THIRD EDITION

Handbook of PTSD

SCIENCE AND PRACTICE

edited by Matthew J. Friedman,
Paula P. Schnurr, and Terence M. Keane

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Preface

With this third edition of the *Handbook of PTSD: Science and Practice*, we will have published this volume approximately every 7 years since 2007. As before, our major goal is to provide an authoritative and comprehensive reference, as well as a textbook for an advanced-level curriculum, on trauma and posttraumatic stress disorder (PTSD). The *Handbook* has enabled us to benchmark all the scientific and clinical progress that has been achieved, both since PTSD was first approved as a diagnosis in 1980 in the American Psychiatric Association's third edition of its *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) and, more specifically, since DSM-5 was published in 2013. While preserving the basic construct that traumatic stress can precipitate the onset of severe and persistent alterations in cognitions, emotions, and behavior, DSM-5 also expanded PTSD's clinical context beyond a narrow, fear-based anxiety disorder to a much broader diagnostic category of its own in which affective, externalizing, and dissociative symptoms are also recognized alongside the original fear-based anxiety diagnosis as clinically significant consequences of exposure to posttraumatic stress.

Because of the accelerating pace of scientific and clinical progress, we have had to combine a few chapters from the last edition in order to make room for brand-new chapters on the latest research on the different DSM-5 and ICD-11 diagnostic criteria for PTSD, the new PTSD brain bank, treatment of comorbid disorders, the psychoneurobiology of resilience, and an implementation science approach to foster best practices for PTSD. In addition, older chapters now contain a great deal of new information and, in some cases, have been almost completely rewritten. There is also a more global perspective in this edition because more international experts have joined colleagues within the U.S. Department of Veterans Affairs' National Center for PTSD, as well as other American scholars, to produce this volume.

The book itself is divided into four parts. Part I, "Historical Overview: Setting the Context," includes an overview of scientific and clinical progress in the field of traumatic stress studies from DSM-III to DSM-5; a detailed discussion of the rationale for the new DSM-5 diagnostic criteria, as well as an update on research with both the new DSM-5 and ICD-11 criteria; and a historical review on the evolution of traumatic stress studies from the 19th to the 21st centuries.

Part II, "Scientific Foundations and Theoretical Perspectives," includes separate chapters on the epidemiology of PTSD among adults and children/adolescents,

respectively; a theoretical chapter on psychological models of PTSD; a review of research on memory and neurocognition; and a chapter on trauma-induced dissociation that includes a section on PTSD's dissociative subtype. Other chapters on scientific findings examine neurocircuitry and neuroplasticity; neurobiological alterations; genetic and epigenetic findings; the new PTSD brain bank; and gender and developmental issues (in both children and older adults).

Part III, "Clinical Practice: Evidence-Based State of the Art," provides comprehensive updates of the empirical literature on assessment and treatment of adults and children. Treatment chapters address early intervention, and individual, couple/family, and group treatments. Other chapters focus on pharmacotherapy, treatment of PTSD and comorbid disorders, and trauma exposure and physical health.

In both the scientific (second) and clinical (third) parts, most chapters have the same format. They usually begin with "Methodological Considerations," which present the scientific techniques needed to acquire the knowledge pertinent to that specific topic. These sections provide thoughtful descriptions of the different techniques needed to investigate brain imaging, memory, gene × environment interactions, epidemiology, psychosocial treatments, pharmacotherapy, and so on. The second section of most chapters, "Current State of the Art," provides a comprehensive and rigorous analysis of the peer-reviewed literature in that particular field. The third section, "Generalizability of Current Findings," considers the relevance of the current empirical literature to scientific or clinical questions that matter most. Finally, each chapter concludes with the section "Challenges for the Future," in which authors identify important new directions for science and practice.

Part IV, "Emerging Territory," contains eight chapters that focus on some of the most exciting new areas in the field, including cultural expression of posttraumatic syndromes and forensic issues. With regard to advances in treatment, chapters on Internet-based psychotherapy, telemental health approaches, and the application of implementation science to disseminate evidence-based treatments offer exciting insight and recommendations by pioneers in these fields. The chapter on the psychoneurobiology of resilience addresses one of the most important spin-offs of PTSD research that focuses on our emerging understanding of health and wellness rather than illness and pathology. The chapter on public health interventions following disasters recognizes that, in addition to traditional clinical concerns, PTSD is a major public health challenge that requires population-based and public health approaches to prevent the onset of PTSD following catastrophic, mass casualty events. Finally, we editors get the last word and present what we consider to be the 19 most important questions for the field. This is always our favorite chapter because it gives us a chance to synthesize all the superb material in the preceding 32 chapters so that we can share our vision for the future of PTSD research. We hope research on these questions will receive the highest priority among investigators and funding agencies.

In closing, we are greatly indebted to the contributing authors with whom we had the privilege to work on this third edition of the *Handbook of PTSD: Science and Practice*. They represent some of the leading PTSD scholars and clinicians in the world today. We also thank The Guilford Press for supporting all three editions of the *Handbook*. We hope this volume serves as a useful textbook for graduate-level and continuing education curricula. We hope it helps PTSD investigators to conceptualize and design studies that have a significant impact on the field. And we hope it will enable practitioners to select and implement the best evidence-based approaches for their clients.

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SETTING THE CONTEXT

CHAPTER 1

PTSD from DSM-III to DSM-5
PROGRESS AND CHALLENGES

Matthew J. Friedman, Paula P. Schnurr, and Terence M. Keane

Since prehistoric times, men, women, and children have been exposed to traumatic life events. Indeed, a literary record of the adverse impact of such exposure can be found in the work of poets, dramatists, and novelists such as Homer, Shakespeare, Tolstoy, Dickens, and Remarque, up to and including contemporary authors. Attempts to record and understand such events and their consequences within a scientific or medical context are much more recent, dating back to the mid-19th century. For example, archival compensation and pension data from the U.S. Civil War indicate that high rates of traumatic exposure were associated with high rates of physical and psychological morbidities (Pizarro, Silver, & Prause, 2006). These latter observations generated a number of somatic (e.g., soldier's heart, effort syndrome, shell shock, neurocirculatory asthenia) and psychological (nostalgia, combat fatigue, traumatic neurosis) conceptual models (see McFarlane & Kilpatrick, Chapter 3, and Bryant, Chapter 6, this volume, on the history and psychological models of posttraumatic stress disorder [PTSD], respectively). Reviewing some of the rich clinical (and literary) reports provided prior to 1980, when the diagnosis was formalized (see below), we see that many authors were describing what would now be labeled PTSD. So, what has been gained by this conceptual and diagnostic construct?

The explication and adoption of PTSD as an official diagnosis in the American Psychiatric Association's (APA, 1980) third edition of its *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) ushered in a significant paradigm shift in mental health theory and practice. First, it highlighted the etiological importance of traumatic exposure as the precipitant of stress-induced alterations in cognition, emotion, brain function, and behavior. Dissemination of this model provides a coherent context within which practitioners have been able to understand the pathway from traumatic exposure to clinical abnormalities. Second, the PTSD model has stimulated basic research (both human and animal), in which it has been possible to investigate the causal impact of extreme stress on molecular, hormonal, behavioral, and social expression. More

recently, investigators began to explore gene–environment interactions and epigenetic expression within this paradigm. Third, as noted earlier, the traumatic stress model has invited the elaboration of therapeutic strategies that have successfully ameliorated PTSD symptoms. Finally, PTSD was a unifying principle at a time when investigators were describing similar symptoms that were specific to different traumatic events, such as child abuse, interpersonal violence, rape, the Holocaust, and Vietnam combat exposure. The important inductive leap of the DSM-III PTSD diagnosis was recognition that the reactions to these different types of events had more commonalities than differences. Subsequent research has shown that the same therapies can be used successfully across different types of traumatic events. All of these extraordinary advances could not have occurred before posttraumatic distress and dysfunction were reconceptualized as PTSD.

It is possible that PTSD would not have been included in DSM-III without strong support from veteran, feminist, and Holocaust survivor advocacy groups. Unlike depression, schizophrenia, and other anxiety disorders, PTSD emerged from converging social movements rather than academic, clinical, or scientific initiatives. As a result, PTSD received an ambivalent, if not hostile, reception in many prominent psychiatric quarters when it was first introduced in 1980. The professional response to this negative reception was an outpouring of research to test the legitimacy of PTSD as a diagnosis. This entire volume documents the current state of the art of such research. Our conclusions are that people who meet PTSD diagnostic criteria exhibit significant differences from nonaffected individuals, as well as from individuals with depression, anxiety disorders, or other psychiatric disorders. Such research spans the spectrum from gene expression to brain imaging to cognitive processing to clinical phenomenology to interpersonal dynamics. Analyses of the PTSD symptom clusters have validated the PTSD construct from DSM-III through DSM-5 (APA, 2013). There can no longer be any doubt about the reliability, validity, and heuristic value of PTSD as a diagnosis.

As detailed in Chapter 2 on the evolution of DSM-5 and in Chapter 3 on the history of trauma-related disorders, the actual term *posttraumatic stress disorder* did not appear in our nosology until 1980. The first *Diagnostic and Statistical Manual of Mental Disorders* (DSM-I; APA, 1952) included "gross stress reaction," a transient disorder following exposure to civilian catastrophes or military combat. Strangely, at the height of the Vietnam War, DSM-II (APA, 1968) eliminated this category. In 1969, John Talbott, future president of the APA, called for the return of this diagnostic category because there was no current DSM diagnosis that captured the symptoms he had treated as a military psychiatrist in Vietnam (Bloom, 2000).

During the 1970s, several social movements in the United States and around the world converged to bring attention to reactions following interpersonal violence, as well as combat. The women's movement focused attention on the sexual and physical assault of women as highlighted by the speak-outs and consciousness-raising groups organized by the National Organization for Women. Laws were changed to reflect the understanding that incidents of abuse within the family were crimes and of societal concern, not merely private family matters. Mandatory reporting of child abuse was enacted in all U.S. states. Rape shield laws, marital rape laws, and the legal recognition that rape could happen to boys and men, and not just girls and women, also changed attitudes and services provided. Landmark studies by Burgess and Holmstrom (1973, 1974), Kempe and his colleagues (Gray, Cutler, Dean, & Kempe, 1977; Schmitt & Kempe, 1975), and Walker (1979) resulted in descriptions of the child abuse syndrome, the rape trauma syndrome, and the battered woman syndrome, respectively,

and spawned a generation of research on those topics. The descriptions of responses to these forms of interpersonal traumas were much like those being described by the millions of Vietnam veterans who had returned from the war (Figley, 1985; Friedman, 1981). As a result, when the revision of the DSM was considered, reactions to all traumatic events were pooled into one overarching category.

In 1980, DSM-III included PTSD for the first time as an official diagnosis. PTSD was classified as an anxiety disorder that had four criteria: (1) the existence of a recognizable stressor that would evoke distress in nearly anyone; (2) at least one of three types of reexperiencing symptoms; (3) at least one indicator of numbing of responsiveness or reduced involvement in the world; and (4) at least two of an array of other symptoms, including hyperarousal or startle, insomnia, survivor guilt, and cognitive difficulties (see Friedman et al., Chapter 2, this volume, for more details). DSM-III also distinguished acute from delayed onset, depending on whether full symptom expression occurred within or after the first 6 months following exposure to trauma (see Friedman et al., Chapter 2, this volume, on DSM-5 diagnostic criteria for PTSD). Introduction of the diagnosis in DSM-III was followed by a wave of prevalence studies to determine who develops the disorder and under what conditions, along with development of valid and reliable assessment instruments for these criteria. Publications on treatment outcome studies began to appear by the mid- to late 1980s.

On the one hand, clinicians, who had been seeking an appropriate nosological category for psychiatrically incapacitated Holocaust survivors, rape survivors, combat veterans, and other traumatized individuals, were delighted. They finally had a DSM-III diagnosis that validated the unique clinical phenomenology of their patients. Recognition of the deleterious impact of a traumatic event provided a conceptual tool that transformed mental health practice and launched decades of research. For the first time, interest in the effects of trauma did not disappear with the end of a war. On the other hand, the new diagnosis also engendered criticisms, some of which continue to the present (see below).

The next revision, DSM-III-R (APA, 1987), produced the criteria that, for the most part, exist today. Six criteria, labeled A–E, were established: (A) the stressor; (B) reexperiencing symptoms; (C) avoidance/numbing symptoms; (D) arousal symptoms; (E) a duration criterion of 1 month; and (F) significant distress or functional impairment. The stressor criterion continued to define eligible stressors as events "outside the range of usual human experience (i.e., outside the range of such common experiences as simple bereavement, chronic illness, business losses, and marital conflict)" and usually experienced with intense fear, terror, and helplessness (p. 247).

Among the questions addressed by the DSM-IV field trials was whether criterion A, the stressor criterion, should be changed or dropped entirely (Kilpatrick et al., 1998) because after the first wave of PTSD prevalence studies, it had become evident that "outside the range of normal experience" was inaccurate. In fact, most people experience at least one qualifying traumatic event in their lives, and some events, though infrequent in one person's life, are all too common across the population. Researchers asked whether people who experienced other stressful events, such as divorce, loss of a job, or the natural death of a loved one, would also develop PTSD. They found that it made little difference whether the definition of the rates of PTSD was strict or nonrestrictive; few people developed PTSD unless they had experienced an extremely stressful (life-threatening) event. Researchers also found support for including a subjective distress component in criterion A (criterion A2) because of consistent findings that the levels of panic, physiological arousal, and dissociation present at the time of the event

were predictors of later PTSD (Kilpatrick et al., 1998; see Friedman et al., Chapter 2, this volume).

DSM-IV was published by the APA in 1994 and was revised slightly in 2000. Several changes in the PTSD diagnosis were formalized, along with the introduction of a new disorder, acute stress disorder (ASD). Despite the PTSD subcommittee's strong interest in moving the disorder out of the anxiety disorders group, the diagnosis remained where it was. Criterion A now had two parts: (1) objective (e.g., exposure to an event or events that involved actual or threatened death or serious injury or a threat to the physical integrity of self or others) and (2) subjective (e.g., experiencing intense fear, helplessness, or horror during the event). Other diagnostic alterations are described in Chapter 2 (Friedman et al., this volume).

The bigger development in DSM-IV was the introduction of ASD, which emerged at the recommendation of the DSM-IV Dissociative Disorders Subcommittee, with the observation that people who had dissociative symptoms during or immediately after the traumatic event were most likely to develop PTSD. ASD was also introduced to bridge the diagnostic gap between the occurrence of a traumatic event and 1 month later, when PTSD could first be diagnosed. Criteria for ASD include the same stressor criterion as PTSD, and the presence of reexperiencing, avoidance, and arousal symptoms. DSM-IV's ASD differed significantly from PTSD in its emphasis on dissociative symptoms. Indeed, DSM-IV stipulated that individuals with ASD must exhibit at least three types of dissociative responses (amnesia, depersonalization, derealization, etc.).

PTSD diagnostic criteria were also revised in DSM-5 (see Friedman, Resick, Bryant, & Brewin, 2011; Friedman et al., Chapter 2, this volume, for details). To briefly summarize:

1. PTSD is no longer categorized as an "anxiety disorder" but is now in a new category, "trauma and stressor-related disorders," alongside acute stress disorder, adjustment disorders, and other related diagnoses.
2. The PTSD construct has been expanded to include other clinical phenotypes; in addition to the DSM-III/IV fear-based anxiety disorder, PTSD now includes anhedonic/dysphoric, dissociative, and externalizing phenotypes.
3. The latent structure of PTSD now comprises four (rather than DSM-IV's three) symptom clusters (i.e., intrusion, avoidance, negative mood and cognitions, and arousal and reactivity).
4. DSM-IV's criterion A2 (i.e., responding to the traumatic event with "fear, helplessness of horror") has been eliminated, given the recognition that many other powerful emotions like shame and rage can contribute to development of PTSD.
5. DSM-IV's 17 symptoms have been retained (though sometimes revised or clarified), and three new symptoms have been added.
6. Two new subtypes have been added: a dissociative subtype for people with derealization or depersonalization, along with the full PTSD syndrome and a preschool subtype for children 6 years of age and younger (see Friedman et al., Chapter 2, and DePrince et al., Chapter 8, this volume).

With regard to ASD, it is no longer necessary for traumatized individuals to exhibit any dissociative symptoms. Nine (out of 14) symptoms are needed for the diagnosis (Bryant, Friedman, Spiegel, Ursano, & Strain, 2011). Given recognition that acute posttraumatic reactions may be expressed differently by different people, individuals who meet DSM-5 ASD diagnostic criteria may or may not exhibit dissociative symptoms.

Research demonstrates that the presence or absence of dissociative symptoms does not affect the severity, morbidity, or longitudinal course of people with ASD (Bryant, Friedman, Spiegel, Ursino, & Strain., 2011).

We begin this third edition of the *Handbook of PTSD* by briefly reviewing the wealth of scientific information that has accrued since 1980 because of the new conceptual context provided by PTSD. Such research has not only transformed our understanding of how environmental events can alter psychological processes, brain function, and individual behavior, but it has also generated new approaches to clinical treatment. Indeed, the translation of science into practice since DSM-III is the major impact of the PTSD diagnosis. Then we consider questions, controversies, and challenges regarding PTSD.

SCIENTIFIC FINDINGS AND CLINICAL IMPLICATIONS

Epidemiology

When PTSD was first operationalized in DSM-III, a traumatic event was defined as "a catastrophic event beyond the range of normal human experience." Epidemiological surveys conducted since 1980 have shown otherwise. More than half (68.7%) of all American adults are exposed to traumatic stress during their lifetimes (Goldstein et al., 2016). In nations at war or subject to internal conflict, traumatic exposure is much higher (Bromet, Karam, Koenen, & Stein, 2018). Surveys of U.S. military veterans suggest, as might be expected, high rates of exposure to war-zone stress, although prevalence estimates vary in magnitude depending on the specific nature of each war and the war-specific demands of each deployment (Magruder & Yaeger, 2009; Marmar et al., 2015; Ramchand, Rudavsky, Grant, Tanielian, & Jaycox, 2015).

One of the most robust findings in epidemiological research on PTSD is a dose–response relationship between the severity or amount of exposure to trauma and the onset of PTSD (Bromet et al., 2018; see Korte et al., Chapter 4, this volume). This dose–response association has held up whether the traumatic experience has been sexual assault, war-zone exposure, natural disaster, or terrorist attack (see Friedman et al., Chapter 2, on DSM-5, and Korte et al., Chapter 4, on epidemiology, this volume). Within this context, however, in the United States, the toxicity of interpersonal violence, such as that in rape, is much higher than that in other types of traumatic events (e.g., Breslau, 2009; Pietrzak, Goldstein, Southwick, & Grant, 2011; see Korte et al., Chapter 4, this volume). In developing nations, however, natural disasters are much more likely to produce PTSD because of the magnitude of resource loss associated with such exposure (see Korte et al., Chapter 4, and Copeland & McGinnis, Chapter 5, this volume, on the epidemiology of PTSD among adults and children, respectively).

It is also important to recognize that PTSD is not the only clinically significant consequence of traumatic exposure. Other psychiatric consequences include depression, other anxiety disorders, and alcohol or drug abuse/dependency (se Korte et al., Chapter 4, this volume, on epidemiology). Finally, accumulating evidence indicates that when traumatized individuals develop PTSD, they are at greater risk to develop medical illnesses (Schnurr et al., Chapter 25, this volume). The clinical implications of these data are clear. Given that exposure to traumatic experiences occurs in at least half of the U.S. adult population (and much more frequently within nations in conflict), mental health and medical clinicians should always take a trauma history as part of their routine intake. If there is a positive history of such exposure, the next step is to assess

for the presence or absence of PTSD (see Livingston et al., Chapter 16, and Briggs et al., Chapter 17, this volume, on assessment of PTSD in adults and children).

Risk Factors

Most people exposed to traumatic stress do not develop persistent PTSD. For example, one study found that even among female victims of rape, the most toxic traumatic experience, 54.1% did not exhibit full PTSD after 1 month, and 78.8 % of female assault survivors did not have PTSD after 3 months (Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992). This means that most people have sufficient resilience to protect themselves from developing the disorder. Research on risk factors generally divides them into pretraumatic, peritraumatic, and posttraumatic factors (see Korte et al., Chapter 4, this volume, on risk factors). Pretraumatic factors include age, gender, previous trauma history, personal or family psychiatric history, educational level, genotype, and the like (see Korte et al., Chapter 4, on epidemiology, and Averill et al., Chapter 30, this volume, on resilience).

It is not clear why some pretraumatic risk factors are associated with PTSD prevalence. It is easy to understand how something like childhood adversity might increase risk of adult disorder. But, for example, female rather than male gender predicts greater likelihood of developing PTSD following exposure to trauma (e.g., Goldstein et al., 2016; see Korte et al., Chapter 4, this volume). It is possible that this is just due to women's greater likelihood of having experienced the events most likely to be associated with PTSD, such as child sexual abuse, rape, or intimate partner violence (Kessler et al., 2005). However, such apparent gender differences may actually represent more complex phenomena, such as gender differences in how trauma is conceptualized, potential gender-related differences in the PTSD construct itself, the social context in which gender differences are expressed, or the way comorbid disorders contribute to this difference (see Kimerling et al., Chapter 13, this volume, on gender issues in PTSD). Finally, there is evidence that whereas female gender predicts greater risk of PTSD, it may also predict more favorable responsivity to treatment.

With the recent characterization of the human genome, it will not be long before pretraumatic factor research includes genotype assessment. Indeed, recent studies identified a number of candidate genes that are being investigated regarding vulnerability versus resilience to PTSD following exposure to traumatic events. Given that genotype, epigenetic methylation, and gene expression differences likely accompany the development of psychopathologies such as PTSD, research incorporating all three forms of genetic information from the same traumatized individuals is needed (see Bustamante et al., Chapter 11, this volume, on the genetics of PTSD).

Peritraumatic risk factors concern the nature of the traumatic experience itself, as well as one's reaction to it. The dose–response relationship between trauma exposure and PTSD onset, mentioned previously, applies here, so that the severity of traumatic exposure predicts the likelihood of PTSD symptoms. Other peritraumatic risk factors include exposure to atrocities, peritraumatic dissociation, panic attacks, and other emotions (see Korte et al., Chapter 4, this volume).

Social support is a very important protective factor that can protect trauma-exposed individuals from developing PTSD (see Korte et al., Chapter 4, this volume, on epidemiology, and Averill et al., Chapter 30, this volume, on resilience, this volume.) Indeed, social support appears to be such a powerful factor that it has been shown to

offset genetic vulnerability among depressed children to adverse life events (Kaufman et al., 2004).

Schnurr, Lunney, and Sengupta (2004) have distinguished between risk factors for the onset of PTSD and those factors that predict maintenance of PTSD. In their study of Vietnam veterans, risk factors for persistence of PTSD emphasized current rather than past factors and included current emotional sustenance, ongoing social support, and recent adverse life events. The clinical significance of these findings is noteworthy. Assessment of risk factors, especially the strength and availability of social support, should be a routine part of any PTSD diagnostic interview. Furthermore, mobilization of social support, whenever possible, should be part of any treatment plan. This applies whether the client has either chronic PTSD or an acute posttraumatic reaction, and whether the clinician is providing treatment within a traditional clinical setting or an early intervention following a mass casualty within a public mental health context (see Morganstein et al., Chapter 31, this volume, on prevention and public health).

Psychological Theory and Practice

PTSD invites explication in terms of classic experimental psychological theory to a far greater degree than any other psychiatric syndrome. It is one of the more interesting and unique disorders as well, inasmuch as researchers, theorists, and clinicians have the rare opportunity to be present at the genesis of a disorder that began at a precise moment in time. Hence, there is a rich conceptual context within which to understand the disorder (see Bryant, Chapter 6, this volume, on psychological models of PTSD). Both conditioning and cognitive models have been proposed. Pavlovian fear conditioning, either as a unitary model (Kolb, 1989) or within the context of Mowrer's two-factor theory (which combined the learning principles of classical and operant conditioning), has influenced research and treatment (Keane & Barlow, 2002; Keane, Zimering, & Caddell, 1985). Such models inspired considerable animal, psychophysiological, and brain-imaging research, in addition to psychological investigations with clinical cohorts. Emotional processing theory (Foa & Kozak, 1986) has also been very influential. This theory proposes that pathological fear structures (i.e., stimulus, response, and meaning propositions; Lang, 1977), activated by trauma exposure, produce cognitive, behavioral, and physiological anxiety. Finally, cognitive models derived from classical cognitive theory (Beck, Rush, Shaw, & Emery, 1979) postulate that it is the interpretation of the traumatic event, rather than the event itself, that precipitates clinical symptoms.

Several cognitive-behavioral therapies (CBTs) are derived from the aforementioned theories and are tested with patients with PTSD. What all CBT approaches have in common is that they elegantly translate theory into practice. The most successful treatments for PTSD are CBT approaches, most notably prolonged exposure, cognitive therapy, cognitive processing therapy, written exposure therapy, and narrative exposure therapy. Several chapters in this volume review the empirical evidence supporting CBT approaches for adults (Galovski et al., Chapter 19), children and adolescents (Cohen & Mannarino, Chapter 20), couples and families (Monson et al., Chapter 21), and in group formats (Beck & Sloan, Chapter 22). Indeed, all clinical practice guidelines for PTSD identify trauma-focused CBT as the treatment of choice (Hamblen et al., 2019).

CBT is also effective in treating acutely traumatized patients with ASD within weeks of exposure to a traumatic event (see Azad et al., Chapter 18, this volume). This approach utilizes briefer versions of the prolonged exposure and cognitive restructuring

protocols that have been so effective in treating chronic PTSD. Also, CBT protocols were modified so that they can be delivered through the Internet (see Ruzek, Chapter 28, this volume), or remotely via telehealth or mobile phone applications (see Morland et al., Chapter 29, this volume).

In addition to CBT, eye movement desensitization and reprocessing (EMDR) has emerged as a first-line therapy for PTSD and is recommended as a front-line treatment in several PTSD practice guidelines (Hamblen et al., 2019). Although there are strong disagreements about the mechanism of action for this approach, especially with regard to the importance of eye movements, the evidence regarding EMDR's efficacy is strong enough for it to be classified as a first-line treatment for PTSD in recent clinical practice guidelines (see Galovski et al., Chapter 19, this volume, on psychosocial treatments).

Although such progress is gratifying, it is the case that there is still much work ahead. Almost all randomized clinical trials for PTSD tested only components of CBT or single medications. Such studies suggest that approximately half of all CBT patients achieve full remission of symptoms, leaving another half that experience partial or less improvement after a course of CBT. Clearly, there is room for more research on new treatments and for a better understanding of how to combine medications and/or psychosocial treatments in real-world settings. Also, questions about optimal strategies for specific phasing of treatments may benefit those who typically drop out of therapy early or do not benefit from a standard course of treatment. Indeed, future research will need to investigate systematically which treatment (or combination of treatments) is most effective for which patients with PTSD under what conditions. Finally, it is imperative that we utilize the most advanced technologies for dissemination of evidence-based practices for the treatment of PTSD in clinical settings (see Stirman, Chapter 32, this volume, on implementation of the best clinical practices).

Recent progress has also been made in developing clinical approaches for PTSD among children and adolescents (see Brown et al., Chapter 14, this volume), thanks in part to establishment of the National Child Traumatic Stress Network in the United States. Yet progress with regard to older adults has lagged behind (see Cook & Simiola, Chapter 15, this volume). In short, there is a real need for better understanding of the consequences of traumatic exposure and for developmentally sensitive treatment approaches for people at either end of the developmental lifespan.

Biological Theory and Practice

Thanks to advances in technology and computational science, biological research has progressed beyond animal models and neurohormonal assays to brain imaging, genetic research, and analysis of brain tissue. It is notable that a book on the neurobiology of PTSD, published in 1995 (Friedman, Charney, & Deutch, 1995), had no chapters on brain imaging, genetics, or neuropathology, unlike this volume. The neurocircuitry that processes threatening stimuli centers on the amygdala, with major reciprocal connections to the hypothalamus, hippocampus, locus coeruleus, and raphe nuclei; and mesolimbic, mesocortical, and downstream autonomic systems. Major restraint on the amygdala is ordinarily exercised by the medial prefrontal cortex. In PTSD, amygdala activation is excessive, whereas prefrontal cortical restraint is diminished. Furthermore, great advances have been made in our understanding of neurocircuitry, neuroplasticity, and neuropathology that mediate both posttraumatic psychopathology and recovery from PTSD (see Averill et al., Chapter 9, this volume, on neurocircuitry and

neuroplasticity, and Girgenti et al., Chapter 12, on neuropathology and research with postmortem brain tissue).

Many different neurohormones, neurotransmitters, and neuropeptides may also play important roles in this stress-induced fear circuit (see Rasmusson et al., Chapter 10, this volume, on neurobiological alterations associated with PTSD), as do different genes that are expressed or suppressed in PTSD (see Bustamante et al., Chapter 11, this volume, on the genetics of PTSD). Thus, there are many potential opportunities to translate such basic knowledge into pharmacological practice and precision medicine.

At present, only two medications, both selective serotonin reuptake inhibitors (SSRIs), have been approved by the U.S. Food and Drug Administration (FDA) as treatments for PTSD. There is growing research with other medications affecting different mechanisms, but many more randomized clinical trials are needed. Given our growing knowledge in this area and the fact that only 30% of patients receiving SSRIs achieve full remission, there is reason to expect that newer agents will prove more effective in the future (see Davis et al., Chapter 23, this volume).

Another significant translation of science into practice concerns the association between PTSD and physical illness (see Schnurr et al., Chapter 25, this volume). Given the dysregulation of major neurohormonal and immunological systems in individuals with PTSD, it is perhaps not surprising that patients with PTSD are at greater risk for medical illness (Schnurr & Green, 2004) and for increased mortality due to cancer and cardiovascular illness (Boscarino, 2006). Again, as a mark of recent progress, in 1995 such relationships were merely hypothesized (Friedman & Schnurr, 1995). Now there is a compelling and rapidly growing database to verify these hypotheses.

Resilience, Prevention, and Public Health

Two epidemiological findings have profoundly affected our understanding about the risk of exposure to trauma and about the consequences of such exposure. First, as noted earlier (see the section "Epidemiology"), exposure to catastrophic stress is not unusual over a lifetime. Second, most exposed individuals are resilient; they do not develop PTSD or some other disorder in the aftermath of traumatic events. Recent world events have thrust such scientific findings into the context of public policy and public health, including terrorist attacks in New York City, Madrid, Moscow, London, Boston, and elsewhere: the South Asia tsunami of 2005; Hurricane Katrina; the wars in the Middle East and Africa; and many other human-made and natural disasters. The scientific question is, Why are some individuals resilient, while others develop PTSD following such catastrophic stressful experiences? The clinical question is, What can be done to fortify resilience among individuals who might otherwise be vulnerable to PTSD following traumatic exposure? And the public mental health question is, Following mass casualties or large-scale disasters, what can be done to prevent psychiatric morbidity in vulnerable populations?

From a historical perspective, these three questions are remarkable. Only because of recent scientific progress can such questions even be conceptualized. The new interest in resilience is emblematic of both maturity in the field and technological advances. Resilience is a multidimensional construct that includes genetic, neurohormonal, cognitive, personality, and social factors (see Averill et al., Chapter 30, this volume, on resilience). From the clinical and public health perspective, the major question is, Can we teach vulnerable individuals to become more resilient? Our emergent understanding

of the multidimensional mechanisms underlying resilience has given the term *stress inoculation* a new meaning in the 21st century. This in turn has raised public policy and public mental health questions about the feasibility of preventing posttraumatic distress and PTSD in the population at large (see Morganstein et al., Chapter 31, this volume, on public health and prevention).

In the United States, the terrorist attacks on September 11, 2001, instigated a national initiative to understand the longitudinal course of psychological distress and psychiatric symptoms following exposure to mass casualties. In this regard, civilian disaster mental health found much in common with military mental health. In both domains, it is recognized that most posttraumatic distress is a normal, transient reaction from which complete recovery can be expected. A significant minority of both civilian and military traumatized individuals, however, do not recover but go on to develop clinical problems that demand professional attention. Thus, several trajectories follow traumatic stress: normal transient distress, early-onset PTSD followed by recovery, or chronic clinical morbidity. On the one hand, the second and third trajectories require treatment by traditional mental health professionals; indeed, evidence-based early interventions have also been developed for acutely traumatized individuals (see Azad, Chapter 18, this volume). On the other hand, the first trajectory, affecting most of the population, demands a public mental health approach that fortifies resilience (see Averill et al., Chapter 30, and Morganstein et al., Chapter 31, this volume, on resilience and prevention, respectively).

The conceptual and clinical advances that have been made in this area during the last decade are very exciting. Future research should produce a wide spectrum of scientific advances that will enhance our understanding of resilience (at genetic, molecular, social, etc., levels), thereby providing needed tools to foster prevention and facilitate recovery at both individual and societal levels.

CRITICISMS OF THE PTSD CONSTRUCT

Criticisms of PTSD as a diagnosis have not abated with the passage of time. Some have probably been exacerbated by concerns about the escalating number of PTSD disability claims recently filed by veterans and civilians (see Friedman et al., Chapter 2, on DSM-5, and Kilpatrick et al., Chapter 27, on forensic issues, this volume). The cross-cultural argument currently rages within the context of natural disasters (e.g., the 2005 South Asian tsunami) or large-scale terrorist attacks (e.g., the bloodshed in Mumbai in 2011) or the endless wars and forced migrations (especially in Africa and the Middle East; see Silove & Klein, Chapter 26, this volume, on culture and trauma). Currently, these arguments also appear within the popular culture, due to mass media's increased attention to ongoing terrorist attacks, natural disasters, wars, and industrial accidents around the world. As a result, scientific debates about PTSD, previously restricted to professionals, have found their way into daily newspapers, popular magazines, radio talk shows, and televised documentaries. Critics of the diagnosis claim that (1) people have always had strong emotional reactions to stressful events, and there is no need to pathologize them; (2) PTSD serves a litigious rather than a clinical purpose; (3) the diagnosis is a European American culture-bound syndrome that has no applicability to posttraumatic reactions within traditional cultures; (4) verbal reports of both traumatic exposure and PTSD symptoms are unreliable; and (5) traumatic memories are not valid. We believe that these criticisms demand a thoughtful and balanced response

because they reflect concerns about PTSD that are shared by the professional community and the public alike.

PTSD Needlessly Pathologizes Normal Reactions to Abusive Violence

This criticism asserts that normal reactions to the abnormal conditions of political repression and torture (or interpersonal violence; e.g., domestic violence) should be understood as appropriate coping responses to extremely stressful events. The argument further states that a psychiatric label such as PTSD removes such reactions from their appropriate sociopolitical-historical context and thrusts them into the inappropriate domain of individual psychopathology. We reject this argument because it fails to acknowledge that some people cope successfully with such events and manifest normal distress, whereas others exhibit clinically significant symptoms and subsequently experience disability. This is another area in which both public health and individual psychopathology models are applicable to different segments of a population exposed to the same traumatic stressor (see Averill et al., Chapter 30, and Morganstein et al., Chapter 31, this volume, on resilience and prevention, and public health, respectively).

As we have learned during the post-9/11 era of posttraumatic public mental health, most people exposed to severe stress have sufficient resilience to achieve full recovery. A significant minority, however, develop acute and/or chronic psychiatric disorders, among which PTSD is most prominent. People who meet PTSD diagnostic criteria differ from nonaffected individuals with regard to symptom severity, chronicity, functional impairment, suicidal behavior, and (both psychiatric and medical) comorbidity. The purpose of any medical diagnosis is to inform treatment decisions, not to "pathologize." Therefore, we reiterate that it is beneficial to detect PTSD among people exposed to traumatic stress to provide an effective treatment that may both ameliorate their suffering and mitigate or prevent future adverse consequences.

PTSD Is a Culture-Bound European American Syndrome

The PTSD construct has been criticized from a cross-cultural perspective as an idiosyncratic European American construct that fails to characterize the psychological impact of traumatic exposure in traditional societies. We acknowledge that certain culture-specific idioms of distress around the world may do a better job describing the expression of posttraumatic distress in one ethnocultural context or another. On the other hand, PTSD has been documented throughout the world, and the cross-cultural validity of PTSD has been demonstrated conclusively (Bromet et al., 2018; Hinton & Lewis-Fernández, 2011; see Silov & Klein, Chapter 26, this volume, on culture and PTSD). An important report, with a unique bearing on this issue, compared people from widely different cultures who were exposed to a similar traumatic event. North and colleagues (2005) compared Kenyan survivors of the bombing of the American embassy in Nairobi with American survivors of the bombing of the Federal Building in Oklahoma City. Both events were remarkably similar with respect to death, injury, destruction, and other consequences. Similar, too, was PTSD prevalence among Africans and Americans exposed to these different traumatic events. Furthermore, a recent randomized clinical trial in the Democratic Republic of the Congo demonstrated the cross-cultural utility of the PTSD diagnosis, as well as the generalizability of evidence-based PTSD treatment in a non-Western arena. Female Congolese survivors of sexual violence who received group sessions of cognitive processing therapy exhibited marked reduction

of PTSD symptoms and significant improvement in functional status compared to a comparison group that received supportive therapy. This improvement was sustained at the 6-month follow-up assessment (Bass et al., 2013). Finally, the World Mental Health Survey demonstrates that PTSD occurs across the globe in low- as well as high-income countries. Its symptom characteristics, risk factors, clinical course, associated disorders, and disease burden appear to be consistent (although prevalence may vary) from one country to the next (Bromet et al., 2018).

PTSD Primarily Serves a Litigious Rather Than a Clinical Purpose

PTSD has played such a prominent role in disability and legal claims in part because it has been assumed that the traumatic event is causally related to PTSD symptom expression and, hence, functional impairment (see Kilpatrick et al., Chapter 27, this volume, on forensic issues). Although traumatic exposure is a necessary condition for the development of PTSD, it is not a sufficient condition. For example, the event most likely to result in PTSD is rape, yet only a minority of rape victims are diagnosable with PTSD after a few months. Other risk factors play a role in symptom onset and duration, as described earlier in the section on risk factors (see Korte et al., Chapter 4, this volume, on epidemiology). Despite the etiological complexity of PTSD onset, the stressor criterion is fundamental in personal injury litigation, and in compensation and pension disability claims. This is because traumatic exposure establishes liability or responsibility for psychiatric sequelae in a context that puts PTSD in a category by itself with respect to other psychiatric diagnoses.

As noted by Kilpatrick and colleagues (Chapter 27, this volume, on forensic issues), the geometric increase in PTSD claims in civil litigation is due to society's growing recognition that traumatic exposure can have significant and long-lasting consequences. Another important factor driving much of this criticism is the sheer magnitude of money awarded for successful personal injury suits or compensation and pension disability claims.

There is also concern that the stressor (A) criterion has opened the door to frivolous litigation in which PTSD-related damages or disabilities are dubious at best. Although DSM-5 has tightened the definition of a "traumatic event" (see Friedman et al., Chapter 2, this volume), it cannot change the behavior of lawyers seeking to win monetary or other benefits for their clients.

There is a significant difference, however, between challenging the utility of PTSD as a clinical diagnosis and questioning how the diagnosis is applied or misapplied in litigation by attorneys or in disability evaluations by mental health professionals. We believe that minimal standards for such evaluations (e.g., utilizing evidence-based assessment instruments; see Livingston et al., Chapter 16, and Briggs et al., Chapter 17, this volume, on diagnostic assessment in adults and children, respectively) must be developed and enforced. This would ensure that people who have a legitimate claim for a favorable judgment or compensation because of their PTSD are not penalized because of misuse or abuse of this diagnosis in civil litigation or in the disability claims process.

Traumatic Memories Are Not Valid

An important scientific question concerns the validity of traumatic memories. A review of the literature on PTSD-related alterations in cognition and memory (see Brewin

& Vasterling, Chapter 7, and DePrince et al., Chapter 8, this volume, on cognition and memory; and dissociation, respectively) indicates that trauma-related alterations in physiological arousal and information processing may affect how such input is encoded as a memory. Furthermore, the retrieval of such information may be affected by both current emotional state and the presence of PTSD. Such appropriate concerns notwithstanding, when external verification has been possible, it appears that most traumatic memories are appropriate representations of the stressful event in question. A particularly newsworthy manifestation of questions about the accuracy of trauma-related memories was sensationalized in the popular media during the 1990s as "the false-memory syndrome." The issue concerned formerly inaccessible memories of childhood sexual abuse that were later "recovered." Some individuals who recovered such memories went on to sue the alleged perpetrators, thereby transforming a complex, controversial, and relatively obscure scientific and clinical question into a very public debate argued in the courtroom and mass media. It is now well documented that accurate traumatic memories may be lost and later recovered, although it is also clear that some recovered memories are not accurate. The veracity of any specific, recovered memory must be judged on a case-by-case basis (Roth & Friedman, 1998; see Brewin & Vasterling, Chapter 7, this volume, on memory).

Verbal Reports Are Unreliable

A major theme throughout modern psychiatry has been the search for pathophysiological indicators or biomarkers that do not rely on verbal reporting. This is a challenge to assessment of not only PTSD but also all DSM-5 diagnoses. We recognize the importance of this concern but see no reason why it should be cited as a specific problem for PTSD, and not for any other psychiatric diagnosis.

Several laboratory findings hold promise as potential non-self-report assessment protocols for refining diagnostic precision (see Averill et al., Chapter 9; Rasmusson et al., Chapter 10; and Girgenti et al., Chapter 12, this volume, on neurocircuitry and neuroplasticity, neurobiology, and neuropathology, respectively). These findings include psychophysiological assessment with standardized cue presentation or script-driven imagery, the startle response, utilization of pharmacological probes (such as yohimbine or dexamethasone), brain imaging, neurohormonal biomarkers, or alterations in gene expression. At the moment, however, none has sufficient sensitivity or specificity for routine utilization in clinical practice.

In the meantime, we should not overlook the remarkable progress we have made in diagnostic assessment through development of structured clinical interviews and self-report instruments with excellent psychometric properties. In addition to improving diagnostic precision, such instruments have been utilized as dimensional measures to quantify symptom severity and to monitor the effectiveness of therapeutic interventions (see Livingston et al., Chapter 16, and Briggs et al., Chapter 17, this volume, on assessment in adults and children, respectively).

A remarkable study by Dohrenwend and colleagues (2006) demonstrated the high reliability of retrospective self-report data among a representative sample of 260 Vietnam War veterans who participated in the National Vietnam Veterans Readjustment Study (NVVRS). The investigators compared verbal reports of combat exposure recorded by NVVRS investigators with a military-historical measure comprising military personnel files, military archival sources, and historical accounts. Results showed a strong positive relationship between the documented military-historical measure of

exposure and the dichotomous verbal report-based assessment of high versus low to moderate war-zone stress previously constructed by NVVRS investigators. In short, this meticulous study indicates that verbal reports are usually quite reliable.

SUMMARY

PTSD has been at the center of multiple controversies. Close examination of these contentious issues indicates that the arguments are generally not about PTSD per se, but about the appropriateness of invoking PTSD within a controversial or adversarial context. Because the issue of causality or etiology is so clearly specified in PTSD, as in few other diagnoses, it will likely continue to be applied or misapplied in clinical, forensic, and disability situations. An important goal is to respect the scientific evidence to ensure appropriate applications in the future. It is also useful to recognize that, as in the recovered memory controversy, such contentious issues spawned important basic and clinical research that has improved mental health assessment and treatment.

Our purpose in this volume is to document how far we have come since DSM-III in 1980, so that we can generate forward momentum in the right directions. Improving our understanding of PTSD so that we can translate the science into better clinical practice is the overarching goal. This book is dedicated to advancing that understanding in order to prevent PTSD in the first place and to optimize assessment and treatment for people who suffer from the disorder and related problems.

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CHAPTER 2

DSM-5 Criteria for PTSD

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The diagnostic criteria for posttraumatic stress disorder (PTSD) have evolved considerably since PTSD was introduced in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association [APA], 1980). The original DSM-III criteria were rationally derived from clinical observations of combatants, concentration camp survivors, and individuals exposed to civilian catastrophes (Andreasen, 2007). Criterion A, the novel and controversial stressor criterion, required exposure to an extraordinary stressor that was outside the range of usual stressors and would elicit significant distress in almost anyone. The symptom criteria included 12 symptoms divided into three clusters. Criterion B required one reexperiencing symptom (distressing intrusive memories, nightmares, or dissociative flashbacks about the trauma). Criterion C required one numbing of responsiveness symptom (loss of interest, social detachment or estrangement, and constricted affect). Finally, criterion D required two of six miscellaneous symptoms (nine when disaggregated—hyperalertness or exaggerated startle, sleep disturbance, survival guilt and guilt about behavior, memory impairment or trouble concentrating, avoidance of trauma-related activities, and intensification of symptoms after exposure to trauma-related events).

Though groundbreaking, the DSM-III PTSD criteria had some notable shortcomings. Criterion A was criticized as being too brief and vague, providing insufficient guidance for determining whether a stressor was traumatic, and confounding objective and subjective aspects (Weathers & Keane, 2007). There also were concerns about the symptom criteria. Criteria B and C comprised thematically consistent symptoms of intrusion and denial, respectively, and thus were conceptually grounded in Horowitz's model of stress response syndromes, which drew on classic Freudian concepts of involuntary repetition of a trauma and defense mechanisms of denial and numbing. In contrast, however, criterion D was a mixed bag of symptoms with no unifying theme. These conceptual limitations became targets for ongoing explication of the PTSD construct.

The next iteration of PTSD emerged seven years later in DSM-III-R (APA, 1987). It involved a more detailed and expanded definition of a traumatic event, as well as

substantial reorganization and reconceptualization of the symptom criteria (Brett, Spitzer, & Williams, 1988). Criterion A was revised to specify life threat or serious injury as the key underlying dimensions of traumatic events, and fear, terror, and helplessness as the salient emotional responses to such events. It was also expanded to include indirect exposure to a stressor as a qualifying event, for example, learning about a traumatic event happening to a close friend or family member. The symptom criteria were expanded from 12 to 17 symptoms, primarily by disaggregating criterion D symptoms. More significantly, symptoms were grouped into reexperiencing, avoidance and numbing, and hyperarousal clusters. The heterogeneous criterion D symptoms were restructured to create a thematically consistent hyperarousal cluster. Guilt was removed altogether, memory impairment was reconceptualized as psychogenic amnesia, and amnesia and effortful avoidance were moved to criterion C with the numbing symptoms. Criterion B was expanded by one symptom with the addition of intense distress at exposure to reminders of the traumatic event but retained its conceptual role of intrusion. Criterion C, now avoidance and numbing, retained its conceptual role as denial.

Of note, only 7 years had passed since the original DSM-III PTSD criteria were derived, which was insufficient time to allow enough studies to accumulate in the literature to empirically guide nosological decisions. Accordingly, the DSM-III-R criteria again were rationally derived. They were a clear improvement over DSM-III, but they laid the groundwork for future debate, particularly regarding the broadened definition of criterion A and the decision to combine effortful avoidance and numbing.

Few additional revisions were made for DSM-IV (APA, 1994). One relatively minor change involved moving cued arousal from the hyperarousal cluster to the reexperiencing cluster. Far more significant and controversial, however, was an expanded definition of a traumatic event, with the introduction of a two-part criterion A requiring both (1) exposure to an event involving life threat or serious injury (A1) and (2) a peritraumatic emotional response of intense fear, helplessness, or horror (A2). On the one hand, DSM-IV criterion A represented a narrower definition of a traumatic event because the two-part definition was a conjunctive requirement that restricted the number of qualifying events. On the other hand, it represented a broader definition by (1) continuing to include indirect exposure; (2) adding vague phrases such as "confronted with" and "threat to physical integrity"; and (3) expanding the list of qualifying stressors. New examples of qualifying stressors included "being diagnosed with a life-threatening illness"; "learning that one's child has a life-threatening illness"; "developmentally inappropriate sexual experiences without threatened or actual violence or injury"; and "learning about the sudden, unexpected death of a family member of close friend." The last-named example turned out to be the most problematic of all in terms of increasing the prevalence of trauma exposure and PTSD (Breslau & Kessler, 2001). DSM-IV criterion A triggered a backlash, with critics charging that it excessively broadened the concept of trauma, a problem referred to as "conceptual bracket creep" (McNally, 2009) or "criterion creep" (Rosen, 2004).

As this brief overview indicates, apart from the continued broadening of criterion A, most of the major revisions of the PTSD criteria occurred with DSM-III-R. Thus, the symptom criteria were essentially unchanged for more than two decades prior to the advent of DSM-5 in 2013. This stability, combined with rapidly growing clinical and scientific interest in the adverse effects of traumatic stress, promoted an explosive increase in the empirical literature on traumatic stress. This led to major advances in assessment, treatment, and etiological models, but also raised several key nosological questions regarding the nature of psychological trauma and the diagnostic

classification of PTSD. This set the stage for the next, and current, iteration of the PTSD criteria in DSM-5.

As described in a series of papers by Friedman and colleagues (Friedman, 2013; Friedman, Resick, Bryant, & Brewin, 2011a, 2011b), the DSM-5 revision of PTSD commenced in 2008 and culminated in the publication of the final version of DSM-5 in 2013. Led by the Posttraumatic and Dissociative Disorders Sub-Work Group (SWG), the revision involved comprehensive literature reviews, input from diverse trauma experts, public commentary, and multiple levels of review by APA committees. The SWG followed a conservative approach, requiring that any changes be founded on the best available scientific evidence. This ensured continuity in the PTSD criteria, while also justifying revisions deemed necessary to address the limitations of previous criteria. This chapter details the criteria now required for a DSM-5 PTSD diagnosis (see Table 2.1), provides the scientific basis and rationale for the DSM-5 PTSD diagnostic criteria, and reviews why certain related constructs were added (i.e., the dissociative subtype), while others were not (e.g., complex and subthreshold PTSD). We conclude with a discussion of how the DSM-5 approach differs from that of the 11th edition of the *International Classification of Diseases* (ICD-11; World Health Organization [WHO], 2018).

RECLASSIFICATION OF PTSD IN DSM-5

Since its introduction in DSM-III, PTSD has been classified as an anxiety disorder. In DSM-5 it was placed in a new category, "trauma and stressor-related disorders." During the early stages of the DSM-5 process, three nosological possibilities were considered: (1) keep PTSD as an anxiety disorder, (2) classify it as a stress-related fear circuitry disorder, and (3) categorize it as an internalizing disorder.

Given the prominence of Pavlovian fear conditioning and stress reactivity models in our current understanding of PTSD, on the one hand, it would appear that PTSD has much in common with other *anxiety disorders*. In addition, it shares a number of symptoms with other anxiety disorders, such as insomnia, irritability, poor concentration, startle, behavioral and cognitive avoidance, physiological arousal, and persistent apprehension manifested as hypervigilance. On the other hand, the numbing, alienation, and detachment seen in PTSD appear to have more in common with affective disorders. Extreme hypervigilance may sometimes be indistinguishable from paranoid thoughts. In addition, PTSD flashbacks have been considered as either dissociative or brief psychotic episodes. In short, there were many reasons to question the appropriateness of classifying PTSD as an anxiety disorder. Perhaps most important, what distinguishes PTSD from anxiety as well as most other psychiatric disorders is the presumed relationship between exposure to a traumatic stressor and the subsequent development of the PTSD symptom profile.

In preparing for DSM-5, the APA examined the evidence favoring a proposed diagnostic cluster, *stress-related fear circuitry disorders,* characterized by abnormalities in the neurocircuitry that mediate the processing of threatening or fearful stimuli. Other disorders considered for this diagnostic group were panic disorder, specific phobia, and social phobia (see Andrews, Charney, Sirovatca, & Regier, 2009). In brief, the rationale was based on research indicating that the neurocircuitry in all four disorders is characterized by excessive amygdala and insula activation associated with reduced activity in the hippocampus and medial prefrontal cortex (mPFC) (Andrews et al., 2009; see Averill et al., Chapter 9, this volume). However, there is increasing evidence for a

TABLE 2.1. DSM-5 Criteria for PTSD

Note: The following criteria apply to adults, adolescents, and children older than 6 years.

For children 6 years and younger, see corresponding criteria below.

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).

      Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

      Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.

   2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

      Note: In children, there may be frightening dreams without recognizable content.

   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)

      Note: In children, trauma-specific reenactment may occur in play.

   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
   5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
   1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
   2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).

D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
   1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
   2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
   3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
   4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
   5. Markedly diminished interest or participation in significant activities.

(continued)

TABLE 2.1. *(continued)*

6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).

E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. **Depersonalization:** Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).
2. **Derealization:** Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Preschool-age children (6 and under)—brief summary of symptoms (consult DSM-5 for precise wording):

- One B and two E symptoms but only one C or D symptom are needed.
- Only four symptoms are included: D4–D7 (e.g., amnesia, negative cognitions and self-blame are not included).
- Reckless behavior (E2) is not included.

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distinctive biological profile associated with PTSD in contrast to these other disorders (see Friedman et al., 2011a). In addition, individuals with PTSD who have high levels of dissociative symptoms exhibit a reversal of this neurocircuitry pattern (see below; see also DePrince et al., Chapter 8, this volume; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012). The stress-related fear circuitry formulation has also been challenged because it neglects other emotions associated with PTSD, such as sadness, grief, anger, guilt, and shame (Rizvi, Kaysen, Gutner, Griffin, & Resick, 2008). Furthermore, it is difficult to understand how a fear-conditioning model applies to a subset of people with PTSD who were never in any direct danger themselves but are overwhelmed by horror or feelings of helplessness during and after a traumatic event. This would apply not only to people who safely witnessed or were indirectly exposed to a traumatic event but also to medical personnel, first responders, families, bystanders, or graves registration personnel (Friedman et al., 2011a).

Watson (2005) proposed collapsing mood and anxiety disorders into an overarching class of *internalizing disorders* that contains three subclasses: the bipolar disorders (bipolar I, bipolar II, cyclothymia); the distress or "anxious misery" disorders (major depression, dysthymia, generalized anxiety disorder, PTSD); and the fear disorders (panic, agoraphobia, social phobia, specific phobia). A fourth cluster, *externalizing disorders* (Krueger & Markon, 2006), includes alcohol dependence, drug dependence, adult antisocial personality disorder, and childhood conduct disorder. Data from the National Comorbidity Survey (Cox, Clara, & Enns, 2002), as well as from the Australian National Survey of Mental Health and Well-Being (Slade & Watson, 2006), showed that, rather than loading with fear disorders, PTSD loaded with the distress/anxiety–misery disorders (Watson, 2005). These results suggested that PTSD may be better characterized by anhedonic mood and anxious rumination than by pathological fear or externalizing behaviors (Resick & Miller, 2009). An important reason not to consider PTSD an internalizing disorder, however, is that there is also an externalizing phenotype of PTSD (see below and Friedman et al., 2011a).

Thus, it appears that traumatic exposure may be followed by a variety of clinical presentations, including a fear-based anxiety subtype, a dysphoric/anhedonic subtype, an externalizing/aggressive/substance-abusing subtype, guilt/shame/other subtypes, a dissociative subtype (see below), as well as combinations of any or all of these. Based on this evidence, DSM-5 removed PTSD from the anxiety disorders cluster and classified it within a separate category, "traumatic and stressor-related disorders," along with acute stress disorder, adjustment disorder, reactive attachment disorder, and disinhibited social engagement disorder.

The A (Stressor) Criterion

A major challenge for PTSD has always been to explicate the distinction between "traumatic" and "nontraumatic" events. In recent years, this challenge has been complicated by the recognition that there are individual differences regarding vulnerability and resilience, so that what one person may perceive as a life-threatening event may be an arduous, but manageable, challenge to another.

The A1 Criterion

One way to avoid this issue would be to completely eliminate criterion A and consider anyone who fulfilled all other diagnostic criteria as meeting the threshold for the PTSD

diagnosis. After considering this alternative (see Friedman et al., 2011b), the DSM-5 Work Group concluded that it was necessary to preserve criterion A1 as an indispensable feature of PTSD because PTSD does not develop unless an individual is exposed to an event or series of events that are intensely stressful. McNally (2009) argued that the memory of the trauma is the "heart of the diagnosis" and the organizing core around which the B–E symptoms can be understood as a coherent syndrome. He noted that "one cannot have intrusive memories in the abstract. An intrusive memory must be a memory of something and that something is 'the traumatic event' " (p. 599). The intrusion and avoidance symptoms are incomprehensible without prior exposure to a traumatic event. The traumatic experience is usually a watershed event that marks a major discontinuity in the life trajectories of individuals affected with PTSD.

A related question was whether A1 should be limited to direct exposure, so that the "learning about" component of the A1 criterion could be eliminated. Several studies have found PTSD among family members whose spouse or child was murdered, assaulted sexually, killed in combat, killed in the September 11, 2001, attack on the World Trade Center, or died violently (see Friedman et al., 2011a). Indirect exposure also applies to professionals who, though never in danger themselves, are exposed to the grotesque details of war, rape, genocide, or other abusive violence to others (see Friedman et al., 2011a). An extensive review (Ursano, Fullerton, & Norwood, 2003) documented the prevalence of elevated PTSD among civilian and military personnel and families indirectly exposed to traumatic death following combat, terrorism, and disasters. Thus, "learning about" the death or traumatic exposure of a loved one has been shown to precede the onset of PTSD in a significant number of family members and significant others, especially in the case of severe traumas such as homicide, violent death, or fatal accidents. In contrast, exposure to such events through television or other electronic media is unlikely to provoke such symptoms (Pfefferbaum et al., 2012).

As a result of this literature review, "learning about" was retained as a component of criterion A. The DSM-5 revision limits such indirect exposure to learning about the traumatic exposure of a close friend or loved one, or learning about aversive details of unnatural (e.g., violent or accidental) death, serious injury, or serious assault to others. This includes learning about the homicide of a family member and gruesome death or grotesque details of rape, genocide, or other abusive violence to significant others. Learning about another person's traumatic experience also applies to work-related exposure to horrific evidence of traumatic events witnessed by police personnel, firefighters, graves registration workers, and emergency medical technicians. Finally, the revised A criterion explicitly excludes (1) learning about any "sudden death" (e.g., from natural causes) of a loved one, as in DSM-IV and (2) witnessing traumatic events through electronic media, television, video games, movies, or pictures, unless this forms part of a person's vocational role (see Table 2.1).

The A2 Criterion

The utility of the A2 criterion was questioned almost as soon as it was introduced in DSM-IV. Brewin, Andrews, and Rose (2000) found that intense levels of immediate postexposure fear, helplessness, and horror are weakly predictive of PTSD 6 months later. They also found evidence that other posttraumatic emotional reactions (e.g., anger or shame) also predicted PTSD. In addition, some people (often military personnel) who denied postexposure A2 emotions often met all other PTSD criteria at 6 months. Indeed, several studies have shown that a substantial minority (19–24%) of A1-exposed

individuals who went on to meet all PTSD B–E criteria failed to receive a PTSD diagnosis because of the absence of A2. It is noteworthy that there were no differences in B–E symptom severity or functional impairment between the A2-positive and A2-negative cohorts in these studies (Creamer, McFarlane, & Burgess, 2005; O'Donnell, Creamer, McFarlane, Silove, & Bryant, 2010).

It has also been shown that the presence or absence of A2 emotions had no effect on PTSD prevalence (Breslau & Kessler, 2001; Brewin et al., 2000; Karam et al., 2010; Schnurr et al., 2000) in the World Health Organization's World Mental Health Survey, which included almost 103,000 respondents. As stated previously, many people, especially trained military and other professionals, can develop PTSD B–E symptoms without having any emotional response to the event at the time. Based on this research, criterion A2 was not included in DSM-5.

Symptom Criteria: B–E

The DSM-IV PTSD construct consisted of three symptom clusters: B, reexperiencing; C, avoidance/numbing; and D, hyperarousal. Questions were raised about how well this construct held together in practice. Many studies utilized confirmatory factor analysis to test whether the three symptom clusters of DSM-IV provided the best model for the latent structure of PTSD. (See Friedman et al., 2011b, for a more extensive review.) Most studies supported a four-factor model (but see Elhai et al., 2011 regarding evidence of a five-factor model for DSM-IV) with reexperiencing, avoidance, and arousal as distinct clusters in all of these studies. There was some disagreement, however, about whether the fourth factor should be "numbing" or "dysphoria" (see Friedman et al., 2011b), but Yufik and Simms's (2010) meta-analysis (which included 40 studies) suggested that both are a good fit to the data.

Taken together, most confirmatory factor analyses supported a four-factor rather than a three-factor model and consistently showed that the avoidance and numbing clusters were distinct from one another, Based on such findings, DSM-5 separated DSM-IV's criterion C (e.g., avoidance/numbing) into two distinct clusters: criterion C (avoidance) and criterion D (negative cognitions and mood) (see Table 2.1 and below).

Criterion B: Reexperiencing Symptoms

The five DSM-IV criterion B symptoms were retained largely unchanged in DSM-5, with some clarifications to B1 and B3. The more complicated clarification concerned B1, "intrusive recollections." DSM-5 makes a clear distinction between such experiences and the rumination seen in depression and other psychiatric disorders (Brewin, Gregory, Lipton, & Burgess, 2010; Resick & Miller, 2009). Intrusive images in PTSD are sensory memories of short duration, have a here-and-now quality, and lack context, whereas ruminative thoughts are evaluative and last longer (see Friedman et al., 2011b). Therefore, B1 in DSM-5 characterizes involuntary and intrusive distressing memories of the event that usually include sensory emotional, physiological, or behavioral components. Since "reexperiencing" is limited to flashbacks while all criterion B symptoms are intrusive, this cluster was renamed "intrusion symptoms" in DSM-5.

Criterion B2 (traumatic nightmares) is essentially unchanged but was loosened somewhat to include trauma-related material rather than requiring the dream to reproduce the traumatic event. Criterion B3 clarifies that the PTSD flashback is a dissociative reaction in which the individual experiences a sense of reliving the experience with

sensory, emotional, physiological, or behavioral reactions and feels or acts as if the traumatic event is recurring. In DSM-5, both B4 and B5 are retained and defined as triggered intrusive emotional and physiological experiences, respectively. B4 is intense emotional distress that may be the only kind of recollection possible in individuals who have sustained a traumatic brain injury (TBI) and have no conscious memories of the traumatic event. There is evidence that trauma survivors with severe TBI and no memory of the event can still meet PTSD criteria because they satisfy B4 or B5 in response to traumatic reminders (Bryant, Marosszeky, Crooks, & Gurka, 2000). In other words, these symptoms exemplify conditioned responses in fear-conditioning models.

Criterion C: Avoidance Symptoms

In keeping with the evidence from confirmatory factor analyses, a four-factor model was proposed. DSM-IV criterion C is now divided into DSM-5 criteria C and D. As suggested by the literature, the criterion C avoidance cluster consists only of the two behavioral avoidance symptoms, which are essentially unchanged from DSM-IV's C1 and C2, as shown in Table 2.1.

Criterion D: Negative Alterations in Cognitions and Mood

DSM-5 criterion D includes several negative appraisals and mood states associated with PTSD that constitute a distinct cluster of symptoms. DSM-IV's numbing (C3–C7) symptoms were retained, sometimes with clarifications or revisions in wording. In addition, two new symptoms were added to this cluster.

People with PTSD often have erroneous cognitions about the causes or consequences of the traumatic event that lead them to blame themselves or others (see review in Friedman et al., 2011b). Addressing such self-blame or erroneous "other-blame" is a consistent component of cognitive-behavioral therapy (CBT) for patients with PTSD (Resick, Nishith, Weaver, Astin, & Feuer, 2002). A related erroneous appraisal is the common belief that one is inadequate, weak, or permanently changed for the worse since exposure to the traumatic event, or that one's expectations about the future have been permanently altered because of the event (e.g., "Nothing good can happen to me," "Nobody can be trusted," "The world is entirely dangerous," "People will always try to control me"). This reframing of DSM-IV's "foreshortened future" became the D2 symptom in DSM-5 (see Friedman et al., 2011b).

In addition to negative appraisals about past, present, and future, people with PTSD have a wide variety of negative emotional states besides fear, helplessness, and horror, including anger, guilt, and shame (see Miller & Resick, 2007). The strength of this evidence led to the inclusion of a pervasive negative emotional state as a new PTSD symptom (DSM-5 criterion D4).

There was abundant evidence that other symptoms included in the DSM-IV numbing (C3–C7) cluster should be retained in DSM-5 diagnostic criteria for PTSD (see Table 2.1). These include dissociative amnesia—the inability to remember at least one important aspect of the traumatic event (criterion D1; Lanius et al., 2005; Sar et al., 2007). Three other DSM-IV symptoms that were retained are diminished interest in significant activities (criterion D5), a feeling of detachment or estrangement from others (criterion D6), and "psychic numbing," represented as the persistent inability to experience positive emotions (criterion D7). It should be noted that the DSM-5 definition reframed "psychic numbing" to reflect difficulty in experiencing positive (but

not negative) emotions because patients with PTSD can definitely experience negative emotional states but, unfortunately, cannot respond to stimuli or situations that would normally elicit a positive response (Litz & Gray, 2002).

Criterion E: Alterations in Arousal and Reactivity

Review of the literature suggested that this symptom cluster encompasses more than hyperarousal and would be better characterized as alterations in arousal and reactivity that are associated with the traumatic event. Such a reframing of this symptom cluster puts the focus on behavioral factors rather than the emotional indicators included in criterion D. Four of the five DSM-IV arousal symptoms—insomnia, problems with concentration, hypervigilance, and startle reations—were retained, unchanged, in DSM-5. In addition, DSM-5 includes a clarification of DSM-IV criterion D2 (e.g., irritability) and the addition of one new symptom (reckless and self-destructive behavior).

The DSM-IV D2 criterion was "irritability or outbursts of anger." This ambiguous criterion conflated an emotional response, "irritability," with a behavioral reaction, "angry outbursts." To improve diagnostic precision, irritability's emotional component was separated from its behavioral component; anger as an emotional response was included in criterion D4 (i.e., "persistent negative emotional state"), whereas the behavioral response (e.g., irritable or angry outbursts that may be expressed as aggressive behavior) became criterion E1. This clarification is also consistent with evidence indicating that aggressive behavior is a bona fide symptom of PTSD (Elbogen et al., 2010; Teten, Schumacher, Bailey & Kent, 2009; Wolf, Miller, Harrington, & Reardon, 2012).

Finally, there is growing evidence that PTSD is associated with reckless and self-destructive behavior, including reckless driving, risky sexual behavior, excessive substance use, and suicidal behavior (see Friedman et al., 2011b, for references). Results from a large randomized controlled trial comparing prolonged exposure with cognitive processing therapy (Resick, Nishith, & Griffin, 2003) showed that successful treatment of PTSD is associated with significant reductions in reckless and self-destructive behaviors. It is of interest that previously such risky behaviors were reported to have been associated with (predominantly female) traumatized individuals who met the criteria for DESNOS/complex PTSD (see below).

Other Criteria: F–H

DSM-5 retained a 1-month duration of symptoms (criterion F) to account for normal recovery and thus avoid pathologizing normal acute posttraumatic distress. In DSM-IV, the demarcation point between acute and chronic PTSD was 3 months, based on a few longitudinal studies of sexual and nonsexual assault victims and motor vehicle accident survivors in which initially high PTSD rates tend to decline greatly and approach an asymptote at 3 months (see Friedman et al., 2011a). Because there was little research validating the distinction between acute and chronic PTSD, it was eliminated in DSM-5.

Delayed onset, a unique aspect of PTSD, has had a significant impact on compensation claims in which the claimant may not have exhibited full PTSD symptoms for many years. A systematic review of 19 group studies indicated that delayed onset accounted for 38.2% and 15.3%, respectively, of military and civilian cases of PTSD (Andrews, Brewin, Philpott, & Stewart, 2007). PTSD in the absence of any prior symptoms, however, was extremely rare. Indeed, delayed onset usually involved subsyndromal PTSD symptoms that later escalated to the full syndrome. Based on such findings, DSM-5 reframed "delayed onset" as "delayed expression" of PTSD (at least 6 months after the event).

DSM-IV added a "significant distress or functional impairment" criterion for PTSD and several other disorders. This means that a person who meets the requisite other criteria would not receive a PTSD diagnosis unless he or she also exhibited clinically significant distress or functional impairment. This criterion was retained in DSM-5 (criterion G). Criterion H also was retained in DSM-5; it stipulated that PTSD symptoms must be due to a criterion A event and not to a substance (e.g., alcohol, medication), medical illness, or neurological condition.

Modified Criteria for Preschool-Age Children (6 Years and Under)

The DSM-5 Developmental Work Group proposed that diagnostic criteria need to be more behaviorally anchored and developmentally sensitive to detect PTSD in preschool children (see Scheeringa, Zeanah, & Cohen, 2011). For the most part, the new DSM-5 preschool subtype retained DSM-IV child/adolescent intrusion symptoms (B) and alterations in both arousal and reactivity (D) symptoms and diagnostic thresholds (e.g., 1B and 2D). Intrusive memories (B1) was broadened to include traumatic memories reenacted in play that did not appear distressing, and irritable/aggressive behavior (D1) was extended to include tantrums.

Because preschool children lack the verbal and abstract cognitive capacities of older children and adults, DSM-5 eliminated symptoms that rely on the capacity to report subjective symptoms, such as amnesia, erroneous other-blame, or lack of positive emotions, for very young children. Therefore, the diagnostic threshold for criterion C (which includes adult DSM-5 cluster C symptoms and four symptoms from cluster D) was lowered from three symptoms to one. Furthermore, the C1 criterion was clarified, since in very young children, it is developmentally problematic to assess avoidance of internal thoughts and feelings related to the traumatic event. Finally, criterion A for this subtype defines loss, injury, or death of a parent or caregiver as a potentially traumatic event. Considerable research supports the preschool subtype, as detailed in Scheeringa and colleagues (2011).

Addition of a Dissociative Subtype

Since Pierre Janet's work during the late 1800s, dissociative symptoms have been linked with traumatic exposure. Lanius and colleagues (2012), summarized four types of evidence to support this link: antecedent validators, neuroimaging data, findings from confirmatory factor analysis, and treatment outcome results. First, dissociation is common among people with trauma-related disorders, including PTSD. Second, neuroimaging data suggest that a distinct neurocircuitry pattern distinguishes individuals with PTSD from those with PTSD plus dissociative symptoms. Those with PTSD alone show heightened amygdala activity and reduced mPFC and anterior cingulate activity. In contrast, those with PTSD plus dissociative symptoms exhibit a reversal of this pattern, showing significantly increased prefrontal activity associated with diminished amygdala activity (see DePrince et al., Chapter 8, this volume; Lanius et al., 2012). Third, latent class analysis identifies a distinct subgroup characterized by high PTSD severity and dissociative symptoms (Lanius et al., 2012). Finally, different treatments may be indicated, depending on the presence or absence of dissociative symptoms (Cloitre, Petkova, Wang, & Lu Lassell, 2012; Resick, Suvak, Johnides, Mitchell, & Iverson, 2012). Based on all this evidence, a dissociative subtype was included in DSM-5 PTSD diagnostic criteria. Continued research on this subtype is poised to further inform our ability to diagnose and treat these individuals and to provide insight into other diagnostic

taxonomies. For example, Friedman (2013) suggested that if future research finds a high association between DSM-5's dissociative subtype and ICD-11's disturbances in self-organization (DSO) symptoms exhibited in complex PTSD (see below), it would provide a better empirical basis for understanding ICD-11's complex PTSD.

NONINCLUSION OF SUBTHRESHOLD PTSD

If a subthreshold PTSD diagnosis had been added to DSM-5, it should have had a similar relationship to full PTSD as dysthymia has to major depressive disorder or as cyclothymia has to bipolar disorder. Approximately 60 publications had reported on the prevalence and morbidity of "partial" (or "subsyndromal") PTSD in a wide assortment of traumatized individuals in which people with subthreshold PTSD often exhibited significantly less symptom severity and functional impairment than those with the full syndrome but significantly more than no-PTSD cohorts. In other studies, few differences were detected between subthreshold and no-PTSD cohorts, whereas both differed significantly from full PTSD. A problem with this research was that subthreshold PTSD had been defined differently by different investigators—in some studies by an adjudication procedure and in other studies by strict criteria that differed from one investigation to the next (Friedman et al., 2011b).

Acknowledging that different definitions of subthreshold PTSD have appeared throughout the literature, a consistent finding has been that it is associated with chronicity; high symptom severity; a broad range of comorbid mental health disorders; suicidal thoughts and attempts; functional impairment; and physical health problems (see Friedman et al., 2011a). In general, the severity of problems associated with subthreshold PTSD has been significantly worse than problems among traumatized nonaffected individuals and significantly less than problems among individuals with full PTSD. Despite these arguments and because of the many different case definitions that have appeared throughout the literature, a new diagnosis, subthreshold PTSD, was not approved for inclusion in DSM-5.

NONINCLUSION OF DISORDERS OF EXTREME STRESS NOT OTHERWISE SPECIFIED/COMPLEX PTSD

The concept of "complex PTSD," renamed "disorders of extreme stress not otherwise specified (DESNOS) by the DSM-IV Work Group, was originally proposed by Judith Herman (1992) to encompass three non-PTSD posttraumatic disorders: dissociative identity disorder, borderline personality disorder, and somatization disorder. It was also meant to provide a diagnostic niche for individuals whose most debilitating symptoms following protracted traumatic exposure included behavioral difficulties (e.g., impulsivity, aggression, sexual acting out, alcohol/drug misuse, and self-destructive actions), emotional difficulties (e.g., affective lability, rage, depression, and panic), cognitive difficulties (e.g., dissociation and pathological changes in personal identity—dissociative identity disorder), interpersonal difficulties, and somatization (Herman, 1992; Linehan, Tutek, Heard, & Armstrong, 1994; van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005). Following field trials, DESNOS was not included in DSM-IV because nearly everyone who met the DESNOS criteria also met criteria for PTSD and was therefore viewed as having a more severe form of PTSD. Unfortunately, what little research had been done on DESNOS between DSM-IV and DSM-5 was insufficient to

establish the construct validity of DESNOS as a distinct diagnosis (Resick et al., 2012). Given the lack of an evidence base to support DESNOS, it was not included in DSM-5.

Interestingly, several key DESNOS symptoms are now included in the DSM-5 PTSD criteria, especially when considering the dissociative subtype. In addition, several D cluster (e.g., negative cognitions and mood) symptoms, such as persistent distorted blame, negative expectations about the future, and persistent negative mood, as well as externalizing behaviors (e.g., irritable, aggressive, impulsive, self-destructive, and suicidal behavior) now explicated in the E cluster (hyperarousal and reactivity), are much closer to DESNOS than was the case with DSM-IV criteria. We look forward to further research in this area.

COMPARING DSM-5 WITH ICD-11

In 2018, ICD-11 introduced an updated conceptualization of PTSD. As with DSM-5, the ICD-11 working group moved PTSD from the anxiety disorders category to a new stress-related disorders category. ICD-11 retained the three symptom clusters included in DSM-IV (APA, 1994). However, unlike the conservative approach taken in DSM-5, the ICD-11 working group was not required to support changes in diagnostic criteria with strong empirical evidence. Instead, the ICD-11 working group relied on expert consensus to make decisions about the diagnosis. As a result, the DSM-5 process was much more conservative and rigorous, while ICD-11 had the latitude to be much more radical.

Due in part to the differential approaches taken by the two working groups, the ICD-11 conceptualization of PTSD varies considerably from that of DSM-5. Unlike DSM-5, ICD-11 introduced two "sibling disorders": PTSD and complex PTSD (CPTSD). ICD-11 PTSD includes three core elements: (1) reexperience of the traumatic event, including intrusive memories, flashbacks, and nightmares; (2) avoidance of traumatic reminders, including avoidance of internal and external stimuli; and (3) a persistent sense of threat, including hypervigilance and increased startle. For a PTSD diagnosis, individuals must meet criteria for at least one symptom from each category, and the symptoms must persist for several weeks and cause significant functional impairment. CPTSD requires meeting criteria for PTSD plus three additional features indicating disturbances in self-organization (DSO): (1) affective dysregulation, (2) negative self-concept, and (3) disturbed relationships. The two ICD-11 disorders are thought to have different etiological triggers, where the etiology of PTSD is general exposure to an extremely threatening or horrific event or events, and the etiology of CPTSD is protracted exposure to prolonged or repetitive events from which escape is difficult or impossible. However, the developers of ICD-11 note that regardless of the nature of the stressor, the diagnosis of PTSD versus CPTSD is determined by the symptom profile (Cloitre, Gavert, Brewin, Bryant, & Maercker, 2013).

The introduction of the ICD-11 sibling disorders has fueled research examining how it might impact who receives a trauma-related diagnosis. Overall, ICD-11 PTSD is substantially less common than either ICD-10 PTSD or DSM-5 PTSD, across cultures and ages (e.g., Brewin et al., 2017; Haravuori, Kiviruusu, Suomalainen, & Marttunen, 2016; Sachser et al., 2018; Shevlin et al., 2018), with low levels of overlap across taxonomies (e.g., La Greca, Danzi, & Chan, 2017). Whereas the prevalence of CPTSD is higher than that of ICD-11 PTSD in clinical samples, nonclinical samples demonstrate the opposite pattern (e.g., Karatzias et al., 2017). The few studies that have examined the prevalence of ICD-11 CPTSD versus DSM-5 PTSD have found that DSM-5 PTSD tends to be the more common of the two (O'Donnell et al., 2010; Powers et al., 2017).

The ICD-11 working group members have argued that these two sibling disorders optimize clinical utility by limiting each of these distinct, but related, diagnoses to a core set of symptoms (Cloitre et al., 2013). In addition, advocates argue that this conceptualization will improve upon past versions by reducing high comorbidity; exclude subthreshold symptomatic individuals; and include only those with the few key PTSD symptoms (based on evidence that short screeners that assess only a few symptoms are excellent at classifying individuals by PTSD diagnostic status; Brewin, 2013). In short, ICD-11 is restricted to seven potential PTSD symptoms (rather than the 20 in DSM-5) and lowers the minimum diagnostic threshold to three symptoms (rather than the six in DSM-5).

Others have argued that the ICD-11 approach to PTSD is problematic because it eliminates symptoms that were core in ICD-10. Furthermore, excluding symptoms that are not unique to PTSD (e.g., many DSM-5 criterion D and E symptoms, such as insomnia, irritability, impaired concentration, and social distancing) is both inconsistent with symptom categorization for other mental disorders and problematic because it will have the unintended consequence of depriving symptomatic individuals of a diagnosis (Friedman, 2013; Vermeteen, Baker, Jetly, & McFarlane, 2016).

Research has begun to test whether three main aspects of the rationale for the ICD-11 PTSD diagnosis have been borne out empirically: that the ICD-11 definition better captures the core symptoms of the PTSD construct; reduces comorbidity, and is more inclusive of symptomatic individuals. Regarding capturing the core construct, although there is empirical support for the procedure used by the ICD-11 expert group to choose the core symptoms (Kliem et al., 2016), network analyses found that only half of the ICD-11 PTSD symptoms are central to the PTSD network (Mitchell et al., 2017), raising questions about whether the symptoms chosen by ICD-11 are indeed central to the diagnosis. In our opinion, eliminating DSM-5's fear-conditioning symptoms (e.g., B4 and B5) is especially problematic.

Examinations of whether ICD-11 PTSD reduces comorbidity have been equivocal. Whereas some studies suggest that ICD-11 PTSD reduces comorbidity compared to DSM-5 PTSD (e.g., La Greca et al., 2017), other research has found that ICD-11 PTSD has higher comorbidity than both ICD-10 (Barbano et al., 2019) and DSM-5 (Green et al., 2017; Shevlin et al., 2018). Still other research has found no difference in comorbidity between ICD-11 PTSD and DSM-5 PTSD (Wisco et al., 2017).

Finally, in considering whether the ICD-11 approach is more inclusive of symptomatic individuals than broader taxonomies, there is some evidence that ICD-11 PTSD can detect some individuals with significant impairment who would not be diagnosed using DSM criteria (Brewin et al., 2017). However, other research has suggested that use of the ICD-11 PTSD taxonomy excludes individuals with clinically significant symptoms. For example, Barbano and colleagues (2018) found that although ICD-11 did identify the more severe cases of PTSD, individuals who met ICD-10 but not ICD-11 criteria *still* had moderate PTSD symptoms according to a clinical interview. Furthermore, research has found that ICD-11 PTSD is associated with lower functional impairment than DSM-5 PTSD among children (Danzi & La Greca, 2016).

In the 7 years that the field has known of the ICD-11 proposal, an impressive body of literature examining the impact of two differential taxonomies has been amassed. However, research on the ICD-11 sibling disorders and on how they compare to DSM-5 PTSD is still in its infancy. Any conclusions about the impact of these taxonomies is preliminary. What is clear, however, is that having two distinct, widely used taxonomies for understanding posttraumatic psychopathology presents a range of challenges for clinicians and researchers alike. Additional research is needed to clarify the best way to

understand trauma-related psychopathology, so that individuals suffering from these debilitating disorders can receive the help they need and deserve.

CONCLUSIONS

Significant changes were made to the PTSD criteria for DSM-5. In some sense, the revised criteria represent a marked departure from DSM-IV PTSD, but in another sense, they represent the next step in an ongoing evolution of the conceptualization of human responses to catastrophic life events. As a result of the dramatic increase in the empirical literature on PTSD, the DSM-5 criteria were the first version of PTSD to be substantially empirically based, rather than being rationally derived from clinical observation and expert opinion. Given the conservative approach to the revision process, the DSM-5 criteria provide continuity in the conceptualization of PTSD and backward compatibility with previous iterations. Changes range from minor clarifications to significant alterations and additions, but all are supported by the best available scientific evidence.

Despite the conservative and rigorous revision process described above, critics strongly objected to several aspects of the DSM-5 PTSD criteria. Some critics were so alarmed by the revisions that they called for a moratorium on their implementation (Hoge, 2016). However, many of the concerns were either based on erroneous assumptions or have proven to be largely unfounded as research accumulates (Weathers, 2017). A legitimate concern is that DSM-5 criteria are too complex. With 17 symptoms in three clusters, DSM-IV PTSD was already one of the most complex disorders, with one of the highest levels of potential diagnostic combinations and disjoint combinations, that is, combinations that satisfy diagnostic criteria but have no symptoms in common. In DSM-5, with 20 symptoms in four clusters, the levels of diagnostic and disjoint combinations were increased eightfold, permitting an extraordinarily high number of potential ways to meet diagnostic criteria and an inconceivably high number of potential comorbid combinations (Galatzer-Levy & Bryant, 2013; Young, Lareau, & Pierre, 2014). This creates the potential for extremely high levels of heterogeneity in PTSD samples, which in turn could thwart efforts to identify biological markers and other risk factors, causal mechanisms, and effective treatments. Although this is a significant concern, in purely theoretical terms, the problem may be overstated and is not specific to PTSD. As Olbert, Gala, and Tupler (2014) demonstrated, in actual samples, heterogeneity is substantially lower than what it potentially could be and is only somewhat higher in PTSD than in depression.

Another possibility is that DSM-5 PTSD encompasses a spectrum disorder that future research will disaggregate into more homogeneous and less complicated PTSD phenotypes. In other words, the heterogeneity and large number of symptoms in DSM-5 may be a necessary prelude to the identification of specific phenotypes that, with the help of biomarkers, will be much easier to diagnose and distinguish in future iterations of the DSM.

Regardless, although this increased complexity and potential for heterogeneity is an important concern, it does not appear to diminish the reliability, validity, or clinical utility of the DSM-5 PTSD criteria. In the DSM-5 field trials, PTSD was among the most reliable diagnoses, outperforming depression, generalized anxiety disorder, and alcohol use (Regier et al., 2013). Furthermore, DSM-5 versions of leading PTSD assessment instruments have been demonstrated to have the same excellent psychometric characteristics as their DSM-IV counterparts. For example, the Posttraumatic Stress Disorder

Symptom Scale—Interview (PSSI-5; Foa et al., 2016) and Clinician-Administered PTSD Scale (CAPS-5; Weathers et al., 2018) have excellent test–retest and interrater reliability and good convergent and discriminant validity (see Livingston et al., Chapter 16, this volume, on diagnostic assessment). Finally, clinicians have responded favorably to the DSM-5 criteria, finding them clinically useful and easy to apply (Moscicki et al., 2013). The DSM-5 criteria have performed well thus far and serve as the foundation for a new wave of empirical investigation into the phenomenology, etiology, and treatment of PTSD.

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CHAPTER 3

Historical Roots of the PTSD Construct
HOW PTSD BECAME A DIAGNOSIS AND LAUNCHED THE TRAUMATIC STRESS FIELD

Alexander C. McFarlane and Dean G. Kilpatrick

> Those who cannot remember the past are condemned to repeat it.
>
> —GEORGE SANTAYANA

> History doesn't repeat itself, but it often rhymes.
>
> —MARK TWAIN

The inclusion of the posttraumatic stress disorder (PTSD) diagnosis in DSM-III in 1980 was a key moment in the history of the traumatic stress field (American Psychiatric Association [APA], 1980). This diagnosis catalyzed the growth of the traumatic stress field by providing a common metric with which to measure the impact of exposure to disparate potentially traumatic events (PTEs), thereby encouraging clinicians, researchers, and activists to recognize commonalities across different types of PTEs. Having the PTSD diagnosis clearly facilitated better assessment, treatment, and research. Having this diagnosis stating that a specific set of symptoms can be caused or aggravated by exposure to PTEs had a major impact on public policy debates in many areas, including whether compensation for disaster survivors, accident victims, crime victims, and veterans is appropriate, as well as on funding priorities for traumatic stress research and treatment services. As we describe in this chapter, the PTSD construct as operationalized in DSM-III had many precursors, none of which were as comprehensive or universal as PTSD.

Given the importance of PTSD in DSM-III to the traumatic stress field, this chapter examines how PTSD achieved diagnostic status at this particular time, thereby obtaining a degree of public, professional, and public policy acceptance that was never possible before. There are important lessons to be learned about how this came to be, and it is critical that we learn them for two reasons. First, as Santayana's quote implies, we must learn from the past to avoid making the same mistakes (i.e., reinventing the flat

tire) but also to learn from and replicate what worked well. Second, as Twain's quote indicates, many of the historical challenges for our field have, and will continue to, repeat themselves in slightly different forms, and we must be ready to recognize and address them.

This chapter does not provide a detailed account of all the important historical contributions of clinicians and researchers that culminated in PTSD in DSM-III. That appears in two excellent chapters in the previous edition of this book (Monson, Friedman, & La Bash, 2007; Weisaeth, 2007). Nor do we describe the evolution of the PTSD construct since 1980 or the tremendous progress made by the traumatic stress field since then because these are described elsewhere in this volume. This chapter does provide an overview of people and events that contributed to developing the societal acceptance of the impacts of psychological trauma and the PTSD construct. However, our primary aim is to examine the barriers that hindered the professional acceptance of the importance of traumatic stress as a fundamental aspect of psychopathology before 1980. We also explore the events and social forces in the 15 years prior to DSM-III in 1980 that enabled the PTSD construct to win acceptance and achieve diagnostic status.

In our view, acceptance of precursors of what we now call PTSD and PTSD itself faced three major barriers. First, professional interest in traumatic stress has never been sustained over time. Interest in and prioritization of traumatic stress have been cyclical in nature, characterized by periods of intense interest followed by dramatic forgetting of the lessons of the past (Kardiner & Spiegel, 1947). Our past is littered with false starts and mistakes as well as successes, but lack of continuity of interest, work in the area, and ability to learn from both successes and failures resulted in much reinventing of both the wheel and the flat tire.

Second, supporters of the many precursors of the PTSD construct often found themselves in the midst of professional and public policy debates with high-stakes consequences, which precluded making policy decisions solely on the basis of facts or logic. The hypothesis that exposure to PTEs can cause substantial harm is a key premise of both the PTSD construct and its precursors. This clearly falls on the environmental side of the nature versus nurture debate that goes back to the Greek philosophers. If exposure to PTEs causes harm, this creates challenges for those making policies regarding treatment of injured members of the armed forces, compensation for victims of war, crime, or torture, and the question of whether the harm is sufficient to require special consideration under the law (Kilpatrick, 2005). As will be described, there are generally strong institutional forces that discount the harm produced by exposure to PTEs or that attribute any harm to nature rather than nurture for political or financial reasons. These vested interests made it more difficult for PTSD and its precursors to gain recognition.

Third, a striking lesson of history is that many clinicians have failed to recognize the trauma experienced by patients and have minimized its etiological significance. For example, the prevalence of incest was described in a major text of psychiatry (Freedman, Kaplan, & Sadock, 1976) as negligible, whereas subsequent research demonstrated the prevalence of this and other types of child victimization to be quite high (e.g., Gelles, 1978; Kilpatrick, Saunders, & Smith, 2003). This statement in a major textbook means that students were taught that child victimization was a negligible problem and is a strong indication that the trauma stories of millions of patients were never heard by generations of clinicians. This highlights how acceptance of PTSD into DSM III was as much driven by exploration of the effects of trauma by writers and the advocacy of activists than by the scholarship of professionals (Young, 1997).

THE SOCIAL AND SCIENTIFIC DYNAMICS OF THE 19TH-CENTURY ENLIGHTENMENT

More than any other psychiatric disorder, PTSD has been embroiled in public debate about its nature and causes that goes beyond mental health professionals (Shephard, 2003). A central reason is that PTEs such as wars, natural disasters, and accidents draw psychiatry and psychology into an interface with political and legal systems, which does not occur with other psychiatric illnesses. Also, over the last two centuries there has been a dramatic change in the social attitudes and capacity for empathy for victims. Scientific and technological advances that have allowed a more focused concern about the nature of pain and the consequences of suffering must be considered if the nature of traumatic stress is to be understood (McFarlane, 2000). The emergence of PTSD into the psychiatric nomenclature has probably been more influenced by these dynamic social, political, and technological changes than by the development of models of post-traumatic psychopathology by leading clinicians.

Many observers of human suffering in the 19th century were not medical professionals. Abolitionists who fought for banning slavery, reformers of prisons, and advocates for humane asylums for the mentally ill were enlightened public policy advocates. In addition, novelists who focused on both civilian and war trauma gave voice to the distress of their traumatized protagonists. It was in this environment that the costs of war and the shocking disability from work-related injuries arising from the industrialization of Europe and America evoked significant public attention (Trimble, 1981). This awareness was slowly acknowledged in legal and pension reforms. The importance of justice and legal protection acknowledged the need to protect individuals and provide care for them if they were injured by no fault of their own. Political, legal, and social reformers took up the cause, and this in turn demanded that medical professionals better understand the psychological dimensions of suffering and how to best manage them. This acceptance first emerged in accepting the legal need to compensate those who suffered psychological injuries because of the negligence of a third party.

COMPENSATION FOR ACCIDENTS

The Liverpool and Manchester Railway in England opened in 1830. The first accident occurred on the very day of this opening when a member of Parliament was fatally injured (Trimble, 1981). This incident became a focal point for those concerned about the risks of this dangerous new form of transport. Accidents remained a constant challenge and problem because of derailments and collisions. One of the victims was Charles Dickens, who described his symptoms as follows:

> I am not quite right within, but believe it to be an effect of the railway shaking. . . . am curiously weak. . . . I cannot bear railway travel yet. A perfect conviction, against the senses that the carriage is down on one side comes upon me, with anything like speed, is inexpressibly distressing. (Trimble, 1981, p. 28)

Development of compensation programs for accident victims became the focal point of many observations about the impacts of trauma in the 19th century. In explaining compensation-related injuries, the medical professionals initially focused on the impact of the rapid deceleration at the point of collision and the musculoskeletal

consequence of the spine. A very influential early work was that of John Erichsen (1818–1895) at University College London, who addressed the impact of "injuries of the spine that may arise from accidents that are often apparently slight, from shocks to the body generally, as well as from blows inflicted directly upon the back" (Trimble, 1981, p. 9). He argued that the nature of the injury was concussion of the spine and concluded that "the primary effects of these concussions or commotions of the spinal cord are probably due to molecular changes in its structure. The secondary effects are mostly of an inflammatory character." These ideas were highly influential in both Europe and the United States.

In 1883, Herbert Page, a surgeon to the London and North Western Railway, published a rebuttal to Erichsen in a volume titled *Injuries of the Spine and Spinal Cord without Apparent Mechanical Lesion*. His view was that concussion created unwanted anxiety in victims of minor accidents. He came to believe that the patient's infirmity was, in reality, attributable to "symptoms of general nervous prostration or shock and pains in the back" (Trimble, 1981, p. 25), which later would be called whiplash. He believed that Erichsen had not considered adequately the possibility of "nervous" symptoms. His views were picked up, and the *Boston Medical and Surgical Journal* in the 1880s carried a series of papers related to "so-called concussion of the spine." G. L. Walton, in 1883, summarized debates between railway spine and traumatic neurasthenia. Hence, a tension arose between whether this injury was due to organic change in the spine or whether it was a consequence of nervous shock. Page argued for a psychological origin, stating that "many errors in diagnosis have been made because fright had not been considered a bit self-sufficient" (Trimble, 1981, p, 26).

Similar investigations occurred in Germany. A further impetus to better understand the consequence of accidental injury came from the introduction of workers' compensation legislation. The first chancellor of Germany, Otto von Bismarck, had to negotiate with the Socialists to bring about the unification of the German states, including Prussia (Macleod, 2019). An important negotiating strategy was the introduction of social benefits, including workers' compensation. It was in this setting that Hermann Oppenheim in 1889 (Sequin, 1890) coined the term *traumatic neurosis,* which he saw as a functional problem produced by subtle molecular changes in the central nervous system. The challenge that remained was how to conceptualize the patient's symptoms and reactions, which included both physical symptoms such as pain and ongoing fears and anxieties, which were also common features.

Intense interest in this question was reported in 1890 in the *Annual of the Universal Medical Sciences,* a major publication reviewing critical advances in medicine. The whole of Volume III dedicated to psychiatry was on the one topic, titled "Traumatic Neurosis." The editorial by Edward Seguin (1890) began:

> The detestable terms, "railway spine" and "railway brain", are still employed by a number of authors, but apparently more with the object of clearly indicating the general classification of the cases they report than with the idea of proper scientific designations. It would do much towards finally setting the status of the topic if those terms (railway spine, railway brain, compensation neurosis) as well as the words "concussion" and "hysteria" were dropped. (p. N1)

Seguin argued that these terms should be grouped under the phrase *traumatic neuroses*. Debates about etiology focused on the relative importance of psychic shock as opposed to vascular changes. This was a thriving field embraced by many clinicians from quite

varying backgrounds, and they reached a consensus that was remarkably similar to the position that DSM-III adopted.

The Crimean War (1853–1856) was fought following the invention of the telegraph and the camera (Ignatieff, 1998). For the first time, distress and the suffering of soldiers was brought to public attention. The British public became outraged at logistic and command failures of the war, such as the Charge of Light Brigade where a cavalry charge into an artillery battery led to terrible carnage. Many troops needlessly died of disease, undernutrition, exposure, and sepsis, which evoked further condemnation of the government.

After an 1855 report by a Royal Commission highlighted the army's blunders in the Crimea, the secretary of war gave Florence Nightingale authority to take a group of nurses to the Scutari Hospital in Istanbul. Her innovations included placing partitions between beds when soldiers were having amputations, so that colleagues did not have to observe the anguish and horror of the procedure, which was often done without anesthesia (Small, 1999). She was also a very able statistician and documented the horrific neglect of the injured and diseased soldiers, as well as needless pain due to prohibition of anesthesia during amputations. After returning to England, she retired to her bedroom and seldom ventured beyond for 9 years. It is probable that she was suffering from what would now be called PTSD because of what she had witnessed. Only after the extreme suffering of hospitalized soldiers was publicized did their psychological suffering became a more salient issue. The medical profession's neglect extended to any serious study of the psychological consequences of war.

Leo Tolstoy (1855/1986) was an artillery officer in the Russian Army who participated in the siege of Sebastopol in the Crimea in 1854, an experience that became the basis for his *Sebastopol Sketches*. Each of the three short stories in this work contained a description of the medical staff amputating a mutilated limb. Unlike the British, the Russians used anesthesia. His epic work *War and Peace* (Tolstoy, 1867/2016) was modeled on his psychological synthesis of what he had observed about war in the Crimea. He articulated the private humanity and suffering in the face of the confusion of battle that was a further beginning to consideration of the costs to the men who fought. He reflected on how the reality of war was not what history captured:

> All these odd and to us incomprehensible discrepancies between the facts and the historical accounts arise only because the historians writing of these events wrote a history of the fine phrases and feelings of the various generals, and not a history of the events themselves. (p. 1283)

The U.S. Civil War (1861–1865) was the first conflict to illustrate the horrors of industrial warfare on a large scale. The death toll of 204,000 men from battlefield injuries and 388,000 from disease highlights the extraordinary suffering, which left a legacy of profound loss to the nation. It was not only the lingering cost of battlefield injuries that preoccupied the medical profession at that time. Important observations were also made about the psychological suffering, which was described in terms of a range of syndromes, including soldier's heart (Da Costa's syndrome) and nostalgia, as well as the scourge of narcotic addiction following attempts to treat both psychological and physical pain (Trimble, 1981). This background likely explains the U.S. Army's better preparation when it finally entered World War I with regard to the probable psychological costs and the need to have effective systems in place. This readiness was in stark contrast to the situation of the British and German armies, who were woefully unprepared when the war began.

Jean-Henri Durant, a social activist and winner of the first Nobel Peace Prize in 1901, had been a key witness to the horrors of war. He witnessed the battle of Solferino in 1859, which was fought in Italy between the Sardinian Army and the French (Ignatieff, 1998). He was shocked and horrified by the sight of the injured and dead who had been left on the battlefield without care or rescue by their armies. In the aftermath of the battle, he recruited local citizens to bring assistance to those casualties who were in a grievous state. This led him to lobby for the Geneva conventions and to establish the International Red Cross, for which he was ultimately awarded the Nobel Prize.

In France, the fervor for political freedom and democracy that followed the Franco-Prussian War of 1870–1871 was an important backdrop to the emerging interest of clinicians such as Jean-Martin Charcot and Pierre Janet in the phenomenology of trauma. Charcot, in Paris, was one of the most famous neurologists of the time, and Janet was a medical graduate who studied hysteria under Charcot.

One of the important debates that emerged was about the role of women in a democracy, and this led to the first international congress of the rights of women, which was held in Paris in 1879. One discussion focused on discrediting many of the superstitious beliefs about women's maladies and on defining the role that medicine had in studying these complaints. Charcot investigated the role of hysteria in the miracles of the Middle Ages (Charcot & Richer, 1881/1984). His interest in hysteria was partly driven by his political interest in human rights. France now entered a state of self-examination where it was open to exploring the costs of war and social trauma, including the sexual abuse of women and accidents.

Hence, the emergence of an intense interest in the effects of psychological trauma in the last decades of the 19th century marked a combination of an increasing awareness of the humanitarian cost of war and the civilian accidents driven by the direct experience of trauma. The scientific revolution that was changing medicine at that time also permitted suffering to be studied and documented. Another factor that influenced the conceptualization of the effects of trauma and its symptoms was the overriding question of how to conceptualize invisible illnesses when there was no observable neural pathology.

MODELS OF DISEASE IN THE 19TH CENTURY

The beginning of modern medicine was very much influenced by René Descartes's dualism. He argued that the mind was separate from matter and that these were two separate independent worlds. This dualism had been encouraged by Christian theologists to avoid conflict with the emerging world of science. However, it led to considerable confusion in understanding the PTSD construct, particularly when psychiatry began to separate from neurology at the end of the 19th century.

Many descriptions of what would now be thought of as PTSD in the 19th century involved an aggregation of both physical and psychological symptoms, such as concussion of the spine. In this context, an important controversy that influenced the conceptualization of PTSD was whether it was a neurological entity with a distinct underlying structural pathology (Trimble, 1981) or another category of disease that was viewed as disturbance of nerve power or neurosis (Trimble, 1981, p. 38). This in turn led to the concept of functional disorders. William Gowers (1893/1970), in an influential textbook, argued for the categorization of neurological disorders as either organic or functional disorders, where functional disorders were thought of in a physiological

sense. Examples of functional disorders were migraine, chorea, and epilepsy. Trimble concluded:

> Molecular changes . . . probably constitute the morbid process in many diseases that are commonly classified as "functional. . . . The primary derangement is in the higher cerebral centers, but the functions of the lower centers in the brain, spinal cord, and of the sympathetic system, may be secondary disorder. (Trimble, 1981, p. 40)

This construct argued for the psychophysiological underpinnings of many presentations and was consistent with Oppenheim's hypothesis that traumatic neurosis was caused by molecular changes in the central nervous system. However, the intersection with hysteria began to cause confusion of terminology. Page, in his examination of patients assessed after railway accidents, came to the view that many of the symptoms were due to nervous shock and hysteria. In this context, "functional" came to have a dramatically different meaning. Charcot, prior to his death in 1893, developed an intense interest in posttraumatic neuroses and their relation to hysteria. He brought the same intellectual discipline to the study of hysteria as he had used in his research on organic neurological disease. He concluded that hysterical states had a neurophysiological underpinning related to abnormal functioning of the brain. He believed that railway spine and railway brain were very often the result of hysteria. He continued to use the word *functional* in the physiological sense, concluding about the etiology of hysterical upper limb paralysis that "[w]e have here unquestionably one of those solutions which escapes our present means of anatomical investigation in which, for want of better term, we designate dynamic or functional lesions" (Trimble, 1981, p. 45).

Janet and Sigmund Freud, both of whom studied under Charcot, increasingly focused on the role of unconscious factors in the development of hysterical symptoms. Janet rejected a neurological theory of hysteria as well as the notion that the symptoms were faked; rather, he proposed that hysteria was a "psychogenic" disease. The concept of psychogenic illness emerged early in the 19th century and was related to conditions "due to activity of mind" (Trimble, 1981). Use of the word *psychogenesis* had become increasingly imprecise and blossomed into popular usage with the writings of Freud.

When Freud lectured about Charcot's ideas, he argued that posttraumatic neuroses equated to hysteria, leading to heated disputes with colleagues. He developed his ideas in his collaboration with Josef Breuer and published the lecture, "On the Psychical Mechanisms of Hysterical Phenomena," in which they concluded:

> Trauma does not simply act as a releasing agent for symptoms. Rather, psychic trauma or more precisely *the memory of the trauma acts like a foreign body* which long after entry must continue to be regarded as the agent that still is at work . . . a psychical pain that is remembered long after the event. Hysterics suffer mainly from reminiscences. (Breuer & Freud, 1955, p. 58)

Freud went on to develop his structural model of the mind and the critical role of the unconscious and thereby redefined the meaning of psychogenic. This construct was where the fracture between psychiatry and neurology was defined, particularly in those who became psychoanalysts, until the publication of DSM-III.

Hence, the term *functional* came to have a psychological meaning. Physician Gordon Kamman (Trimble, 1981) stated that posttraumatic neurosis was psychogenic and that it resulted from conflicting forces or drives within the personality structure of the

individual. This was viewed as a reaction rather than as being related to the event or injury caused. Symptoms were viewed as conflicts between internal systems of the mind and failed adaptations to a new environment. Words such as *functional* and *psychogenic* became so distant from their original definitions that they lost any conceptual utility. Progressively, the view emerged that psychiatric illnesses such as PTSD were functional, which in turn took on a pejorative undertone. They had lost any connection with their psychophysiological underpinnings as characterized by the emerging field of neurophysiology. Modern neuroscience has shown that any attempt to distinguish functional from organic symptoms is meaningless.

However, prejudice regarding the use of these words in relation to the effects of traumatic stress continued into the 20th century. A legacy was to focus on psychological mechanisms in traumatic neurosis at the exclusion of the centrality of the physical symptoms to the patient's experience. Ignoring the centrality of these physical symptoms in PTSD is ironic, given that one of its original formulations was as railway spine. Thus, the dominance of psychoanalysis in the 20th century led to psychophysiological dysregulation being largely ignored as being part of traumatic neurosis. This was partly a consequence of Charcot's successor, Joseph Babinski (1857–1932), who chose to diminish his mentor's legacy. Babinski postulated that the symptoms Charcot observed in posttraumatic neuroses were a consequence of suggestion created by hypnosis (Bailey, 1918).

The legitimacy of traumatic neurosis was always subject to debate when compensation claims were instituted. Questions were raised about how malingering and suggestion were mechanisms underlying the clinical presentations assessed in litigation settings. Much of the early attention on traumatic neurosis was in the context of compensation cases involving railway accidents. The defendant's case depended on casting doubt on the credibility of the litigant. As the field became linked to the study of hysteria and the role of the unconscious, the influence of secondary gain received increasing attention. This added to suspicions about the legitimacy of symptoms, particularly when the individual's motivation was in question. This dynamic played out in the different conceptualizations of PTSD in World War I and the intellectual battles that took place in deconstructing shellshock. Were the mind and the brain separated? Was this a physical or psychological injury, or was shellshock primarily a motivational problem?

THE STUDY OF PATHOGENESIS AND THE ROLE OF TRAUMATIC EVENTS

Models of etiology rapidly developed in medicine in the second half of the 19th century. The basic mechanisms of pathology, such as healing, inflammation, and infection, were described, but the cause of many illnesses remained obscure. Moreover, even when etiological agents were identified, little could be done to modify their effect. The role of environmental factors in illness was still in its infancy. In contrast, Charles Darwin's *On the Origin of Species,* published in 1859, which set out the theory of evolution, had a dramatic impact on theories of what caused mental illness. The hereditary factor was viewed as a critical causal feature of these illnesses (Macleod, 2019). Darwin's observations about the phylogenetic nature of emotion among patients in mental asylums added to his influence about the origins of mental illness. Hence, the predominant paradigms focused on the host rather than the nature of the external environment that led to symptom formation. This formulation was particularly influential in the debates regarding the cause of psychiatric casualties suffered in World War I.

Importantly, at this time Russian Nobel Prize winner Ivan Pavlov (1849–1946) was making important observations about conditioned reflexes. He had an interest in the physiology of gastric function and the saliva gland. In the course of this research, in 1901 he described the phenomenon of classical conditioning and involuntary reflex actions. This work became the foundation of modern behaviorism. At the time, this work did not have a significant influence on the common understanding of the nature of the response to PTEs, or early 20th-century theories about the etiology of traumatic neurosis. However, classical conditioning was later applied by psychologist John Watson and psychiatrist Joseph Wolpe in the development of key behavioral treatments (Monson et. al, 2007). Psychologists Dean Kilpatrick, Lois Veronen, and Patricia Resick (e.g., 1977, 1979) were the first to apply the concept of classical conditioning to understanding fear and anxiety in victims of rape. Their work influenced the subsequent development of fear-conditioning models of PTSD as well as cognitive-behavioral treatments for PTSD (Monson et al., 2007).

The original view of the pathogenic agent in traumatic neurosis was nervous shock. However, there was little discussion of the exact mechanisms through which it exerted its effects. Charcot's previous work led to postulation about possible mechanisms, including dissociation and the importance of traumatic memory. Janet's 1889 doctoral dissertation made a seminal contribution to the origins of modern traumatology. He hypothesized that the symptoms of hysterical patients were manifestations of a lack of synthesis, which dissociated their personality into different "systems of ideas and functions" (Janet, 1907). In many cases, traumatic experiences were seen as critical.

These ideas were further developed by Freud, who stated that the traumatic event was responsible for neurotic symptoms. In most of his patients, the event identified was childhood sexual abuse. He then made a dramatic shift in 1897, rejecting his previous opinion. Freud's recanting of his earlier views had a dramatic impact on the acceptance and management of sexually abused children. Thus, according to Brown (1968), "Freud had to change his mind concerned with these supposed sexual seductions of childhood [as] from the accounts of relatives it seemed clear that the patient was either lying or imagining an event which had never happened" (McFarlane, 2000, p. 54). This recanting of Freud's original formulation and denial of the reality of sexual abuse unraveled the critical role of the memory of PTEs in adult psychopathology for 80 years.

Mental health practitioners continued to accept Freud's assertions, despite the accounts of sexual abuse reported by millions of patients. As a result, clinicians had difficulty acknowledging the existence of trauma. Based on the theoretical assumptions of psychoanalysis, many clinicians assumed that the symptoms caused by the experience of traumatic events were due to existing personality traits. This shift in Freud's views and the growing influence of psychoanalysis, combined with Babinski's negative view of many of Charcot's observations, was a critical historical turning point. Blocking the development of the inquiry into the impact of traumatic events had catastrophic consequences both for generations of patients and for the development of this area of psychiatry and psychology.

WORLD WAR I AND THE SHELLSHOCK DEBATE

Human imagination failed to prepare the world for the consequences of the carnage of World War I. In the postwar years, countries were preoccupied with the grief associated with the death of between 22 and 25 million men in their prime. Those who survived

without physical wounds were considered the lucky ones, and hence psychological injuries were not a predominant focus of concern. The estimated 50 million killed by the 1918 Spanish influenza pandemic added to the sense of carnage and loss.

At the beginning of the war, a fundamental question that confronted the medical officers was whether inability to function in battle was a moral or mental problem. Was it simply a matter of conscious will when individuals broke down? This question was described as "the psychic no-man's land that separates malingering from hysteria and which links free will with determinism" (Butler, 1943, p. 43). The absence of a clear diagnostic framework was fertile ground for the acceptance of the emerging concept of shellshock. The various diagnostic labels used included traumatic neurasthenia, hysteria, disordered action of the heart, and shellshock. The medical profession was confronted with soldiers who broke down in battle. The focus was on the nature of acute disorders and how to manage them, with the primary goal being to return soldiers to active duty (Salmon, 1917).

Despite the enormity of the exposures and losses, a continued debate existed about the cause of these psychiatric disorders rather than about the role of emotions such as fear and horror. Rather, debate continued as to whether it was due to the "seed" rather than the "soil." Arthur Butler (1943), who wrote the history of the Australian Medical Corps, summarized the issue as "the [preexisting] nervous and moral constitution of the force and of the individuals comprising it rather then that particular kind of strain to which they were subjected—was the essential element in determining the total amount of nervous breakdowns" (p. 89). Hence, despite the extraordinary conflagration experienced in battle and the strains of 4 years of fighting, the view that individual vulnerability was the critical diathesis leading to war neurosis remained the predominant one.

The problem of acute mental casualties also focused debate on psychogenic and functional disorders. Speculations about the role of motivation and courage were rife. This focus prevailed despite the carnage of trench warfare, the brutality of intense artillery barrages, and the constant threat of being poisoned by chemical agents. Chemical weapons also produced an element of psychological warfare in which there was a constant threat of these invisible agents. In this context, the debate about the concussive effects of being exposed to shells exploding emerged. As with railway spine, the debate was about whether the critical issue was the physical effect of the explosion or the threat of death and injury.

Myers (1915), the British physician who first published research on shellshock, attributed the symptoms to the concussive effects of exploding shells. This formulation viewed an external agent as the cause of symptoms rather than individual vulnerability. This theory had obvious appeal to soldiers, but the military hierarchy saw the inability of the medical corps to prevent the popularization of concepts such as shellshock or "war neurosis" as "a devastating menace," fearing that it would lead to "military and social exploitation and mass suggestion" (Butler, 1943, p. 93).

The public accepted the reality of shellshock, but many doctors argued that it provided too easy an exit from the battlefield. These views were challenged by the soldiers, particularly those who became renowned war poets in Great Britain, such as Siegfried Sassoon (1983):

> How many a brief bombardment had its long-delayed after-effect in the minds of these survivors, many of whom had looked at their companions and laughed while inferno did its best to destroy them. Not then was their evil hour; but now; now, in the

> sweating suffocation of nightmare, in paralysis of limbs, in the stammering of dislocated speech. (p. 51)

Sassoon's account highlighted the fact that many soldiers who had bravely fought broke down after battle. Hence, the concept of shellshock went beyond its original formulation, and this created considerable consternation. A battle emerged between neurologists and psychiatrists about "the no-man's land between neurology, the medicine of the brain, and psychiatry, the medicine of the mind" (Butler, 1943, p. 93). This rivalry did little service to those who were suffering, for the military command continued to see this both as an urgent disciplinary problem and a reflection of the soldiers' failure to manage the fear of battle.

The Challenge of Dealing with Secondary Gain and Prolonged Disability

The challenge of maintaining the fighting force in the face of the rising number of casualties became an increasing preoccupation of the medical services. Shellshock implied the need to remove individuals from the battlefield in order to prevent further injury. Similar discourse among professionals occurred on both sides of the war, partly due to a regularly published letter in the *Journal of the American Medical Association* that kept the English-speaking world abreast of the thinking of German psychiatrists (Macleod, 2019). In 1916, German psychiatrists, led by Emil Kraepelin, decided that a traumatic neurosis diagnosis was not in the national interest. They argued that having a name/diagnosis caused disability, reduced the will to fight, and showed that symptoms were not the consequence of combat (Macleod, 2019). Although the term continued to be used, this politically driven consensus statement had the effect of largely banishing traumatic neurosis from the psychiatric nomenclature until DSM-III reintroduced the diagnosis as PTSD in 1980 (APA, 1980).

Given this conclusion, the challenge became how to limit secondary gain. If a soldier broke down, the aim of the doctor was to stop him from falling into the trap of accepting "the insidious motivation" of "defeat and dependence" (Butler, 1943, p. 103). Delaying diagnosis was one strategy, and the label of the "not yet diagnosed: nervous" emerged. The absence of a diagnosis was supposed to promote early recovery and a rapid return to duties (Salmon, 1917). In adopting this practice, medical officers prioritized responsibilities to military command rather than acting in the best interests of the patient, thereby neglecting the risks of symptom exacerbation through further combat exposure.

As the end of the war approached, the prevailing view remained that individual vulnerability was the primary cause of psychiatric casualties and that inadequate selection had failed to exclude those who could not cope with war service. Lack of discussion about the risk of cumulative combat exposure during World War I is one of the striking lacunae of the literature of the era. Medical ideas of causation also assumed that any adverse effects of battle would be immediately apparent. The idea of a delayed onset of morbidity was not accepted in the medical literature. However, once the war ended, the numbers of those who could not function and sought pensions increased.

In general, psychiatry and psychology were at a loss to explain the delayed emergence of psychopathology. Rather, an alternative discourse emerged which was notable in the way that pension claims were managed. Delayed presentation was seen to be a consequence of suggestibility (Bailey, 1918). Exaggerated disability and compensation neurosis were dominant rubrics that were used to dismiss emerging symptoms. The

individual was stigmatized in his suffering as being poor "seed" rather than having been injured by the horror of war. However, an interesting strain developed between views of the medical establishment and broader popular perceptions of this issue. This matter remained an ongoing controversy in which social attitudes favored an understanding of the veterans' suffering, but concerns about the cost of pensions fueled prejudice in other circles.

Many of these issues were revisited after the war when the results of an inquiry into shellshock by the British War Office was published. The Lord Francis Southborough Committee (1922) concluded that shellshock was not due to concussive injury. The psychogenic view of etiology had evolved to the position that psychological mechanisms were an unconscious escape into disease. Retreat into illness provided a solution to the unendurable emotional tension faced by the soldier. Secondary gain was seen to be acceptance that this was a wound that allowed removal from duty (Wessely, 2006). Ultimately, it was accepted that war neurosis/traumatic neurosis was not a consequence of some immediate physical "shock to the brain that had led to microscopic neurological lesions" (Butler, 1943, p. 99). However, the burden of proof in the minds of many soldiers was weighted between acceptance of vulnerability due to these psychological constructs (because of the stigma of mental illness) versus disability due to a direct injury.

There were few certainties and much debate as to what the most effective treatments were. Medical officers were generally "left to work out their own salvation" (Butler, 1943, p. 104). Treatments ranged from hypnosis to galvanism (e.g., electrical shocks), rest, and psychotherapy. Notable contributions were made by clinicians such as W. H. R. Rivers, who saw that repression was the central mechanism of the failure to process the traumatic memory. Equally, he saw that it was the attempt to keep the traumatic event at bay, rather than the primary experience at the time of combat, which was critical to the emergence of later symptoms (Rivers, 1918).

In retrospect, historical observers did not have models to address or tools to measure the dysregulation of the function of neurohormonal systems and the effects of conditioning on neural functioning. The fact that certain underlying neurobiological processes underpinned the emergence of psychological symptoms due to the horrendous trauma of warfare was not considered. The mind–body split remained supreme based on an overly simplistic dichotomy of a biological/neurological illness or a disorder of mental mechanisms. The latter dominated due to the ascendency of Freudian psychology.

THE INTERWAR PERIOD

The end of the war brought a period of reflection and memorialization of the dead. The challenge of dealing with injured soldiers led to building the veterans' health systems in the United States, Canada, and Australia. It had been expected that the psychiatric casualties would recover with the end of the war. However, with the passage of time, many soldiers who coped with the heat of battle became unwell. Progressively, the number of pensions issued for psychiatric illness increased. For example, between 1916 and 1920 in the United Kingdom, only 4% of pensions were for "neurotics." By 1932, 36% of pensions in the United Kingdom were for psychiatric cases. By 1942, neuropsychiatric cases represented 58% of all the World War I veterans on pensions in the United States (Micale & Lerner, 2001).

There was minimal recognition of the delayed impact of combat exposure, and any delayed problems were attributed to secondary gain. Pension systems were blamed, and benefits were reduced or terminated altogether, as occurred in Germany. In 1938, the United Kingdom determined that there would be no pensions for psychiatric injuries in future wars. In Germany, the Nazis began exterminating psychiatric patients, many of whom were World War I veterans (Jones & Wessely, 2001). In short, Germans failed to consider the prolonged impact of war trauma on patients because they were reminders of defeat.

The interest of the psychiatric profession waned, and "the limited ability to cope with combat was deemed the result of faulty personality development and thus conformed to the psychoanalytic model of the psychoneuroses and was so generally diagnosed" (Glass, 1974, p. 802).

Veterans continued to advocate for those suffering because of their service. Increased concern was voiced about the premature mortality and general physical debility of those who had fought, and this led to the claim that there was a 'burnt-out' soldier syndrome. A large-scale epidemiological study in Australia found that combatants who had fought on the Western Front had a decreased life expectancy of 4 years (Butler, 1943). Despite these observations and the continued increased presentation of delayed-onset PTSD, as it would now be known, mental health professionals had little interest in the trauma field. Rather, the suffering of the soldiers and the exploration of their experience were captured by war poets and authors, including Robert Graves, Siegfried Sassoon, and German veteran Eric Marie Remarque (1987), who wrote the great World War I epic, *All Quiet on the Western Front* (1929). These writers gave voice to the suffering of those who fought, and they captured the phenomenology of their experience.

WORLD WAR II

When World War II began, Allied forces were unprepared for the psychological casualties, and it took months to relearn the lessons of World War I. U.S. forces undertook major screening programs, but these programs did not stop the problem of acute combat breakdowns (Glass, 1974). A direct result of overreliance on screening was that there was little preparation for an overwhelming incidence of psychiatric disorders. During the Tunisian campaign in 1943, the U.S. Army suffered large numbers of psychiatric casualties who were generally lost to fighting units. More than 2 years elapsed before sufficient organizational and operational capability was developed to adequately deal with the large incidence of psychiatric disorders.

One consequence of the continued reluctance to diagnose mental disorders was seen in the United Kingdom's Royal Airforce. A tour of duty was 30 missions, based on a calculation that there was a 50% chance of being shot down after 30 sorties. If an airman could not fly due to a psychiatric disorder, it was not diagnosed, and he was deemed to show "lack of moral fibre" (McCarthy, 1984). This label was highly stigmatized and led to loss of rank and dishonorable discharge. This policy reflected the idea that secondary gain was a critical driver of symptoms and impairment, not the cumulative stress of battle (Wessely, 2006).

World War II psychiatrists did begin to reconsider these views because of research on the epidemiology of combat stress casualties. Prospective studies by Stouffer and colleagues (1949) demonstrated that units with good morale and leadership had fewer

combat stress casualties than those without, controlling for combat intensity. A direct relationship was also found between combat intensity (as measured by rates of wounded and killed in action) and psychiatric casualties (Beebe & Apple, 1958). "New" or inexperienced troops were more likely to become a psychiatric casualty, but with increasing exposure to combat, after one or two combat months, older troops were also likely to suffer from combat stress.

While the focus was on acute combat stress reactions, Grinker and Spiegel (1945) proposed that some people develop excessive responses under stress and that such responses are often transformed into prolonged disorders They highlighted the lack of a clear diagnostic system: "The clinical description of the neurotic reactions to severe combat stress is thus a passing parade of every type of psychological and psychosomatic symptom, and of maladaptive behavior" (p. 82).

In the postwar period, extreme stress was accepted as an important determinant of acute symptoms with the inclusion of "gross stress reaction" in DSM-I (APA, 1952). However, the need for a separate category to account for the chronic disorder remained elusive. In DSM-II (APA, 1968), a shift toward including less severe events was reflected in the category "transient situational disturbance." This diagnosis was used to describe acute symptomatic distress following a range of aversive events, whereas more prolonged disorders were categorized as anxiety or depressive neuroses. The suspicion remained that diagnosis led to disability through suggestion, and the term *compensation neurosis* was synonymous with traumatic neurosis, despite the systematic evidence about the long-term effects of traumatic stress.

POST-1945

When the war ended, there was again no anticipation of the continued burden of psychiatric casualties. The expectation remained that the effects of combat were acute and would resolve with effective frontline psychiatry. There was little interest in studying the long-term effects, except for a few enlightened clinicians such as Abram Kardiner, who characterized traumatic neurosis as a physioneurosis (Weisaeth, 2007). Albert Glass, who wrote the main report on the psychiatric casualties of World War II in the U.S. forces, commented, "Curiously, during the early postwar years, as following World War I, military psychiatry, like civil psychiatry, ignored the lessons of wartime experiences. Instead, attention was focused in the then prevalent psychoanalytic concepts and practice" (1974, p. 804).

An intense interest in the acute effects of stress remained, however, as reflected in the categories "gross stress reaction" and "transient situational disturbance" included in DSM-I and DSM-II. Many psychiatrists had seen service in World War II, including Thomas Holmes and Richard Rahe, who developed the life events research field. However, this body of work did not differentiate the effects of events such as unemployment or divorce from traumatic stressors. It did lead to bereavement research, and early pioneers such as Colin Murray Parkes and Beverly Raphael developed interventions to address the morbidity of loss (Weisaeth, 2007).

This work in the area of bereavement was one of the early origins of disaster research that contributed to the emerging interest in PTSD. While the earliest studies of disasters were by Edouard Strielin, who documented a Swiss mine disaster and the impact of the Messina earthquake, there had been little accumulated experience from the investigation of these events (Weisaeth, 2007). In the United States, several tragic

nightclub fires gave new impetus to this field and to the role of crisis intervention in assisting victims. A turning point of interest was the Buffalo Creek disaster in 1972, documented by James Titchener, who conducted a long-term follow-up of the affected community in the context of the litigation that followed for compensation from the mining company responsible for the dam's collapse (Weisaeth, 2007).

In the aftermath of World War II, repatriation of refugees highlighted the horrors of the Holocaust and the need for some long-term reparation. Pioneers of the field who were survivors included the psychiatrist Henry Krystal, who fought for adequate pensions for Holocaust survivors from the German government (Weisaeth, 2007). In the Netherlands, resistance fighters who had been brutally treated by the Nazis sought long-term recognition and were assisted by Professor Jan Bastiaans, another veteran. In Norway, Leo Eitinger, who had survived Auschwitz, studied the impact of stress on survivors of the Holocaust as well as on merchant mariners in the convoys that traversed the Atlantic Ocean during the war. His research demonstrated the long-term effects of war on the mental and physical health of both groups (Weisaeth, 2007). Because of this work, Norway emerged as a leader in understanding the effects of disasters and trauma.

ADVOCACY MOVEMENTS IN THE 1960s AND 1970s THAT CATALYZED THE BIRTH OF PTSD IN DSM-III

The Vietnam War and Its Aftermath

The political and social turmoil surrounding the conduct of the Vietnam War and the treatment of veterans led to a critical turning point in the traumatic stress field. The rates of psychiatric casualties were not anticipated since tours of duty were limited to a year. Upon returning to the United States, veterans who sought treatment from the Department of Veterans Affairs (VA) were often humiliated and felt that their struggles were not dealt with empathically (e.g., Scott, 1990; Shatan, 1973).

In the context of the Vietnam War protest movement, the VA began to set up "rap" groups, which were essentially a self-help movement. A group of psychiatrists and psychologists, some of whom were themselves veterans of the war, began participating and engaging with these groups; among them were Charles Figley, Sarah Haley, and Art Blank. (Blank later went on to become the director of the Vietnam Veterans Readjustment Counseling Service.) Other political activist clinicians, such as Robert Lifton and Chaim Shatan, became actively engaged and advocated for the Vietnam veterans. One of the inadequacies of the veterans system was its essential denial and lack of curiosity about the nature of stress response syndromes. Veterans were so distrustful of the DVA system that they demanded separate services.

The Women's Movement

The National Organization for Women (NOW) was founded in the United States in 1966. In the late 1960s and early 1970s, speak-outs and consciousness-raising groups organized by NOW and other feminist groups provided women with the opportunity to discuss problematic issues in their lives. A common theme was the devastating impact of sexual and physical violence against women and children. This issue focused attention on the abysmal treatment of victims of these crimes by the criminal justice system, health care professionals, and society in general. Freud's legacy had contributed to the

denial of child abuse and sexual violence and the lack of interest in the topic by most researchers and mental health professionals. To address the problem of rape specifically, feminist grass roots activists established the first four rape crisis centers (RCCs) in the United States in 1972. By 1979, every U.S. state had at least one RCC (Koss & Harvey, 1987). In 1978, the National Coalition Against Sexual Assault was founded to advocate for sexual assault prevention, services, and victims.

Anti-rape activists lobbied the U.S. government to pass legislation appropriating funds to support RCCs, but the public policy process worked in mysterious ways. A bill was enacted into law in 1975 that established the National Center for Prevention and Control of Rape (NCPCR) within the National Institute of Mental Health, but it did not provide funds for RCCs to deliver services. Instead, the NCPCR's mission was to provide funding for rape research. As Koss (2005) notes, NCPCR funding had a profound effect on the quality and quantity of rape research during its existence from 1976 to 1987. Prior to 1973, only 16 articles on rape had been published in the English literature. From 1974 to 1989, there were 453 such publications. The first NCPCR grant was funded in 1976, and 58 grants were funded as of 1981 (NCPCR, 1981). Many more grants were funded from 1981 until the NCPCR and its funding for rape research were abolished in 1988 upon the recommendation of the politically conservative Reagan administration (Koss, 2005). Two historical lessons from the NCPCR are that its existence and successes would not have been possible without anti-rape activists from the women's movement and that even highly successful programs are subject to elimination by the vicissitudes of politics.

Many influential individuals in the PTSD/traumatic stress field got their start in rape research funded by the NCPCR. A partial list of these pioneering traumatic stress researchers includes Susanne Ageton, Judith Becker, Ronnie Janoff-Bulman, Karen Calhoun, David Finkelhor, Edna Foa, Mary Harvey, Judith Herman, Dean Kilpatrick, Mary Koss, Patricia Resick, Barbara Rothbaum, Murray Strauss, and Lois Veronen. Work done by these pioneers provided theories, data on the prevalence of rape and its mental health consequences, and treatments for these problems that provided justification for the PTSD construct in DSM-III and that advanced the traumatic stress field.

Battered Women and Child Abuse

The woman's movement also highlighted the problem of family violence, much of which was directed at women, as well as the devastating mental and physical consequences of such violence. These observations by activists were confirmed by researchers who provided sound data documenting the extent of these problems (e.g., Gelles, 1980; Gelles & Straus, 1979; Walker, 1978). In 1978, the National Coalition Against Domestic Violence was established to advocate for battered women's shelters. Victims of these experiences described symptoms consistent with what would be included in the PTSD diagnosis.

There was also a growing understanding about the rights of children and about the extent of child abuse. In the United States, C. H. Kempe and colleagues (1962) published a seminal paper about the "battered child syndrome." The suffering of children whose parents had been murdered was an area that began to explore the impact of traumatic loss on children, documented, for example, by the British child psychiatrist Dora Black (Weisaeth, 2007). A national advocacy group in the United States, Parents of Murdered Children, was formed in 1978 by parents whose daughter had been murdered. Lenore Terr (1981) carried out a seminal study of the impact of a school

kidnapping that occurred in 1976. Richard Gelles (1978) conducted the first national study in the United States documenting the high prevalence of parent-to-child violence. Again, many survivors described symptoms consistent with PTSD.

The Crime Victims Movement

Core beliefs of the crime victims movement included (1) that victims are frequently mistreated by the criminal justice system, (2) that victims should have the same rights as criminal defendants, (3) that victims suffer harm from crime as well as from being mistreated by the criminal justice system, (4) that harm from treatment by the criminal justice system should be mitigated, and (5) that harm from the crime should be remediated. The National Organization for Victim Assistance (NOVA) was founded in 1975 and brought together a broad array of individuals who approached this problem from many perspectives. NOVA members included criminologists, mental health professionals, members of the criminal justice system, legal scholars, and crime victims themselves.

The crime victims movement highlighted that crime produces psychological injuries as well as physical ones and that a barrier to cooperation with the criminal justice system is lack of assistance in dealing with the extreme stress of interacting with the criminal justice system. Descriptions of crime-related psychological injuries included many symptoms that subsequently were included in the PTSD diagnosis. Also highlighted was the importance of providing crime victims with enforceable rights to be notified about and participate in criminal proceedings, to make impact statements to the court about how they had been affected by the crime, and to receive crime victim compensation and restitution for crime-related injuries they had sustained.

This movement was incredibly successful in achieving public policy change. By the 1970s and 1980s, all 50 U.S. states had enacted a Crime Victims Bill of Rights. This was accomplished by building a potent public policy coalition to improve victim rights and services. The coalition included social progressives who supported improving victim rights and services because it was the right thing to do based on the human rights tradition and humanitarian ideals that demanded fair treatment for all people, including crime victims. It also included social conservatives who supported these changes because "getting tough on crime" was impossible without the cooperation of crime victims. These two factions agreed on virtually nothing else but were united on this one issue. The lesson this history teaches us is that we can accomplish more if we put aside areas of disagreement and ideological purity fights and focus on areas of agreement.

Other Key Contributors

A group of independent clinician–researchers understood the limitations of the existing formulations of traumatic stress and made important contributions (Weisaeth, 2007). Two individuals who had particular impact were Mardi Horowitz and Nancy Andreasen. Horowitz's (1978) seminal work on "stress response syndromes" characterized the phenomenology of intrusion and avoidance, which are central to our understanding of PTSD today. Andreasen, best known for her prolific research on schizophrenia, conducted a series of studies in the early 1970s with patients who had sustained major burn injuries (e.g., Andreasen, Noyes, & Hartford, 1971). She reported that "traumatic neurosis" was the most frequent psychiatric complication in this cohort of burn patients. These observations, as well as her distinguished status in the academic medicine field and her familiarity with the emerging findings on the mental health

consequences of exposure to PTEs among civilians, would make her a key player in how PTSD was defined and explained in DSM-III.

PTSD IN DSM-III: HOW IT ALL CAME TOGETHER

DSM-III was published in 1980, but preliminary work on it began in the mid-1970s. It was a radical departure from its predecessors due to the recognition that more reliable definitions of psychiatric disorders and improved methods of diagnosis were needed. Scott (1990) provides a fascinating account of events that resulted in PTSD becoming a diagnosis that includes media accounts and personal interviews with many of the key parties who were involved. His account places a great deal of emphasis on the following. First, there was no diagnosis in DSM-II that captured the symptoms clinicians were seeing among Vietnam veterans. Second, a group of anti-Vietnam War clinicians (Sarah Haley, Robert Lifton, and Chaim Shatan) advocated strongly for inclusion of a new diagnosis in DSM-III that would address this deficit. Among their candidate names for this proposed new diagnosis were "post-Vietnam syndrome," "post-combat disorder," and "catastrophic stress disorder."

Third, word got out that there were no plans to include any type of combat-related disorder in DSM-III, which prompted members of the antiwar clinicians group to contact Robert Spitzer, leader of the DSM-III revision process, to press him to include a diagnosis. Fourth, Spitzer was skeptical, citing opposition by prominent psychiatrists and researchers, including John Helzer and Lee Robins who concluded that no new diagnosis was needed. However, Spitzer agreed to appoint a six-person APA Committee on Reactive Disorders, with Nancy Andreasen as chair to report to the DSM-III Task Force. Spitzer served as a member, as did three antiwar supporters of a new diagnosis for veterans (Lifton, Shatan, and Jack Smith, an antiwar Vietnam combat veteran). The charge to Lifton, Shatan, and Smith was to provide convincing evidence to their fellow committee members that would justify a new diagnosis. They in turn engaged others from the Vietnam veterans groups, as well as Henry Krystal and William Niederland who had been studying Holocaust survivors, including those who had been in German concentration camps.

Fifth, Andreasen was the key figure in deciding whether there would be a diagnosis and in determining what its nature would be. Scott (1990) indicates that the antiwar members of the committee viewed her as the key vote. Andreasen describes herself as "the psychiatrist who was also the midwife at the birth of PTSD" (2004, p. 1323). In her account of these events, she did not favor a "post-Vietnam syndrome" because it was too narrow and because the types of symptoms that were being described occurred among victims of civilian trauma as well as veterans. Her work with burn victims clearly reinforced these views. Scott notes that the committee then began to broaden its focus to include extensive information about all types of stress disorders that already existed, much of which is described in this chapter.

Sixth, these justification efforts were clearly successful, and PTSD was born as an official diagnosis that included civilian as well as war-related trauma. Specific types of PTEs included rape or assault, military combat, natural disasters, accidental human-made disasters, or deliberate human-made disasters such as bombings, torture, and death camps. As noted previously, this was a stellar achievement because it united a previously fractured field and provided a strong foundation that facilitated rapid progress in the traumatic stress field. It can also be argued that the comprehensiveness of the

PTSD diagnosis and the diversity of the traumatic stress groups who supported it made PTSD more resilient to attacks from critics than its narrower precursors had been.

CONCLUSIONS

PTSD science and practice exploded after PTSD was included in DSM III. The traumatic stress field has also had far-reaching effects beyond clinical practice, but it emerged as an entity, probably as much due to the voices of many groups of victims and survivors (some of whom were health professionals themselves) as because of mainstream health professionals. Delayed acceptance of the PTSD diagnosis was due to fear of suggestion and inappropriate compensation seeking. Mainstream psychiatry and psychology failed to document the suffering and impact of traumatic stress for complex reasons. The traumatic stress field has changed the landscape of many domains outside mental health, such as public policy, human rights, public health, cinema, and literature.

However, many age-old dilemmas remain. The challenge of how to incorporate the neurophysiology, neurochemical, cognitive, and psychodynamic processes into a unified whole remains, particularly as current diagnostic criteria do not fully capture the range of physical symptoms that were central to the initial descriptions of traumatic syndromes. The field has also documented the cumulative effects and prevalence of PTEs as a major public health challenge that affects many more people than those who develop PTSD. Furthermore, the impacts of traumatic stress go beyond PTSD and are central to the range of psychiatric morbidity. History teaches us that minimizing the impact of trauma fails those that health professionals are supposed to serve. Psychoanalysis was a major force driving this denial, which arose from Freud's recanting of his earlier observations about child abuse. Seeing the reality of the suffering arising from traumatic events allows clinicians to advocate for the broader social and political changes required to ensure that we live in a society safe for all.

We must be mindful that PTSD is widely accepted now, but forces always exist that minimize traumatic stress and its consequences for a host of reasons. The traumatic stress field is always in peril, so we must remember that numerous social and political advocates shaped the PTSD construct and made it a mental health/public policy priority. These forces united to advocate for inclusion of PTSD in DSM-III. Building and maintaining broad coalitions that extend beyond the mental health field are essential to ensure that traumatic stress remains a priority and does not, once again, fade away into the mist of the forgotten.

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PART II

SCIENTIFIC FOUNDATIONS AND THEORETICAL PERSPECTIVES

CHAPTER 4

Epidemiology of Trauma and PTSD in Adults

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Traumatic events, such as natural disasters, accidents, sexual assault, and child abuse, are common throughout the world. Mental health consequences of these events, such as posttraumatic stress disorder (PTSD), are also pervasive. In this chapter, we discuss the epidemiology of trauma exposure and PTSD. Specifically, we review the prevalence and distribution of traumatic events, PTSD, and other associated disorders (including physical and mental health consequences), and describe differences in the distribution of trauma and trauma-related disorders across populations. Furthermore, we discuss the course of PTSD as well as functioning and treatment seeking among persons with PTSD. Finally, we describe methodological considerations regarding the research in this area to date.

CURRENT STATE OF THE LITERATURE

Epidemiology of Traumatic Event Exposure

Traumatic events are common globally, with each person experiencing an average of three traumatic events during their lifetime (Kessler et al., 2017). The best estimates of the global prevalence of trauma exposure come from the World Health Organization's World Mental Health Surveys (WMHS), which found that approximately 70% of respondents experienced one or more traumatic events (Kessler et al., 2017). The most common types of traumatic events were witnessing death or serious injury, experiencing the unexpected death of a loved one, being mugged or assaulted, being in a life-threatening automobile accident, and experiencing a life-threatening illness or injury (Benjet et al., 2016). These five traumatic events together accounted for over half of all instances of traumatic events experienced across 24 countries between 2001 and 2012 (Benjet et al., 2016).

Although this study illuminates the pervasiveness of traumatic events globally, an important limitation of this study is that it used the fourth edition of the *Diagnostic and*

Statistical Manual of Mental Disorders (DSM-IV) definition of a traumatic event, which is somewhat broader than that of DSM-5. In many studies using DSM-IV criteria, experiencing the sudden, unexpected, nonviolent death of a loved one was one of the most highly endorsed criterion A events, but this event is no longer considered to meet the criteria for a traumatic event in DSM-5. (The impact of the DSM modifications on estimates of trauma is discussed in Kilpatrick et al., 2013.) In the National Epidemiologic Survey on Alcohol and Related Conditions–III (NESARC-III), a nationally representative sample of U.S. adults that used DSM-5 criteria, nearly 69% of respondents reported at least one potentially traumatic event. This study found that the prevalence of traumatic events varied by PTSD diagnostic status. Among respondents with PTSD, the most commonly reported potentially traumatic events were sexual abuse before age 18, seeing a dead body or body parts, victimization by intimate partner violence, and own serious or life-threatening injury and illness (Goldstein et al., 2016). Among respondents without PTSD, the most commonly reported traumatic events were someone else's serious illness, seeing a dead body, one's own serious illness, someone else's serious injury, and one's own serious injury (Goldstein et al., 2016).

Predictors of Traumatic Event Exposure

The distribution of exposure to traumatic events varies across sex, age, race/ethnicity, sexual orientation, educational attainment, marital status, occupation, genetics, risk-taking behavior, and neighborhood of residence (Benjet et al., 2016; Kessler et al., 2017). In the WMHS, the types of traumatic events that affect men and women differed: Men were more likely to experience physical violence and unintentional injuries, whereas women were more likely to be exposed to sexual violence, intimate partner violence, and the unexpected death of a loved one. Gender was not associated with having a child with a serious illness, being a civilian in a war zone, and exposure to a self-nominated other traumatic event (Benjet et al., 2016). Findings from the NESARC-III indicated that compared to men veterans, women veterans were more likely to report child abuse, interpersonal violence, and a greater number of past-year stressful life events, but less likely to report combat or war-zone exposure and other traumas (Lehavot, Katon, et al., 2018).

According to the WMHS, the median age-of-occurrence of interpersonal violence is 17 years; intimate partner sexual violence, 18 years; war-related traumas and traumas happening to other people, 20 years; and unintentional injuries, unexpected deaths of loved ones, and other traumas, later median ages-of-occurrence (ages 24–31). The distribution of traumatic events across ages may be explained by differences in life circumstances and behaviors across the life course (Kessler et al., 2017). There are also differences in types of traumatic events experienced based on racial/ethnic factors. Black and Hispanic persons are more likely than White persons to report witnessing domestic violence and child maltreatment. Findings from the 2004 to 2005 wave of NESARC showed that Black men, Hispanic women, and Asian populations have greater risk of exposure to war-related traumatic events (Roberts, Austin, Corliss, Vandermorris, & Koenen, 2010) than White persons (Roberts et al., 2010). Sexual orientation is associated with exposure to violence and other types of traumatic events; findings from the 2004–2005 wave of NESARC indicated that persons reporting any same-sex partners during their lifetime were more likely to report childhood maltreatment, interpersonal violence, trauma to a close friend or relative, and unexposed death of someone close in comparison with people who did not report having same-sex partners (Roberts et al., 2010).

Low educational attainment is associated with increased risk of some traumatic events (e.g., violence, unintentional injuries, and natural disasters), whereas higher levels of educational attainment are associated with lower risk of being raped, being beaten up by a spouse or romantic partner, or stalked, but were associated with increased risk of nonpenetrative sexual assault and traumatic events to a loved one (Kessler et al., 2017). Individuals who are married have lower risk of most types of traumatic events compared with persons who have never been married. A potential reason for this finding is that married individuals may spend less time outside the home at later hours, unaccompanied, and in potentially vulnerable situations (Benjet et al., 2016). Certain occupations also carry greater risk of exposure to traumatic events. Military members, veterans, and first responders are likely to have experienced traumatic events, including combat exposure, coworkers being injured or killed intentionally, and being seriously injured intentionally or unintentionally (Brunet, Monson, Liu, & Fikretoglu, 2015; Geronazzo-Alman et al., 2017; Richardson, Frueh, & Acierno, 2010). Genetic factors may also influence risk of traumatic events, possibly through mechanisms involving individual personality traits that influence environmental choices (Stein, Jang, Taylor, Vernon, & Livesley, 2002). Furthermore, individual factors such as impulsivity and risk-taking may increase the risk of traumatic event exposure (Romer, 2010). Highly disorganized neighborhoods (e.g., neighborhoods with high levels of poverty, family disruption, and residential instability) are associated with increased risk for trauma exposure (Butcher, Galanek, Kretschmar, & Flannery, 2015).

Having experienced a traumatic event increases one's risk of experiencing additional traumatic events (Benjet et al., 2016). More than 30% of respondents in the WMHS reported being exposed to four or more traumatic events (Kessler et al., 2017). Childhood abuse is strongly associated with additional traumatic event exposure in adulthood. Exposure to interpersonal violence is a strong predictor of subsequent exposure to interpersonal violence (Benjet et al., 2016; Coid et al., 2001; Kessler et al., 2017). Perpetrators may target individuals who have low self-esteem, are socially isolated, feel powerless, or have other psychological sequelae of previous victimization (Benjet et al., 2016; Coid et al., 2001; Grauerholz, 2000). Furthermore, impulsivity and risk-taking could also increase the risk of experiencing more than one traumatic event (e.g., injuries; Benjet et al., 2016).

EPIDEMIOLOGY OF PTSD AND OTHER PSYCHOLOGICAL CONSEQUENCES OF TRAUMA EXPOSURE

Although the majority of people exposed to traumatic events recover naturally and follow a normative pattern of resilience (Galatzer-Levy, Huang, & Bonanno, 2018), a substantial proportion of traumatized individuals do develop problems. Traumatic event exposure can lead to elevated levels of distress, significant problems in psychological functioning, and in some cases, to the development of mental health disorders. This is especially true in conflict zones where trauma exposure tends to be ongoing and in refugee populations where rates of psychological distress are higher (de Jong et al., 2001; Tinghög et al., 2017). Many psychological consequences can emerge after exposure to a traumatic event, including but not limited to acute stress disorder, complicated grief, adjustment disorder, and depression (Lewis et al., 2019). However, PTSD is among the most common, with approximately a 5.6% lifetime prevalence among the trauma exposed across the globe (Koenen et al., 2017), and it tends to be the focus when studying the psychological consequences of trauma exposure.

PTSD is among the most prevalent mental health disorders in the United States, with approximately 2.5% (Karam et al., 2014) to 4.7% (Goldstein et al., 2016) of the general population meeting diagnostic criteria in any given year. Approximately 6.1% of the population in the United States (Goldstein et al., 2016), 7.8% to 8.1% in the United Kingdom (Lewis et al., 2019; White et al., 2015), and 7.2% in Australia (Chapman et al., 2012; McEvoy, Grove, & Slade, 2011) will be diagnosed with PTSD in their lifetime. PTSD prevalence is significantly higher in certain subgroups of the population, such as the U.S. veteran population, where the lifetime PTSD prevalence ranges from 13.2% for female veterans and 6.2% for male veterans (Lehavot et al., 2018). It is notable that the lifetime prevalence of PTSD in the general population is second only to that of depression diagnoses in the United States and Australia (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012; McEvoy et al., 2011).

PTSD prevalence varies based on the socioeconomic status of a given country, with high-income countries reporting higher prevalence estimates of lifetime PTSD (6.9%) than those in upper-middle-income (3.9%) and lower-middle-income countries (3.0%; (Koenen et al., 2017). This pattern is similar to that of past 30-day prevalence of PTSD, with high-income countries reporting the highest prevalence (1.9%) and upper-middle-income (0.7%) and low-income (0.6%) countries reporting lower prevalence of PTSD. Although these prevalence estimates may reflect true differences in the prevalence of PTSD across cultures, it could also be a function of misclassification leading to underestimates of PTSD prevalence in low-income countries, variations in reporting due to cultural factors such as mental health stigma, and less understanding of mental health issues (Wang et al., 2007). High-income countries tend to report younger age of onset of PTSD than low- and middle-income countries, with the median age of onset in high-income countries being 25–28 years of age, whereas the median age of onset is before the age of 43 in lower-income countries (Koenen et al., 2017).

Correlates and Risk Factors of PTSD

Numerous pretrauma and posttrauma psychological and socioeconomic factors have been shown to increase risk for the development and maintenance of PTSD. Preexisting psychological factors, such as poor coping responses, personality traits, such as elevated levels of neuroticism, and preexisting mental health disorders have been associated with greater risk of PTSD (Perrin et al., 2014). Sociodemographic factors have also been shown to be associated with increased risk for PTSD. These sociodemographic variables include lower income and less education, prior exposure to traumatic events, and preexisting mental health disorders, White ethnicity has been implicated in risk for PTSD, but these findings have been somewhat equivocal. Furthermore, female sex has been shown to be associated with higher risk of PTSD, with women having twice the risk of PTSD as men (Kessler et al., 2005; Perrin et al., 2014). Emerging genomic and epigenetic research is identifying specific differences in gene expression associated with posttraumatic vulnerability or resilience (see Bustamante et al., Chapter 11, this volume).

The type of traumatic event one experiences has also been shown to be associated with risk for PTSD. Sexual assault and other forms of interpersonal trauma have been shown to lead to more severe and disabling psychological consequences than other types of traumatic event exposures (Breslau, 2009; Pietrzak, Goldstein, Southwick, & Grant, 2011). Women are more likely to experience sexual assaults such as rape and child sexual abuse, whereas men are more likely to experience nonsexual assaults,

accidents, injury, witnessing deaths, and combat-related events (Tolin & Foa, 2006). "Intentional" events (e.g., assault) are associated with more enduring symptoms of PTSD than traumatic events perceived to be "nonintentional" (e.g., natural disorders; Santiago et al., 2013).

Furthermore, the number of traumatic events one encounters is also associated with elevated risk. Experiencing four or more events has been shown to significantly increase risk for PTSD and may reflect a "risk threshold" for this disorder (Karam et al., 2014). Life course theories have been proposed to explain pathways to experiencing multiple traumatic events, including the view that living in certain environments (e.g., low-resource urban neighborhoods) can increase risk for adversity and trauma exposure (McCall-Hosenfeld, Mukherjee, & Lehman, 2014). Furthermore, it is also possible that exposure to the initial traumatic event may begin a negative feedback loop whereby the initial event places an individual in circumstances resulting in posttrauma variables that lead to subsequent adversity and increased risk for trauma exposure (Fink & Galea, 2015), and in some cases increased risk for PTSD. In particular, posttrauma variables such as subsequent life stressors (e.g., financial problems) and low perceived social support are associated with increased risk and maintenance of PTSD (Brewin, Andrews, & Valentine, 2000; Bryant et al., 2017; Ozer et al., 2003).

A key issue in some of the aforementioned literature is the difficulty in determining which variables are associated with the development versus the maintenance of PTSD. Although some variables likely influence both development and maintenance of PTSD, other factors may be more influential in the development rather than the maintenance of PTSD and vice versa. This line of research is further complicated by the tendency for research on predictors of PTSD to often fail to differentiate between current, acute PTSD and chronic PTSD. When investigating risk factors for PTSD, careful consideration of methodological design is needed. For example, Schnurr, Looney, and Sengupta (2004) examined the predictive pattern of variables associated with PTSD by comparing groups of those without a history of PTSD to those with PTSD. This allowed for the identification of variables associated with increased risk for the development of PTSD. Furthermore, for those who had PTSD, the authors were able to identify predictors associated with the short-term, remitted PTSD compared to predictors that were associated with chronic cases of PTSD. This methodological approach allowed for the ability to distinguish between predictors associated with the development versus the maintenance of PTSD in their sample.

Course of PTSD

PTSD tends to lead a chronic course if left untreated. However, it is not unusual for individuals to experience a fluctuation in symptoms, including the remission and reemergence of symptoms over time (Bryant, O'Donnell, Creamer, McFarlane, & Silove, 2013; Magruder et al., 2016; Solomon & Mikulincer, 2006). The WMHS reports that anywhere from 25 to 40% of PTSD cases will remit within 12 months, with a majority of those cases remitting within the first 6 months (Kessler et al., 2017). However, meta-analytic findings have shown that close to 50% of PTSD cases will be chronic (Morina, Wicherts, Lobbrecht, & Priebe, 2014; Steinert, Hofmann, Leichsenring, & Kruse, 2015)

The course of PTSD may also be influenced by the number of traumatic events an individual experiences. Those experiencing four or more traumatic events reported having an earlier age of onset, greater disability and functional impairment, more

persistent PTSD symptoms, and higher prevalence of comorbidity with other mental disorders than those experiencing fewer than four traumatic events. Such evidence supports the concept of a "risk threshold" whereby those with PTSD experiencing four or more traumatic events follow a more severe and debilitating course of PTSD (Karam et al., 2014), and possibly a more chronic trajectory of PTSD than those reporting lower level of traumatic event exposure. In addition, type of traumatic event experienced may influence the course of PTSD, and there is some evidence suggesting that individuals who have experienced "intentional" traumatic events, such as physical or sexual assault, may have more enduring courses of PTSD than those who experienced "nonintentional" traumatic events, such as natural disasters (Santiago et al., 2013).

PTSD and Co-Occurring Disorders

PTSD and Commonly Co-Occurring Mental Health Disorders

A majority of individuals diagnosed with PTSD also meet the criteria for at least one additional mental health disorder in their lifetime (Koenen et al., 2017). The comorbidity of PTSD and substance use disorders (SUDs) is high (Simpson, Rise, Browne, Lehavot, & Kaysen, 2019; Smith, Goldstein, & Grant, 2016), with approximately 35.8–46.0% of individuals with PTSD also meeting the criteria for a co-occurring SUDs (Blanco et al., 2013; Pietrzak et al., 2011). Findings from NESARC-III data showed that a PTSD diagnosis was associated with greater odds (odds ratio [OR] = 1.3, 95% confidence interval [CI] = 1.1–1.6) of having an SUD (Pietrzak et al., 2011). SUDs tend to develop after PTSD diagnosis (Kessler et al., 2005), and theories explaining this pattern suggest that those with PTSD may use substances as a self-medicating strategy to mitigate the distressing symptoms of PTSD (Gradus, Farkas et al., 2015; Stewart & Conrod, 2003). Thus, the development of PTSD may serve as a risk factor for the subsequent development of SUDs.

The comorbidity of PTSD with mood disorders, especially unipolar depression, is high. Over half of those with PTSD also meet criteria for a depression diagnosis (Flory & Yehuda, 2015; Kessler et al., 2005). Specifically, those with PTSD have greater odds of having a major depressive (OR = 1.6; 95% CI = 1.3–1.9) or a dysthymic disorder (OR = 1.5; 95% CI = 1.2–1.8; Goldstein et al., 2016). Likewise, the comorbidity of PTSD and anxiety disorders is also high (Goldstein et al., 2016; Gradus, Farkas, et al., 2015). Findings from NESARC-III data showed that a PTSD diagnosis was associated with greater odds (OR = 2.8, 95% CI = 2.5, 3.3) of having an anxiety disorder (Pietrzak et al., 2011). In contrast to SUDs, mood and anxiety disorders tend to be present before the onset of PTSD and may represent a risk factor for PTSD in certain cases (Balachandran, Cohen, Le Foll, Rehm, & Hassan, 2020; DiGangi et al., 2013; Smith et al., 2016). However, the opposite has also been found, reflecting a pattern in which mood and anxiety disorders more commonly develop after the onset of a PTSD diagnosis (Gradus, Farkas, et al., 2015). To explain the high levels of comorbidity among mood and anxiety disorders and PTSD, it has been suggested that there may be a shared underlying vulnerability factor across the disorders (e.g., neuroticism; Brown & Barlow, 2009) or shared genetic vulnerability (Duncan et al., 2018). Other theories have also suggested that high comorbidity may reflect a distinct phenotype (Flory & Yehuda, 2015) or may be due to the overlap in diagnostic symptom clusters that are shared across the disorders, such as the presence of dysphoric symptoms in both depression and PTSD (Biehn et al., 2013; Elhai et al., 2011).

Epidemiological studies have also shown that PTSD is associated with increased risk for suicide (Kessler, Borges, & Walters, 1999; Sareen et al., 2005). PTSD is associated with approximately a sixfold increase in risk for suicide attempts and fivefold increase in risk for suicidal ideation (Kessler et al., 1999; Sareen et al., 2005). To illustrate, a Danish cohort study showed that the rate of suicide among PTSD patients was 13 times the rate of suicide in patients without PTSD (Gradus, Antonsen, et al., 2015). In addition, studies have found that the comorbidity of PTSD and depression is a stronger predictor of suicidal ideation (DeBeer, Kimbrel, Meyer, Gulliver, & Morissette, 2014; Ramsawh et al., 2014) and suicidal attempts (Kimbrel, Meyer, DeBeer, Gulliver, & Morissette, 2016) than a PTSD diagnosis alone. This raises the question of whether the association between PTSD, depression, and increased suicidal ideation is driven more by the depression than by PTSD, or whether it is the comorbidity of these two disorders that drives this effect. The high comorbidity of PTSD and other mental disorders, such as anxiety, depression, and SUDs, paired with elevated levels of problematic anger (McHugh, Forbes, Bates, Hopwood, & Creamer, 2012; Olatunji, Ciesielski, & Tolin, 2010), guilt (Lee, Scragg, & Turner, 2001), dissociation (Bryant, 2007; Stein et al., 2013), and increased occurrence of suicidality, make this clinical profile an important target for prevention and treatment efforts.

Comorbidity of PTSD and Physical Health Problems

The comorbidity of PTSD and physical health problems has been recognized (Gradus et al., 2017; Kessler, 2000; Schnurr & Jankowski, 1999); see Schnurr et al., Chapter 25, this volume). PTSD has long been implicated as a risk for developing various physical health disorders. It has been shown to be associated with somatic disorders (Pacella, Hruska, & Delahanty, 2013), gastrointestinal disorders (Gradus et al., 2017; Kessler, 2000; Schnurr & Jankowski, 1999), cardiovascular disease (Sumner et al., 2016), and pain disorders (Otis, 2003). Findings have been equivocal for somatic and gastrointestinal disorders (Pacella, Hruska, & Delahanty, 2013); however, evidence for an association between PTSD and cardiovascular disease (CVD; Gradus, Farkas, et al., 2015; Sumner et al., 2016) and pain disorders (Asmundson, Coons, Taylor, & Katz, 2002; Otis, Keane, & Kerns, 2003) is stronger.

There is sound evidence for an association between PTSD and CVD. The link between PTSD and CVD has been demonstrated in both the general population (Gradus, Farkas, et al., 2015) and the veteran population (Beristianos, Yaffe, Cohen, & Byers, 2016; Vaccarino et al., 2013). A PTSD diagnosis increases the odds (OR = 3.4, 95% CI = 1.9, 6.0) for CVD (Spitzer et al., 2009). It is unclear whether the association between PTSD and CVD is due to an underlying shared vulnerability, or whether having a PTSD diagnosis increases the risk of CVD; however, there is evidence of a dose–response relationship in which higher levels of PTSD symptoms are associated with higher levels of hypertension, which in turn is associated with increased risk for CVD (Sumner et al., 2016).

There is a strong association between PTSD and pain disorders (Otis et al., 2003). It is estimated that 20 to 30% of those with PTSD also report chronic pain (Asmundson et al., 2002). Potential mechanisms underlying the comorbidity of PTSD and chronic pain may be illuminated by mutual maintenance models whereby the presence of PTSD symptoms increases pain-related distress and vice versa (Asmundson & Katz, 2009; Sharp & Harvey, 2001) and by shared vulnerability models whereby elevated levels of anxiety sensitivity increases risk for PTSD and pain disorders (Asmundson et al., 2002).

Methodological Considerations

Changes in the Definitions of Traumatic Event and PTSD

A number of methodological considerations may change our understanding of the epidemiology of trauma exposure and PTSD. One of the most important considerations is the change in the definition of a traumatic event. The newest iteration of the DSM, the main diagnostic classification system used in the United States, resulted in three major changes in the definition of trauma from DSM-IV (American Psychiatric Association [APA], 1994) to DSM-5 (APA, 2013) that may impact the incidence and prevalence of trauma and PTSD (see Friedman et al., Chapter 2, this volume). Most data show slightly lower prevalence of exposure to traumatic events in DSM-5 than in DSM-IV, which may be partly explained by the modification of the A1 stressor criterion in DSM-5, which involved excluding some stressor events defined as criterion A1 events in the DSM-IV. For example, unexpected deaths from natural causes are no longer considered to be a traumatic event in DSM-5. Furthermore, indirect exposure to the actual or threatened death of a family member or friend must be violent or accidental. A second change to the definition of a traumatic event from DSM-IV to DSM-5 was the elimination of criterion A2, which required that the A1 stressor event cause fear, helplessness, or horror. Research examining the necessity of the traumatic event meeting criterion A2 found that most individuals reporting events that met criterion A1 also reported experiencing fear, helplessness, or horror (Breslau & Kessler, 2001), indicating that removal of this criterion may not increase the prevalence of trauma exposure meaningfully. A third change to the definition of a traumatic event in DSM-5 is that criterion A includes repeated or extreme work-related exposure to adverse details of the traumatic event(s). This applies to service professionals, including police officers, firefighters, ambulance personnel, and health care personnel. Finally, DSM-5 does not include "indirect trauma" as experienced through electronic media, television, movies, or pictures, unless this exposure is work-related (APA, 2013).

Another important methodological consideration is whether changes in the PTSD diagnostic criteria from DSM-IV to DSM-5 would impact prevalence estimates. Recent investigations have shown comparable prevalence estimates of PTSD when using DSM-IV in comparison to DSM-5 criteria (Hoge, Riviere, Wilk, Herrell, & Weathers, 2014; Kilpatrick et al., 2013; Stein et al., 2014). When expanding beyond the DSM classification system to the *International Classification of Diseases, 11th revision* (ICD-11), several important differences are apparen (see Friedman et al., Chapter 2, this volume). ICD-11 uses a narrower definition of PTSD than DSM-5 in order to increase the specificity of PTSD diagnoses. ICD-11 removes "nonspecific symptoms" common to other disorders, particularly mood and anxiety disorders. ICD-11 narrows the scope of PTSD by focusing on three core elements: trauma reexperiencing in the present, avoidance of traumatic reminders, and persistent perceptions of heightened current threat. ICD-11 omits all seven of the DSM-5 negative alterations in cognitions and mood symptoms and circumscribes the definitions of reexperiencing and hyperarousal symptoms by omitting emotional or physiological reactivity to trauma reminders, irritability, reckless or self-destructive behavior, concentration difficulties, and sleep disturbance. Thus, PTSD prevalence in ICD-11 tends to be lower than in DSM-5 (Wisco et al., 2016, 2017). Perhaps, more importantly, a substantial portion of those meeting criteria using one diagnostic system did not meet criteria using the other system (O'Donnell et al., 2014).

Generalizability of Findings

The generalizability of findings on trauma exposure and PTSD across countries and cultures is another important consideration. The prevalence of traumatic exposure varies across countries. The WMHS found that the prevalence of exposure to any traumatic event ranged from a high of 85% in Ukraine and to a low of 29% in Bulgaria (Benjet et al., 2016). Varying prevalence estimates of traumatic event exposure across countries may be due to true differences, differences in willingness to disclose traumatic events, and measurement error (Benjet et al., 2016).

Traumatic Event Exposure and Natural Recovery

It is common to experience some psychological distress and PTSD-related symptoms immediately after enduring a traumatic event, such as fear, somatic symptoms, and sleeping disturbance (Sayed, Iacoviello, & Charney, 2015). However, most individuals experiencing a traumatic event will not develop PTSD (Atwoli, Stein, Koenen, & McLaughlin, 2015; Galatzer-Levy et al., 2018; Isaacs et al., 2017). Of those experiencing some PTSD-related symptoms, most, if not all, of the symptoms will dissipate within a month for a large majority of individuals (Littleton, Axsom, & Grills-Taquechel, 2011) or will show trajectories of resilience (Feder et al., 2016; Galatzer-Levy et al., 2018) reflecting a course of natural recovery.

Multilevel and Life Course Perspectives and Risk for Traumatic Event Exposure

The literature on traumatic event exposure tends to focus on individual factors influencing the risk for traumatic exposure; however, expanding beyond individual factors to include multilevel and life course perspectives in the risk for trauma exposure provides a more nuanced approach to the study of risk. A multilevel perspective holds that health is explicitly linked to the context surrounding us and how this context influences our behaviors and can impact individual risk factors for the development of disease (Galea & Vaughan, 2018). For example, living in an impoverished neighborhood may lead to unhealthy lifestyle behaviors, such as eating food with low nutritional value, due to the lack of good-quality grocery stores or engaging in a sedentary lifestyle due to lack of exercise programs in the community. Over time, the impact of these unhealthy lifestyle behaviors can affect health, such as increasing blood pressure or weight gain, and may result in increased risk for cardiovascular disease or obesity over the life course. Relatedly, a life course perspective holds that an individual's health over the course of the lifetime shapes an individual's health at any given point in time (Lynch & Smith, 2005). It is known that highly disorganized neighborhoods (i.e., neighborhoods with high levels of poverty, family disruption, and residential mobility) are associated with higher levels of exposure to violence and crime. The accumulation of these multilevel factors over the life course can directly affect risk of traumatic event exposure (Butcher et al., 2015) and subsequent risk for PTSD and other health problems.

CONCLUSION: CHALLENGES FOR THE FUTURE

Our understanding of the epidemiology of trauma and PTSD continues to evolve, with the first national general population-based studies published less than 30 years

ago (Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993). However, epidemiology has already made major contributions to our understanding of trauma and PTSD from a public health perspective. First, traumatic event exposure is common and not random—individual and social factors predict exposure. Also, only a minority of persons who experience traumatic events develop PTSD, and who falls into this group is largely dependent on individual and contextual factors. Second, it is difficult to obtain accurate measurements of trauma exposure and PTSD. It is not feasible to administer gold standard assessments of trauma exposure and PTSD in routine clinical settings; as a result, lay interviews are used instead, which may lead to measurement error in prevalence estimates. Third, PTSD is a prevalent, potentially chronic, and debilitating disorder that is often comorbid with other mental disorders (e.g., depression, anxiety, and SUDs), and increases risk of adverse physical health outcomes (e.g., cardiovascular disease; Gradus, Farkas, et al., 2015). Fourth, the majority of PTSD is not treated. This is particularly unfortunate, given our knowledge of how to treat PTSD. A remaining challenge to trauma epidemiology is to work to develop effective methods to identify persons at risk of PTSD for targeted prevention and treatment initiatives (Shalev et al., 2019). Finally, if we are to make a sustainable impact on mental health and disease prevention, the field must move beyond a focus on individual factors and address the impact of multilevel and life course factors on trauma exposure and PTSD.

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CHAPTER 5

Epidemiology of Trauma and PTSD in Childhood and Adolescence

William E. Copeland and Ellen W. McGinnis

Posttraumatic stress disorder (PTSD) is distinct among psychiatric disorders in being defined by its etiology (March, 1993). PTSD and its epidemiology cannot be studied without giving equal attention to its precipitating event—the traumatic stressor. A review of the epidemiology of PTSD and traumatic stressors in *childhood* must also address contextual issues. PTSD was first proposed as a disorder in adults in 1980, based primarily on study of war veterans (Grinker & Spiegel, 1945; Haley, 1974), rape victims (Burgess & Holmstrom, 1974; Trimble, 2013), and concentration camp survivors (Krystal, 1968). The definition of qualifying traumatic events and the elaboration of clinically problematic symptomatology continue to be strongly linked to these origins in specific adult populations, likely contributing to long-standing cultural narratives showing that early exposure to trauma is rare. A core challenge to epidemiological work in childhood has been to address the question about how well this model of traumatic events and PTSD developed in specific adult samples applied to childhood populations.

Childhood is a heterogeneous period of multiple developmental stages. It begins with the preschool years characterized by limited language and emotional regulation skills coupled with high levels of dependence on and attachment to caregivers. In this period, trauma and the reaction to trauma must be studied in the relational context of the caregiver and child (Scheeringa & Zeanah, 2001; see Brown et al., Chapter 14, this volume, on developmental issues, this volume). School-age children are characterized by rapidly increasing intellectual, language, and social skills that allow for increased exploration, autonomy, and competence. The end of this period is punctuated by puberty, a biologically driven developmental transition with complex secondary effects on social, emotional, and sexual development. The final stage of childhood—adolescence—is characterized by a duality in which peak physical health, advanced abstract thinking. and problem-solving skills are coupled with still-developing emotional dysregulation that can place the child at risk for substance use, relational problems, and risky sexual behaviors. The ever-changing experience of childhood may affect both the events that

are experienced as traumatizing and the emotional, behavioral, and cognitive ways in which the child responds to the events.

Epidemiology, the basic science of public health, provides vital information about diseases that threaten the health and well-being of the population (Rothman & Greenland, 1998). This information can and should be used to estimate public health burden, identify groups of individuals at risk, inform the types of interventions that are needed, and monitor the effects of those interventions. As such, the story of the epidemiological literature is one that needs to be conveyed to the general public and scientific community alike. Herein, we review and discuss the epidemiology of childhood trauma and PTSD.

METHODOLOGICAL CONSIDERATIONS

Perhaps related to the challenge of applying adult definitions to childhood, heterogeneity in the study of childhood traumatic events and PTSD is the norm. This heterogeneity extends to the key methodological decisions that may have substantial and substantive effects on prevalence estimates of traumatic events and PTSD, as well as associations with early risk factors. For the purposes of this review, we focus on three such sources of heterogeneity that are salient in the child literature: criteria for potentially traumatic events, criteria for PTSD, and data collection from varied informants.

Criteria of Potentially Traumatic Events

The first source of heterogeneity in the study of childhood PTSD stems from differing criteria of potentially traumatic events. Prior to DSM-IV, the stressor definition reflected the implicit view that only certain relatively rare and extreme events commonly elicit PTSD (March, 1993), several examples of which were not applicable to children (e.g., military combat). The stressor criterion was expanded in DSM-IV to incorporate information about the individual's response to the event and be inclusive of indirect exposures (American Psychiatric Association, 1994). Including indirect exposures was an important change for children specifically, which may have increased rates of PTSD from DSM-III to DSM-IV, as indirect exposures affected 74.7% of adolescents and significantly predicted PTSD disorder between 16.5% and 40.8% of the variance in one study (Christiansen, Hansen, & Elklit, 2014). Clarifications were added to DSM 5 in the interest of narrowing the definition of "trauma" (American Psychiatric Association, 2013), which may or may not have impacted trauma prevalence in childhood. For instance, "hearing about the death of a loved one" was modified to only be included if the death was violent or accidental (e.g., no sickness). This would likely decrease the prevalence of trauma, yet the death of a loved one itself (e.g., the trauma of acknowledging primary caregivers can and may die) may be traumatic for young children. Similarly, the clarification that exposure to traumatic events would not include exposure through media may be problematic in children less desensitized to viewing negative events through news media (Pfefferbaum, 2005).

The field trials of DSM-5 changes typically included mostly adults, a few adolescents, and no children (see Friedman, 2013). The evidence from studies of children strongly suggests that children do display posttraumatic stress symptoms in response to experiences that do not meet the DSM-5 stressor criterion, such as witnessing fearful scenes on TV, attending a funeral, learning about the death of a pet, reacting

to parental divorce, going to a haunted house, and getting shots (Copeland, Keeler, Angold, & Costello, 2010; Kousha & Tehrani, 2013; Verlinden et al., 2013; Willard, Long, & Phipps, 2016).

Specific to childhood, caregiver neglect can be life threatening and yet does not meet PTSD stressor criteria. Neglect is common globally (16% in a meta-analysis; see Stoltenborgh, Bakermans-Kranenburg, & van IJzendoorn, 2013), can compromise brain and behavioral development (De Bellis, Hooper, Spratt, & Woolley, 2009; Hunt, Slack, & Berger, 2017), and is vastly understudied compared to other types of childhood maltreatment. Neglect does commonly co-occur with physical or sexual abuse (in 35.7–52.7% of children with neglect; Dong et al., 2004) and with witnessing domestic violence (Hartley, 2002) which may lead some neglected children to be counted in trauma prevalence rates, but not all and likely not most such children. Some epidemiological studies of trauma in childhood assess neglect (e.g., Elklit, 2002), but those focusing on strict DSM criteria have not.

What is considered a reasonable definition of an extreme stressor in adulthood (Kilpatrick et al., 2013) may be insufficient to capture the experience of trauma in childhood. As such, it is not surprising that some studies of trauma and extreme stress in childhood have included events that may fail to meet strict DSM criteria as an extreme stressor. A number of included studies were not focused on PTSD-qualifying potentially traumatic events (PTEs) per se (e.g., focus on prevalence of violence in children). For the purposes of this review, we have included studies that have adopted a broader definition of PTEs than is typically seen in adult reviews.

Diagnostic Criteria for PTSD

Like the criteria of traumatic events themselves, the criteria for PTSD is a second source of heterogeneity. Specifically, there is some evidence that posttraumatic stress symptoms in young children may differ from those seen in adults. Again, this is not entirely surprising given the origins of PTSD. Research with young children (6 years and younger) in which parents are the only source available suggest that the optimal algorithm for PTSD may require substantially fewer symptoms than is required for diagnosis of the disorder in adults (Carrion, Weems, Ray, & Reiss, 2002; Scheeringa, Peebles, Cook, & Zeanah, 2001; Scheeringa, Zeanah, Myers, & Putnam, 2003, 2005). Research by Scheeringa and colleagues has paved the way in making changes to DSM-5 criteria for young children, such as (1) removing certain symptoms such as the A2 criterion, (the need for intrusions to be distressing, which has also been removed for adults), as well as impaired recall and sense of shortened future; (2) including other symptoms (i.e., "emphasized play"); (3) redefining "psychic numbing" as restricted positive (but not negative) emotions); and (4) making changes to diagnostic thresholds (i.e., requiring only one numbing/avoidance symptom). With the changes, preschoolers demonstrate similar and or higher levels of PTSD compared to adults, such that in the same sample DSM-IV criteria suggest that PTSD prevalence is at 13% versus 44% using DSM-5 (Scheeringa, Myers, Putnam, & Zeanah, 2012). There is evidence that including these specific PTSD criteria for very young children in DSM-5 is more developmentally sensitive in that age group (see more details in Azad et al., Chapter 18, this volume) and may also be appropriate for those in middle childhood (whose PTSD criteria have not been altered; see Mikolajewski, Scheeringa, & Weems, 2017). It is important to note that only one epidemiological study included herein uses DSM-5 PTSD criteria as they apply to children under 6 years of age (Briggs-Gowan, Carter, et al., 2010). Thus, we are

unable to draw conclusions about PTSD prevalence rates for this early age group based on these symptom criteria.

Finally, it is a consistent finding across a number of epidemiological studies that the symptomatic sequelae of traumatic events well extend beyond the domains of posttraumatic stress as they are currently defined. This broad scope may be due to variations in age, timing, and duration of traumatic events that children experience, which are key for symptom presentation from adults (Hyland et al., 2017; see Cook & Simiola, Chapter 15, and Azad et al., Chapter 18, this volume).

Informants

The third source of heterogeneity is a methodological one: who to rely upon for accurate information about exposure to traumatic events and subsequent symptoms. In adulthood, the answer is both obvious and convenient: Ask the person themselves. Indeed, every large survey of traumatic events and PTSD in adulthood has relied on single-informant self-report data (Atwoli, Stein, Koenen, & McLaughlin, 2015). Who else would one ask? In childhood, there is an obvious answer to that question: It is not the child. Parent report is the most commonly used information to assess childhood psychiatric symptomatology (De Los Reyes & Kazdin, 2005; Jensen et al., 1999). In school-age children, information is sometimes also collected by teachers and in adolescence (or even middle childhood) information is also collected from the children themselves.

These sources of information are only modestly correlated, but each is independently associated with symptom-related impairments (Achenbach, McConaughy, & Howell, 1987). (The same may be true for additional informants in adulthood, e.g., Achenbach, Krukowski, Dumenci, & Ivanova, 2005.) Studies of multiple informants suggest that agreement between parent and child reports of exposure to PTEs is modest (Tingskull et al., 2015) to nonsignificant (Stover, Hahn, Im, & Berkowitz, 2010). This agreement is particularly low when trauma was interpersonal (e.g., domestic violence, physical abuse; Tingskull et al., 2015). In summarizing their work, Tingskull and colleagues (2015) described agreement as "outstandingly poor." There are a number of reasons why this is the case, including underreporting from parents regarding concern about stigma, institutional responses (e.g., Child Protective Services), the involvement of caregivers, lack of knowledge about events, or consideration of the event as being severe enough to report (Briggs-Gowan, Ford, Fraleigh, McCarthy, & Carter, 2010; Daviss et al., 2000; Ford et al., 2000). Low levels of agreement for PTSD are similarly modest (Meiser-Stedman, Smith, Glucksman, Yule, & Dalgleish, 2007; Stover et al., 2010). This has led to some recommending that best practice would involve data collection from both a parent and a child. Although recommended, this is not common across childhood studies of traumatic stress and PTSD. It is also simply not possible in studies of children too young to provide reliable information.

CURRENT STATE OF THE ART

Only a few nationally representative surveys use interview-based assessments of PTEs and PTSD and cover a broad age span. For the purposes of our review, we focus on those surveys that are representative and that have assessed a broad range of traumatic events. Table 5.1 provides an overview of the epidemiological studies of PTEs

TABLE 5.1. Epidemiological Studies on the Prevalence of Trauma in Childhood

Study	Location	Design	*N*	Informant	Assessment	Age group	Prevalence; most common
Alisic, van der Schoot, van Ginkel, & Kleber (2008)	Netherlands	Community representative	1,770	Self	UCLA PTSD Reaction Index for DSM-IV	8–12	Lifetime: 14%; sudden death of loved one most common
Bödvarsdóttir & Elklit (2007)	Iceland	Nationally representative	206	Self	Ad-hoc questionnaire	13–15	Lifetime: 76.5%; 42.7% death of loved one; 27.1% traffic accident
Breslau et al. (2004)	Mid-Atlantic city	Nationally representative of low and very low middle class	1,698	Self	Ad-hoc interview from 1996 Detroit Area Survey	19–24	Lifetime: 82.5%; 15.4% witnessed event; 13.4% mugged/threatened
Briggs-Gowan, Ford, et al. (2010)[R]	Greater New Haven Area	Community representative	1,152	Parent	PAPA and the Child Life Events Scale	2–4	Lifetime: 26.3%; 14.5% noninterpersonal; 13.8% violence exposure
Copeland, Keeler, Angold, & Costello (2007)[R]	Southeastern United States	Community representative	1,420	Parent and self	CAPA life events module*	9–16	Lifetime: 67.8%; 23.7% witnessed event; 21.4% learned about event
Cuffe et al. (1998)	Southeastern United States	Community representative	490	Parent and self	Ad-hoc interview	16–22	Lifetime: 11.6 to 25.2%
Domanskaité-Gota et al. (2009)	Lithuania	Nationally representative	183	Self	Ad-hoc questionnaire	13–17	Lifetime: 80%; 29.7% threatened; 26.4% near-drowning
Elklit (2002)	Denmark	Nationally representative	390	Self	Ad-hoc questionnaire	13–15	Lifetime: 87%; 51.8% death of loved one; 26.9% threatened
Finkelhor & Dziuba-Leatherman (1994)	United States	Nationally representative	2,000	Self	Ad-hoc interview	10–16	Lifetime: 51.3%; 12-month: 37.1%

Finkelhor, Ormrod, Turner, & Hamby (2005)	United States	Nationally representative		Parent or self	Juvenile Victimization Questionnaire*	2–17	12-month: 53% physical assault; 35.7% indirect violence; 8.2% sexual abuse;
Finkelhor et al. (2015)	United States	Nationally representative	4,000	Child or parent	Juvenile Victimization Questionnaire*	0–17	12-month: 37.3% physical assault; 24.5% indirect violence; 5.0% sexual offense
Giaconia et al. (1995)	Northeastern United States	Community representative	384	Self	Diagnostic Interview Schedule*	18	Lifetime: 43.0%; 13.0% learned about event; 12.8% witnessed event
Kilpatrick et al. (2000)	United States	Nationally representative	4,023	Self	Ad-hoc interview	12–17	Lifetime: 47%; physical assault most common
Landolt et al. (2013)	Switzerland	Nationally representative	6,787	Self	UCLA PTSD Reaction Index*	14–17	Lifetime: 56.1%; 22.4% learning of event; 19.3% witnessed event
Lewis et al. (2019)	England and Wales	Nationally representative	2,232	Child Report	JVQ* adapted interview	18	Lifetime: 31.1%; 27.9% learned about event; 21.5% assault/threat
McLaughlin et al. (2013)[R]	United States	Nationally representative	6,483	Self	CIDI*	13–17	Lifetime: 61.8%; 28.2% sudden death of loved one; 14.8% disasters
Perkonigg & Wittchen (2000)[R]	Munich, Germany	Community representative	3,021	Self	M-CIDI*	14–24	Lifetime: 21.4%; 9.7% physically attacked; 7.8% serious accident
Petersen et al. (2010)	Faroe Islands	Total population	687	Self	Ad-hoc PTE questionnaire	13–16	Lifetime: 91.5%; 53.3% death of loved one; 31.9% threatened

Note. Asterisks (*) indicate references for life events measures with published reliability and validity: CAPA life events module (Costello et al., 1998); Juvenile Victimization Questionnaire (Finkelhor, Hamby, et al., 2005); Child Life Events scale (Carter & Briggs-Gowan, 1998); Preschool Age Psychiatric Assessment (Egger & Angold, 2004); NIMH Diagnostic Interview Schedule–Version IIIR (Robins, Helzer, Cottler, & Goldring, 1989); DAWBA (Development and Well-being Assessment; Goodman et al., 2000); Composite International Diagnostic Interview (Kessler & Üstün, 2004); UCLA PTSD Reaction Index (Steinberg, Brymer, Decker, & Pynoos, 2004); M-CIDI (Munich Composite International Diagnostic Interview; Wittchen, Lachner, Wunderlich, & Pfister, 1998).

[R]Highly rigorous studies as defined by criteria on pages 77–78.

in childhood. In addition to the considerations above, heterogeneity was common in terms of sampling, measures, period assessed, and representativeness. Despite these caveats, we have structured the review of the empirical literature to focus on those areas in which the science—particularly based on specific notable studies—is sufficient to draw summary conclusions.

A few studies meet a number of criteria for high methodological rigor: large ($N > 500$), representative samples; valid trauma and PTSD measures that are interview-based; and multiple informants across a broad age range (for within-study age comparisons). As such, these studies should be weighted more heavily when drawing conclusions about prevalence. The British Child and Adolescent Mental Health Survey was a nationally representative study conducted in 1999 (Ford, Goodman, & Meltzer, 2003). This study surveyed 10,438 children 5–15 years of age using the multimodal (questionnaire, interview, clinician rating), multi-informant (teachers, parents, self) Development and Well-Being Assessment (DAWBA) to assess mental health. The Great Smoky Mountain Study (GSMS) began in 1992 (Costello, Copeland, & Angold, 2016) and interviewed 1,420 children ages 9–16 and their parents using the Child and Adolescent Psychiatric Assessment in a representative community sample in rural southeastern United States. Like the British study, GSMS used structured interviews to assess trauma and symptoms and covered both middle childhood and adolescence.

Additional studies upheld rigorous standards but were limited in informant (self only) and/or age scope (adolescents or preschoolers only). The National Comorbidity Survey Replication Adolescent Supplement (NCS-A) was a nationally representative study conducted between 2001 and 2004 (Kessler et al., 2009). This study surveyed 10,148 adolescents ages 13– 17 via nationwide phone interviews using an age-informed version of the Composite International Diagnostic Interview (CIDI). Perkonigg and Wittchen (2000) conducted a community representative study of 3,021 adolescents and young adults ages 14–24 using the age-modified CIDI in Munich, Germany. Finally, Briggs-Gowan and colleagues conducted a community representative study of 1,152 young children ages 2–4 using the Preschool Aged Psychiatric Assessment interview in the greater New Haven, Connecticut, area (Carter et al., 2010). Notably, these rigorous epidemiological studies represent only Western cultures and focus more on adolescents, without specific attention to high-risk groups. Thus, it is important to expand our accounting of prevalence of child trauma and PTSD to studies beyond these few, but also to weight them more prominently due to their representative designs and highly rigorous methodology.

Prevalence of PTEs

Across the studies reviewed, over a dozen different interviews and questionnaires were used to assess PTEs. Few of these measures had any published test–retest reliability and validity information, with a few notable exceptions. The Child and Adolescent Psychiatric Assessment (Costello, Angold, March, & Fairbank, 1998), a structured interview, demonstrates an exemplary assessment, reporting intraclass correlations of PTEs by informant, which ranged from 0.58 (parent reports on low-magnitude traumas) to 0.83 (parent report on high-magnitude traumas) and 2-week test–retest reliability, which ranged from a kappa of 0.25 (for learning about a traumatic event) to 0.88 (diagnosis of a serious illness). Discriminant validity was tested by comparing prevalence of traumatic events in clinic as compared to community samples. The Juvenile Victimization Questionnaire reported 4-week test–retest reliability mean kappa by informant of

0.50 (caregivers) and 0.63 (self-report) and construct validity (moderate to high correlations with trauma-related emotional symptoms) (Finkelhor, Hamby, Ormrod, & Turner, 2005). The Child Life Events Scale (CLES) demonstrated good 2- to 4-week test–retest reliability with a single "even exposure" variable kappa of 0.78 and discriminant validity-based dichotomous comparison (those who experienced at least one event on CLES had more PTSD symptoms compared to no event (Mongillo, Briggs-Gowan, Ford, & Carter, 2009).

Other standardized instruments measuring PTEs, including the Diagnostic Interview Schedule (DIS), Preschool Age Psychiatric Assessment (PAPA), CIDI interviews, and UCLA PTSD Reaction Index questionnaire, report reliability and validity statistics ranging from acceptable to excellent for PTSD, but not for PTEs (Breslau et al., 1998; Steinberg et al., 2013). Several traumatic event assessments were created post hoc, including events from "the relevant literature and from clinical experience" (Elklit, 2002). Moreover, trauma assessments included only events meeting the A1 DSM-IV criterion for PTSD, while others cast a wider net, "covering possible life-threatening experiences and distressing family condition" (Elklit, 2002, p. 179). This wider net may be particularly valuable given the differences in what is likely to be considered traumatic by children as opposed to adults. Epidemiological studies assessed anywhere between 5 and 34 PTEs, almost certainly impacting the prevalence rates of traumatic events in children. These measures assessed periods as broad as 30 months to 18 years. The longer the time frame, the higher the potential is for forgetting or recall bias (Coughlin, 1990; Hardt & Rutter, 2004). While studies covered preschool and school-age participants, the vast majority of the studies focused exclusively on adolescents.

Estimates of lifetime exposure to PTEs vary greatly, ranging from 12.6 to 91.5%. The lower estimates tend to be for those studies that assessed young children and/or omission of specific traumas (e.g., child abuse due to concern about the sensitive nature of the asking-parents-by-mail survey; Briggs-Gowan, Carter, et al., 2010). The method of data collection also had a significant impact on trauma prevalence across studies. Studies with structured interviews tended to demonstrate lower prevalence of trauma (weighted M = 46.3%) than questionnaires (weighted M = 61.5%). Those studies with the highest estimates tended to include more PTEs (including those that might not meet the PTSD A1 criterion) from ad-hoc measures. For example, several representative studies that used a post-hoc survey inclusive of 21 items assessing both direct or *indirect* exposure to trauma yielded four of the five highest prevalences (76.5–91.5%) of lifetime trauma included in Table 5.1 (Bödvarsdóttir & Elklit, 2007; Domanskaité-Gota, Elklit, & Christiansen, 2009; Elklit 2002; Petersen, Elklit, & Olesen, 2010). Another study showing a high prevalence of trauma (82.5%) was conducted with a high-risk, low-socioeconomic-status (SES) sample. As such, this study affirms the association between SES and trauma risk (Breslau, Wilcox, Storr, Lucia, & Anthony, 2004).

Overall, the weighted mean lifetime prevalence of exposure to traumatic events was 49.0% (range: 21.4–67.8%) among the four more highly rigorous epidemiological studies (see "R" references in Table 5.1). Not surprisingly, these estimates are less than the rates found in adult samples (68.6% and 70.4%, respectively, Goldstein et al., 2016; Kessler et al., 2017), but they also suggest that exposure to a PTE within childhood is not uncommon. In high-risk samples or those assessing a broader range of events, a substantial proportion reported exposure to more than one traumatic event (range 40–65%: Breslau et al., 2004; Elklit, 2002; Finkelhor, Turner, Shattuck, & Hamby, 2015). The most common PTEs for children and adolescents were events affecting the child's social network, including unexpected loss of a loved one and learning details

of a trauma affecting others (Elklit, 2002; Lewis et al., 2019; McLaughlin et al., 2013). These were followed by being physically attacked or experiencing a serious accident.

The overall likelihood of being exposed to at least one traumatic event did not tend to vary significantly by gender, although there were exceptions (e.g., male > female; Breslau et al., 2004; Perkonigg & Wittchen, 2000; female > male, Cuffe et al., 1998). The prevalence of *individual* categories of trauma exposure did vary by gender. Males were more likely to have been exposed to a serious accident (e.g., 6.6% vs. 4.3% in Perkonigg & Wittchen, 2000) or violence (e.g., 41.6% vs. 33.0% in Finkelhor et al., 2015; 62.6% vs. 33.7% in Breslau, Wilcox, et al., 2004; and 10.1% vs 4.9% in Perkonigg & Wittchen, 2000). Females were more likely to be exposed to sexual assault (e.g., 0.9% vs. 1.9% in Cuffe et al., 1998; 0.3% vs. 3.7% in Perkonigg & Wittchen, 2000).

Prevalence of trauma exposure did seem to increase with age (e.g., Finkelhor et al., 2015; McLaughlin et al., 2013). For instance, Finkelhor and colleagues (2015) showed an increase in the prevalence rates of childhood maltreatment by age group (0–1 years, 2.2%; 2–5 years, 8.1%; 6–9 years, 7.8%; 10–13 years, 12.0%; 14–17 years, 16.6%). Higher prevalence with age tended to be confounded with higher age of assessment and retrospective design, with few studies available to make such comparisons prospectively. Evidence on the clustering of exposure to PTEs in low-SES families was mixed with some studies finding an association (e.g., more than twice as high in low vs. middle/high income, Finkelhor et al., 2015; Perkonigg & Wittchen, 2000), or in association with certain types of trauma and gender (1.6 times higher for children with subsidized school lunch for assaultive violence of males in Breslau et al., 2004) and others finding no association (e.g., Giaconia et al., 1995; McLaughlin et al., 2013).

Overall, the evidence supports exposure to PTEs as a common experience in childhood, perhaps the norm. The most common types of trauma are those that occur to loved ones. While males and females are equally likely to experience trauma, their risk for specific types of trauma does vary. Children from disadvantaged backgrounds may be exposed to higher levels of exposures, but no child or category of children is immune to trauma exposure—a finding that is consistent with the literature on adverse childhood experiences (Merrick, Ford, Ports, & Guinn, 2018).

Prevalence of PTSD

Table 5.2 provides an overview of the studies included in the review of the epidemiology of PTSD in childhood. Although, not highlighted in Table 5.2, some of the same sources of heterogeneity for estimates of PTE exposure also apply to the assessment of PTSD (e.g., sampling, periods assessed). As a diagnostic entity, PTSD was more likely to be measured with a questionnaire or structured interview with established reliability and/or validity compared to PTEs. Although most of the assessment of PTEs focused on lifetime exposure, the majority of PTSD assessments focused on more proximal periods (e.g., past year, past month) to maximize recall for symptoms (e.g., Ford et al., 2003; Kilpatrick et al., 2003). This strategy is informed by evidence suggesting that retrospective recall is associated with much lower levels of symptom reports (Compton & Lopez, 2014; Moffitt et al., 2010). As with PTEs, the majority of studies focused on self-report data from adolescent respondents. Typically, the questionnaire or interview would ask the individual to respond about the worst or most distressing event. Studies comparing this "worst-event" approach to other approaches (e.g., "random event" chosen from the list of traumatic events experienced; three worst traumas) suggest that this decision has nontrivial effects on conditional prevalence estimates for PTSD in

adult populations, such that choosing the "three worst events" makes PTSD more likely than "worst," and the "worst event" makes PTSD more likely than choosing a random traumatic event (Beals, Manson, et al., 2013; Breslau et al., 1998). In a subset of studies, a link between the specific symptoms and a particular event was not clearly established (Cuffe et al., 1998; Kilpatrick et al., 2000).

Across our highly rigorous epidemiological studies, PTSD was assessed using structured diagnostic interviews. The CAPA interview demonstrated excellent test–retest reliability (kappa was 0.94 for self-report and 0.99 for parent report) and discriminant validity (in clinic compared to community samples (Costello et al., 1998). The Development and Well-Being Assessment (Goodman, Ford, Richards, Gatward, & Meltzer, 2000) has demonstrated good discriminant validity between clinic and community samples (Aebi et al., 2012). The age-informed CIDI demonstrated good test–retest reliability (kappa = 0.62), and discriminant validity. Researchers noted that the computer-modified version of the CIDI had a broadened C criterion for PTSD diagnosis and showed good convergent validity with a clinician diagnosis (overall kappa = 0.85), except for items on diminished/restricted interest questions in adolescent samples (Perkonigg & Wittchen, 2000). Finally, PAPA demonstrated acceptable test–retest reliability (kappa = 0.73) and moderate convergent validity (Egger et al., 2006).

Other studies used other interviews: the National Women's Study (NWS) PTSD Module (Kilpatrick, Resnick, Saunders, & Best, 1989); the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule, Version IIIR, demonstrating good convergent validity with each other (Spitzer, Williams, Gibbon, & First, 1992); and the Diagnostic Interview of Children and Adolescents for Parents of Preschool Children (DICA-PPC; Ezpeleta, de la Osa, Granero, Domènech, & Reich, 2011), which reported good 8-day test–retest reliability (kappas ranged from 1.0 to 0.39) and convergent validity for "any diagnosis" but did not detail PTSD specifically. Other studies administered standardized questionnaires: The Adolescent Version of the University of California Los Angeles PTSD Reaction Index (UCLA-RI; Steinberg et al., 2013) and the Harvard Trauma Questionnaire-Part IV (HTQ; Mollica et al., 1992) both demonstrated good reliability and convergent and/or discriminant validity. Two studies used interviews made specifically for the reported studies (Cuffe et al., 1998; Lewis et al., 2019). Each created semistructured interview questions based on DSM PTSD criteria.

The prevalence estimates for lifetime PTSD in childhood varied greatly, ranging from 1.3 to 20% in all epidemiological samples. The two highly rigorous epidemiological studies that reported lifetime prevalence showed 1.3% (Perkonigg & Wittchen, 2000) and 4.7% (McLaughlin et al., 2013), which were both adolescent samples. Mean prevalence in studies that administered structured interviews (4.1%) was on average less than half compared to studies that administered questionnaires (11.1%). The absolute variability in the prevalence estimates of childhood PTSD is less than that of PTEs, but the range goes from relatively uncommon to vanishingly rare. It's notable that the two studies of younger children (aged 2–7 years) did not demonstrate any PTSD (0.0%: Carter et al., 2010; Ezpeleta, de la Osa, & Doménech, 2014); however, novel DSM-5 PTSD criterion for children age 6 and younger were not assessed in either study. Studies reporting the highest rates of PTSD tended to involve high-risk or convenience samples (e.g., Karsberg & Elklit, 2012). Overall, these lifetime rates are not entirely dissimilar, albeit modestly lower, than what has been found in adult studies (2.5–8.8%: Atwoli et al., 2015; Kessler, Chiu, Demler, & Walters, 2005). Current PTSD in highly rigorous epidemiological studies of childhood varied from 0.0 to 0.5% for the past 1–3 months (Carter et al., 2010; Copeland, Keeler, Angold, & Costello, 2007) and 0.7%–0.14% for

TABLE 5.2. Epidemiological Studies on the Prevalence of PTSD in Childhood

Study	Location	PTSD measure	Prevalence; conditional prevalence	Sex diff?	Other predictors of PTSD
Alisic et al. (2008)	Netherlands	CRTI*	Conditional risk: 15%		
Bödvarsdóttir & Elklit (2007)	Iceland	Ad-hoc PTE questionnaire	Lifetime: 16%	F > M	Multiple traumas
Breslau et al. (2004)	Mid-Atlantic city	WHO CIDI*	Lifetime: 7.1%; Conditional risk: 8.8%	ns	Assaultive violence
Briggs-Gowan, Ford, et al. (2010)[R]	Greater New Haven area	Child Life Events scale	3-month: 0.0%		
Cisler et al. (2011)	United States	PTSD module of NWS*	Lifetime: 3.9%		
Copeland et al. (2007)[R]	Southeastern United States	CAPA life events module*	3-month: 0.5%	ns	Violent or sexual trauma; multiple traumas, anxiety; other adversities
Cuffe et al. (1998)	Southeastern United States	Ad hoc interview	Lifetime: 0.1–3.5%	F > M	Sexual assault; witnessing serious accident; other life events
Domanskaité-Gota et al. (2009)	Lithuania	HTQ*	Lifetime: 6.1%	F > M	Living with a single parent; multiple trauma; recent exposure
Elklit (2002)	Denmark	HTQ*	Lifetime: 9.0%	F > M	Sexual assault; physical abuse; exposure to multiple trauma; single parent
Ezpeleta et al. (2014)	Spain 3–7 years	DICA-PPC*	Lifetime: 0.0%		
Ford et al. (2003)[R]	Great Britain	DAWBA*	1-month: 0.14%		

Giaconia et al. (1995)	Northeastern United States	Diagnostic Interview Schedule*	Lifetime: 6.3%; Conditional risk: 14.5%	F > M	Sexual assault
Kilpatrick et al. (2003)	United States	PTSD module of NWS*	6-month: 3.7% for boys; 6.3% for girls	F > M	Higher age; Black or Hispanic
Landolt et al. (2013)	Switzerland	UCLA PTSD Reaction Index*	Lifetime: 4.2%; Conditional risk: 7.4%	F > M	Multiple trauma; physical abuse; not with biological parents; low parent education
Lewis et al. (2019)	England and Wales	Ad-hoc interview	Lifetime: 7.8%; 12-month: 4.4%; Lifetime conditional risk: 25.0%	F > M	Childhood victimization, exposure to direct interpersonal assault
McLaughlin et al. (2013)[R]	United States	CIDI*	Lifetime: 4.7%; Conditional risk: 7.6%	F > M	Interpersonal violence; prior trauma; fear and distress disorders; < two biological parents in home
Perkonigg & Wittchen (2000)[R]	Munich, Germany	M-CIDI*	Lifetime: 1.3%; 12-month: 0.7% Conditional risk: 7.8%	F > M	Sexual assault; older; low SES; multiple traumas; anxiety and mood disorder diagnosis
Petersen et al. (2010)	Faroe Islands	HTQ*	Lifetime: 20%	F > M	Multiple traumas; single parent; recent negative event

Note. Asterisks (*) indicate references for PTSD measures with published reliability and validity: HTQ = Harvard Trauma Questionnaire—Part IV (Mollica et al., 1992); M-CIDI = Munich Composite International Diagnostic Interview(Wittchen et al., 1998); UCLA PTSD Reaction Index(Steinberg et al., 2004); Composite International Diagnostic Interview (Kessler & Üstün 2004); Impact of Events—Revised (Weiss, 2007); DAWBA = Development and Well-Being Assessment (Goodman et al., 2000); DISC-IV = Diagnostic Interview Schedule for Children (Schaffer et al., 1996); PTSD module of National Women's survey (Cisler et al., 2011); World Health Organization Composite International Diagnostic Interview (Andrews & Peters, 1998); Children's Responses to Trauma Inventory (Alisic & Kleber, 2010); Diagnostic Interview of Children and Adolescents for Parents of Preschool Children (Ezpeleta et al., 2011).

[R]Rigorous studies as defined by criteria presented on pages 78–79.

the past 6–12 months (Ford et al., 2003; Perkonigg & Wittchen, 2000), which appear significantly less than 12-month prevalence data in adults (4.7%: Goldstein et al., 2016). Together, these studies provide a basis for the argument that either PTSD is less common in childhood than in adulthood or that the phenomenology of traumatic stress differs in childhood.

Conditional risk for PTSD (i.e., prevalence in those exposed to trauma) was less likely to be reported than base prevalence. Conditional prevalence clustered around 7–10% (e.g., Elklit, 2002; Landolt, Schnyder, Maier, Schoenbucher, & Mohler-Kuo, 2013; McLaughlin et al., 2013). A few studies that had reported lower PTE prevalence reported higher conditional rates for PTSD. For example, Lewis and colleagues (2019) reported 31.1% trauma prevalence and 7.8% PTSD lifetime prevalence. Studies reporting low prevalence of PTSD were less likely to report associated conditional rates (Carter et al., 2010; Ezpeleta et al., 2014; Ford et al., 2003). Conditional rates were also higher in studies with longer periods in which the symptoms were assessed (lifetime vs. past year vs. past 3 months: Giaconia et al., 1995; Lewis et al., 2019). Overall, there is insufficient evidence to conclude that conditional prevalence of PTSD in childhood is dissimilar from that in adult samples of around 2.5– 4% (Atwoli et al., 2015; Kessler et al., 2017). This is surprising given the remaining challenges to defining posttraumatic stress in childhood populations (see above).

A key question for clinicians and researchers alike has been determining which children are most likely to meet the criteria for PTSD (or at least display significant posttraumatic stress symptomatology) following PTE exposure. A number of risk factors for PTSD have emerged. First, while both males and females are likely to have been exposed to a PTE, females are more likely to meet the criteria for PTSD (e.g., Lewis et al., 2019; Perkonigg & Wittchen, 2000). This pattern is remarkable across a broad range of studies with differing methodological features and rates of PTEs and PTSD overall, and it is not accounted for by the different types of exposures that are more common in females than males (e.g., sexual assault). Similar findings are found in the adult literature (Olff, Langeland, Draijer, & Gersons, 2007).

Second, children who had been exposed to multiple traumatic events were at higher risk for PTSD (e.g., Landolt et al., 2013; McLaughlin et al., 2013). It is not an uncommon finding that cumulative risk exposure in childhood is associated with higher levels of psychopathology (Appleyard, Egeland, van Dulmen, & Sroufe, 2005; Copeland, Shanahan, Jane Costello, & Angold, 2009). This pattern extends to PTEs and PTSD as well. Finally, PTSD risk was associated more with some types of exposures than with others. Conditional risk for PTSD or posttraumatic symptoms was highest for serious motor vehicle accidents (Lewis et al., 2019), direct assault or violence (e.g., Copeland et al., 2007; McLaughlin et al., 2013), or sexual assault (e.g., Lewis et al., 2019; Perkonigg & Wittchen, 2000). Again, these findings mirror those found in adults (Beals, Belcourt-Dittloff, et al., 2013).

Finally, additional childhood adversities, including prior psychiatric disorders and experience of other life stressors, predicted higher conditional risk (e.g., Copeland et al., 2007; Landolt et al., 2013), especially simple phobia (85.7% prior to PTSD onset; see Perkonigg & Wittchen, 2000). Together, these risk factors provide clinicians with some guidance as to which trauma-exposed children will struggle with posttraumatic stress. Recently, Lewis and colleagues (Lewis et al., 2019) developed a PTSD risk calculator based on their multivariate analyses in the Environmental Risk Longitudinal Twin Study sample. The risk calculator displayed adequate discrimination of trauma-exposed

individuals who met the criteria for PTSD. The calculator variables included female sex, IQ, ethnicity, psychotic internalizing or externalizing symptoms, experience of traumatic events such as serious accidents and victimization, socioeconomic disadvantage, fewer than two biological parents in the home, and a family history of mental illness.

In summary, childhood PTSD is uncommon among the vast majority of children exposed to PTEs not meeting DSM criteria. Children who do eventually meet PTSD criteria are more likely to be female, have been exposed to multiple traumatic events, have a history of mood or anxiety problems, and have been directly exposed to violence or sexual assault.

CHALLENGES FOR THE FUTURE

The literature to date has done well in establishing an important foundation for understanding the experiences of trauma and PTSD in childhood. Trauma is a normative experience that affects all groups of children without regard for gender, race/ethnicity, or socioeconomic strata. Most of these children do not go on to meet the criteria for PTSD, and the risk factors for PTSD are well established. This area has matured sufficiently to provide an important context for understanding the experience of trauma in childhood. There are several important next steps, as follows.

Need to Focus on Long-Term Effects, Rigorously Studied

One term that has not yet been mentioned in this review is ACEs, or adverse childhood experiences. This term refers to nine early adverse experiences, some of which include a number that meet the criteria as DSM extreme stressors (e.g., physical and sexual abuse), while others do not (e.g., parental incarceration, divorce). ACE has been popularized as a result of a series of studies that linked these early exposure experiences to poor health outcomes in adulthood (Brown et al., 2009; Felitti et al., 1998; Geoffroy, Gunnell, & Power, 2014; Mars et al., 2014; Steptoe, Marteau, Fonagy, & Abel, 2019). The potential for early trauma and ACEs to affect behavior and functioning across the lifespan is now commonly accepted. Though widely accepted, support for this hypothesis has often rested on studies that assess childhood exposures retrospectively, while failing to account for other childhood factors that commonly co-occur with trauma exposure. The next challenge for researchers of early trauma and ACEs in childhood is to follow these samples prospectively to characterize rigorously the effects of such early exposures in adulthood, as a few studies have done thus far (Copeland et al., 2018). In this study, cumulative childhood trauma exposure to age 16 years was associated with higher rates of adult psychiatric disorders (odds ratio for any disorder, 1.2; 95% CI, 1.0–1.4) and poorer functional outcomes, including key outcomes that indicate a significantly disrupted transition to adulthood (e.g., failure to hold a job and social isolation). Childhood trauma exposure continued to be associated with higher rates of adult psychiatric and functional outcomes after adjusting for a broad range of childhood risk factors, including psychiatric functioning and family adversities and hardships (adjusted odds ratio for any disorder, 1.3; 95% CI, 1.0–1.5). Such studies have the potential to clarify the true impact of trauma on physical and mental health throughout the lifespan—apart from recall bias and forgetting and childhood confounders—and provide a strong empirical basis for lifespan public health efforts.

Need to Get Beyond PTSD

Trauma and PTSD are commonly studied jointly, as they are in this chapter. It is now well established, however, that the effects of trauma on health are much broader than PTSD (Copeland et al., 2007; Perkonigg & Wittchen, 2000). This finding is perhaps appreciated better by the research community than the general public where PTSD and trauma are closely linked. Trauma exposure is associated with increased incidence of every type of common childhood psychiatric disorder, as well as disruptions in all areas of life functioning—anywhere from 2 times for depressive disorders to 10 times for panic disorder (Perkonigg & Wittchen, 2000). The majority of children with PTSD (76.6–87.5%) had comorbid diagnoses (Lewis et al., 2019; Perkonigg & Wittchen, 2000). Perkonigg analyzed the timing of diagnosis onset of children with PTSD and found that obsessive–compulsive disorder (OCD) and panic disorder were the most common to onset around the same time as PTSD and that generalized anxiety disorder (GAD), agoraphobia, and substance use/dependence most commonly developed secondary to developing PTSD (61–67%: Perkonigg & Wittchen, 2000). Overall, Lewis and colleagues list the most common comorbidities as depression (54.7%), conduct disorder (27.0%), and alcohol/nicotine dependence (21.3–25.6%). Trauma, in addition to being a specific risk factor for a single DSM diagnosis, is a nonspecific risk factor for almost all common psychiatric problems. Importantly, the public health burden of trauma is greater for these more common disorders as they affect many more children than for PTSD itself, which affects only a few. Future work should focus on these broad, pleiotropic effects to better estimate the cumulative public health burden of trauma exposure in childhood.

Focus on Surveillance and Prevention

Review of the epidemiology of trauma and PTSD is a way of pulling together the patchwork data available to draw general conclusions. Such studies provide enough evidence to help us understand the basic epidemiological facts of trauma in childhood. What is now needed is a means of tracking the exposure of children to trauma over time to aid in public health efforts to minimize risk. The findings from this review and others suggest that targeted efforts to reduce exposure to trauma in children are unlikely to be successful. Exposure to trauma affects too many strata of individuals to justify such targeted efforts. What is needed are broad-based public policy efforts to reduce trauma exposure and ameliorate the effects of exposure, rather than informing the development of precision–medicine models to influence or predict individual responses to treatment (Psaty, Dekkers, & Cooper, 2018). Such prevention efforts can only be conducted in concert with surveillance efforts that allow for a target index to measure policy effectiveness.

SUMMARY

Childhood is a heterogeneous period with multiple developmental stages and frequent biological, educational, and social transitions. This heterogeneity extends to the events that children find traumatic (e.g., neglect; death of a pet) and the emotional and behavioral responses to those events. This heterogeneity is overlaid with differing research methodologies for estimating prevalences, as there are a range of informant

and age-related differences, which are not necessarily considered in adult samples. Due, in part, to these issues, obtaining precise estimates of the public health burden of traumatic events in childhood is a challenge, and not all studies meet multiple criteria for high rigor. Despite these challenges, there is evidence that lifetime event prevalence is less than in adults but still relatively common. The most common of these experiences affect the child's social network. The likelihood of exposure for specific events did differ by gender and age, but fewer differences were seen by SES. Lifetime PTSD prevalence in childhood appears to be similar, but it is modestly lower than in adults. This is due to either true differences in prevalence or to differing symptom phenomenology in childhood. There is insufficient evidence on this point to draw a clear conclusion. In the studies described here, childhood PTSD was more likely among female children, those with multiple PTEs, and prior psychiatric disorders, mirroring adult literature. A few traumatic events such as serious motor vehicle accidents, violence, and sexual assault yield higher conditional rates of PTSD. Nevertheless, and perhaps most importantly, the vast majority of children exposed to trauma do not meet the criteria for PTSD. There is a need for rigorous, long-term studies of childhood trauma to better understand how children continue to cope and function as they transition within childhood and then to adulthood. Surveillance and prevention efforts are important tools that can help us keep children safe and well; thus, they should be a priority for future research and policymaking.

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CHAPTER 6

Psychological Models of PTSD

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Understanding the mechanisms of how posttraumatic stress disorder (PTSD) develops, maintains, and remits has been the focus of theoretical and empirical attention for many decades. Psychological models have been seminal in our understanding of how PTSD functions and increasingly have merged with more biologically oriented models. This chapter outlines the major psychological models of PTSD, commencing with the early behavioral conceptualizations (that actually predated official recognition of PTSD as a disorder) and progressing to models that incorporate cognitive processes.

EARLY BEHAVIORAL MODELS

The early models of posttraumatic stress disorder (PTSD) understandably evolved from conceptualizations of phobic behavior, which was the precursor of current understandings of posttraumatic stress. Development of phobias was initially conceptualized as being a function of Pavlovian classical conditioning, in which a previously neutral stimulus is associated with a fearful experience; as a result, the previously benign stimulus acquires a fearful quality such that it triggers the expectation of threat (i.e., it becomes a conditioned stimulus). In the initial study of this process conducted in 1920, John Watson and Rosalie Rayner paired a rat with a loud noise (the unconditioned stimulus) for 9-month-old Albert, who subsequently developed a fear of the rat. In many subsequent studies, this process was understood to underpin the development of anxiety disorder.

Although this model has certain parsimony in explaining the acquisition of anxiety, it does not readily account for avoidance behaviors. Mowrer (1960) attempted to explain phobic behaviors with his two-factor model that proposed a combination of classical and operant conditioning processes. Specifically, Mowrer proposed that one may respond to the anxiety that develops following the acquisition of fear (via classical conditioning pairing of conditioned and unconditioned stimuli) by avoiding the stimulus and thereby enjoying reduced anxiety. The resulting reduction in anxiety can reinforce the avoidance behavior, and accordingly the operant processes contribute to

ongoing avoidance tendencies. This model has received criticism because people can develop fear in the absence of an overt threatening experience and can also have fear without accompanying avoidance. In addition, phobias often develop cognitive or social features that the Mowrer model does not explain (Levis, 1981). As a result, this model has been updated over the years in an attempt to refine it. For example, one iteration of this model has recognized the major limitation of the two-factor model, which is that reduction of fear does not necessarily predict reduction in avoidance (Cook, Mineka, & Trumble, 1987). This model proposes that avoidance can persist despite reduced anxiety because learned avoidance becomes habitual and is not dependent on reinforcement related to fear reduction (Maia, 2010).

The therapies based on this early model were largely responsible for initiating most frontline therapies of PTSD that have evolved over time. At their core, these treatments aim to reduce the symptoms of PTSD by reducing avoidance of the feared stimuli via maintaining proximity to these stimuli until fear abates. Numerous case studies and case series involving Vietnam veterans were reported in the 1980s which required the patient to repeatedly focus on traumatic memories (Keane, Fairbank, Caddell, & Zimering, 1989; Keane & Kaloupek, 1982); Basic to this therapy is the idea that the trauma memory is the core trigger of fear and that exposure to these memories would reduce the associated distress.

PTSD-SPECIFIC FEAR-CONDITIONING MODELS

After the introduction of the PTSD diagnosis in DSM-III, fear-conditioning models were developed that built on earlier behavioral models and were specifically related to PSTD (Milad, Rauch, Pitman, & Quirk, 2006). These models are actually very similar to earlier conditioning models, but they also describe in more detail the biological underpinnings of conditioning processes, as well as the parameters of conditioning processes. These models posit that when a traumatic event (an unconditioned stimulus) occurs, the trauma-exposed person responds with intense fear (an unconditioned response); subsequent reminders of the trauma (the conditioned stimuli) prompt fear reactions, such as reexperiencing symptoms and distress (the conditioned response). For example, the survivor of combat may learn that the sound of a car backfiring or the smell of burnt steak may trigger the sense of imminent threat; in this way, previously benign events acquire threatening qualities. Fear-conditioning models propose that increased activation of stress hormones (including norepinephrine and epinephrine) results in overconsolidation of trauma memories (Rauch, Shin, & Phelps, 2006). It is also argued that most people are able to recover from a traumatic experience because extinction learning occurs in the weeks and months following the experience, in which there is repeated exposure to trauma reminders or memories that do not result in further harm. That is, new learning occurs so that these reminders no longer signal threat (Myers & Davis, 2007).

These models are supported by research showing that, in response to trauma reminders, people with chronic PTSD display elevated psychophysiological responses, including heart rate, skin conductance, and facial electromyogram (EMG) relative to trauma survivors without PTSD (Bauer et al., 2013). People who develop PTSD also display higher resting heart rates in the immediate period after trauma, reflecting possible elevated conditioning (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2008; Shalev et al., 1998). Consistent with the notion that PTSD reflects impaired extinction

learning, multiple studies involving military or emergency service personnel have shown that impaired extinction learning (measured on experimental tasks) prior to commencement of active duty predicts subsequent PTSD levels after personnel have been exposed to traumatic events (Guthrie & Bryant, 2006; Lommen, Engelhard, Sijbrandij, van den Hout, & Hermans, 2013). Another study that tried to understand the risk for different susceptibilities for fear conditioning compared the responses of monozygotic twins who either did or did not serve in the Vietnam War; this design allowed the researchers to disentangle genetic and exposure factors. This study found evidence of more slowly habituating skin conductance startle responses in veterans with PTSD and their noncombat-exposed co-twins, compared to veterans without PTSD and their noncombat-exposed co-twin. This finding suggests that habituating skin conductance responses to startle stimuli (which may reflect a predisposition to have a conditioned response) may represent a pretrauma vulnerability factor for PTSD (Orr et al., 2003).

Building on fear-conditioning models, much work has also addressed the issue of how trauma exposure can make one more susceptible to subsequent stressors. Sensitization models propose that after trauma-related distress a person can have a predisposition to an excessive response to less severe subsequent stressors. In short, neural circuitry (particularly the limbic system) is sensitized following an initial traumatic experience (Post, Weiss, & Smith, 1995), which has been shown in animals and humans who have been exposed to a prior stressful aversive event (Stam, 2007a, 2007b). Consistent with this model, prior traumatic events are linked to more reactivity to subsequent stressors (Breslau, Davis, & Andreski, 1995); delayed-onset PTSD is predicted by posttrauma stressors (Smid et al., 2012); and people who develop PTSD do not display elevated startle responses immediately after the traumatic event but do so in the following months (Griffin, 2008; Shalev et al., 2000).

Much attention has also been given in recent years to how initially conditioned memories are altered over time. This attention has focused on memory reconsolidation, a process that recognizes that when one activates a previously encoded memory (by recalling it), the memory becomes temporarily destabilized as a result of synaptic plasticity, and during this time it is susceptible to modification (Nader, Schafe, & LeDoux, 2000). This pattern has been observed in rats (Nader, Schafe, & LeDoux, 2000) and humans (Kindt, Soeter, & Vervliet, 2009) and appears to alter the affective qualities of the associative learning rather than the memory itself (Kindt et al., 2009). This has led to numerous attempts to alter trauma memories by administering manipulations following memory reactivation; there is evidence that both pharmacological (Brunet et al., 2018) and psychological (Bryant & Datta, 2019) interventions can impact posttraumatic-type responses, such as intrusive memories. It is worth noting, however, that the process of reconsolidation is the subject of much debate, with questions remaining over the extent to which it is distinct from consolidation and extinction processes (Haaker, Golkar, Hermans, & Lonsdorf, 2014).

Treatments emerging from fear-conditioning models have built on those treatments developed in the wake of the two-factor models but have placed greater emphasis on the processes involved in extinction learning and retention. In practice, this approach (generally referred to as trauma-focused cognitive-behavioral therapy [TF-CBT]) also involves repeated exposure to the conditioned stimuli, which in the case of PTSD is primarily the trauma memories and avoided situations that trigger the distress. Many controlled trials have been conducted over the years demonstrating that this approach is the treatment of choice for PTSD (Institute of Medicine, 2008; National Institute of Clinical Excellence, 2005). It should be noted that at least one-third of PTSD patients

may not respond optimally to this treatment (Bradley, Greene, Russ, Dutra, & Westen, 2005; Loerinc et al., 2015). Although this response rate is consistent with treatment success across anxiety disorders (Springer, Levy, & Tolin, 2018), it nonetheless points to the need to develop additional approaches to augment current treatment strategies. As knowledge of the parameters of extinction learning has grown, application of TF-CBT has been adapted to address issues of fear reinstatement and fear renewal (Weisman & Rodebaugh, 2018). One of the developments to emerge from the neural understandings of extinction learning has been attempts to augment TF-CBT by combining exposure with a range of pharmacological and direct stimulation methods to enhance the benefits of TF-CBT. Unfortunately, these attempts have been only modest to date (Lebois, Seligowski, Wolff, Hill, & Ressler, 2019).

INFORMATION-PROCESSING MODELS

Despite the success of behavioral models in explaining many PTSD phenomena, there was increasing recognition that they did not fully account for a range of PTSD reactions, including cognitive features of the disorder. Earlier iterations of more cognitively based models focused on information processing. These models explain PTSD in terms of information processing and memory function (Foa, Steketee, & Rothbaum, 1989; Litz & Keane, 1989). The models can be traced back to Lang's (Lang, 1977) proposal that emotions are stored in memory networks that contain information about (1) stimuli that elicit the emotional response, (2) verbal, cognitive, physical, and behavioral responses evoked by the stimuli, and (3) the meaning of the stimuli and associated response (Lang, 1977). Foa and colleagues' (1989) information-processing model proposed that following trauma exposure, a fear network is formed that stores information about what is threatening. This theory holds that because trauma-related stimuli are highly represented in the fear network, they are readily activated by many internal and external cues. It is proposed that this ready activation triggers reexperiencing symptoms and hypervigilance to potentially threatening events. Intrusive memories can have two distinct outcomes in information-processing theories: They may promote processing and resolution of the traumatic memories, or they may prompt attempts to avoid or control trauma memories, which can compound the disorder. Inherent in this theory is that the predominance of threat-related cognitions in the fear network leads a lower threshold for interpreting stimuli as threatening, as well as a bias toward searching for and identifying threatening information. The attentional bias to threat-related stimuli has been repeatedly demonstrated in studies that have employed the modified Stroop color-naming test. This paradigm requires participants to name the color of either printed threat or nonthreat words, and the extent to which speed on this task is impaired reflects a bias to those stimuli. Numerous studies have found that individuals with PTSD display slower color naming of threat words (Bryant & Harvey, 1995; McNally, Kaspi, Riemann, & Zeitlin, 1990). Furthermore, studies that have employed the masked Stroop paradigm indicate that this bias toward threat stimuli in PTSD occurs at a preattentive stage of processing (Harvey, Bryant, & Rapee, 1996). The attentional bias to threat has also been demonstrated in dot-probe (Bryant & Harvey, 1997) and eye-tracking (Bryant, Harvey, Gordon, & Barry, 1995) paradigms. This form of attention bias is seen across many anxiety disorders (Schmidt, Richey, Buckner, & Timpano, 2009). It is to be noted, however, that PTSD is also characterized by bias to *avoidance* (Bar-Haim et al., 2010; Wald et al., 2013). That is, PTSD appears to be

distinguished by greater attention variability involving attentional biases toward and away from threat (Naim et al., 2015).

Treatments related to these models also utilize TF-CBT approaches. Treatments directly informed by these models are strongly influenced by fear-conditioning models but also build on the cognitive focus of information processing. This approach recognizes the importance of narrating the experience of the trauma in order to not only achieve proximity to the feared stimulus but also to integrate the information into one's normal memory network. It is argued that this achieves reduced predominance of threat-related memory representations, less attentional bias to the threat, and consequent reductions in reexperiencing symptoms (Foa et al., 2006).

DISSOCIATIVE MODELS

One school of thought that can be loosely described as a cognitive model places emphasis on dissociation as a core mechanism in traumatic stress. This school emphasizes that traumatized people can manage their distress by dissociating awareness of the experience. In the latter part of the 19th century, Jean-Martin Charcot documented the dissociative reactions he observed in traumatized patients seen at the Salpêtrièfre Hospital in Paris (Micale, 2001); he highlighted the extreme disturbances in perception, cognition, or motor ability in patients with few overt physical injuries. Although Charcot was somewhat vague about the specific mechanisms for these responses, he posited that in the wake of a traumatic experience, one can experience a dissociation of the ego, such that there is a temporary state of hypnotic-like trance, in which one is suggestible to representations of the accident or experience. This could result in more permanent physical and sensory dysfunction as the individual maintains these symptoms (Charcot, 1889). This position was further developed by one of Charcot's students, Pierre Janet, who posited that the foundation of mental health was self-awareness, which involved being aware of one's memories (Janet, 1907). According to Janet, overwhelming experiences that can occur during trauma may be dissociated from awareness, but he argued that these patients paid the cost of having their psychological energy depleted by the effort required to maintain the dissociated state, which resulted in poor functioning.

This position was largely ignored for the first half of the 20th century but became popular again in the latter part of that century (van der Kolk & van der Hart, 1989). Prior to DSM-IV, there was a very strong movement in Western psychiatry to promote dissociation theories into models of PTSD (Butler, Duran, Jasiukaitis, Koopman, & Spiegel, 1996). In short, these models posited that dissociative responses after trauma (potentially including dissociative amnesia, emotional numbing, and depersonalization) represent a strategy used to reduce awareness of aversive emotions. Although this had little influence on DSM-IV's criteria for PTSD, it was exemplified in DSM-IV's new diagnosis of acute stress disorder, which placed a major emphasis on dissociative symptoms. The rationale for this emphasis was that dissociative reactions may limit access to trauma memories and associated emotions, which may impede processing of trauma memories and thereby may predict PTSD. Supporting this emphasis was evidence that people diagnosed with PTSD report higher levels of hypnotizability (Spiegel, Hunt, & Dondershine, 1988) and dissociation (Bernstein & Putnam, 1986), people with dissociative disorders have higher rates of traumatic histories (Kluft, 1987), and dissociative responses during traumatic experiences are predictive of subsequent PTSD (Ehlers, Mayou, & Bryant, 1998).

Much emphasis has been placed on the potential for peritraumatic dissociation to predict subsequent PTSD. This emphasis was supported by evidence from longitudinal studies that indicated a relationship between peritraumatic dissociation and PTSD (Murray, Ehlers, & Mayou, 2002; Shalev et al., 1998; Spiegel, Koopmen, Cardeña, & Classen, 1996). There is evidence, however, that questions the predictive role of peritraumatic dissociation. Although peritraumatic dissociation has been found in nonsexual assault victims, it has not been replicated in rape victims (Dancu, Riggs, Hearst-Ikeda, Shoyer, & Foa, 1996). There is also evidence that the relationship between peritraumatic dissociation and PTSD may occur because dissociation interacts with other factors rather than occurring in a linear manner (Breh & Seidler, 2007; van der Velden et al., 2006). For example, the relationship between initial dissociation and later PTSD may be mediated by the level of acute hyperarousal (Friedman, 2000). Disturbances in awareness and perception commonly occur when we are highly aroused. For example, flashbacks can be triggered by administering yohimbine to PTSD individuals (Southwick et al., 1993), during panic attacks people often dissociate (Krystal, Woods, Hill, & Charney, 1991), and recently trauma-exposed people experience dissociation if asked to hyperventilate (Nixon & Bryant, 2006). The latter finding is relevant because panic attacks are very common during trauma and more than half of trauma-exposed people experience some panic in the period immediately after the event (Nixon & Bryant, 2003). The possibility that arousal influences dissociation is underscored by evidence that the extent to which peritraumatic dissociation is associated with acute stress reactions depends on the degree of peritraumatic panic (Bryant & Panasetis, 2005; Fikretoglu et al., 2006, 2007). Furthermore, the relationship between peritraumatic dissociation and later PTSD is influenced by peritraumatic panic (Bryant et al., 2011).

Dissociative models have not contributed significantly to the treatment literature for PTSD. One avenue that has been explored is to utilize hypnosis to augment TF-CBT. One school of thought holds that hypnotherapy can address dissociative barriers (Spiegel, 1993), which raises the possibility that it can facilitate exposure therapy. One study randomized to patients with acute stress disorder to either TF-CBT, TF-CBT associated with hypnosis, or supportive counselling (Bryant, Moulds, Guthrie, & Nixon, 2005). Patients who received TF-CBT combined with hypnosis had greater reduction of reexperiencing symptoms after treatment than those in the TF-CBT condition.

COGNITIVE MODELS

Current prevailing cognitive models emphasize the pivotal roles of (1) maladaptive appraisals of the trauma and its aftermath and (2) disturbances in autobiographical memory (Ehlers & Clark, 2000). These models emphasize the role of excessively negative appraisals of the traumatic event, how one is responding to it, and how one perceives the future. In short, it is proposed that engaging in maladaptive appraisals will exaggerate the level of threat or worsen the evaluation of oneself. Common maladaptive appraisals focus on different domains. Ehlers and Clark (2000) suggest some common themes, including the extent to which people generalize from the trauma to other situations (e.g., "The world is always dangerous") and appraisals of symptoms and coping (e.g., "These flashbacks mean I am going crazy"). There is considerable evidence that maladaptive appraisals of the traumatic experience are associated with both acute stress disorder (Smith & Bryant, 2000) and PTSD (Dunmore, Clark, & Ehlers, 1997), and that such appraisals made shortly after trauma exposure are highly predictive of

subsequent PTSD (Ehlers, Mayou, & Bryant, 1998). There is also much evidence that the tendency to ruminate about negative experiences is also predictive of subsequent PTSD symptoms (Clohessy & Ehlers, 1999; Ehring, Frank, & Ehlers, 2008).

There is also convergent evidence that possessing these cognitive styles prior to trauma exposure predisposes people to PTSD when they are exposed to trauma. One study assessed tendency to engage in maladaptive appraisals in newly recruited firefighters and found that negative appraisals regarding self-blame predicted PTSD levels after trauma exposure (Bryant & Guthrie, 2005, 2007). Another study assessed 1,372 women early in their pregnancy for their "sense of coherence," which involves perceiving a stressor as manageable, predictable, and explicable (Engelhard, van den Hout, & Vlaeyen, 2003); among 126 women assessed one month after experiencing a pregnancy loss, and a month afterward, a sense of coherence prior to the loss predicted subsequent PTSD symptoms. The tendency to ruminate also poses greater risk for developing PTSD. A study of university students found that ruminative thinking assessed immediately prior to the Loma Prieta earthquake in 1989 predicted later PTSD symptoms (Nolen-Hoeksema & Morrow, 1991). Similarly, soldiers who report a ruminative thinking style prior to deployment are at higher risk for PTSD symptoms following deployment (Engelhard & van den Hout, 2007).

The other major component of Ehlers and Clark's model involves autobiographical memories, which are normally retrieved in two ways. One involves a concerted effort to follow search paths to identify a specific memory. The other route is via direct involuntary retrieval, which is triggered by associations. Prevailing models of autobiographical memory models posit that memories are stored as "event-specific knowledge," which describe the mental representations of highly specific events encoded in one's autobiographical memory base (Conway & Pleydell-Pearce, 2000). In the Ehlers and Clark (2000) model, the sensory nature of encoded information during trauma results in this information not being integrated into one's normal autobiographical memory base, which purportedly contributes to intrusive memories. According to this model, elevated arousal during trauma results in preferential encoding of sensory information rather than verbal or semantic information. This model posits that these sensory impressions are typically visual, such as someone reporting images of red blood splattered on a windscreen but lacking any contextual information. This "data-driven processing," which is fragmented and dominated by sensory impressions, results in PTSD patients experiencing these perceptual memories with a strong sense of "nowness"; this involves memories that are relived in the "here and now" rather than recalling the memory in a broader autobiographical memory base, which allows the knowledge that they are remembering back to a previous event. This model posits that these memories are strongly conditioned to the events that occurred at the time of the trauma. In this sense, this cognitive model has overlap with fear-conditioning models insofar as conditioned stimuli at the time of trauma serve to trigger the sensory memories that are experienced as involuntary.

There is considerable evidence that trauma memories do tend to be fragmented and to lack a coherent narrative. When asked to recount their trauma narrative, people with PTSD tend to report the events out of order or with patchy details (Amir, Stafford, Freshman, & Foa, 1998; Foa, Molnar, & Cashman, 1995) and that perceptual processing of the traumatic experience is predictive of later PTSD (Sundermann, Hauschildt, & Ehlers, 2013). Furthermore, data-driven processing is associated with intrusive memories and PTSD (Ehring, Ehlers, & Glucksman, 2008;). The same pattern is found in the acute phase after trauma, in that people with acute stress disorder report narratives

that are more fragmented than people without the disorder (Harvey & Bryant, 1999). Furthermore, as treatment progresses, trauma narratives tend to become more coherent (Foa et al., 1995). Although there is some evidence that people with PTSD do not have more fragmented memories (Rubin et al., 2016), these findings may be attributed to methodological factors (Brewin, 2016). Overall, this line of qualitative investigation supports the importance of a contextual coherence in the autobiographical narrative of the trauma memory, possibly because it allows the person to understand the experience in relation to the broad range of causes, consequences, and possible explanations.

It is worth reviewing another major cognitive model that emphasizes how memories are encoded. Brewin's dual representation theory proposes that the encoding of emotionally arousing events generates two memory representations: (1) a verbally processed system called the verbally accessible memory system (VAM) and (2) a perceptually processed system called the situationally accessible memory system (SAM) (Brewin, Dalgleish, & Joseph, 1996; Brewin, Gregory, Lipton, & Burgess, 2010). Whereas the VAM contains consciously processed, contextualized information about the traumatic event, the SAM consists of fragmented, highly detailed sensory and physiological information. According to Brewin and colleagues (1996, 2010), PTSD is characterized by SAM-based memories that result in perceptually dominated memories, which are responsible for the reliving nature of flashback memories.

Relatedly, Holmes has conducted a series of studies investigating the roles of verbal and visual processing in trauma memories. In these studies, the paradigm involves watching a traumatic film and simultaneously doing a visuospatial or verbal task. This approach has shown that performing a visuospatial task interferes with encoding perceptual information, resulting in fewer intrusive memories, while the verbal task results in impoverished conscious representation of the film and more intrusive memories (Holmes, Brewin, & Hennessy, 2004). Numerous studies have now been reported pointing to the role of visual processing in contributing to intrusive memories (e.g., Holmes, James, Coode-Bate, & Deeprose, 2009). Importantly, initial evidence suggests that interfering with visual processing immediately after trauma exposure can reduce subsequent posttraumatic intrusions (Iyadurai et al., 2018).

Implicit in many cognitive models is that people with PTSD will have difficulty in accessing specific autobiographical memories that could otherwise be retrieved on demand. Extending from prior research with suicide attempters and depressed patients, many studies have investigated how efficiently people with PTSD can retrieve highly specific personal memories (e.g., events that may have occurred on a specific day). Numerous studies have found that PTSD individuals retrieve fewer specific memories than trauma-exposed people without PTSD (e.g., McNally, Lasko, Macklin, & Pitman, 1995; Sutherland & Bryant, 2007). Furthermore, difficulties in retrieving specific memories prior to trauma exposure seems to be a risk factor for developing PTSD (Bryant, Sutherland, & Guthrie, 2007), and impaired retrieval of specific memories in the acute phase after trauma predicts development of subsequent PTSD (Kleim & Ehlers, 2008). These findings may suggest that people with PTSD have difficulty contextualizing their memories, including their trauma memories, into a broader autobiographical memory base, which limits their capacity to process and contextualize their experience in an adaptive manner. This interpretation would be consistent with Ehlers and Clark's (2000) model.

Another component of the role of autobiographical memories is the content of the memories. Conway and Pleydell-Pearce's (2000) self-memory system (SMS) model proposes that autobiographical information is reciprocally connected to one's "working

self," which is composed of personal goals, self-representations, and expectations. It is proposed that the working self influences which autobiographical information is retrieved. Relevant to this proposal in the context of PTSD is evidence in an early study of autobiographical memory in Vietnam veterans with PTSD that found that those who attended the research wearing Vietnam-defining regalia (e.g., war insignia, combat fatigues) were more likely to report memories of the war (McNally et al., 1995). This finding accords with other evidence that when people with PTSD are asked to provide "self-defining" memories (i.e., memories that reflect pivotal events that have shaped who we are), they tend to focus on those memories that relate to trauma (Sutherland & Bryant, 2008). This is similar to repeated findings that rating of trauma memories of people with PTSD shows that these memories are central to one's identity and one's "life story" (Rubin et al., 2016).

Importantly, Ehlers and Clark (2000) note that dysfunctions in memories and appraisals interact. It is proposed that people with PTSD preferentially retrieve memories that are consistent with their excessively negative appraisals of the trauma and its aftermath. Furthermore, those who believe that threat is imminent may selectively focus on potential sources of threat. On the other hand, memories that are experienced in the "here and now" may compound appraisals about a sense of threat because these experiences can reinforce the subjective sense of danger and fear.

Several treatments now in use are strongly influenced by cognitive models. Ehlers's cognitive therapy is directly rooted in her cognitive model (Ehlers & Clark, 2000), which involves narrating the trauma experience to facilitate it within the normal autobiographical memory base and systematically challenging maladaptive interpretations of events (Ehlers, Clark, Hackmann, McManus, & Fennell, 2005; Ehlers et al., 2014). Although initially developed with a primary focus on emotional processing, cognitive processing therapy has evolved to focus predominantly on altering unhelpful and unrealistic appraisals about the traumatic experience; this therapy has been validated across many trials (Resick et al., 2008, 2015). Finally, although it draws upon its own theories that are essentially unproven, eye movement and desensitization does involve restructuring people's interpretations of the trauma memory prior to reliving the memory (Shapiro, 2002). Furthermore, it places considerable weight on eliciting saccadic eye movements during the reliving, which may accord with cognitive models that interfering with visual processing may reduce intrusive memories (Iyadurai et al., 2018).

SOCIAL MODELS

Although most influential models of traumatic stress focus on biological, conditioning, or cognitive mechanisms, there are also emerging models that indicate the role of other factors. Increasingly, the role of social factors in how one adapts to a traumatic event is being recognized. Although not traditionally regarded as a model of PTSD, traditional models of attachment theory recognize that people are hard-wired to turn to others during times of threat because from an evolutionary perspective humans have always done this in order to survive. Attachment theories posit that we all rely on primary caregivers when we are upset, frightened, and/or aroused, especially in times of threat. Bowlby (1982) popularized the notion that people internalize attachment representations, such that mental representations of attachment figures acquire soothing effects that are comparable to the actual presence of an attachment figure. It is argued that the development of our attachment systems represents a core emotion regulation strategy

because from the cradle we learn to turn to trust others in times of threat. Consistent with this proposal is much evidence that individuals tend to seek attachment representations when they are presented with either real or symbolic threats (Mikulincer, Gillath, & Shaver, 2002).

Supporting the importance of attachments for management of adversity is evidence that the actual or symbolic presence of social supports ameliorates fundamental stress responses at experiential and neural levels (Coan, Schaefer, & Davidson, 2006). Activating mental representations of attachment figures (e.g., by presenting an image of a mother holding a baby) can reduce attentional bias to threat (Mikulincer et al., 2002), diminish noradrenergic activation to a stressor (Bryant, & Chan, 2015), increase the parasympathetic response (Bryant & Hutanamon, 2018), and impede fear conditioning (Toumbelekis, Liddell, & Bryant, 2018).

Inherent in attachment theory is the recognition that people vary in the extent to which they have a sense of attachment security. Attachment theorists posit that diminished support early in life can lead to an insecure attachment system that involves an inadequate internal working model of attachment. This produces difficulties in accessing attachments later in life as a means to manage threats (Mikulincer & Shaver, 2016). Early studies conducted by Ainsworth and colleagues regarding infants when they were temporarily separated from their mothers documented that upon reunion infants were either securely comforted by the parent or blunted or intensified their emotional expressions in order to maintain the relationship and maximize their caregiver's availability (Ainsworth, Boston, Bowlby, & Rosenbluth, 1956). It was proposed that these early experiences would establish subsequent working models of attachment systems that would influence how people would process social information, and also how they could use social factors to moderate threat response (Mikulincer & Shaver, 2007). Attachment styles are typically conceptualized in two dimensions: attachment-related anxiety and attachment-related avoidance (Brennan & Shaver, 1998). Attachment-related anxiety is a dimension that reflects the extent to which an individual worries about the proximity and/or availability of their partner in times of need. The second dimension, attachment-related avoidance, reflects the extent of a person's distrust of others and the extent to which an individual maintains behavioral independence and emotional distance from their partner to avoid abandonment (Fraley & Shaver, 1997).

Having an insecure attachment style predisposes people to be less able to manage stressors, and there is convergent evidence that they are more likely to develop PTSD (Dieperink, Leskela, Thuras, & Engdahl, 2001). One longitudinal study assessed situations in which children were separated from their parents during a major disaster and found that 30 years later this separation predicted insecure attachment styles, which were associated with more severe PTSD (Bryant et al., 2017). People with avoidant attachment tendencies distance themselves during threat processing as a means of coping. Supporting this proposal is evidence that during threat, avoidantly attached individuals inhibit proximity-seeking behavior and are less likely to activate attachment representations (Mikulincer, Birnbaum, Woddis, & Nachmias, 2000). Consequently, they are less likely to benefit from attachment availability when they are exposed to stressors. Convergent research suggests that although avoidantly attached people appear to cope, their psychological problems often become exacerbated over time (Mikulincer, Horesh, Eilati, & Kotler, 1999). The eventual deficits in emotion regulation can undermine coping with stress, thereby rendering these individuals more vulnerable to psychological problems, including PTSD (Ein-Dor, Doron, Solomon, Mikulincer, & Shaver, 2010). Meanwhile, avoidant individuals may not benefit from security priming due to

their inherent distrust of others and their preference for distance (Mikulincer, Hirschberger, Nachmias, & Gillath, 2001). Studies have shown that when provided with an attachment prime in conjunction with a stressor, securely but not avoidantly attached individuals report reduced noradrenergic response (Bryant & Chan, 2015), increased heart rate variability (Bryant & Hutanamon, 2018), and reduced intrusive memories (Bryant & Datta, 2019). In one Israeli study, students who had survived terrorist bombing attacks and had either elevated or low PTSD responses were administered the Emotional Stroop Test; on each trial prior to presentation of the words, they were subliminally presented with an attachment-security or a nonrelated word (Mikulincer, Shaver, & Horesh, 2006). This study found that the presentation of attachment reminders prior to threat words reduced the expected attentional bias to threat that one normally sees in PTSD. In a replication study with prisoner-of-war survivors from the Yom Kippur War that used the same protocol, the beneficial effect of providing attachment primes was not observed (Mikulincer, Solomon, & Shaver, 2014). The authors concluded that the experience of being a prisoner of war may have so damaged these individuals' attachment systems that they were not able to access internal attachment systems in a way that was helpful for them.

These models also need to be considered in the context of much research that has been done on the role of social support in PTSD (Andrews, Brewin, & Rose, 2003). Some research has linked negative (but not positive) social support to subsequent posttraumatic distress (Andrews et al., 2003; Zoellner, Foa, & Brigidi, 1999), or has found that the relationship between social support and PTSD symptoms changes over time (Cook & Bickman, 1990; Robinaugh et al., 2011). This pattern may be consistent with the social support deterioration model, which holds that trauma may lead to disruptions in social support, which can be compounded by changes in people's expectations of social support, which in turn weakens interpersonal relationships (Wheaton, 1985). In a longitudinal study, King and colleagues observed that more severe PTSD 2 years after combat was associated with lower positive social support 5 years later among male veterans (King, Taft, King, Hammond, & Stone, 2006). Although Kaniasty and Norris (1993) found that positive social support at 6 months predicted lower levels of PTSD 12 months following a natural disaster, between 12 and 18 months, high levels of positive social support predicted decreases in PTSD, and high levels of PTSD symptoms predicted decreases in social support. Taken together, there seems to be evidence that PTSD symptoms are associated with subsequent decreases in positive social support. Considering the potential benefits that social attachments can confer on people, this detrimental impact of PTSD on social support may compound trauma survivors' difficulties. It is probable, however, that these effects may be moderated by one's predisposing attachment security tendencies.

THE ROLE OF EMOTION REGULATION

One process that is worth highlighting and transverses all models is the role of emotion regulation in PTSD. Emotion regulation is a complex construct that comprises a person's ability to monitor, evaluate, and modulate emotional states. This process is strongly represented in most fear-conditioning and associated neurobiological models of PTSD, which rely strongly on prefrontal cortical regions regulating limbic-based arousal (Shalev, Liberzon, & Marmar, 2017). The important component of this model is that prefrontal networks, which are strongly implicated in promoting extinction learning,

are inadequately recruited in PTSD (Greco & Liberzon, 2016). Cognitive models also emphasize emotion regulation by noting cognitive strategies that allow better management of stress response after trauma exposure, and thereby facilitate healthy adaptation. This view is supported by repeated demonstrations of impaired emotion regulation in PTSD symptom severity (Seligowski, Lee, Bardeen, & Orcutt, 2015), as reported in cross-sectional studies (Mazloom, Yaghubi, &Mohammadkhani, 2016), experimental paradigms (Badour & Feldner, 2013), and longitudinal designs (Bardeen, Kumpula, & Orcutt, 2013). The role of emotion regulation has been particularly important in conceptualizations of PTSD development in children, who by the nature of the limited cognitive abilities associated with developmental stages have restricted capacities for emotion regulation (Salmon & Bryant, 2002). These developmental limitations in emotion regulation may increase the susceptibility of youth to developing PTSD (Salmon & Bryant, 2002). It is for this reason that children's mental health after trauma is often determined by parental distress (Lambert, Holzer, & Hasbun, 2014) and by the impact of this distress on parenting behaviors (McLeod, Weisz, & Wood, 2007), and consequently on the emotional difficulties in their children (Bryant et al., 2018).

CONCLUDING COMMENTS

Although it is parsimonious to categorize models of PTSD as being primarily biological, behavioral, cognitive, or social, a more accurate way to conceptualize most contemporary models of PTSD is to state that most models incorporate mechanisms from diverse schools of thought. Considering the various models available to us, it seems that when we are faced with trauma, we initially respond with the evolutionary-driven biological reaction that prepares us for managing threat: Our noradrenergic and glucocorticoid systems interact to prepare the body for the threat and subsequently to adapt once the threat has subsided. As a result of the strong activation of stress hormones, fear-conditioning processes are occurring in which aversive emotional reactions are associated with the trauma-related stimuli. This leads to strong aversive reactions to subsequent reminders of the trauma until extinction occurs. Cognitive models show that the elevated arousal resulting from the stress hormones impacts how we encode information and how memories are stored. There is consequent attentional focus on the source of threat, which can lead to fragmented and sensory-based information being encoded rather than a coherent narrative. The resulting lack of integration of trauma memories in our autobiographical memory can limit how these memories are processed and then contextualized to a point at which we can master them.

As time progresses after the trauma, biological and cognitive processes continue to interact. Sensitization processes may contribute to ongoing reactivity to subsequent stressors, but maladaptive appraisals and biases in the nature of memories that are retrieved can compound the sense of threat one perceives in the aftermath of trauma. As memories recur in the posttraumatic period, during which time they are labile and can be reconsolidated in either adaptive or maladaptive ways, trauma memories can be updated via psychological, pharmacological, or environmental inputs. Importantly, trauma rarely occurs in a social vacuum, and so typically a multitude of social processes will occur that can moderate how one adapts to trauma; this will depend in part on one's predisposing capacity to benefit from supportive social factors.

It cannot be overstated that there are many nuanced variations of how these factors can function and interact. Factors related to genotypic predisposition, sex, menstrual

phase, and a much broader range of individual differences can all contribute to how the person is responding at each phase of the posttrauma period. The notion that adaptation to trauma will be solely influenced by appraisals, memories, or conditioned responses is naïve, and so it is only by considering processes from multiple models that we can begin to understand the complexity of factors that contribute to the development of PTSD and recovery.

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CHAPTER 7

Alterations in Memory and Other Neurocognitive Processes

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Posttraumatic stress disorder (PTSD) is often described as a disorder of memory, but it is also associated with deficits on clinical neuropsychological tests that measure skills such as attention or response inhibition and with information-processing biases in the context of emotionally relevant information. In this chapter, we review current knowledge in these areas, considering their relevance to theoretical conceptualizations of the disorder. We additionally discuss how these processes relate to the prediction of course and treatment outcome, and to aging and dementia.

MEMORY FOR THE TRAUMATIC EVENT

The symptoms of PTSD include both vivid and detailed intrusive (i.e., repeated, involuntary) memories of the traumatic event and difficulty in deliberately recalling all the important details of the events in an orderly fashion. It is not uncommon that recollections of the traumatic event include blanks or periods during which memory for the details of the event is vague and unclear. Periods during which events were completely forgotten have also been reported. Research has correspondingly focused on the characteristics of involuntary memories and the intentional recall of the traumatic event, as well as on the reported forgetting of the event.

Involuntary Memories

Involuntary memories are usually brief and perceptually detailed. Typically, between one and four different scenes may recur, sometimes in the form of videotape replaying events (Ehlers & Steil, 1995; Hackmann, Ehlers, Speckens, & Clark, 2004; van der Kolk & Fisler, 1995). Their content generally appears to the person as a literal record of

events during or surrounding the traumatic event, but it is sometimes an imaginative extension of what has been experienced (Merckelbach, Muris, Horselenberg, & Rassin, 1998; Reynolds & Brewin, 1998). Intrusions based on imaginative reconstructions may also occur following head injury that has resulted in posttraumatic amnesia (Harvey & Bryant, 2001). Over the course of treatment, the frequency of these intrusions diminishes, as do their vividness, the associated distress, and the sense of how much the events appear to be happening all over again (Hackmann et al., 2004; Speckens, Ehlers, Hackmann, & Clark, 2006).

Although most, if not all, psychiatric disorders are frequently accompanied by unwanted memories and images of distressing events (Brewin, Gregory, Lipton, & Burgess, 2010), the intrusive memories of people with PTSD appear to contain significantly more sensory elements than those of people who are depressed (Ashbaugh, Marinos, & Bujaki, 2018; Parry & O'Kearney, 2014). Moreover, intrusive trauma memories in PTSD have the special feature of being reexperienced in the present or the here and now (Brewin, 2015; Kleim, Graham, Bryant, & Ehlers, 2013; Schönfeld & Ehlers, 2017). This distortion in the sense of time demarcates much reexperiencing in PTSD from normal reliving, in which even events that are vividly recalled nevertheless feel as though they belong to the past.

Reexperiencing in the present has traditionally been acknowledged within the DSM in the form of a PTSD flashback. Both DSM-5 and ICD-11 define flashbacks as encompassing a spectrum of reexperiencing from a very brief sense that the events are happening again in the here and now to a total absorption in the traumatic memory in which the person loses all contact with their current environment, being temporarily unable to see or hear people in their immediate vicinity. These symptoms are specific to PTSD (Bryant, O'Donnell, Creamer, McFarlane, & Silove, 2011). Although they generally begin shortly after the traumatic event, their onset may be delayed by months or even years ("with delayed expression" in DSM-5) (Andrews, Brewin, Philpott, & Stewart, 2007).

Intentional Recall

Trauma narratives intentionally recalled by individuals with clinical disorders are often described as being disorganized and containing gaps (Foa, Molnar, & Cashman, 1995; Harvey & Bryant, 1999). This claim has now been extensively tested, with the best studies utilizing independent blind ratings of narrative quality. Six such methodologically superior studies, four with adult and two with juvenile samples, have unanimously reported that the trauma narratives of patients with PTSD or acute stress disorder are more disorganized than those of trauma victims without those disorders (Brewin, 2014). This disorganization has also been shown to be specific to the trauma memories of these groups (Halligan, Michael, Ehlers, & Clark, 2003; Jelinek, Randjbar, Seifert, Kellner, & Moritz, 2009; Salmond et al., 2011).

Higher levels of fragmentation in trauma narratives are often found to be related to self-reported dissociation either during or after the traumatic event (Engelhard, van den Hout, Kindt, Arntz, & Schouten, 2003; Halligan et al., 2003; Harvey & Bryant, 1999; Murray, Ehlers, & Mayou, 2002). During psychotherapy, it is common for patients to say that details are returning to them and that they now recall numerous aspects of the event that had been forgotten. However, the evidence that fragmentation and disorganization of trauma memories decrease as patients recover from PTSD is inconsistent (Bedard-Gilligan, Zoellner, & Feeny, 2017; Foa et al., 1995; Halligan et al., 2003; Jones, Harvey, & Brewin, 2007; van Minnen, Wessel, Dijkstra, & Roelofs, 2002).

One group of researchers has consistently failed to find evidence for more disorganization or fragmentation in the trauma memories of people with PTSD, and on this basis they claim that these memories are no different from ordinary autobiographical memories (Rubin, 2011; Rubin et al., 2016). Notably, however, the measures used by this group involve self-ratings or computer-based analyses. Their results likely have differed from the consensus of clinical opinion for two reasons: (1) Their methods do not require the person with PTSD to systematically report the worst moments of the trauma and (2) their data generally involve the memory narrative as a whole rather than the individual units analyzed in the clinical studies. It is plausible that disorganization and fragmentation are characteristic, not of the whole traumatic narrative, but of those moments when the person was most afraid or helpless (Brewin, 2016; Ehlers, Hackmann, & Michael, 2004).

THEORETICAL ACCOUNTS OF MEMORY ALTERATIONS IN PTSD

Ehlers and Clark's Model

Ehlers and Clark (2000) proposed that the memory of the traumatic event is poorly elaborated, not given a complete context in time and place, and inadequately integrated with other autobiographical knowledge and memories. The worst moments (e.g., when a victim of assault thought they would die or felt ashamed for complying with the perpetrator's requests) typically need to be updated (e.g., with the information that they did not die or that they complied with the perpetrator because he or she threatened to kill them). Until the update is integrated with the memory of this particular moment, the original threatening meaning will be retrieved (Ehlers et al., 2004; Evans, Ehlers, Mezey, & Clark, 2007).

Lack of integration is brought about in part by higher levels of data-driven processing (an increased focus on sensory impressions during the traumatic event), which in turn enhance perceptual priming, defined as a reduced perceptual threshold for trauma-related sensory stimuli (Kleim, Ehring, & Ehlers, 2012; Michael, Ehlers, Halligan, & Clark, 2005). Additionally, the theory proposes that lower levels of conceptual processing (a decreased focus on the meaning of the situation during the traumatic event) hinder integration of the trauma memory with the autobiographical database. This shift from conceptual to data-driven processing may be related to extreme fear reactions such as panic. Other responses during the trauma that would increase the risk of later PTSD are an inability to establish a self-referential perspective while experiencing the trauma, dissociation, mental defeat, emotional numbing, and lack of cognitive capacity to evaluate aspects of the event accurately. All these factors, with the exception of conceptual processing, have been empirically supported.

The lack of integration accounts for difficulties in intentional recall, the absence of a context accounts for reexperiencing in the present, and the lack of connection with other relevant information accounts for the unchanged threatening meaning of the moments that are reexperienced. The easy triggering by a wide range of cues is explained by strong associations involving sensory elements from the traumatic situation and by the enhanced perceptual priming.

Dual Representation Theory

Dual representation theory (DRT; Brewin, Dalgleish, & Joseph, 1996) proposed that memories of the traumatic events were stored not only in ordinary episodic memory

but in a separate, partly image-based memory system that was unable to contextualize how and when the information was acquired. More sensory detail could be captured by this automatic system, but images could only subsequently be reexperienced in the form of flashbacks when triggered by reminders. In contrast, episodic memory recorded aspects of the event that had been consciously attended to, located these in a full temporal and spatial context, and provided accessible memories that could be used flexibly to reflect on, appraise, and communicate about the event. Posttrauma, paying deliberate attention to the flashbacks and their content results in recoding this information into the episodic memory system. However, avoidance of flashbacks and reminders results in the information in the image-based memory remaining unintegrated and prone to being triggered.

Recent evidence has confirmed that briefly fixated information appears to be encoded automatically and to form a relatively stable representation in long-term memory (Brewin, 2014). The revised DRT proposes that the dorsal visual stream is able to represent this information, which is close to the sensory input and recorded from an egocentric perspective, transmitting it quickly and automatically to the motor cortex (Brewin et al., 2010). In contrast, a contextualized memory system operates on information that is much more highly processed within the ventral visual stream and medial temporal lobe, leading to the creation of more flexible allocentric representations and an accompanying spatial and temporal context. According to the revised DRT, extreme stress results in these normally integrated systems becoming functionally disconnected, so that some moments of great fear or horror are reexperienced as decontextualized flashbacks. As the theory suggests, people with PTSD appear to have a more general difficulty in forming allocentric spatial memories (Smith, Burgess, Brewin, & King, 2015).

Even in healthy people, negative material induces an upregulation of the amygdala, leading to improved item memory, accompanied by a down-regulation of the hippocampus such that items are bound less to their context which is more poorly recalled (Bisby, Burgess, & Brewin, 2020). According to the revised DRT, these are the same processes that are illustrated more extremely in people with PTSD and that explain why intentional recall is at least in part fragmented and incoherent, while involuntary sensory memories and flashbacks are easily triggered by reminders. Trauma-related nightmares may also be seen as decontextualized intrusions.

FORGETTING THE TRAUMA

Contrary to the argument that trauma cannot be forgotten, several studies have reported the forgetting of documented traumatic events in adulthood (Means & Loftus, 1991; Raphael, Cloitre, & Dohrenwend, 1991; Schraedley, Turner, & Gotlib, 2002). In fact, forgetting has been regularly observed in treatment of combat veterans with PTSD (T. M. Keane, personal communication). A substantial proportion of those reporting childhood sexual abuse described periods when they say they had completely forgotten that the abuse had occurred (DePrince et al., 2012). Forgetting may occur because the event is deliberately not thought about (Ghetti et al., 2006) or is not registered at the time as something that is significant in the person's life going forward. Children exposed to abusive environments often have great difficulty developing a coherent sense of themselves, experiencing internal conflict between multiple selves and disruptions to the continuity of the self over time (Harter, 1998). Changes in family members, parent

figures, and accommodation may lead to environments in which important retrieval cues are no longer present. Recovery of traumatic memories has also been observed in the treatment of war veterans with PTSD.

The argument that trauma cannot be forgotten is often deployed to contest the validity of claims that traumatic memories of child sexual abuse have been recovered after a period of amnesia. The main alternative hypothesis is that such memories have been suggested through inappropriate therapy (Loftus, 1993). Key propositions include the following: (1) The content of recovered memories is usually stereotypical, conforming to therapists' preconceptions about child sexual abuse as a ubiquitous cause of psychological disorder, or highly implausible (e.g., Satanic rituals with human sacrifices); (2) the age at which the events are supposed to have occurred may precede the development of explicit event memory; (3) there is typically no independent corroboration of the events; (4) recall generally occurs within therapy; and (5) the idea that trauma can be forgotten is contrary to established knowledge about how memory works.

These claims have been systematically evaluated elsewhere (Brewin, 2003): To summarize, surveys indicate that the content of recovered memories is extremely varied and may include undergoing traumatic medical procedures and witnessing violence or death; that few apparent recovered memories of abuse involve events that fall completely within the first 5 years of life; that there is frequently some degree of corroboration for the memories; and that one-half to one-third of recovered memories are recalled prior to any therapy or in a nontherapeutic context. These data strongly suggest that although some recovered memories may be false, others appear to be perfectly plausible. This is the position adopted by most independent commentators and by professional bodies such as the American Psychiatric Association and the British Psychological Society.

There is now extensive research demonstrating that people can deliberately forget a wide variety of material, including autobiographical memories, when they choose to do so (Anderson & Huddleston, 2012; Noreen & MacLeod, 2013). This research has also delineated some of the brain mechanisms involved (Anderson & Hanslmayr, 2014; Bekinschtein, Weisstaub, Gallo, Renner, & Anderson, 2018; Schmitz, Correia, Ferreira, Prescot, & Anderson, 2017). Moreover, some individuals are particularly adept at forgetting negative material (Gleaves, Smith, Butler, & Spiegel, 2004), despite exposure to greater adversity in childhood (Myers & Brewin, 1994).

GENERAL IMPAIRMENTS IN COGNITIVE FUNCTIONING

In addition to distinctions in the way people with PTSD remember their trauma and other autobiographical events, people with PTSD often have greater difficulty learning and remembering new information, as well as with other types of cognitive processes. Cognitive domains that appear particularly relevant to PTSD include learning and retrieval of new information, verbal intellectual functioning, certain aspects of attention and executive functioning, and speed of information processing.

Learning and Memory for Emotionally Neutral Information

Anterograde memory (i.e., new learning and subsequent retrieval of newly learned information) is among the most studied aspects of neurocognition in PTSD. Three meta-analytic studies provide converging evidence that new learning is impaired in

PTSD (Brewin, Kleiner, Vasterling, & Field, 2007; Johnsen & Asbjornsen, 2008; Scott et al., 2015). Difficulties surface on both measures of immediate and delayed recall but do not necessarily indicate a deficit in memory retention. Specifically, although delayed recall can be used as a measure of the ability to remember newly learned information over time, delayed recall depends to some extent on how well the information was initially learned. Studies that have taken into account immediate recall of information when examining delayed recall suggest that initial learning may be more compromised than memory retention in PTSD (e.g., Vasterling et al., 2002; Yehuda, Golier, Halligan, & Harvey, 2004). Consistent with these findings, effect sizes in a meta-analytic study were larger for new verbal learning, as compared with verbal memory retention (Scott et al., 2015).

PTSD-related weaknesses in new learning may reflect deficits in executive control of memory, as evidenced by more intrusive errors (e.g., Vasterling, Brailey, Constans, & Sutker, 1998), less effective use of organizational strategies (e.g., Johnsen & Asbjornsen, 2009), and retrieval failures in the context of intact recognition (e.g., Cohen et al., 2013) among individuals with PTSD. Finally, people with PTSD show heightened sensitivity to interference on memory tests (e.g., Samuelson, Krueger, Burnett, & Wilson, 2010; Vasterling et al., 2002) and impaired ability to generalize prior learning to novel situations (Levi-Gigi et al., 2012). Of relevance to theoretical frameworks such as DRT that emphasize the degraded encoding of the trauma as a risk factor for PTSD, longitudinal (e.g., Parslow & Jorm, 2007; Vasterling et al., 2018) and twin (Gilbertson et al., 2007) studies suggest that the integrity of pretrauma anterograde memory processes moderate PTSD symptoms following trauma exposure.

Emerging evidence suggests that prospective memory, or the ability to remember to carry out intended actions in the future (e.g., taking medication according to a set schedule), is also degraded among people with PTSD. Prospective memory may be time-based (i.e., taking action after a specified amount of time has passed) or event-based (i.e., performing a future action in response to an external cue). Scott and colleagues (2016) found that people with PTSD have relative difficulty performing future actions in response to time cues but not in response to event-based cues. In contrast, McFarland and colleagues (2016) found that PTSD symptom severity was inversely related to performance on a prospective memory using event-based cues. Because of the relevance of prospective memory to daily functioning, including health behaviors, it will be important to understand more fully the nature of prospective memory impairment in PTSD.

Attention, Executive Functioning, and Processing Speed

PTSD is associated with abnormalities in some, but not all, aspects of attention and executive functioning. In particular, difficulties in sustaining optimal levels of vigilance over time (with implications for both insufficient attention to important yet nonthreatening information and overattentiveness to perceived threat), in temporarily retaining and manipulating information (i.e., working memory), in monitoring (as displayed by perseveration), and in suppressing or inhibiting task-irrelevant information and automatic responses accompany PTSD (see Aupperle, Melrose, Stein, & Paulus, 2012, for a review). Deficits in inhibitory control likely hold particular relevance to PTSD (DeGutis et al., 2015; Reinhard, Allen, Wong, & Schwartz, 2017; Swick, Honzel, Larsen, & Ashley, 2013). More specifically, deficits on cognitive inhibitory control tasks have been associated with more pronounced reexperiencing symptoms (e.g., Bomyea, Amir, & Lang,

2012; Catarino, Küpper, Werner-Seidler, Dalgleish, & Anderson, 2015; Swick, Honzel, Larsen, Ashley, & Justus, 2012; Vasterling et al., 1998), raising the possibility that diminished inhibitory control impedes disengagement from thoughts and memories of the traumatic event (Aupperle et al., 2012). A meta-analytic study additionally suggests that associations between PTSD and executive dysfunction may be more pronounced in men than in women, in response to combat as opposed to civilian trauma, and as a function of older age and more significant depression symptoms (Polak, Witteveen, Reitsma, & Olff, 2012).

Intellectual Functioning

Typically, PTSD is inversely related to performance on intellectual tasks, most commonly measured on tasks of verbal intelligence (e.g., Saltzman, Weems, & Carrion, 2006; Vasterling et al., 2002). In general, studies using archived test data (e.g., Macklin et al., 1998) and prospective methodology (e.g., Nissen et al., 2017; Orr et al., 2012) indicate that higher pretrauma intelligence buffers the impact of trauma exposure on subsequent PTSD symptom expression, although this finding is not universal (cf. Milan, Zona, Acker, & Turcios-Cotto, 2013). Some research has additionally suggested that as trauma severity increases, premorbid IQ becomes less influential on subsequent PTSD expression (Sørensen, Andersen, Karstoft, & Madsen, 2016; but see Nissen et al., 2017, for findings to the contrary). Finally, one prospective study using item response theory modeling revealed that PTSD might also affect test taking on intellectual tasks, as evidenced by a performance decline from pre- to posttrauma on a vocabulary task used to estimate verbal intelligence (Rutkowski, Vasterling, Proctor, & Anderson, 2010). Thus, there may be a bidirectional relationship between PTSD and IQ test performance.

COGNITIVE BIASES

Memory Bias

Overgeneral Memory

The term *overgeneral memory* refers to a deficit in autobiographical memory, such that, in response to a variety of predetermined positive and negative cue words, participants struggle to retrieve specific memories as instructed and instead tend to retrieve memories that are overgeneral in that they refer to repeated or long-lasting events. One explanation for this bias is that people may be trying to avoid the activation of specific distressing memories from their past (Williams et al., 2007). Recent meta-analytic studies (Barry, Lenaert, Hermans, Raes, & Griffith, 2018; Ono, Devilly, & Shum, 2016) have reported that trauma exposure alone increased overgenerality and reduced specificity. The two meta-analyses differ in the importance they attribute to the additional presence of PTSD symptoms, one finding this to amplify the effect of exposure and the other finding a marginal effect. The study by Ono and colleagues (2016) also suggested greater generality when trying to deliberately retrieve memories to negative cue words, contrasting with the involuntary activation of highly specific trauma memories associated with PTSD. Additional evidence shows that memory becomes more specific with recovery from PTSD (Sutherland & Bryant, 2007) and that explicitly targeting memory specificity may reduce PTSD symptoms (Callahan, Maxwell, & Janis, 2019).

False Recognition

The Deese–Roediger–McDermott (DRM) paradigm measures an associative illusion, the tendency to falsely recall that an associated item (e.g., "sleep") was presented in a list of thematically related words (e.g., "bed," "pillow," "dream"). Tests of PTSD patients with verbal and visual versions of this task have not been entirely consistent. A recent review has argued that this is because the effects are present for emotional materials but absent or inconsistent for neutral materials (Otgaar, Muris, Howe, & Merckelbach, 2017). There is little evidence that this kind of associative illusion is related to the tendency to produce false memories in any other situation, for example, as a result of suggestion.

An alternative method of studying false memories is to ask patients with PTSD to distinguish between words and phrases from their own previously supplied trauma narrative and those belonging to the narrative of another patient (Brewin, Huntley, & Whalley, 2012). Not surprisingly, this kind of task often elicits spontaneous flashbacks, the kind of vivid recall experience normally associated with a true rather than false memory. When flashbacks occurred to their own words, patients were usually more accurate in their recognition judgments. However, occasionally flashbacks occurred in response to words from the other patient's narrative (probably reflecting some similarity in their experience), and these tended to be misremembered as being from the patient's own narrative. This suggests a possible mechanism that could account for patients being convinced of the truth of a memory even if it is objectively false.

Other Biases

Future Thinking

Similar to their recall of past life events, people with PTSD also have greater difficulty than those without PTSD in imagining future specific events (Brown et al., 2013, 2014), particularly when asked to imagine positive future events (Kleim, Graham, Fihosy, Stott, & Ehlers, 2014). That ability to imagine the future parallels ability to recall the past is not surprising, given that future thinking and autobiographical recall appear to share common underlying neuroanatomy (e.g., prefrontal cortex, medial temporal lobe; Schacter, Addis, & Buckner, 2008). Difficulties imagining a positive future may have considerable clinical implications, contributing to trauma-related self-views and difficulties formulating future goals (Krans et al., 2017) that could be hypothesized to lead to maladaptive behaviors (e.g., increased suicide risk; hesitancy to engage in emotionally challenging treatment interventions if the eventual benefits of those interventions cannot be imagined).

Attention Biases

Attention bias refers to the disruption of ongoing cognitive activity due to either preferential engagement with, or avoidance of, emotionally relevant information. It is thought to contribute to the development and maintenance of PTSD symptoms such as hypervigilance and increased responsivity to trauma-related stimuli (Chemtob, 1988; Litz & Keane, 1989). In PTSD, the strongest biases occur in response to trauma-relevant stimuli, as compared to more generally negatively valenced emotional stimuli (Cisler et al., 2011) and nonrelevant trauma stimuli (Fleurkens, Rinck, & van Minnen, 2011). For example, in the Emotional Stroop Task, people with PTSD name the color in which

trauma-related words are printed more slowly than they do non-trauma-related words. Initially thought to reflect facilitated threat detection related to vigilance, PTSD-related bias to perceived threat likely also reflects difficulties disengaging from trauma cues (e.g., Pineles, Shipherd, Mostoufi, Abramovitz, & Yovel, 2009). Interestingly, in one study, PTSD-diagnosed survivors of a building collapse showed both greater vigilance to general threat and greater avoidance of stimuli highly specific to their trauma, suggesting that both engagement and avoidance processes may occur in PTSD depending on the specificity of the threat to the trauma event (Zinchenko et al., 2017). Discrepancies across studies may also reflect differences in the experimental paradigms used to examine attentional bias, which have included, for example, emotional Stroop, dot-probe, visual search, rapid serial visualization, and eye-tracking paradigms, given that these tasks also measure different components of attention (e.g., engagement vs. disengagement) or require other cognitive processes (e.g., inhibitory control) and behavioral responses (e.g., keyboard vs. verbal responses) (see Bomyea, Johnson, & Lang, 2017, for a review).

Still other research has suggested that people with PTSD do not consistently attend to or avoid threat. Instead, people with PTSD, as compared with trauma-exposed and non-trauma-exposed healthy or minimally symptomatic individuals, show greater variability in directing their attention toward or away from threat over time (Alon, Naim, Pine, Bliese, & Bar-Haim, 2019; Bardeen, Tull, Daniel, Evenden, & Stevens, 2016; Iacoviello et al., 2014; Naim et al., 2015). This phenomenon, referred to as "attention bias variability," is thought to reflect instability in threat monitoring caused by competing urges to attend to and avoid threatening stimuli (Swick & Ashley, 2017).

Interpretation Biases

Consistent with cognitive theories that suggest people with PTSD interpret ambiguous information as threatening (Chemtob et al., 1988; Ehlers & Clark, 2000), previous research has found that PTSD-diagnosed individuals are more likely to interpret ambiguous words, sentences, and videos of social situations as threatening (Amir, Coles, & Foa, 2002; Kimble, Batterink, Marks, Ross, & Fleming, 2012). Although interpretive biases remain relatively understudied as compared with attention and memory biases, preliminary evidence from randomized controlled trials suggests that preventative (i.e., pre-exposure) interventions focused on modification of interpretive biases may be successful in reducing PTSD symptoms at least among certain subgroups (e.g., Pyne et al., 2019).

PREDICTION OF COURSE AND TREATMENT OUTCOME

Certain changes in memory and cognitive functioning may be related to the course of the disorder or to treatment outcome, rather than simply being correlates of PTSD symptoms. In particular, features of the trauma memory itself, such as reexperiencing them in the present, are predictive of the course of the disorder over and above the effects of initial symptom levels (Kleim, Ehlers, & Glucksman, 2007; Michael et al., 2005). Similarly, a greater level of memory disorganization may present as early as the first week posttrauma and predicts a poorer outcome, even when initial symptoms are controlled (Brewin, 2014; Jones et al., 2007).

Both of these processes predict concurrent and subsequent PTSD symptoms in line with clinical theories (Ehlers, Mayou, & Bryant, 1998; Evans et al., 2007; Halligan

et al., 2003; Murray et al., 2002). Similar results have been found with children and adolescents (Ehlers, Mayou, & Bryant, 2003; Meiser-Stedman, Dalgleish, Smith, Yule, & Glucksman, 2007; Meiser-Stedman et al., 2019). Consistent with the Ehlers and Clark model, the degree of priming at two weeks posttrauma has also been found to predict the course of PTSD (Michael et al., 2005), including when levels of initial symptoms and priming for other words were controlled (Ehring & Ehlers, 2011). There is less evidence that other changes in memory and cognition play a functional role in the disorder. One exception is the reduced specificity/increased overgenerality of autobiographical memory, which has been found to predict the course of the disorder (Bryant, Sutherland, & Guthrie, 2007; Kleim & Ehlers, 2008).

Better treatment outcome has been associated with enhanced verbal memory abilities (Haaland, Sadek, Keller, & Castillo, 2016; Nijdam, de Vries, Gersons, & Olff, 2015; Scott et al., 2017; Wild & Gur, 2008). According to DRT, this is because verbal memory assists in the creation of contextualized representations of the traumatic event.

PTSD, Aging, and Dementia

As people continue to live longer, the potential interaction between aging and PTSD has emerged as an area of interest. Like younger adults, older adults with PTSD demonstrate greater cognitive impairment than age peers without PTSD, with the largest effects demonstrated on memory tasks (Schuitevoerder et al., 2013). Larger effect sizes among older adults with PTSD (≥ 0.7), as compared with those found in the more general PTSD population (cf. Brewin et al., 2007; Scott et al., 2015), raise the question of whether PTSD accelerates cognitive aging and/or leads to increased risk of dementia. Previous research suggests, for example, that exposure to stressful life events, as well as PTSD and other psychological sequelae of traumatic stress exposure, are associated with more significant cognitive aging in later life (Burri, Maercker, Krammer, & Simmen-Janevska, 2018).

The relationship between PTSD and disorders of aging, such as progressive dementia, may be particularly complex and reflect bidirectional influences (see Desmarais et al., 2020, for a review). An archival study of over 181,000 predominantly male military veterans 55 years of age revealed that veterans diagnosed with PTSD at baseline were more than twice as likely to receive a new-onset dementia diagnosis 6 years later (Yaffe et al., 2010). More recently, similar findings in a sample of over 109,000 female veterans 55 years of age or older indicated that women were almost twice as likely to develop dementia within 4 years (Yaffe et al., 2019). Qureshi and colleagues (2010) found that PTSD, irrespective of war-zone injury as indicated by Purple Heart status, was associated with a twofold increase in dementia diagnosis in a cross-sectional study of older military veterans.

These findings are consistent with longitudinal research indicating more general links between earlier and late-life chronic stress and increased risk of subsequent dementia (e.g., Johansson et al., 2010; Peavy et al., 2012). Mechanisms linking stress to dementia of various etiologies are as yet poorly understood. A study of Vietnam veterans found that although PTSD was associated with worsened cognitive functioning, it was not associated with neuropathological indices of Alzheimer's disease, including medial temporal lobe atrophy and positron emission tomography measures of amyloid (Weiner et al., 2017). Other potential biological pathways, however, may exist, including, for example, increased cerebrovascular risk (Henderson et al., 2013; Kubzansky, Koenen, Spiro, Vokonas, & Sparrow, 2007) and inflammatory processes resulting in

oxidative stress (Johansson et al., 2010). Recent work suggests that PTSD may also be associated with epigenetic changes (i.e., DNA methylation) that accelerate cognitive aging (Wolf et al., 2016, 2018) and interact with genetic vulnerabilities to increase risk of dementia (Averill et al., 2019).

In addition to PTSD increasing risk of dementia, dementia may also spark the reemergence of PTSD symptoms. Although no epidemiological or cohort studies have examined the course of PTSD symptoms in relation to new-onset dementia, several case reports have described exacerbated and/or reemergent PTSD symptoms in patients following cerebrovascular events (e.g., Cassiday & Lyons, 1992) and nonvascular dementia (see Lapp, Agbokou, & Ferreri, 2011, for a review). The onset of dementia is often associated with psychosocial (e.g., loss of social support, changes in living environment), neurocognitive (e.g., reduced cognitive control of intrusive thoughts), and biological (e.g., diminished prefrontal inhibition of limbic structures) factors, which may contribute to the onset or exacerbation of PTSD symptoms.

CONCLUSIONS

The processes and deficits described in this chapter are integral to understanding the nature of PTSD. General intelligence and other aspects of neurocognitive functioning may protect against the initial development of PTSD, while verbal memory abilities allow greater benefit from treatment. Conversely, PTSD erodes neurocognitive integrity, potentially increasing vulnerability via a negative feedback loop, and is associated with increased risk of cognitive decline. The findings are consistent with a bidirectional relationship between PTSD and neurocognition in which treatment may help to restore cognitive functioning and break the negative cycle (Jacob, Dodge, & Vasterling, 2019).

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CHAPTER 8

Trauma-Induced Dissociation

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> A man who had seen his greatest friend killed beside him developed the following symptoms. At first he struck several of his comrades, but later he assumed a semi-stuporose condition, in which he would stare curiously at such objects as shining buttons and play with them as a child. He became depressed, tearful, vacant, speechless and heedless of what was said to him. . . . He took no notice of a pin-prick until it had been repeated several times, whereupon he gazed at the spot without attempting to withdraw from the pricking. . . . Two days later, he suddenly sat up and exclaimed: "Where am I." Then he got out of bed and sat by the fire, speaking quite intelligently to the orderly, but with no memory of his military life. After a few minutes he relapsed into his former state. The next day he became very restless, and on being quieted and assured that he was in hospital, he gradually came to himself, but had completely lost all memory of what had occurred since he left the trenches. . . . he began to complain of shakiness, bad dreams, attacks of headache and dizziness, which, when severe, caused "fainting attacks." Finally after a sudden shock he was readmitted to hospital, suffering from complete "functional paraplegia."
>
> —Charles S. Myers (1940, pp. 46–48)

Hysteria, soldier's heart, and *shellshock* are among many terms used across the history of grappling with human responses to trauma. The roots of traumatic stress studies began as early as the 19th century, when philosopher and physician Pierre Janet drew a connection between traumatic experiences and "hysteria" in adult women (van der Kolk, Weisaeth, & van der Hart, 1996). Janet was the first to articulate the basic principles of dissociative phenomena and among the first investigators to elucidate the adaptive nature of dissociation for dealing with acute and/or chronic trauma (van der Hart & Friedman, 2019). While the foundation for traumatic stress studies was established by Janet and his peers, a subsequent period of neglect ensued with limited interest in trauma and dissociation outside World Wars I and II (Herman, 1992; van der Kolk et al., 1996). For example, Myers (1940) described dissociative reactions to combat exposure, as in the quotation opening this chapter. Not until the 1980s did sustained attention to dissociation reemerge.

METHODOLOGICAL CONSIDERATIONS

Defining Dissociation

Over the last three decades, definitions of dissociation have varied along many dimensions. Among the issues that need to be considered in defining dissociation are distinctions between continuum and taxon, mechanism (e.g., structure) and outcome (e.g., phenomena), state and trait, detachment and compartmentalization and normative, adaptive, and maladaptive elements of dissociation. Our review focuses on trauma-induced dissociation, setting aside other alterations in consciousness unrelated to trauma, such as meditative states. Trauma is consistently and moderately correlated with dissociative symptoms, though the presence of trauma varies somewhat in dissociative disorders, with approximately half of those with depersonalization/derealization disorder reporting a trauma history, while such a history is nearly universally reported in those with dissociative amnesia and dissociative identity disorders (e.g., Dalenberg et al., 2012).

Various Definitions of Dissociation

Definitions of dissociation have generally converged on lack of integration at some level of functioning (e.g., sensory, somatic, cognitive, affective, representational, personality), though theorists vary in estimates of the scope, type, and nature of disintegration necessary to characterize experiences meaningfully as trauma-induced dissociation (e.g., Chefetz, 2015; Steele, Dorahy, van der Hart, & Nijenhuis, 2009). Van der Hart, Nijenhuis, Steele, and Brown (2004, p. 906) define dissociation as a "lack of integration among psychobiological systems that constitute personality." Putnam (1997) argued that pathological dissociation is "characterized by profound developmental differences in the integration of behavior and in the acquisition of developmental competencies and metacognitive functions" (p. 15). Beere (1995, 2009), focusing on perceptual experiences associated with trauma, viewed dissociation as trauma-induced alterations, degradations or losses in the experience of I–self (e.g., divided to produce dissociative identities), mind (e.g., feeling one's mind is not one's own), body (e.g., out-of-body experiences, automatic behaviors), world (e.g., derealization), and time (e.g., losing time, time speeding up or slowing down). Dell (2009a) argued that dissociative symptoms reflect "recurrent, jarring, involuntary intrusions into executive functioning and sense of self . . . thus dissociative symptoms are startling, alien invasions of one's mind and one's experience" (p. 226). Cardeña and Carlson (2011) characterized dissociation symptoms as involving

> (a) a loss of continuity in subjective experience with accompanying involuntary and unwanted intrusions into awareness and behavior (so-called positive dissociation); and/or (b) an inability to access information or control mental functions, manifested as symptoms such as gaps in awareness, memory, or self-identification that are normally amenable to such access/control (so-called negative dissociation) and/or (c) a sense of experiential disconnectedness that may include perceptual distortions about the self or environment. (pp. 251–252)

Continuum–Taxon

Janet's early conceptualization of dissociation suggested that a subset of individuals experience dissociative states that nondissociative individuals do not experience (see

van der Hart & Friedman, 2019). Despite Janet's view that dissociation involved a distinct category of experience, the prevailing view in the 1980s and early 1990s placed dissociation on a continuum, from common experiences like highway hypnosis or absorption in a book to more uncommon dissociative symptoms. Implicit in the construction of widely used measures, such as the Dissociative Experiences Scale (see Table 8.1), was the assumption that everyone dissociates to some degree.

In the 1990s, findings from taxometric analyses were used to argue that pathological dissociation was a taxon whose symptoms (e.g., amnesia, dissociative identities) were distinct from the continuum of more common dissociative experiences (e.g., Waller, Putnam, & Carlson, 1996). Taxon views of dissociation affect theories about the nature as well as the development, maintenance, and measurement of dissociation. For example, existing measures include nonpathological experiences that may not be informative or related to pathological degrees of dissociation. The taxon view influences theory building by assuming those individuals who pathologically dissociate differ in their basic cognitive organization (Putnam, 1997).

The issue of whether dissociative phenomena fall on a continuum or a taxon invokes consciousness. Many experiences (e.g., absorption, daydreaming, trance states) can cause alterations in consciousness; however, the quality of such experiences may be better described as something other than dissociation. For example, van der Hart and colleagues (van der Hart, Nijenhuis, & Steele, 2006; Steele et al., 2009) argued that daydreaming or trance involves alterations in the level of consciousness (the degree to which the individual has awareness of consciousness) and the field of consciousness (the stimuli available to consciousness), and that it is structural dividedness that separates nondissociative experiences (e.g., absorption) from dissociation. "Structural dividedness" in its most rudimentary form involves alternations between an apparently normal part of the personality and an emotional part (van der Hart et al., 2006).

This chapter focuses on trauma-induced dissociation as pathological dissociation. We do not address directly alterations in consciousness that are more typically distributed in the population (e.g., absorption) or that are not trauma-induced (e.g., neurologically-based alterations in consciousness).

State–Trait

Much as discussions of continuum versus taxon are important to conceptualizations of dissociation, so too are issues of state versus trait dissociation. Some dissociative experiences appear transitory and state-like, such as dissociation during trauma. The experience of such peritraumatic dissociation has been characterized as including "emotional numbing, altered time sense, reduction in awareness of one's surroundings, depersonalization, and amnesia" (Bryant et al., 2011, p. 805). Other forms of dissociation are persistent and trait-like, reflecting a more general "tendency to dissociate across the lifespan" (Fleming & Resick, 2016, p. 267). The term *acute dissociation* has been used to refer to dissociation in the month posttrauma (Harvey & Bryant, 2002), whereas the term *persistent* refers more broadly to dissociation after the event, but not limited to one month (Bryant et al., 2011).

The degree to which peritraumatic, acute, and persistent dissociation relate to one another and predict later posttraumatic stress disorder (PTSD) symptoms remains an area with equivocal findings. Some of the equivocation may be due to measurement problems, ranging from whether participants are asked to retrospectively report peritraumatic dissociation, which can be influenced by current psychopathology, to the

operationalization of peritraumatic dissociation across studies. For example, researchers vary in whether they have operationalized peritraumatic dissociation as dissociative experiences only at the time of the trauma or also in the aftermath of the event (see Bryant et al., 2011; Harvey & Bryant, 2002).

Much attention has been paid to whether peritraumatic dissociation predicts later PTSD. Individual studies have long identified peritraumatic dissociation–PTSD links (e.g., McCanlies, Sarkisian, Andrew, Burchfiel & Violanti, 2017), with evidence that peritraumtic dissociation may partially mediate the relationships between emotional regulation difficulties as well as distress at the time of trauma and PTSD development (Jones, Badour, Brake, Hood, & Feldner, 2018; Otis, Marchand, & Courtois, 2012). A meta-analysis of 35 studies found a medium effect linking peritraumatic dissociation to later PTSD, regardless of whether studies asked for retrospective or quasi-prospective reports of peritraumatic dissociation and PTSD symptoms (Breh & Seidler, 2007). Yet, people who do not report peritraumatic dissociation can go on to be diagnosed with PTSD, and those with high levels of peritraumatic dissociation do not necessarily end up meeting criteria for PTSD (Bryant et al. 2011; Harvey & Bryant, 2002). Thus, peritraumatic dissociation may be a correlate of, rather than a risk factor for, PTSD or reflect some other shared variable, such as history of childhood abuse, which increases the risk of dissociative responses and PTSD (Bryant et al., 2011). Peritraumatic dissociation may also contribute to persistent dissociation, which in turn, contributes to PTSD (e.g., Briere, Scott, & Weather, 2005; Fleming & Resick, 2016).

Over the years, reports of connections between peritraumatic, acute dissociation, and later PTSD have inspired questions about the degree to which dissociation at the time of trauma is normative, adaptive, and/or maladaptive. The answer may be all of the above. Peritraumatic dissociative states have been documented across a range of traumas (Harvey & Bryant, 2002). That they are so commonly experienced suggests that they might be elicited by arousal (Harvey & Bryant, 2002) or injury (Fleming & Resick, 2016) during the event and therefore are not related to psychopathology. Adding to the links observed between peritraumatic dissociation and PTSD across multiple studies (Breh & Seidler, 2007), one study found both cost and benefit. Peritraumatic dissociation predicted PTSD symptom severity *and* posttraumatic growth in civilians living in a conflict zone (Greene, 2018). Moderate levels of peritraumatic dissociation were particularly associated with more PTSD, while higher levels were connected with growth.

Elucidating the connections between peritraumatic, acute, and persistent dissociation is important to theory development. For example, peritraumatic dissociation's link to PTSD has been argued to arise out of mechanisms such as avoidant coping and negative beliefs about self (e.g., Pacella et al., 2011; Thompson-Hollands, Jun, & Sloan, 2017). Yet, others have made the opposite argument that peritraumatic dissociation may limit encoding of trauma material and should therefore be protective against later PTSD; rather, persistent dissociation may reflect avoidance of emotion memories and increase subsequent PTSD symptoms (Bryant et al., 2011).

Outcome–Mechanism

Dissociation is variably referred to as an outcome, a mechanism, or both. For example, dissociation as an outcome can include organization of the personality (e.g., the personality divided into separate components, each with a different sense of self and set of motivations, memories, feelings, and behavioral repertoires), failures in information

processing (e.g., hyper- and hypomemory for trauma-related material), and posttraumatic distress (e.g., dissociation symptoms on a measure such as the Dissociative Experiences Scale [DES]). As a mechanism of trauma-related phenomena (e.g., of memory problems), dissociative symptoms are created by a personality becoming (dis)organized (i.e., dissociative structure) and information (dis)integrated (i.e., breakdown in integrated processing). For example, a dissociative structure of mind/personality (i.e., the mind being organized in a dissociative manner) and dissociative processing (i.e., failure of integrated processing with or without dissociation at the level of personality organization) has been used to explain trauma-related memory impairment, like amnesia (e.g., Chefetz, 2015; van der Hart et al., 2006). Thus, a dissociative structure and dissociative processing are outcomes of trauma but also become mechanisms that give rise to dissociative symptoms, just like a damaged fender is an outcome of a car crash and also the mechanism of the noise caused by a tire rubbing on it.

More than simply semantics, dissociation as outcome and mechanism have led to debates about the very nature of the phenomena, including what constitutes symptoms themselves. For example, are dissociative symptoms the result of, and limited to, a more static dissociative structure or a more fluid process by which information is disintegrated? Van der Hart and colleagues (2006) argued that dissociative symptoms reflect phenomena that result from a dissociative structure. From this viewpoint, amnesia, auditory hallucinations, flashbacks, dissociative identities, and conversion manifestations all constitute dissociative symptoms as they reflect the dynamic outcome of dissociation at the level of personality organization (e.g., amnesia results from information being processed and stored in another part of the personality). Van der Hart and colleagues argued that derealization and most depersonalization symptoms reflect alterations in consciousness that are not reliant on a dissociative structure and therefore should not be classed as dissociative symptoms. Alternatively, Chefetz (2015) argued not to limit dissociative phenomena to a dissociative structure but suggested that dissociative symptoms come from a dissociative process that results from information being isolated, excluded, or deflected from awareness. These issues are as yet unresolved in the field.

Detachment–Compartmentalization

Building on earlier work (e.g., Allen, Console, & Lewis, 1999), Holmes and colleagues (2005) proposed that dissociation reflects two distinct but related experiences: (1) alterations in consciousness involving detachment of one's self, body, or experience and (2) compartmentalization involving deficits in the intentional ability to control psychological and behavioral actions. Dell (2009b) argued that detachment is a metaphor for dissociative phenomena or experience, while compartmentalization is a structural metaphor, capturing how the mind is organized to give rise to compartmentalization symptoms, such as amnesia, automatic actions, and flashbacks. Studies have differentiated detachment symptoms from compartmentalization symptoms, with both types higher in psychiatric groups than controls (Butler, Dorahy, & Middleton, 2019; Mazzotti et al., 2016). In addition, those with dissociative disorders report higher compartmentalization symptoms than those with other disorders, while those with borderline personality disorder report higher compartmentalization than those with other personality disorders (Mazzotti et al., 2016). Consequently, compartmentalization symptoms appear elevated in psychiatric disorders with a higher rate of traumatic experience (Dorahy, Middleton, Seager, Williams & Chambers, 2016). DSM-5's dissociative specifier of

PTSD, which allows a diagnosis of PTSD with dissociative features to be given to those experiencing depersonalization or derealization alongside PTSD symptoms, integrates detachment more fully into the PTSD diagnosis. The central dissociative features of PTSD—flashbacks and amnesia—reflect compartmentalization experiences.

Development of Dissociation: Motivation

The discrete behavioral states model of dissociation argues that pathological dissociation is the result of developmental processes whereby children do not learn to integrate across behavioral states (Putnam, 1997). Putnam (1997) links the development of dissociation to early childhood abuse and notes three primary defensive functions of dissociation: automatization of behavior, compartmentalization of information and affect, and alteration of identity and estrangement from self. These forms of dissociation can also operate in adulthood, especially in association with chronic and/or severe interpersonal trauma (e.g., torture, intimate partner violence).

Maldonado, Butler, and Spiegel (2002, p. 463) stated that dissociative symptoms "should be understood as failures in integration, defects in control systems, rather than the creation of multiple identities" that result in distress and dysfunction. This statement captures a common view that dissociation is a deficit with negative consequences. An alternative viewpoint is that dissociation is a creative adaptation to external insult. For example, dissociative automatization of behavior may allow children to endure painful abuse without full awareness of what is happening and/or their own actions (Putnam, 1997). These two perspectives in their extremes may have profoundly differing implications for those who experience high levels of dissociation that necessitate treatment.

One issue implicit in distinguishing between dissociation as deficit versus adaptation is the origin or motivation for developing dissociation. Theorists have long argued that dissociation can serve a protective or defensive function to keep trauma-related information out of awareness at the time of the trauma or later. Yet, peritraumatic dissociation correlates with later distress (e.g., Ozer, Best, Lipsey, & Weiss, 2003), raising questions about its adaptive value. Evaluating the adaptive–maladaptive nature of dissociation requires thinking about the function of dissociation given the individual's context. Betrayal trauma theory (Freyd, 1996), discussed below in more detail, argues that dissociation enables victims who are dependent on abusive caregivers to maintain necessary attachments. Under conditions in which survival depends on structural dissociation—that is, lack of awareness of the trauma-related information by the part of the personality that must manage tasks necessary to survival, such as attachment with caregivers—dissociation may very well serve an adaptive function. By analogy, one might consider the plight of a creature in a trap. In order to get out, the creature might have to sacrifice a limb. Without that sacrifice, the creature would likely perish, so it is adaptive to sacrifice the limb, but in the long run the missing limb will likely cause problems. Similarly, dissociation may play a role in helping people survive traumas as well as in later distress, perhaps mediating or moderating the relationship between some traumas (e.g., abuse) and later psychological symptoms. There may also be contexts in which dissociation puts individuals at a distinct disadvantage. For example, day-to-day disruptions in information processes arising from dissociation may result in missing danger cues that increase revictimization risk (DePrince, 2005).

The adaptive–maladaptive nature of dissociation may also vary with time and context. For example, dissociation may be adaptive to the immediate goal of surviving

childhood abuse, but maladaptive later in life when caring for children due to the potential impact of unresolved dissociation on parenting. Hulette, Kaehler, and Freyd (2011) found that mothers who experienced high betrayal trauma in childhood and were revictimized in adulthood had higher levels of dissociation than mothers who were not revictimized. In turn, maternal revictimization was associated with child interpersonal trauma history, suggesting that dissociation may involve a persistent unawareness of threats to self and children with implications for interventions.

Whether dissociation is adaptive or maladaptive has implications for understanding individual differences. If individuals do differ in their tendency to dissociate, perhaps due to heredity (Becker-Blease, Deater-Deckard, et al., 2004), then a diathesis–stress model may be applied to suggest that the underlying tendency is a vulnerability provoked by trauma. An alternative would be to see the underlying tendency as a resilience factor that is awakened by trauma. In this view, dissociation protects the individual from greater harm.

A dialectical view may help resolve issues of how adaptive or maladaptive dissociation is viewed. Specifically, dissociation may be both a creative adaptation to an environmental insult that threatens survival (e.g., child abuse by a caregiver) and a deficit that causes problems in other domains of life (e.g., difficulty in school, revictimization risk). When researchers examine adults high in dissociation to evaluate whether dissociation is adaptive or maladaptive, studies suffer from the classic problem of looking at "survivor data": We are not able to see what these individuals would be like had they not dissociated. Consequences may have been far worse for some individuals had they not dissociated.

Observing Dissociation

Measuring dissociation requires thought about both the definition of dissociation (e.g., pathological vs. normative) and conditions under which it occurs. Measuring trauma-induced dissociation should include pathological dissociation versus alterations in consciousness that are more normally distributed in the population. Several reliable and validated self-report measures in children, adolescents, and adults are available (see Table 8.1 for a listing of several widely used measures; see Butler et al., 2019).

Observing Dissociation Posttrauma

Trauma–dissociation correlations have frequently been interpreted as evidence that trauma is a causal factor in the development of dissociative symptoms, though the assumption of causality has been questioned (e.g., Lynn et al., 2014). Dalenberg and colleagues (2012, 2014) laid out specific predictions derived from two alternative models explaining dissociation–trauma links: The trauma model posits that trauma is causally related to pathological dissociation; the fantasy model posits that fantasy proneness mediates, overlaps with, or leads to reports of dissociation (e.g., amnesia, dissociative identities), which in turn contributes to false reports of abuse. Overall, the authors documented strong, consistent support for the trauma model (see also Kate, Hopwood, & Jamieson, 2020).

Research has also addressed the issue of whether societal and cultural expectations play a role in dissociation. For instance, could a trauma survivor learn from others (e.g., therapists) or the culture at large (e.g., through media) to present dissociative symptoms as a socially accepted response to trauma? If so, we would expect to see

TABLE 8.1. Examples of Common Self-Report Measures of Dissociative Experiences

Measure name	Relevant references	Respondent	Comments
Adolescent Dissociative Experiences Scale (A-DES)	Armstrong, Putnam, Carlson, Libero, & Smith (1997); Putnam (1997)	Adolescent	Emphasis on dissociation of mental functions (vs. movement, sensation, and perception).
Child Dissociative Checklist (CDS)	Putnam (1997); Putnam, Helmers, & Trickett (1993)	Parent	Emphasis on dissociation of mental functions.
Dissociative Experiences Scale (DES)	Bernstein & Putnam (1986); Putnam (1997)	Adult	Emphasis on dissociation of mental functions.
Peritraumatic Dissociative Experiences Questionnaire (PDEQ)	Marmar, Weiss, & Metzler (1997); Marshall, Orlando, Jaycox, Foy, & Belzberg (2002)	Adult	Assesses retrospective reports of dissociative experiences at the time of the event.
Somatoform Dissociation Questionnaire (SDQ)	Nijenhuis, Spinhoven, van Dyck, van der Hart, & Vanderlinden (1998)	Adult	Emphasis on somatoform dissociation symptoms. Five- and 20-item measures available.
Multidimensional Inventory of Dissociation (MID)	Dell (2006)	Adult	Assesses 14 facets of dissociation and includes validity items.

lower trauma–dissociation correlations in societal contexts in which individuals were less exposed to suggestive influences regarding this relationship. Dalenberg and Palesh (2004) evaluated the links between dissociative symptoms and trauma in a Russian population that was relatively unexposed to these suggestive sources. They documented the often-replicated positive relationship between trauma and dissociation, noting that rates of dissociation were higher than in comparable American samples. A substantive meta-analytic review found no indication that sociocultural factors explain the relationship between trauma and dissociation, though such factors may shape dissociative symptom presentation (Kate et al., 2020).

Observing Dissociation in PTSD

Dissociative symptoms are observed in conjunction with a range of diagnostic categories (see Lyssenko et al., 2018). We focus here on the co-occurrence of PTSD and trauma-induced dissociation. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) now includes a dissociative subtype of PTSD (PTSD+DS), characterized by depersonalization/derealization in response to traumatic cues. This addition was prompted by evidence (e.g., Lanius et al., 2010) that some patients respond to traumatic reminders with emotional detachment, including symptoms of depersonalization and derealization, as opposed to hyperemotionality and hyperarousal typically associated with PTSD. Ongoing research demonstrates that PTSD+DS is associated with a distinct neurobiological profile that includes, but is not limited to, increased activity in frontal areas that inhibit the fear response through connectivity with the amygdala and the periaqueductal gray matter (see Fenster, Lebois, Ressler, & Suh, 2018). PTSD+DS is not limited to the fear system, however, and is characterized by alterations in a range of brain areas that

mediate, for example, sensory integration and own-body processing, which may help explain the subjective experience of dissociation. These areas include the temporal lobe, the cerebellum, and the periaqueductal gray matter (Daniels, Frewen, Théberge, & Lanius, 2016; Harricharan et al., 2016; Rabellino, Densmore, Théberge, McKinnson, & Lanius, 2018).

Approximately 16–45% of patients with PTSD present with the dissociative subtype (Frewen, Brown, Steuwe, & Lanius, 2015; Hansen, Ross, & Armour, 2017; Kim et al., 2019; Müllerová, Hansen, Contractor, Elhai, & Armour, 2017; Tsai, Armour, Southwick, & Pietrzak, 2005; Wolf, Luney, & Schnurr, 2016). Varying definitions of trauma and dissociation have led to heterogeneous findings, but generally a trend suggests greater illness severity, and more complex trauma history (larger number of traumatic events and earlier age of first exposure) (Hansen et al., 2017). Some studies suggest that PTSD+DS represents a similar phenotype to what is captured in the ICD-11 as complex PTSD, involving emotion dysregulation, negative views of self, and impairments in interpersonal relationships (Frewen et al., 2015). Additionally, while this is not captured in the DSM-5 criteria, PTSD+DS is characterized not just by depersonalization/derealization, but by a wide range of dissociative symptoms that do not only occur in the presence of traumatic cues. Such symptoms include trance, gaps in awareness, and memory disturbances (Armour, Contractor, Palmieri, & Elhai, 2014; Frewen et al., 2015; Ross, Banik, Dědová, Mikulášková, & Armour, 2018).

Overall, exposure-based treatments such as prolonged exposure and cognitive-processing therapy have the most evidence in PTSD. Multiple studies have found no difference in response rates between PTSD and PTSD+DS (Burton, Feeny, Connell, & Zoellner, 2018; Resick, Suvak, Johnides, Mitchell, & Iverson, 2012; Wolf et al., 2016). Patients with PTSD+DS, however, have been found in some studies to both begin and end treatment with a higher overall burden of symptoms, though they experience a similar magnitude of response to treatment (see, e.g., Hagenaars, van Minnen, & Hoogduin, 2010). Some experts have suggested a role for multicomponent treatments that focus on stabilizing dissociation prior to exposure therapy, though research is limited. One study found that while baseline dissociation did not moderate treatment outcome at the end of treatment, only those with PTSD+DS who received both components continued to make gains at posttreatment follow-up (Cloitre, Petkova, Wang, & Lu Lassell, 2012). Other research points to the role specific components of dissociation may play in treatment, such as state dissociation during the therapy session itself (Kleindienst et al., 2016).

DISSOCIATION AND INFORMATION PROCESSING

While the underlying cognitive mechanisms of dissociation have not always been the primary focus of empirical work (Dorahy & Green, 2019), we highlight some information-processing approaches because better understanding of mechanisms underlying dissociation promises to inform interventions. Dissociation has long been implicated in trauma-related memory disruption. Betrayal trauma theory predicts that dissociating information from awareness is mediated by the threat that the information poses to the individual's system of attachment (Freyd, 1996). With few exceptions (see Zurbriggen & Becker-Blease, 2003), links between closeness or dependence in the victim–offender relationship and memory of abuse have been documented in multiple datasets (e.g., DePrince et al., 2012; Freyd, DePrince, & Gleaves, 2007; Schultz, Passmore, & Yoder,

2003). Betrayal and dissociation have also been linked across datasets (e.g., Plattner et al., 2003; DePrince, 2005; DePrince, Chu, & Pineda, 2011).

Phenomenologically, dissociation involves alterations in attention and memory; thus, basic cognitive processes involved in attention and memory may play a role in dissociating explicit awareness of traumas (see Brewin & Vasterling, Chapter 7, this volume). Laboratory tasks link dissociation with alterations in basic cognitive processing (e.g., Becker-Blease, Freyd, & Pears, 2004; DePrince et al., 2012; DePrince, Weinzierl, & Combs, 2009) and provide evidence that dissociation is linked with less awareness of trauma-related information under some conditions (see also Moulds & Bryant, 2002). Although dissociation may be one route to memory impairment, many routes exist. For example, trauma memories may be impaired because of incomplete, unelaborated, or fragmented encoding. Alternatively, forgetting may occur as a by-product of rehearsing new related information without invoking dissociative processes (see Anderson et al., 2004).

Another line of research focuses on memory in individuals diagnosed with dissociative identity disorder (DID) and other dissociative disorders, including examinations of working memory (e.g., Dorahy, McCusker, Loewenstein, Colbert, & Mulholland, 2006), as well as interidentity amnesia in DID (e.g., Huntjens, Verschuere, & McNally, 2012; Marsh et al., 2018). Taken together, the advancement of the use of cognitive methods to examine dissociation, memory, and attention points to exciting discoveries that prime growing literature on intervention for trauma-induced dissociation.

CURRENT STATE OF THE ART

The march toward the 2013 publication of DSM-5 and the 2018 working form of ICD-11 brought renewed focus on trauma-related dissociation. Dissociative symptoms have been and remain a core feature of PTSD in DSM-5 and ICD-11. Yet, debates about the relevance, viability, and clinical utility of a stand-alone complex PTSD diagnosis for DSM-5 (see the special section on "complex PTSD" in Volume 25, issue 3, of the *Journal of Traumatic Stress,* 2012) fueled efforts to understand the connection between dissociation and more complicated manifestations of posttrauma pathology (Dalenberg & Carlson, 2012). Dissociation had been central to the initial formulation of complex PTSD (Ford, 2009; Herman, 1992) and the empirical work that followed it (e.g., Dorahy et al., 2013; Pelcovitz et al., 1997; Zucker, Spinazzola, Blaustein, & van der Kolk, 2006). The DSM-5 working group for the trauma disorders weighed multiple issues before deciding not to proceed with the inclusion of a formal diagnosis of complex PTSD (Friedman, 2013). Because of strong evidence that a significant minority (15–30%) of individuals with PTSD did experience dissociative symptoms in the form of depersonalization and/or derealization, a dissociative subtype was added to DSM-5 (see Friedman et al., Chapter 2, this volume). Research shows that those with depersonalization/derealization in addition to PTSD symptoms are more likely to have earlier and more severe trauma histories and a more complicated symptom presentation (e.g., Armour, Elklit, Lauterbach, & Elhai, 2014; Stein et al., 2013; Steuwe, Lanius, & Frewen, 2012; Wolf et al., 2012).

ICD-11 included a complex PTSD diagnostic category as a stand-alone disorder (i.e., not a specifier or subtype of PTSD; Brewin et al., 2017) in its working draft, which awaits ratification and formal implementation in 2022. While DSM-5's dissociative specifier of PTSD and the ICD-11's complex PTSD both require the presence of a PTSD

diagnosis, complex PTSD in the ICD reflects a more diverse symptom presentation that goes beyond depersonalization and derealization. Consequently, empirical work associated with validating the ICD-11 complex PTSD category has been less focused on dissociative symptoms specifically. For a diagnosis of complex PTSD, the symptoms of PTSD are augmented with severe and ensuring symptoms associated with (1) affect dysregulation, (2) negative beliefs about self, and (3) relationship difficulties. Dissociative symptoms of numbing, depersonalization, and derealization characterize the symptoms captured under affect dysregulation. Scales designed to assess the ICD-11 complex PTSD constellation have a small number of dissociative items (e.g., derealization, emotional numbing) among the other symptoms assessed (e.g., Complex Trauma Inventory [Litvin, Kaminski, & Riggs, 2018]; International Trauma Inventory [Cloitre et al., 2018; Cloitre, Roberts, Bisson, & Brewin, 2015]). In short, trauma-related dissociation is evident in the trauma disorders of both DSM-5 and ICD-11. Beyond the core dissociative symptoms of PTSD in both classification systems, like flashbacks, the DSM-5's dissociative PTSD is characterized by the presence of depersonalization and/or derealization, while complex PTSD in the ICD-11 has dissociative symptoms that are present, though less visible, among the broader array of diagnostic symptom clusters.

CHALLENGES FOR THE FUTURE

With continued work toward conceptual clarity about the operationalization of dissociation comes the promise of increased capacity to identify dissociative developmental pathways and mechanisms. Generalizability of findings remains limited due to definitional and measurement challenges. For example, findings based on a continuum view of dissociation may or may not fully generalize to pathological dissociation. With increased precision in defining and measuring dissociation, we reduce the risk of pathologizing experiences that include alterations in consciousness that do not involve structural dissociation (e.g., trance or religious experiences not viewed as pathological in their cultural context).

Further exploration is needed regarding the implementation of standard exposure therapies in dissociative patients, including whether patients with high levels of dissociation or particular dissociative profiles require phase-oriented therapy consisting of stabilization of dissociative symptoms prior to exposure (e.g., Blue Knot Foundation, 2019) or not (De Jongh et al., 2016). Dissociation symptoms in PTSD can vary from absorption, derealization, and persistent emotional numbing to ego-dystonic episodes of depersonalization (e.g., not recognizing oneself in the mirror; experiencing body movements as outside willed control), chronic trance states, analgesia, ongoing flashbacks, body pain, auditory hallucinations, and amnesia. Given this complexity, dissociation has been defined and measured differently across the treatment-response literature, making it difficult to determine which aspects of dissociative symptomatology should be assessed and addressed in treatment in order to characterize the impact of dissociation on treatment response. The role of state versus trait dissociation and the presence of dissociation during therapy sessions have been raised as relevant to clinical considerations, as has the need for longer-term follow-up to assess durability of treatment gains in this population (Cloitre et al., 2012; Kleindienst et al., 2016; Price, Kearns, Houry, & Rothbaum, 2014).

Future research should leverage understudied dissociation correlates as well as emerging areas of study. For example, constructs that may (or may not) be dissociative

in nature, such as alexithymia, have not yet been included routinely in analyses. Alexithymia is the inability to label emotions, a phenomenon that may be consistent with the lack of integration observed in dissociation. Recent research also suggests that posttraumatic appraisals—and in particular alienation—distinguish individuals diagnosed with DID from PTSD (DePrince, Huntjens, & Dorahy, 2015). Alienation, defined as feeling disconnected from self and others, was more strongly related to DID. While concepts about the structure of the self are common in descriptions of dissociation and theory about definitions, research has less frequently focused on measuring concepts of self. Better understanding of concepts of self and others in relation to trauma-induced dissociation may have implications for treatment.

As researchers and clinicians improve definitions of dissociation and deepen understanding of related issues (alexithymia, alienation), we will be in a better position to evaluate the relationship between dissociation and other psychiatric phenomena. With more precise definitions and measurement of dissociation, researchers can begin to untangle the complicated picture of comorbidity between dissociation and other forms of trauma-related distress (see Dalenberg & Carlson, 2012; Simeon, 2007).

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CHAPTER 9

Examining Neurocircuitry and Neuroplasticity in PTSD

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A vast literature demonstrates that traumatic stress has deleterious effects on the brain; however, the precise mechanisms through which these neural alterations occur is not fully elucidated. Neurocircuitry and neuroplasticity have been identified as critical components in determining an individual's stress tolerance and response (Abdallah, Averill, Akiki, et al., 2019; Abdallah, Southwick, & Krystal, 2017; Akiki, Averill, & Abdallah, 2017; L. A. Averill et al., 2017; Kamiya & Abe, 2020; Sheynin & Liberzon, 2017). In this abridged review, we present selected current data concerning neurocircuitry and neuroplasticity in trauma-exposed samples; review traditional intertwined circuitry-based models of posttraumatic stress disorder (PTSD) focused on fear learning/processing, contextual processing, and emotional regulation; discuss a network-based model of PTSD grounded in synaptic dysconnectivity and the vicious cycle of chronic stress pathology; review considerations regarding the generalizability of findings; and discuss challenges and future directions. For reference, we provide a list of abbreviations for potentially less commonly known abbreviations (see Figure 9.1).

STATE-OF-THE-ART NEUROBIOLOGICAL EVIDENCE

Neurons and the Impact of Trauma-Induced Synaptic Loss and Dysconnectivity

Considerable evidence, gathered from both preclinical and clinical investigations, suggests that traumatic stress influences the connections between the 86 billion neurons in the average adult human brain, with respect to information processing and transmission (Abdallah, Southwick, & Krystal, 2017). Neurons communicate with one another through chemical connections called synapses, with each neuron suspected to have as many as 10,000 synapses. Primary brain functions, then, are thought to

ABP	Amino acid-based pathology
ACC	Anterior cingulate cortex
AMPAR	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF	Brain-derived neurotrophic factor
CEN	Central executive network
CSP	Chronic stress pathology
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
fMRI	Functional magnetic resonance imaging
GM	Gray matter
ICN	Intrinsic connectivity network
lPFC	Lateral prefrontal cortex
MBP	Monoamine-based pathology
MDMA	3,4-Methylenedioxymethamphetamine
mPFC	Medial prefrontal cortex
sMRI	Structural magnetic resonance imaging
NAc	Nucleus accumbens
NMDAR	*N*-methyl-D-aspartate receptor
PET	Positron emission tomography
PFC	Prefrontal cortex
pgACC	Pregenual anterior cingulate cortex
PTSD	Posttraumatic stress disorder
RAAD	Rapid-acting antidepressant effect
RAAS	Rapid-acting anti-suicidal effect
sgACC	Subgenual anterior cingulate cortex
SNRI	Selective norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
SN	Salience network
vmPFC	Ventromedial prefrontal cortex

FIGURE 9.1. List of abbreviations.

be fundamentally dependent on a sufficient number of synaptic connections, between neurons, supporting the efficient flow of information. A phenomenon referred to as synaptic plasticity, is the continuous process of change and adaptation of synaptic connections based on day-to-day biopsychosocial experiences, with each new experience or insult/injury potentially sparking the formation of new or removal of old synaptic connections (Abdallah, Southwick, & Krystal, 2017). Although the brain generally works as a whole unified unit, distinct and specific brain regions are implicated in distinct and specific functions. When multiple brain regions are highly interconnected, a neural circuit is formed, such as the limbic circuit that is composed of the hippocampus, amygdala, and prefrontal cortex (PFC). Thus, connectivity between brain regions is critical to balanced, effective, and efficient circuits that can support adaptive cognitive function, behavior, and emotion regulation (Sheynin & Liberzon, 2017).

Neural Circuitry Underlying Fear Learning, Processing, and Extinction

PTSD is associated with deficits in fear extinction, increased fear generalization, negative bias toward viewing threat from neutral stimuli, and, relatedly, feeling danger in safe environments (Kamiya & Abe, 2020; Milad et al., 2009; Sheynin & Liberzon, 2017). Studies suggest that patients with PTSD exhibit hyperactive amygdala and anterior cingulate cortex (ACC) and hypoactive hippocampus and ventromedial PFC (vmPFC) activity (Abdallah, Averill, Akiki, et al., 2019; Abdallah, Southwick, & Krystal, 2017; Kamiya & Abe, 2020; Milad et al., 2009; Sheynin & Liberzon, 2017). More specifically, it is suspected that the amygdala processes sensory stimuli sent from the thalamus and immediately coordinates a response to perceived threat by alerting the basal ganglia, hypothalamus, and brainstem (Sheynin & Liberzon, 2017). The amygdala also works in tandem with the ACC and insular cortex to perform general threat detection by reviewing salient cues in the internal and external environment. It is further suspected that the PFC exerts some top-down control over the amygdala to aid in appropriate fear learning (Sheynin & Liberzon, 2017) and that decreased connectivity between the mPFC and basolateral amygdala may underlie problems with generalization of fear (Morey et al., 2015).

Although a great deal of evidence suggests the critical role of fear learning and processing, the mechanisms through which trauma exposure induces dysregulated fear and impaired extinction are not yet determined. Moreover, effective psychopharmacological interventions for PTSD (and other stress-related disorders without known fear dysregulation) are antidepressants, which are believed to reverse or normalize stress- and trauma-induced synaptic loss and dysconnectivity (Abdallah, Sanacora, Duman, & Krystal, 2015; L. A. Averill et al., 2017), rather than directly targeting fear. In fact, drugs that target fear (e.g., D-cycloserine) have been largely unsuccessful so far (L. A. Averill et al., 2017), raising concern as to whether fear is the optimal target for novel drug development.

Neural Circuitry Underlying Contextual Processing

Evidence from empirical investigations and clinical interactions have repeatedly demonstrated that a reaction to a stressor is dependent on each individual's unique and subjective interpretation and appraisal of the event and that abnormalities in contextual processing have been noted in PTSD (Averill, Averill, Kelmendi, Abdallah, & Southwick, 2018; Garfinkel & Liberzon, 2009; Kamiya & Abe, 2020). The hippocampus

has been a key brain region studied relative to contextual processing and is thought to interact with the mPFC to regulate contextually based fear learning, generalization, and extinction (Kamiya & Abe, 2020; Maren, Phan, & Liberzon, 2013; Sheynin & Liberzon, 2017). Studies have also suggested reduced activity in the vmPFC and increased activity in the dorsal ACC during contextual processing (Sheynin & Liberzon, 2017), as well as associating extinction recall with increased activity in the ACC and decreased activity in the hippocampus and mPFC (Garfinkel & Liberzon, 2009; Milad et al., 2009). Disruption or dysfunction in the context processing circuitry may cause maladaptive or inappropriate interpretations of events, rigid or inflexible perceptions, and emotional and behavioral responses, and it may ultimately contribute to the development of PTSD (Liberzon & Abelson, 2016; Maren et al., 2013; Shalev, Liberzon, & Marmar, 2017). It is interesting to consider pharmacological and behavioral interventions for PTSD as they relate (or not) to contextual processing. Psychopharmacologic interventions for PTSD that are currently in use do not directly target context processing; however, two of the gold-standard psychotherapeutic interventions for PTSD—cognitive processing therapy (Resick, Monson, & Chard, 2017) and prolonged exposure therapy (Foa, Hembree, & Rothbaum, 2007)—rely heavily on collaborative efforts between therapist and patient to adjust maladaptive thoughts, emotional responses, and behaviors based on potentially false, incomplete, or inappropriate contextual perceptions and interpretations. An investigational approach that may be targeting contextual processing that has shown promising results is 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy, currently in Phase 3 clinical trials for PTSD (Mithoefer et al., 2018).

Neural Circuitry Underlying Emotion Regulation

Emotion regulation plays a key role in adaptive and resilient reactions to trauma exposure, and dysregulated emotional reactions (e.g., significant over- or underreactions), impulsivity, irritability are commonly seen in PTSD (Kamiya & Abe, 2020; Liberzon & Abelson, 2016; Shalev et al., 2017). Evidence supports a prefrontal–subcortical circuit of emotion regulation in which it is suspected that decreased amygdala activation reflects top-down modulation of the emotional salience of any given stimuli, while the PFC maintains cognitive control by aiding in interpretation (Buhle et al., 2014; Sheynin & Liberzon, 2017). It is suspected that trauma-induced prefrontal neural alterations may underlie the onset, worsening, or maintenance of PTSD and that deficits in this brain region include executive impairment (e.g., attention, impulsivity, inhibitory function) that can interact with connections between dorsal and ventral cortical systems and emotional and trauma-related contexts (Sheynin & Liberzon, 2017). Decreased activity in the dorsolateral PFC (dlPFC) has been implicated in dysregulated or impaired working memory, behavior, and cognitive and emotional control (Koch et al., 2016; Patel, Spreng, Shin, & Girard, 2012). Cognitive reappraisal of aversive stimuli has been associated with increased activation of the dlPFC and dmPFC and parallel decreased activation of the amygdala and medial orbitofrontal cortex (Buhle et al., 2014; Sheynin & Liberzon, 2017). Regarding pharmacological and psychotherapeutic interventions, as with fear and contextual processing, no medications used in the treatment of PTSD target emotion regulation specifically. However, similar to fear and context processing, the commonly used trauma-focused psychotherapeutic treatment approaches target emotion regulation to some extent through supporting adaptive cognitive reappraisal and attention control (Abdallah et al., 2019a).

THE SYNAPTIC MODEL OF TRAUMA RESPONSE

Although brief (minutes-to-hours) stress responses may enhance plasticity, improve cognition, and promote resilience (Yuen et al., 2009, 2011), chronic exposure to inescapable or unmanageable stressors is often associated with chronic (days-to-weeks) stress responses that are detrimental to the brain. These responses can include reductions in prefrontal glutamatatergic synaptic strength (affecting both *N*-methyl-D-aspartate [NMDA] and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptors). with sustained elevations in extracellular glutamate (Abdallah, Sanacora, Duman, & Krystal, 2018), often in parallel with behavioral disturbances (McEwen, 2017; Yuen et al., 2012). Animal models of stress have shown that chronic stress pathology-related behavioral alterations and neuronal synaptic loss are evident within days to weeks of traumatic stress and are reversible within 2–4 weeks after removing the stressor (McEwen, 2017; Popoli, Yan, McEwen, & Sanacora, 2012). Depending on the brain region, traumatic or repeated stressors induce neuronal remodeling consistent with both reduced and increased synaptic connectivity. These chronic stress pathology-related reductions in synaptic connectivity have been mostly demonstrated in the PFC and the hippocampus, while the increases in synaptic connectivity were most evident in the nucleus accumbens (NAc) and the basolateral amygdala (McEwen, 2017; Russo & Nestler, 2013).

In the PFC and hippocampus, prolonged stress responses have been associated with disruption in glucocorticoid signaling, increased neuroinflammation, reduced brain-derived neurotrophic factor (BDNF), and induced astrocytic deficits, along with reduced uptake of synaptic glutamate, leading to increased extracellular glutamate and excitotoxicity (Abdallah, Sanacora, et al., 2015; Duman & Aghajanian, 2012; Sanacora & Banasr, 2013). Prolonged stress responses, in particular, maintain a paradoxical increase in extracellular glutamate despite a considerable reduction in glutamate neurotransmission, NMDA and AMPA receptors, and synaptic strength (Banasr et al., 2010; S. X. Li et al., 2017; Yuen et al., 2012). These molecular changes precipitate neuronal atrophy consistent with reduced dendritic length and arborization, and reduction in synaptic density and strengths. In preclinical studies, this synaptic loss and hypoconnectivity is directly associated with behavioral abnormalities, consistent with mood and anxiety dysregulation (Duman, Aghajanian, Sanacora, & Krystal, 2016; McEwen, 2017). Moreover, these chronic stress pathology-related behavioral disturbances are normalized following the reversal of the synaptic deficit, by both slow-acting antidepressants (SAADs; e.g., traditionally available antidepressants such as selective serotonin reuptake inhibitors [SSRIs]) and rapid-acting antidepressants (RAADs; e.g., ketamine) (Hare, Ghosal, & Duman, 2017).

Chronic stress pathology is further associated with functional and structural changes consistent with reduced synaptic connectivity in the medial amygdala, but increased BDNF and synaptic connectivity in the basolateral amygdala (Bennur et al., 2007; Lakshminarasimhan & Chattarji, 2012). Notably, a single stressor is sufficient to upregulate BDNF in the basolateral amygdala, which is evident one day post-stress and persists 10 days or more (Lakshminarasimhan & Chattarji, 2012). The single stressor also induces a gradual increase in basolateral amygdala synaptogenesis over a 10-day period, which is paralleled by a gradual increase in anxiety-like behavior (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005). Moreover, while the hippocampal/PFC synaptic loss, downregulation of BDNF, and related behavioral disturbances recover within 2–4 weeks of withholding the stressor, the basolateral amygdala synaptic hyperconnectivity,

upregulation of BDNF, and related anxiety-like behavior require a longer recovery time (Lakshminarasimhan & Chattarji, 2012). In the NAc, chronic stress pathology is also associated with neuronal hypertrophy, including increased BDNF, dendritic length and branching, and synaptic density and strength (Chaudhury et al., 2013; Walsh et al., 2014; Wook Koo et al., 2016). Similarly, the NAc hypertrophy is associated with anxiety-related behavioral impairment and is reversed by both SAADs and RAADs (Melo et al., 2015; Russo & Nestler, 2013).

INTRINSIC CONNECTIVITY NETWORKS AND THE TRIPLE-NETWORK MODEL

As above, the overwhelming majority of brain-based research in PTSD to date has focused on alterations in a three-region frontolimbic model that includes the hippocampus, amygdala, and PFC, including the chronic stress pathology model described above. As technology and science forge ever onward (Nemati et al., 2019), it has become quite clear that our understanding of the scope of functional disturbances will benefit from a more inclusive and encompassing approach that investigates the many neurocircuitry complexities associated with PTSD. Recently, compelling work suggests that the brain is organized into functionally distinct networks with a high degree of intrinsic connectivity—referred to as intrinsic connectivity networks (ICNs; Akiki & Abdallah, 2019; Yeo et al., 2011). Mounting evidence suggests large-scale network alterations in PTSD that extend beyond the aforementioned circuit-based models of PTSD and that focus primarily on three networks. This unifying *triple-network model* (see Figure 9.2) (Akiki, Averill, & Abdallah, 2017; Menon, 2011) is composed of the default mode

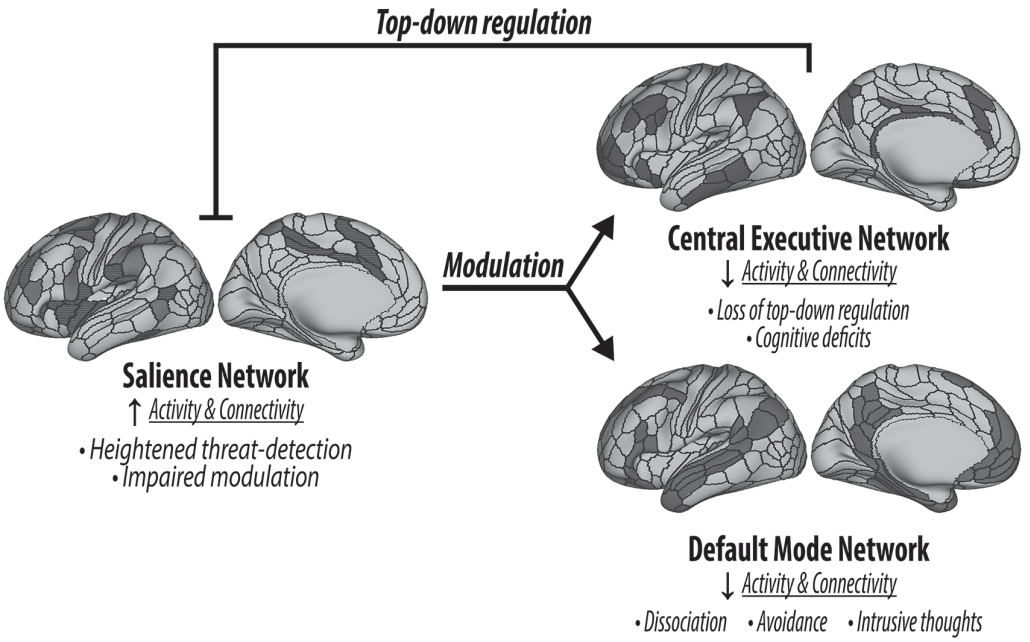

FIGURE 9.2. A proposed triple-network model of PTSD. Adapted with permission from the Emerge Research Program (*emerge.care*).

network (DMN), central executive network (CEN), and salience network (SN). Similar to the synaptic model of chronic stress pathology, the triple network model is not specific to PTSD, but rather to a broad range of psychopathological presentations (Menon, 2011).

Figure 9.2 portrays representations of the SN, CEN, and DMN. The gray-shaded regions depict the specific brain regions involved in each network. It is suspected that alterations within and between these three networks may underlie the psychopathology of PTSD. The SN comprises primarily the dorsal ACC, amygdala, and insula. Within PTSD, the SN demonstrates both increased activity and intrinsic connectivity and is implicated in heightened threat-detection/hyperarousal and impaired modulation of the CEN and DMN. The CEN is composed primarily of the dorsolateral prefrontal cortex (dlPFC) and precuneus. Within PTSD, the CEN demonstrates both decreased activity and intrinsic connectivity and is implicated in cognitive impairment (primarily executive functions) and loss of top-down SN regulation. The DMN is composed primarily of the vmPFC, posterior cingulate cortex, and medial temporal lobe/hippocampus. In PTSD, the DMN demonstrates both decreased activity and intrinsic connectivity and is implicated in internal processes such as intrusions and reexperiencing, dissociative symptoms and altered sense of reality, and fear generalization and avoidance.

Default Mode Network

The DMN is perhaps the most robustly identifiable network, spanning important regions in the posterior cingulate cortex, mPFC, and medial temporal lobe, including the hippocampus (Buckner, Andrews-Hanna, & Schacter, 2008). This network is known to engage in self-referential, introspective processes, and autobiographical memory. Consistent with its function, it is most active at rest and hypoactive during goal-oriented tasks. In individuals with PTSD, the DMN is known to be hypoactive and weakly interconnected (Akiki, Averill, & Abdallah, 2017; Sripada et al., 2012), which is thought to parallel symptoms of dissociation, avoidance, and intrusions (Akiki, Averill, & Abdallah, 2017; Menon, 2011).

Resting-state functional connectivity studies have shown reduced coupling between known structures of the DMN in PTSD that appear to correlate with symptom severity (Bluhm et al., 2009; Sripada et al., 2012). The anterior part of the hippocampus is implicated in stress response, emotion-related memory, and pattern completion and is mediated via strong connections to the amygdala (Kishi, Tsumori, Yokota, & Yasui, 2006; Strange, Witter, Lein, & Moser, 2014). The posterior portion, anchored in the DMN proper, is thought to be more involved in spatial functions and pattern separation (Buckner et al., 2008; Strange et al., 2014). Focused structural alterations have been described in the literature, with evidence of shape and volume alterations in the anterior hippocampus (Akiki, Averill, Wrocklage, et al., 2017; Vythilingam et al., 2005), and particular hippocampal subfields (C. L. Averill et al., 2017; Pitman et al., 2012; Wang et al., 2010). A pattern of functional dysconnectivity between the anterior hippocampus and the rest of the brain is also an emerging finding (Abdallah, Wrocklage, et al., 2017). A positive response to therapy has been linked to normalization of DMN abnormalities. For example, a trial of paroxetine showed increased hippocampal volume posttreatment linked with overall PTSD symptom improvement (Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003). Furthermore, psychotherapy studies have reported treatment-induced normalization in structural changes in the ACC (Dickie, Brunet, Akerib, & Armony, 2013; Helpman et al., 2016) and hippocampus (Rubin et al., 2016).

Central Executive Network

The CEN—known to engage in goal-directed behavior and top-down regulation of emotions—is anchored primarily in the dlPFC with core regions in the middle frontal gyrus, precuneus, and portions of the premotor cortex (Akiki & Abdallah, 2019; Menon, 2011). Dysconnectivity in the CEN is thought to mirror a loss of modulation over fear/threat-detection circuits and deficits in cognition and executive function. Within PTSD, there is evidence of weaker functional connectivity within the CEN, between the premotor cortex and middle frontal gyrus (with increasing trauma exposure), and between the premotor cortex and parietal cortex/middle frontal gyrus (with increased PTSD symptom severity) under emotional tasks (Cisler, Steele, Smitherman, Lenow, & Kilts, 2013). The middle frontal gyrus shows hypoactivity both at rest (Koch et al., 2016) and across several cognitive-emotional tasks (Patel et al., 2012). These findings have been paralleled in the structural magnetic resonance imaging (sMRI) literature, with evidence showing reduced middle frontal gyrus thickness in PTSD (L. Li et al., 2014; Wrocklage et al., 2017). In contrast, other regions such as the precuneus may be hyperactive under emotional tasks (Patel et al., 2012). Connectivity between the CEN and DMN appears to be critical in treatment response (King et al., 2016). Enhanced connectivity in the CEN was noted following completion of cognitive processing therapy (CPT; Resick et al., 2017) and related improvement in PTSD symptoms (Abdallah et al., 2019a). In a longitudinal study of trauma victims, increased dlPFC thickness was found after trauma and was linked to improved PTSD symptom reduction (Lyoo et al., 2011).

Salience Network

The SN has important nodes in the insula, the dorsal anterior cingulate cortex, and possibly the amygdala. The SN is implicated in the response to subjective salience and arbitrates between the CEN (task-positive) and DMN (task-negative; Akiki, Averill, & Abdallah, 2017; Goulden et al., 2014). Dysconnectivity in the SN is thought to impair this arbitration function, resulting in a low threshold for saliency and a hypervigilant state (Brown et al., 2014; Sripada et al., 2012). The dorsal ACC (dACC), unlike the ventral regions of the PFC, is hyperactive in PTSD (Patel et al., 2012), as is the amygdala. This is not surprising given the affiliation of the dACC to the SN (in contrast to the vmPFC, which is part of the DMN; Menon, 2011). In the insula, while there have been some mixed results with regard to its activity in PTSD (Abdallah et al., 2019b), a pattern is emerging where the anterior part shows increased activity at rest and under various emotional and cognitive paradigms, while the posterior insula is hypoactive (Koch et al., 2016; Patel et al., 2012). Structurally, the integrity of core elements of the SN has been shown to be altered in PTSD, for example, via gray matter (GM) alterations in the amygdala (Akiki, Averill, Wrocklage, et al., 2017; Morey et al., 2012) and GM reductions in the dACC (Meng et al., 2016; O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015). Furthermore, PTSD-related changes in the insula include decreased GM (Meng et al., 2016); decreased cortical thickness (Mueller et al., 2015; Wrocklage et al., 2017), fractional anisotropy (a measure of how much water is diffusing along a single or multiple directions in a given voxel; thought to reflect fiber density, axonal diameter, and myelination) in the white matter (Sun et al., 2013); and increased betweenness centrality (a measure indicating a node—such as the insula—is a hub/bridge for other nodes in the network) (Mueller et al., 2015).

Increased functional coupling, or seed-to-seed connectivity between paired regions of the SN, such as amygdala–insula (Rabinak et al., 2011; Sripada et al., 2012), and

amygdala–dACC (Brown et al., 2014), has been generally described in PTSD at rest. On the other hand, there is decreased connectivity between the dACC and the rest of the SN during an autobiographical memory task (St. Jacques, Kragel, & Rubin, 2013). Increased insula–hippocampus (Sripada et al., 2012) and amygdala–vmPFC (Brown et al., 2014) connectivity at rest have also been described and represent increased SN–DMN connectivity. Increased SN to CEN coupling was also evident in PTSD under a threat-processing paradigm (Rabellino et al., 2015). Increased functional coupling and hyperactivity within the SN at rest may indicate a state of "primed" saliency. In contrast, decreased connectivity between the dACC and the rest of the SN during an autobiographical memory task may indicate a weakened top-down inhibition function under challenge. Increased connectivity between the SN–DMN and SN–CEN, and SN–DMN dysmodularity leading to greater affinity of the amygdala to the DMN (i.e., a relative loss of the amygdala to the DMN) may reflect SN-initiated destabilization of the DMN and CEN. Considering the critical role of SN in arbitration between DMN and CEN, these findings suggest that an increased salience network connectivity in PTSD underlies the disruption in DMN and CEN, as well as their corresponding functions. Most importantly, targeting the SN overactivity may provide therapeutic benefit in reducing PTSD symptoms; for example, successful treatment was reported to normalize SN connectivity in soldiers suffering from PTSD (Abdallah et al., 2019a, 2019b).

GENERALIZABILITY OF FINDINGS

Generalizability of findings is always a concern in empirical studies, and replication does seem to be an issue in neurobiologically based PTSD research as well as other stress- and trauma-related disorders due, at least in part, to heterogeneity, in both the samples and the empirical methods. Careful documentation of eligibility criteria and related sample characteristics, behavioral assessment measures, and neuroimaging methods, including specific details regarding scanning sequences, procedures, and analysis methods, are critical to improved reproducibility. The careful investigation of possible biomarkers is paramount to the chances that we will better understand PTSD, and stress- and trauma-related psychopathology, more broadly. Chronic stress pathology appears to generalize well to the whole PTSD population. Considerable evidence supports the critical role this takes in the onset, worsening, and/or exacerbation of symptoms as well as neurobiological alterations. Furthermore, more recently a dual-pathology model has been proposed that seems to capture more fully the complexities and heterogeneity in both the samples and the empirical methods.

Chronic Stress Pathology and a Dual-Pathology Model

There may be two independent pathways in which chronic stress pathology interacts with characteristics of the stressor(s) and individual biopsychosocial predispositions to differentially affect synaptic connectivity in the PFC/hippocampus and amygdala/NAc (Abdallah, Averill, Akiki, et al., 2019; Abdallah et al., 2018; Akiki, Averill, & Abdallah, 2017; Averill, Averill, & Abdallah, 2019). First, the monoaminergic-based pathology (MBP) model posits that trauma- and stress exposure induce increases in catecholamine activity (i.e., adrenaline, noradrenaline, and dopamine). These increases simultaneously weaken dlPFC synaptic connectivity and strengthen neuronal activity in the amygdala and striatum, including localized NAc elevations in synaptic gain and BDNF (Arnsten,

2015; Chaudhury et al., 2013; Walsh et al., 2014; Wook Koo et al., 2016). There is also evidence of enhanced response to monoaminergic interventions such as SAADs and increased volume in the NAc (Abdallah et al., 2018; Abdallah, Jackowski, et al., 2015, 2017). The amino acid-based pathology (ABP) model proposes that prefrontal and hippocampal excitotoxicity and synaptic deficits may result in altered glutamatergic input in the amygdala and NAc, along with PFC amino acid impairment, resistance to monoaminergic SAADs, and GM reductions in the hippocampus and PFC (Abdallah, Averill, Akiki, et al., 2019; Abdallah, Jackowski, et al., 2017; Averill et al., 2019).

The dual-pathology model was initially proposed in the context of major depression (Abdallah, Jackowski, et al., 2015, 2017). However, various lines of evidence provide support for this model in PTSD. For example, it has been shown that individual characteristics dictate whether an animal is susceptible or resilient to a stressor without developing behavioral disturbances and NAc hypertrophy (Krishnan et al., 2007). Furthermore, animal studies have shown that the type and magnitude of a stressor determine the extent and nature of the dopaminergic response in the NAc (Holly & Miczek, 2016; Valenti, Gill, & Grace, 2012), and its related behavioral pathology, namely, the excitation or inhibition of reward and motivation (Chaudhury et al., 2013; Tye et al., 2013). Therefore, the stressor characteristics may dictate the pattern of biological injury and related behavioral abnormalities (Flandreau & Toth, 2018; Goswami, Rodriguez-Sierra, Cascardi, & Pare, 2013). Comparably, differing brain regions may have variable responses to a unique stress; for example, brief uncontrollable stress was found to induce synaptic loss in the infralimbic (mPFC, involved in extinction), but not prelimbic area (dorsal PFC, involved in fear acquisition) (Izquierdo, Wellman, & Holmes, 2006).

Similar to studies in depression, GM deficits have been found only in some, but not all cohorts of PTSD (Logue et al., 2018; Wrocklage et al., 2017). In fact, PTSD has been found to be associated with both amygdala hypertrophy and hypotrophy (Akiki, Averill, Wrocklage, et al., 2017; Kuo, Kaloupek, & Woodward, 2012; Morey et al., 2012), raising the possibility of a subgroup of PTSD with prominent MBP and synaptic gain compared to others with ABP and synaptic loss. Notably, the "vicious cycle" of chronic stress pathology suggests that initial MBP leading to behavioral disturbance, which further exacerbates the magnitude of the stressor, could eventually lead to ABP and synaptic loss. Thus, the discrepancy in the amygdala findings in PTSD may also reflect the time course of the disorder, with chronic suffering from severe PTSD leading to more prominent ABP and synaptic loss.

CHALLENGES AND FUTURE DIRECTIONS

Parallel to innovations in technology, the last two to three decades have supported a great influx of studies using neuroimaging techniques to advance knowledge of neurobiological mechanisms associated with PTSD. Despite these impressive advancements, a fine-grained understanding of the underlying neurobiology is yet to be elucidated, and available psychopharmacologic treatment options are limited, with only two approved medications—both of which are SAADs (Krystal et al., 2017).

While each of the various neurocircuitry and neuroplasticity models of PTSD discussed provides a framework to understand psychopathology, none fully accounts for all commonly noted clinical presentations, highlighting the considerable heterogeneity and multifaceted nature of this disorder and the critical need to continue pursuing data-driven exploratory methods. For example, there is great interest in the

endophenotypes of PTSD, including the dissociative subtype of the disorder. Neuroimaging studies using machine learning (Terpou et al., 2018) and network analysis (Cramer, Leertouwer, Lanius, & Frewen, 2020) have added important findings to the literature that help us understand the derealization and depersonalization that occur in PTSD. Future studies that combine behavioral data, multimethod neuroimaging data, and state-of-the-art analytic methods have great potential to advance our understanding of endophenotypes of PTSD, including integrating the subgroup stratification into the triple network model. Continued efforts to advance our understanding and to identify reliable and reproducible biomarkers will likely come from a combination of efforts including (but not limited to): continued MRI efforts to further explore neural connectivity and circuitry; molecular imaging such as positron emission tomography (PET) to elucidate neurochemical underpinnings; pharmacoimaging trials specifically aimed at exploring treatment response in parallel to neurobiological changes, and normalizations, such as the RAAD ketamine that may support mechanistically interventional biomarker development (Averill et al., 2019); and advanced technological and mathematical methods, such as machine learning, artificial intelligence (Nemati et al., 2019), network science, and continued work with animal models of chronic and traumatic stress (Fogaça & Duman, 2019; Girgenti, Hare, Ghosal, & Duman, 2017). The discovery of reliable biomarkers has significant potential to advance the field through identification of prospective treatment targets, supporting progress toward improved clinical management and better patient outcomes (Akiki, Averill, & Abdallah, 2017; Abdallah, Averill, Akiki, et al., 2019; Garfinkel & Liberzon, 2009). Biomarkers may also advance our understanding of brain-based risk factors that may be useful in detecting individuals who may be at elevated risk for deleterious, versus resilient responses to trauma exposure. Given the transdiagnostic nature of trauma and stress response, findings in PTSD may not only be beneficial for this specific population but could have positive implications for all stress- and trauma-related psychopathology, a constellation of symptoms afflicting millions across the globe.

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CHAPTER 10

Neurochemistry, Neuroendocrinology, and Neuroimmunology of PTSD

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Examination of the neurobiological processes associated with posttraumatic stress disorder (PTSD) over 35 years has allowed experts to conclude that no single dysregulated system characterizes PTSD, as defined by the symptom-based phenotype in the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association [APA], 2013). Rather, many biological systems, as well as components within each system, interact to optimize or diminish functional adaptation to traumatic stress. Furthermore, dysfunction within one or several of these systems may occur in different individuals with PTSD (e.g., Kim et al., 2020; Southwick et al., 1997). In addition, chronic, nontraumatic stress or injuries (e.g., traumatic brain injury [TBI]), as well as behaviors adopted to cope after trauma (e.g., social isolation vs. interpersonal reprocessing of trauma, psychoactive substance use vs. exercise) may impact these systems in ways that influence PTSD risk, severity, and trajectory.

The biological heterogeneity of PTSD and the consequent need for subpopulation-specific PTSD treatments thus have become evident. This means that scientific approaches to treatment target identification and treatment development itself must change. Exploring only linear associations and mean differences in our analytic models must give way to analytic approaches that capture the multiple random, as well as individual or subpopulation-specific nonrandom, factors that contribute to PTSD risk, severity, and treatment response. *In short, we must begin to delineate biological "endophenotypes" to which different treatment modalities can be targeted.*

There has been progress in this direction. Preclinical and clinical research has defined dynamic, interactive neurophysiological and molecular processes involved in the acute expression of PTSD symptoms—allowing us to better understand PTSD patients' general responses to stressors and trauma reminders, as well as the effects of a range of current treatments (e.g., psychotherapies and prescribed or self-adopted

psychotropics). Molecular processes underlying synaptic plasticity and neural connectivity changes induced by traumatic stress or modified during recovery also have been defined. Establishing links between these (1) quantifiable, higher-level neurobehavioral and cognitive phenomena pertinent across PTSD patients, and (2) underlying individually variable molecular processes will be important to define mechanism-based, treatment-relevant PTSD endophenotypes.

This review therefore explores the pathophysiology of PTSD at two organizational levels: brain regional activity and connectivity broadly relevant to PTSD acquisition and recovery, and the array of highly variable underlying molecular mediators and moderators that allow for multiple etiologies and pathogenic features of PTSD.

NEUROBIOLOGICAL RESPONSES TO TRAUMATIC STRESS

Stress Intensity and PTSD-Relevant Regional Brain Activity

Interactions between prefrontal cortex (PFC) and amygdala/anterior cingulate activation during stress govern the expression of PTSD symptoms (Pitman et al., 2012; see Averill et al., Chapter 9, this volume). In rodent models these interactions favor execution of the species-specific defense response (SSDR)—a set of highly conserved, reflexive sympathetic nervous system (SNS), cardiovascular, hypothalamic–pituitary–adrenal (HPA) axis, behavioral (fight, flight, freezing), and cognitive reactions devoted to survival. Activation of the SSDR is mediated by the amygdala, which activates brainstem monoaminergic inputs to the PFC, insula, nucleus accumbens, amygdala, hippocampus, and other brain regions to regulate these stress reactions (Goldstein, Rasmusson, Bunney, & Roth, 1996).

During *mild stress,* activation of high-affinity noradrenergic (NE) α_2 receptors in PFC allows finely discriminated sensory inputs and relevant experiential probabilities coded in the hippocampus to converge within the frontal lobe and inform executive decision making and guidance of behavior. During such mildly aroused states, the PFC can effectively inhibit the amygdala via glutamatergic pyramidal neuron projections to intra-amygdalar γ-aminobutyric acid (GABA)-releasing interneurons (Grace & Rosenkranz, 2002). In contrast, *intense threat* stimulates the amygdala to activate mesocortical monoamine neurons (Goldstein et al., 1996) more intensely, resulting in engagement of low-affinity norepinephrine (NE)-α_1, dopamine $(DA)_1$, and serotonin $(5\text{-}HT)_{2A}$ receptors in PFC. This interferes with PFC integration of sensory and hippocampus input, as well as PFC-mediated working memory, executive function, and inhibitory control of the amygdala (Arnsten, 2009). In the meantime, synapses on basolateral amygdala (BLA) neurons coincidentally activated by nonthreatening (i.e., "neutral") contextual stimuli are strengthened due to the intense co-activation of synapses on the same BLA neurons by "unconditioned threat stimuli" (US)—a process called *associative long-term potentiation* (LTP). Such unconditioned threat stimuli are rapidly routed to the amygdala through the thalamus (LeDoux, Romanski, & Xagoraris, 1989) or parabrachial nucleus, in the case of pain (Bernard & Besson, 1990). Subsequent exposure to the formerly neutral, but now "conditioned threat stimuli" (CS) can then trigger the full-blown SSDR (Goldstein et al., 1996)—or, in clinical parlance, PTSD reexperiencing symptoms.

The state of high arousal associated with the SSDR (during which access to current contextual information, experiential probability computations, working memory, and PFC inhibitory control of the amygdala may be unavailable) persists until high brain monoamine levels subside. This results from catabolism and synaptic reuptake

of released monoamines, as well as the production of negative feedback factors that inhibit further monoamine release (e.g., neuropeptide Y $[NPY]_{3\text{-}36}$, a metabolite of $NPY_{1\text{-}36}$, and GABA-ergic neurosteroids such as allopregnanolone [Allo]; Rasmusson & Pineles, 2018). Once monoamine levels subside, the processing of context-dependent "safety information" can proceed and the infralimbic PFC brake on the amygdala can reengage in the service of extinction (see below).

The amplitude and duration of aroused states stimulated by unconditioned and threat-conditioned stimuli (i.e., trauma reminders) are correlated, individually variable (even in inbred rodent species; Morrow, Elsworth, Rasmusson, & Roth, 1999), and magnified by *chronic* stress. Responses to trauma reminders thus range from aroused interest or mild discomfort along with thoughtful, modulated behavioral reactions to intense fear or terror and reflexive fight, flight, freezing, or dissociative reactions. As previously reviewed (Rasmusson & Pineles, 2018), intense or chronic stress sensitizes neurons of the amygdala central and basolateral nuclei to stimulation by other stressors, in part by (1) upregulating amygdala $5\text{-}HT_{2C}$ receptors, and (2) downregulating expression of GABA-synthesizing enzyme genes, NE-α_1 receptor-stimulated GABA release from BLA interneurons, expression of benzodiazepine-sensitive *synaptic* $GABA_A$ receptors, and synthesis of neurosteroids that positively modulate GABA effects at $GABA_A$ receptors. These processes reduce the signal-to-noise ratio of sensory inputs tightly associated with unconditioned threat stimuli vs. adventitious contextual stimuli—and thereby facilitate threat generalization and risk for chronic PTSD. However, while synaptic $GABA_A$ receptors are downregulated in amygdala, *benzodiazepine-resistant extrasynaptic* $GABA_A$ receptors are upregulated. These receptors are more sensitive than synaptic $GABA_A$ receptors to positive modulation by GABA-ergic neurosteroids (e.g., Allo) and ethanol. As they *tonically* reduce gain in the firing rate of stimulated neurons, their activation may be critical to modulating amygdala reactivity during recovery from traumatic stress.

Rodent studies indicate that high glucocorticoid and catecholamine responses during chronic stress reduce the plasticity of PFC–hippocampus circuits that inform context-specific defensive responding (Arnsten, 2009; Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007). In addition, even brief chronic stress induces dendritic atrophy in PFC neurons that subserve working memory and attentional set-shifting, although dendrites of infralimbic PFC pyramidal cells that project to the amygdala to inhibit defensive responding are preserved. This may facilitate the SSDR to threat-conditioned cues and promote immediate survival, while preserving capacities for extinction and stress recovery. Yet it also should be noted that acute, uncontrollable stress causes dendritic retraction in the infralimbic cortex and resistance to fear extinction (Izquierdo, Wellman, & Holmes, 2006). Together this work suggests mechanisms by which very high stress states experienced during trauma-focused psychotherapies for PTSD might diminish their efficacy.

The experience of high-amplitude, long-lasting stress states triggered by trauma reminders or other stressors is characteristic of severe PTSD and may be mediated by the dysregulation of several neurobiological systems referenced above and discussed below. In addition, tactical behaviors adopted by PTSD patients to quell intense conditioned stress reactions (e.g., social isolation; use of tranquilizers, tobacco, alcohol, opiates, or other drugs) are construed as avoidant symptoms of PTSD. These may inadvertently interfere with PTSD recovery by preventing the *necessary reactivation* of brain circuits to be modulated during recovery or by dysregulating neurobiological systems critical to modifying these circuits when activated. Genetic factors also modulate these

general stress responses to shift individual outcomes in the direction of risk or resilience (see Bustamante et al., Chapter 11, and Cohen & Mannarino, Chapter 20, this volume).

A Biological Perspective on PTSD Recovery

PTSD recovery is thought to involve reconfiguration of brain and peripheral nervous system circuits so that trauma reminders no longer trigger *intensely* distressing physiological, cognitive, and behavioral reactions that derail the individual from desired human interactions, rewarding daily activities, or necessary tasks. Effective treatments for PTSD include trauma-focused psychotherapies, such as cognitive processing therapy (CPT) or prolonged exposure (PE) (see Galovski et al., Chapter 19, this volume), and pharmacotherapy (see Davis et al., Chapter 23, this volume). Several factors may contribute to widely disparate responses to these therapies, however, including *genetic* (see Bustamante et al., Chapter 11, this volume) *and environmentally influenced neurobiological factors* that impact the reprocessing of trauma memories and consolidation of reconfigured neuronal circuits. Thus, a brief survey of these processes may point to individually variable pathophysiological factors that could be targeted for rectification.

Activation of a threat-related memory renders the memory "labile" and engages two competing processes: *extinction* and *reconsolidation* (Monfils, Cowansage, Klann, & LeDux, 2009), both of which may be exploited in the treatment of PTSD. *Extinction* relies on PFC inhibition of the amygdala-mediated SSDR, as well as acquisition and consolidation of new learning (e.g., the CS no longer signals threat in the new time–space context) (Pitman et al., 2012). Extinction thus involves both synaptic long-term depression (LTD) and LTP (Maren, 2015) and results in a progressive reduction in the magnitude of the SSDR upon repeated reexposure to the CS or mental representations of the US. During extinction, PFC inhibitory input to the BLA is restored by activation of infralimbic PFC pyramidal neuron noradrenergic β-receptors and resultant increases in protein kinase A (PKA) and protein synthesis (e.g., Mueller, Porter, & Quirk, 2008). In response to extinction, amygdala synaptic $GABA_A$ receptors downregulated during threat conditioning are reexpressed (Heldt & Ressler, 2007). Thereafter, *extinction recall* is accompanied by NMDA receptor–activated burst firing of infralimbic pyramidal neurons projecting to the BLA stimulated by convergent sensory and hippocampus-derived contextual information that defines the circumstances under which extinction should be recalled (Corcoran & Quirk, 2007).

Extinction thus reduces PTSD symptoms and improves function, but has limitations. Extinguished amygdala-mediated defense responses may be "renewed" in a new context, "reinstated" upon reexposure to the US, or "recovered spontaneously" over time (Monfils et al., 2009). Furthermore, PTSD is associated with deficits in extinction learning (e.g., Jovanovic, Kazama, Bachevalier, & Davis, 2012) and/or extinction recall/retention (Milad et al., 2008; Pineles et al., 2016). Reactivation of trauma circuits under conditions that do not promote extinction then may result in threat circuit reconsolidation or threat generalization.

Blockade of threat circuit reconsolidation—perhaps most specifically at the level of the amygdala—may constitute another mechanism by which recovery from PTSD may occur (Elsey, van Ast, & Kindt, 2018). In contrast to extinction, conditioned amygdala-mediated defense responses 'lost' after *reconsolidation blockade* are not subject to renewal, reinstatement, or spontaneous recovery, even though episodic memory for the unconditioned threat event remains. In rodents, protein synthesis inhibitors (too

toxic for humans), protein kinase A (PKA) inhibitors, and β-blockers (e.g., propranolol) prevent reconsolidation of threat memory-related defensive responses if given within an hour of *brief* threat memory reactivation. The latter two agents limit incorporation of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors into synapses, a prerequisite for memory consolidation and reconsolidation (Monfils et al., 2009). Some, but not all, human cognition studies have demonstrated blockade of episodic and aversive memory reconsolidation by propranolol (Elsey et al., 2018). PTSD symptoms also improved moderately in response to acute treatment with propranolol vs. placebo before trauma memory reactivation in a paradigm that appeared to combine reconsolidation blockade and extinction opportunities (Brunet et al., 2018).

Further work is thus needed to refine and translate our knowledge of these recovery mechanisms into reliable clinical interventions that may benefit individual PTSD patients.

SPECIFIC MOLECULAR SYSTEMS RELEVANT TO PTSD

Monoamines

There is evidence for sympathetic system hyperreactivity in many, though not all, individuals with PTSD (e.g., Southwick et al., 1997). Noradrenergic hyperreactivity may be a pre-trauma trait or develop with exposure to stress and contribute to negative emotional reactions (Neumeister et al., 2005) and the formation of durable trauma memories (Southwick et al., 2002). Factors that contribute to increased NE release in response to SNS activation in PTSD include genetic or stress-related decreases in NPY and decreased expression or affinity of NE-α_2 autoreceptors (Pitman et al., 2012). Factors that otherwise enhance amygdala reactivity also may increase NE responses to novelty and unconditioned or conditioned threat.

Some studies suggest that NE reactivity in PTSD patients with comorbid major depressive disorder (MDD) and/or chronic nicotine use is decreased (e.g., Yehuda et al., 1998). Recent smoking appears to suppress SNS hyperreactivity in PTSD (Familoni et al., 2016); smoking also increases inflammation, which decreases catecholamine synthesis (see below). Individual differences in NE reactivity may account for varied responses to adrenergic medications. Clinical probes of noradrenergic system reactivity thus may be useful in stratifying clinical trials or predicting treatment response to adrenergic drugs.

Much less research has been done on the DA system in PTSD because peripheral and central measures of DA system function correlate poorly. Nevertheless, rodent studies show that DA release in the amygdala promotes unconditioned and conditioned stress responding and thus may promote threat generalization (e.g., Rosenkranz & Grace, 2001) and PTSD risk. DA also mediates nucleus accumbens reward signaling, which appears to be decreased in PTSD (e.g., Elman et al., 2009), a phenomenon to which inflammation also may contribute (see below).

Neuropharmacological studies, treatment trials, and genetic epidemiological studies also support involvement of the 5-HT system in the pathophysiology of PTSD (Pitman et al., 2012). The only medications currently approved by the FDA for PTSD treatment are 5-HT selective reuptake inhibitors (SSRIs; see Davis et al., Chapter 23, this volume). However, SSRIs show only small to moderate effect sizes and marked individual variability in treatment response, Understanding subpopulation differences in the function of the 5-HT system or other neural systems influenced by 5-HT may help

with the targeting of these drugs. For example, women show greater stress-induced depletion of tryptophan, the amino acid precursor for 5-HT (Rasmusson & Friedman, 2002). SSRIs also may be useful in some individuals with noradrenergic system hyperreactivity, as 5-HT acting at 5-HT_{1A} receptors reduces glutamate activation of the locus coeruleus.

On the other hand, increasing synaptic 5-HT levels may worsen PTSD in some individuals. Meta-chlorophenylpiperazine (mCPP), which interacts with the 5-HT transporter to release 5-HT and acts as a potent direct agonist at $5\text{-HT}_{2A,}$ $5\text{-HT}_{2B,}$ and 5-HT_{2C} receptors, provoked anxiety, panic attacks, flashbacks, and other PTSD symptoms in about half of a cohort of medication-free male combat veterans with PTSD (Southwick et al., 1997). The capacity of phasic increases in 5-HT to increase PTSD symptoms is also supported by (1) the work of Harada, Yamaji, and Matsuoka (2008) showing that stress-induced increases in amygdala 5-HT_{2C} receptor gene expression contribute to conditioned contextual fear and (2) clinical trials showing that reductions in serotonergic activity at 5-HT_2 receptors may be associated with clinical improvement (Kennett et al., 1994; Villarreal et al., 2016). Furthermore, the efficacy of combined mirtazapine and paroxetine treatment in PTSD (Schneier et al., 2015) suggests that there may be therapeutic synergism in raising levels of 5-HT (and/or Allo, as discussed below) by SSRI administration, while antagonizing or downregulating 5-HT_{2A} receptors. It follows that rapid dose escalation of SSRIs in patients with upregulated 5-HT_2 receptors could worsen PTSD symptoms, including impulsive aggression (Burghardt, Bush, McEwen, & LeDoux, 2007).

Together, these findings suggest two different PTSD endophenotypes, one associated with a deficiency and one with an excess of serotoninergic activity. Future studies of medications that impact the 5-HT system thus should include biomarkers to help predict benefits and side effects.

GABA and Glutamate

PTSD has been associated in cross-sectional studies with decreased and increased resting plasma GABA levels and reactivity to laboratory stressors; there are also mixed findings for cortical GABA levels and GABA_A receptor benzodiazepine binding (reviewed in Hall et al., 2021; Rasmusson & Pineles, 2018). Prospective research findings also are mixed. One study demonstrated a link between low plasma GABA after trauma and PTSD risk (Vaiva et al., 2006). In contrast, a large, mostly male military cohort showed increases in plasma GABA levels between pre-deployment or 1-month post-deployment and 6 months post-deployment in association with increases in PTSD, depression, and other mental health symptoms (Schür et al., 2016). The relationship was stronger when individuals who started or stopped alcohol, medication, or tobacco over that time span were excluded. Thus, further research will be needed to resolve the discrepant relationships of GABA to PTSD.

Acute stress increases glutamate transmission in association with improvements in working memory. Chronic repeated stress, however, impairs glutamate neurotransmission in the PFC (Yuen et al., 2012)—perhaps related to chronic stress-induced inflammation and attendant increases in extrasynaptic glutamate (see below). Studies of glutamate in PTSD have been mixed. One study found high plasma glutamate levels in PTSD, but brain glutamate levels have been variable in PTSD subjects compared to trauma-exposed and unexposed healthy controls (Averill et al., 2017). Nevertheless, interest in the glutamate system in PTSD increased after FDA approval of ketamine, a

rapid-acting *N*-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of refractory MDD. Several clinical trials of acute ketamine administered alone or to augment psychotherapy are currently underway or have been recently completed in PTSD, yielding mixed results (*clinicaltrials.gov*; see Schnurr et al., Chapter 25, this volume). There also remains uncertainty about whether ketamine exerts its therapeutic effects by direct antagonism of the NMDA receptor or due to indirect stimulation of glutamate release and engagement of downstream mechanisms. Convergent downstream mechanisms implicated in the "therapeutic" effects of both glutamate-based NMDA receptor antagonists like ketamine and novel allosteric NMDA receptor complex modulators recently characterized in rodent models of stress and depression include brain-derived neurotrophic factor (BDNF) release, augmentation of TrkB-mTORC1 signaling, and increases in synapse formation. Insight into these mechanisms may eventually help identify individuals likely to benefit from such treatments, as well as spur development of new therapeutics with fewer acute side effects than ketamine (Duman, Shinohara, Fogaça, & Hare, 2019).

STEROIDS

Glucocorticoids

Given the critical role of cortisol in adapting to stress, researchers have studied cortisol regulation in PTSD extensively (Rasmusson & Pineles, 2018). Early studies revealed a pattern of low cortisol output and increased sensitivity to glucocorticoid negative feedback in some PTSD subpopulations, but other studies have shown no difference in cortisol levels or glucocorticoid feedback between subjects with and without PTSD, or increased cortisol levels and/or cortisol reactivity in PTSD. In a large, unselected, trauma-exposed cohort presenting to an emergency room, there were no differences in cortisol levels between those who did and did not develop PTSD up to 5 months later (Shalev et al., 2008).

While these data indicate that there is no single pattern of glucocorticoid system findings in PTSD, they do not preclude a role for the glucocorticoid system in the pathophysiology of PTSD in at least some subpopulations. The glucocorticoid system impacts energy availability during stress, regulates genes critical to longer-term stress adaptation, and plays a role in memory (Sandi, 2011). Low levels of glucocorticoids activate high-affinity mineralocorticoid receptors that increase presynaptic glutamate release and excitatory postsynaptic potentials, thus facilitating LTP. High levels of glucocorticoids (as occur during unconditioned and conditioned stress) activate low-affinity glucocorticoid receptors (GRs) that facilitate installment of AMPA receptors in neuronal synapses, thus enhancing their strength under conditions conducive to LTP—while the genomic effects of GR activation play out over hours to impact memory consolidation.

To more effectively evaluate the possible role of glucocorticoid system dysregulation in PTSD, study findings must be considered carefully within the context of experimental design and possible adventitious effects of individually variable pharmacological agents that alter HPA axis reactivity, cortisol metabolism, or brain GR expression or function (e.g., recent and chronic use of psychiatric medications, nicotine, and alcohol; Rasmusson, Vythilingam, & Morgan, 2003). The body fluid assayed (Baker et al., 2005) and the type of assay used to measure cortisol also may influence the findings. For example, lower cortisol levels measured by immunoassay predicted greater PTSD severity and poorer PE outcomes. However, when cortisol was measured instead by more

accurate mass spectrometry, low levels of a structurally similar but inactive cortisol metabolite synthesized by 5α-reductase predicted PTSD severity and PE outcome (see the next section of this chapter) (Yehuda, Bierer, Andrew, et al., 2009; Yehuda, Bierer, Sarapas, et al., 2009).

Once such confounds are addressed, we can have greater confidence in the relevance of findings to treatments that in the end must target glucocorticoid system dysregulation in individual patients. To illustrate the possibilities, Logue and colleagues (2015) found that most genes with increased or decreased expression in PTSD were normally downregulated or upregulated, respectively, by dexamethasone (a synthetic glucocorticoid)—suggesting a link between PTSD risk and *inadequate glucocorticoid signaling*. These findings could be accounted for by (1) reduced GR gene expression (Logue et al., 2015), (2) downregulation of intraceullular GR signaling whether or not GR expression is altered (e.g., Klengel et al., 2013), or (3) *inadequately* upregulated GR number or sensitivity (Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004) in the context of low cortisol levels (Yehuda, Halligan, Grossman, Golier, & Wong, 2002). Primary reductions in the expression or function of glucocorticoid-regulated neurobiological factors might also have contributed to the findings (e.g., Hou, Lin, & Penning, 1998; Kuo et al., 2007). Abnormal glucocorticoid-system function might also result from dysregulation of nonglucocorticoid-system factors (e.g., Allo; Barbaccia, Serra, Purdy, & Biggio, 2001). Development of clinical testing paradigms to more fully characterize glucocorticoid system dynamics in individual patients thus will be important to the targeting of possible glucocorticoid system-based therapeutics (e.g., Jovanovic et al., 2011; Zohar et al., 2011). Both human and rodent studies, however, suggest that the timing and dose of glucocorticoid administration may affect therapeutic outcomes (Rasmusson & Pineles, 2018).

GABA-ergic Neurosteroids

Extensive preclinical and clinical research extending from the discovery of Allo in the adrenal gland in 1938 to its characterization as a potent positive modulator of GABA effects at $GABA_A$ receptors in 1986, and its approval by the U.S. Food and Drug Administration (FDA) as a fast-acting treatment for postpartum depression (Paul, Pinna, & Guidotti, 2019) supports the promise of Allo-based therapeutics for the treatment of PTSD. In 2006, Rasmusson and colleagues demonstrated markedly reduced cerebrospinal fluid (CSF) levels of Allo and its equipotent stereoisomer pregnanolone (PA), measured together by gas-chromatography/mass-spectrometry, in women with PTSD. CSF Allo+PA levels also correlated negatively and strongly with PTSD reexperiencing and depressive symptoms. A decrease in the CSF ratio of Allo+PA to the immediate Allo precursor 5α-dihydroprogesterone (5α -DHP) suggested a block in synthesis of Allo and PA from progesterone at 3α-hydroxysteroid dehydrogenase (3α-HSD). Pineles and colleagues (2018) subsequently confirmed a PTSD-related reduction in the *plasma* ratio of Allo+PA to 5α-DHP in women during the early follicular and mid-luteal phases of the menstrual cycle. In contrast to healthy trauma-exposed women, women with PTSD also failed to increase this ratio in response to a moderately stressful differential fear-conditioning paradigm. Recent work in men also demonstrated a strong negative relationship between CSF Allo+PA levels and PTSD symptoms, although the apparent block in Allo synthesis was at 5α-reductase, not 3α-HSD (Rasmusson et al., 2019). This accords with work by Gillespie and colleagues (2013) identifying a PTSD risk polymorphism in the 5α-reductase II gene in men but not in women.

These findings in humans align with those in rodents with experimental Allo deficiency that show anxiety- and depression-like behaviors, aggression, enhanced contextual fear conditioning, poor extinction, and poor extinction retention (Rasmusson et al., 2017). It is thus notable that Pineles and colleagues (2020) report strong correlations between extinction retention and resting plasma Allo+PA levels in women with PTSD. Pinna and Rasmusson (2014) also showed that a single dose of ganaxolone (an Allo analogue) administered to Allo-deficient mice after a single brief extinction training session markedly increased rates of extinction and prevented spontaneous recovery of conditioned fear after extinction—suggesting a potential therapeutic role for GABA-ergic neurosteroids in blocking reconsolidation. Locci and Pinna (2019) demonstrated similar effects of the endocannabinoid congener *N*-palmitoylethanolamine (PEA) that binds to the peroxisome proliferator-activated receptor (PPAR)-α to induce Allo biosynthesis. Effects of PEA were prevented by pretreatment with finasteride, which inhibits 5α-reductase II activity and the synthesis of Allo.

Together these studies suggest a possible therapeutic role for GABA-ergic neurosteroids in PTSD patients with deficits in Allo synthesis. Although Allo and PA are synthesized in brain neurons, as well as in the adrenal gland and gonads of both men and women, such a neuroendocrinopathy could potentially be identified by careful assessment of resting baseline plasma Allo+PA levels or the use of adrenocorticotropic hormone (ACTH) stimulation testing—as long as population norms and certified laboratory mass spectrometric methodologies are established. Given that Allo also has anti-inflammatory effects (see below), promotes stage 2 spindle sleep that promotes memory consolidation, protects against neurotrauma, induces neurogenesis, and plays a critical role in myelination, Allo-based interventions also may help to prevent or treat prevalent PTSD-comorbid conditions (e.g., depression, chronic pain, alcohol dependence or withdrawal, nicotine dependence, traumatic brain injury (TBI), preterm labor, postpartum depression, and long-term neurodegenerative disorders; Rasmusson et al., 2017). Future research must then determine whether Allo-based medications should be dosed to steady state in accordance with usual psychopharmacological practices, dosed to supraphysiological levels in the short term, as approved for the treatment of postpartum depression, or dosed "on-demand" to mimic natural phasic increases in GABA-ergic neurosteroid synthesis stimulated by stress and neuronal activation. SSRIs have been shown to increase synthesis of Allo at doses less than one-tenth of the ED_{50} for 5-HT reuptake blockade in association with resolution of PTSD and depression-like symptoms in a rodent model of PTSD (Pinna, Costa, & Guidotti, 2009). Investigating whether SSRI resistance in many patients with PTSD is related to deficient Allo synthesis capacity also may be of benefit to the field.

Dehydroepiandrosterone

Production of dehydroepiandrosterone (DHEA [5-androsten-3-β-ol-17-one]) by the adrenal gland is thought to be the sole source of DHEA and its more potent sulfated metabolite, DHEAS, in the human central nervous system (CNS). In addition, DHEA(S) appears to have a complex relationship to PTSD that presents challenges in translating its therapeutic potential. DHEA is the precursor for testosterone and estrogen. Both DHEA and DHEAS antagonize $GABA_A$ receptors and facilitate NMDA function, although DHEAS is four times more potent than DHEA. Given that activation of amygdala NMDA receptors is essential to fear conditioning and extinction, DHEA(S) likely play(s) an important role in both processes. DHEA is also neuroprotective and increases

metabolism of cortisol to its inactive metabolite cortisone, reverses cortisol-induced impairments in LTP, protects against excitatory amino acid- and oxidative stress-induced neuronal damage, regulates programmed cell death, and promotes neurogenesis. DHEA is also converted to androsterone, another GABA-ergic neurosteroid (Dor, Marx, Shampine, Rubinow, & Schmidt, 2015), and 5-androsten-3β,17β-diol (ADIOL; Saijo, Collier, Li, Katzenellenbogen, & Glass, 2011). ADIOL promotes estrogen receptor (ER) β recruitment of C-terminal binding protein (CtBP) co-repressor complexes to activator protein (AP)-1 dependent promoters in genes that synthesize GABA-ergic steroids. This may contribute to increases in Allo in perimenopausal women treated with DHEA—in association with improvements in postmenopausal symptoms (Genazzani et al., 2003) or to the antidepressant effects of DHEA observed in refractory MDD in middle-aged adults (e.g., Schmidt, et al., 2005)

While therapeutic studies of DHEA in PTSD have not yet been undertaken, many studies link DHEA(S) to stress resilience. Increased resting plasma DHEA(S) levels and adrenal DHEA release have been associated with PTSD diagnosis, but with decreased PTSD and negative mood severity in PTSD patients. A lower resting DHEA/cortisol ratio was linked to childhood trauma and low PTSD recovery rates in male veterans (Yehuda, Brand, Golier, & Yang, 2006), whereas higher DHEA(S) levels and a higher ratio of DHEA to cortisol were positively linked to performance under stress in male military personnel (e.g., Morgan, Rasmusson, Pietrzak, Coric, & Southwick, 2009). Insomnia, however, has been uniquely associated with increases in adrenal DHEA release (Rasmusson et al., 2004) and rising DHEAS levels after trauma (Söndergaard, Hansson, & Theorell, 2002)—an important topic for future research. The balance between levels of DHEA(S) and inhibitory GABA-ergic steroids also may be important, as the ratio of CSF Allo+PA to DHEA is even more strongly inversely related to PTSD and negative mood symptoms than CSF Allo+PA levels alone (Rasmusson et al., 2006, 2019). These observations may be relevant to the use of DHEA in treating PTSD or PTSD-comorbid pain (e.g., Naylor et al., 2016a), since identifying individuals most likely to benefit from DHEA vs. suffer side effects will be important. Additional factors to consider include age-related changes in DHEA and markedly increased levels of DHEA that may be associated with some types of congenital adrenal hyperplasia (e.g., Witchel, Lee, Suda-Hartman, Grucco, & Hoffman, 1997).

17β-Estradiol and Related Systems

17β-Estradiol is synthesized in the ovaries, adrenal glands, and brain, and may impact PTSD risk, comorbidity, and recovery through a variety of mechanisms (Rasmusson et al., 2017). 17β-estradiol is trafficked by external neuronal membrane estrogen receptors (ERα and ERβ) to nuclear estradiol response elements (EREs) in a variety of genes. ERα activation in the amygdala induces anxiety, while activation of ERβ (expressed in the hippocampus, amygdala and PFC) reduces anxiety and facilitates extinction retention. Activation of ER1, an *intracellular,* non-nuclear G-protein coupled receptor, impacts neuronal signaling and gene transcription, and has antidepressant and neuroprotective effects.

Low estradiol in women with PTSD is associated with poor fear inhibition and extinction (Glover et al., 2013). Low estradiol in healthy women and in rodents of both sexes is associated with poor extinction retention (Pineles et al., 2016). 17β-Estradiol increases 3α-HSD expression. Deficient estradiol signaling in women with PTSD thus may contribute to reductions in GABA-ergic neurosteroid synthesis and thereby to

extinction retention deficits, which are more severe in women with PTSD during the luteal phase (Pineles et al., 2016). However, the effects of 17β-estradiol on many other neurotransmitters and neuronal systems also may impact PTSD risk and recovery.

As previously reviewed (Rasmusson & Pineles, 2018), high 17β-estradiol levels also may negatively impact PTSD risk and severity. 17β-Estradiol decreases NPY synthesis and increases 5-HT_{2A} receptors in the frontal cortex of male and female mammals, including humans. Increases in 5-HT_{2A} receptors in the frontal lobe have been associated with violent suicide and with impulsive aggression in humans and dogs. In humans, activation of 5-HT_{2A} receptors is associated with gating disturbances, hallucinations, and flashbacks; in mice, activation of 5-HT_{2A} receptors on cortical layer V pyramidal projection neurons mediates conflict-related anxiety (Weisstaub et al., 2006). Such mechanisms may underlie the observations of Bryant and colleagues (2011) wherein trauma during the mid-luteal phase of the menstrual cycle when 17β-estradiol is high conferred a fourfold increased risk of flashbacks and PTSD assessment during the mid-luteal phase yielded a fivefold increased rate of flashbacks.

17β-Estradiol levels peak in women shortly before and after ovulation. In both sexes, high brain 17β-estradiol levels also may occur in well-characterized endocrine disorders, such as 21-hydroxylase deficiency, which reroutes cortisol precursors into the androgen pathway. Heterozygosity for 21-hydroxylase deficiency is common, but often undiagnosed, especially in males (Witchel et al., 1997). In women, 21-hydroxylase deficiency is associated with hirsuitism, infertility, and polycystic ovary syndrome. In both sexes, it is associated with early-onset insulin resistance and increased mental health symptoms (Kyritsi et al., 2017), yet has not so far been studied in relation to PTSD. Of note, inhibition of aromatase, which converts testosterone to estrogen, reduces aggression in male fish, birds, and rodents, as does knockout of the *Esr1* gene coding for ERαs in ventromedial hypothalamus neurons (Anderson, 2012). Nicotine and cotinine (a metabolite of nicotine with a long half-life) also inhibit aromatase expression, perhaps accounting for the onset and increases in smoking observed after trauma (Japuntich et al., 2016) and in PTSD (Koenen et al., 2005). Thus, defining both low and high estradiol and testosterone endophenotypes in PTSD may aid in targeting new PTSD therapeutics.

PEPTIDE NEUROHORMONES

Neuropeptide Y

NPY is a 36-amino-acid peptide co-localized with a variety of neurotransmitters across the central and peripheral nervous systems. Across systems, NPY behaves like a biological "capacitor" or "high-pressure valve," conserving bioenergy for use in high-demand situations. For example, during low stress, NPY acts at presynaptic NPY-Y_2 receptors on sympathetic neurons to restrain their firing rate and the release of NE. Once sympathetic neurons are intensely activated (e.g., by psychological stress or pain), NPY is released to act at postsynaptic NPY-Y_1 receptors that potentiate the effects of co-released NE at postsynaptic α_1 receptors.

In the brain, the balance between regional NPY effects is critical to stress adaptation and recovery. NPY acting in the amygdala decreases the expression of conditioned fear and enhances extinction (e.g., Gutman, Yang, Ressler, & Davis, 2008). In the anteroventral bed nucleus of the stria terminalis (BNST), activation of NPY-Y_2 receptors also enhances extinction and dampens reinstatement of fear (Verma, Jamil,

Tasan, Lange, & Pape, 2018). Chronic stress decreases NPY in the amygdala to promote defensive responding, but increases NPY in the PFC (McGuire, Larke, Sallee, Herman, & Sah, 2011). In the PFC, NPY-containing GABAergic neurons that project from the infralimbic to prelimbic cortex *inhibit* pyramidal output neurons that project to the BLA and *increase* conditioned fear expression. In contrast, NPY facilitates GABA inhibition of infralimbic pyramidal neurons that project to amygdala and *inhibit* conditioned fear while enabling extinction (e.g., Vollmer et al., 2016). Consistent with these rodent data, healthy humans with low NPY haplotypes show higher trait anxiety and amygdala reactivity to emotionally provocative stimuli (Zhou et al., 2008), as well as increased negative affect and decreased brain opioid neurotransmission in response to pain (Mickey et al., 2011).

Preclinical studies also show that NPY enhances DA-mediated reward in the nucleus accumbens. Consistent with this work, low NPY haplotypes in humans are associated with decreased ventral striatum activation by "low-salience stimuli," but increased ventral striatum activation by "high-salience stimuli" linking performance to reward (Warthen et al., 2019). These studies suggest that low NPY may contribute to the combination of anhedonia and risk-taking or thrill-seeking often observed in patients with PTSD.

As seen in male rodents, exposure to severe stress was associated with reduced resting plasma NPY in separate samples of male active-duty personnel and combat veterans (Morgan et al., 2003). The effects of stress on plasma NPY levels may be individually variable, however; NPY levels decreased across survival training in non-Special Forces trainees, but not in Special Forces (Morgan et al., 2001) who generally demonstrate lower risk for PTSD. Consistent with effects of trauma on peripheral NPY levels, male combat veterans with severe chronic PTSD demonstrated both low resting plasma NPY levels and markedly blunted NPY responses to SNS activation; lower resting plasma NPY levels also were associated with increased noradrenergic system activation and PTSD severity (Rasmusson et al., 2000). In addition, higher plasma NPY levels in active-duty males at the peak of intense survival training were associated with lower dissociation and distress, as well as better military performance (Morgan et al., 2002).

Higher resting plasma NPY also has been associated retrospectively and prospectively with PTSD improvement over time (Yehuda, Brand, & Yang, 2006; Yehuda et al., 2014). Resting NPY did not, however, discriminate pre- to post-deployment PTSD trajectories in two recently characterized male military cohorts (Reijnen et al., 2018). Unfortunately, use of an enzyme immunoassay with insufficient sensitivity and specificity reduces confidence in the Dutch Prospective Research in Stress-related Military Operations (PRISMO) cohort findings. NPY levels measured with a sensitive and specific NPY radioimmunoassay (RIA) in the American Marine Resiliency cohort, which had a low PTSD rate, approximated higher NPY levels found in resilient groups in other studies using similar RIAs.

CSF NPY levels have varied in relation to PTSD across studies using different types of NPY assays (Kim et al., 2020; Sah, Ekhator, Jefferson-Wilson, Horn, & Geracioti, 2014). Results also may have been influenced by differences in participant characteristics, such as trauma exposure, PTSD severity, and smoking rates. Additional studies using validated NPY assays thus will be important.

Finally, given the broad role of NPY across organ systems, genetic or stress effects on NPY function may contribute to common PTSD-related comorbidities, such as obesity, cardiovascular disorders, metabolic syndrome, insomnia, irritable bowel syndrome, and chronic pain (Rasmusson & Pineles, 2018). Targeting the NPY system in

PTSD may therefore yield long-term medical benefits as well. Novel drugs targeted to specific NPY receptors in discrete disorders (e.g., obesity) can induce undesired off-target effects, however, suggesting that epigenetic approaches to restoring normal NPY system function in PTSD may hold greater therapeutic promise.

Corticotropin-Releasing Hormone

Corticotropin-releasing hormone (CRH) activates extrahypothalamic brain systems to produce physiological and behavioral manifestations of anxiety, many of which are reproduced by CRH infusion into the amygdala, where CRH antagonizes the anxiolytic effects of NPY (Rasmusson & Pineles, 2018). CRH released by neurons projecting from the hypothalamus to the anterior pituitary also activates ACTH release. Increased CSF levels of CRH, which are derived predominantly from extrahypothalamic CRH sources, have been consistently observed in men with PTSD (e.g., De Kloet et al., 2007). However, CSF CRH levels decreased, while NE levels increased along with negative mood and blood pressure in male veterans with PTSD watching trauma-related videos—suggesting that we have more to learn about CRH dynamics in PTSD (Geracioti et al., 2008). Interest in CRH system-based drugs to prevent or treat PTSD remains, despite the discontinuation of clinical trials of CRH receptor antagonists in PTSD and MDD due to lack of efficacy or to drug-related hepatic toxicity. Given that NPY reduces CRH-induced stress symptoms, including sleep disturbance (Ehlers, Somes, Seifritz, & Rivier, 1997), NPY-based therapeutics may be an alternative for PTSD patients with elevated CRH levels.

Adrenocorticotropic Hormone

ACTH released in response to CRH from the pituitary gland into the circulation activates the *de novo* synthesis and release of an array of steroids from the adrenal gland (e.g., cortisol, DHEA, Allo, and PA). Studies of ACTH levels or reactivity to CRH in men with PTSD have been inconsistent (De Kloet et al., 2008; Golier, Caramanica, & Yehuda, 2012). Such variability may be influenced by a variety of factors, including time of day, sex, depression, childhood and cumulative trauma, genetic factors, and use of psychotropic medications, illicit substances, and nicotine use.

ACTH-related findings in women have been more consistent. A longitudinal study by Shalev and colleagues (2008) showed that high ACTH levels accounted for ~10% of the variance in PTSD risk after trauma in women. Rasmusson and colleagues (2001) demonstrated increased and sustained ACTH responses to CRH challenge in unmedicated women with current PTSD who, for the most part, had childhood trauma and lifetime MDD. These findings aligned with work by Heim and colleagues (2000) showing increased ACTH responses to the Trier Social Stress Test in women with MDD and childhood trauma, most of whom had PTSD. Several factors may contribute to this female PTSD endophenotype: deficient synthesis of Allo and PA, which provide delayed negative HPA axis feedback, possession of a loss-of-function pituitary adenylate cyclase-activating polypeptide (PACAP) receptor (Ressler et al., 2011), and GR insensitivity, related in some cases to an *FKBP5* gene polymorphism that interacts with early childhood stress to increase FKBP5 (Klengel et al., 2013; see Bustamante, Chapter 11, this volume). The mechanistic link between ACTH hyperreactivity and PTSD risk in women is not clear, as adrenal reactivity is critical for extinction. It may be that the relative proportions of neuroactive steroids released in response to ACTH (e.g., deficits

in Allo or cortisol) are more relevant to PTSD risk while contributing to high ACTH levels. At a practical level, controlling for ACTH levels or use of ACTH stimulation testing may help in evaluating potential downstream blocks in adrenal steroid synthesis in PTSD (e.g., Rasmusson et al., 2019).

Pituitary Adenylate Cyclase-Activating Polypeptide

PACAP is a member of a peptide family that includes vasoactive intestinal protein (VIP) and contributes to multiple somatic and brain processes, including neuronal development, metabolism, cell signaling, learning and memory, and neuroprotection (Rasmusson & Pineles, 2018). PACAP and VIP act at two classes of G-protein coupled receptors: PAC1 (eight variants) and VPAC (VPAC1, VPAC2). PAC1 receptors preferentially bind PACAP, while VPAC receptors bind PACAP and VIP with similar affinities. These receptors activate multiple cellular signal transduction pathways [adenylyl cyclase to cAMP → protein kinase A (PKA), phospholipase C (PLC) → inositol 1,4,5 triphosphate (IP3)/diacyl glycerol (DAG) → PKC, and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)] that lead to the transcription of genes for peptides such as BDNF, CRH, and the regulatory proteins and enzymes involved in synthesis of steroids, including Allo and PA.

Ressler and colleagues (2011) reported increased PACAP levels in women (but not men) with PTSD in association with PTSD severity. PACAP was not elevated in PTSD patients with comorbid MDD, however. A polymorphism in the estrogen response element of the *PAC1* gene (i.e., downstream from PACAP) in women (but not men) was linked to PTSD, dark-enhanced startle, and failure to distinguish safety cues from threat cues in a differential fear-conditioning paradigm. In human brain, the CC allele of the *PAC1* gene PTSD risk polymorphism was linked to low PAC1 receptor expression. Stevens and colleagues (2014) also linked the *PAC1* gene risk polymorphism CC allele to increased amygdala and hippocampus reactivity to fearful faces and decreased amygdala-hippocampus coupling. Methylation of the *PAC1* gene also has been associated with PTSD diagnosis and severity, regardless of sex.

These findings suggest that failed activation of signaling pathways downstream from the PAC1 receptor may contribute to PTSD risk and severity (Rasmusson & Pineles, 2018). In rodents, Ressler and colleagues (2011) observed increases in PACAP levels and *PAC1* gene expression after fear conditioning during the period of memory consolidation. It thus may be important to differentiate individuals with high PACAP levels and normal PAC1 and downstream signaling vs. those with high PACAP but inadequate PAC1 receptor function (and resulting deficiencies in protective factors such as BDNF, GABA-ergic neurosteroids, etc.)—as these groups may show different recovery trajectories and response to trauma-focused psychotherapies.

Oxytocin and Vasopressin

Oxytocin (OT) and vasopressin (AVP), as well as their receptors are expressed in brain regions relevant to defensive behavior and PTSD, including the forebrain, amygdala, BNST, hippocampus, and brainstem (Bredewold & Veenema, 2018). OT receptors are also expressed in the breast and uterus; V_{1b} receptors in anterior pituitary where they regulate osmolality; and V_2 receptors are expressed in the kidney. Studies of these peptides have been limited, however, by inconsistent assay methods, lack of pharmacological tools, and difficulty discriminating their roles. For example, OT and AVP differ

by a mere two amino acids and bind promiscuously to AVP and OT G-protein coupled receptors.

OT and AVP have been thought to antagonize one another in regulating responses to threat, with OT registering safety, and AVP registering danger, but this model is now considered too simplistic. These peptides also show discrepant effects in animal anxiety models, but both modulate SNS and HPA axis responses. AVP specifically mediates increases in ACTH responses to novelty after exposure to chronic stress (Aguilera, 1994).

Intranasal AVP in healthy men increased corrugator electromyography (EMG) responses to neutral faces, thus reducing typical differences in response to neutral and angry faces. Thompson, George, Walton, Orr, and Benson (2006) found that AVP increased skin conductance and heart rate responses to neutral faces in both sexes. However, in men, AVP increased corrugator reactivity and threat perception, while in women, AVP decreased corrugator reactivity and increased affiliative ratings. Another study found that AVP decreased amygdala responses to angry faces in men, an effect blocked by an AVP_{1a} receptor antagonist (Lee et al., 2013).

OT-AVP studies in humans with PTSD also have yielded variable but intriguing findings. Among children in war zones, PTSD development was associated with an OT-AVP genotype comprising five risk alleles on three genes: *OXTR, CD38,* and *AVPR1a* (Feldman, Vengrober, & Ebstein, 2014). In adults, the relationship of OT-AVP levels to PTSD risk or diagnosis has been inconsistent (De Kloet et al., 2008; Frijling et al., 2015; Reijnen, Geuze, & Vermetten, 2017).

Intranasal OT improved working memory in participants with PTSD, but not in trauma controls (Flanagan et al., 2018), while intranasal OT given soon after trauma was associated with decreased PTSD symptoms over time in individuals with high baseline symptoms (van Zuiden et al., 2017). In contrast, AVP increased arousal indexed by frontalis EMG during trauma recall in males with PTSD (Pitman, Orr, & Lasko, 1993); thus, a V_{1a} antagonist (SRX246) is being tested in PTSD (clinicaltrials.gov). However, as regards other neurobiological factors to which new treatments are being targeted, development of OT and AVP-related treatment response predictors, which might include factors such as sex, disorder severity, or genetic risk alleles, would be helpful.

THE IMMUNE SYSTEM AND INFLAMMATION IN PTSD

Evidence of a role for dysregulation of the immune system in PTSD has exploded since observations of uniquely unmethylated immune system genes in PTSD were reported (e.g., Smith et al., 2011). For example, pro-inflammatory markers within 24 hours of trauma were found to correlate with PTSD development (Vaccarino, 2019), while inflammation has been associated with PTSD severity, possibly representing a PTSD subtype (Eswarappa et al., 2019). Elevated pro-inflammatory markers and cytokines in PTSD have included C-reactive protein (CRP), interferon-γ (IFN-γ), interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α (e.g., Passos et al., 2015). Studies also have reported elevated peripheral monocytes (e.g., Lindqvist et al., 2017) and NF-κB mRNA levels in monocytes in PTSD (O'Donovan et al., 2011). Pro-inflammatory markers are also increased in psychiatric conditions that are commonly comorbid with PTSD (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017). For example, monocyte chemoattractant protein-1 (MCP-1), which is essential for monocyte recruitment to the

brain, is elevated in PTSD, alcohol abuse, anxiety, and depression (An, Salyer, & Kao, 2014).

Acute stress upregulates and propagates inflammatory responses by activating the Toll-like receptor-4 (TLR-4)/NF-κB) inflammatory cascade, which increases the production and release of pro-inflammatory cytokines and inflammasomes by peripheral immune cells and their CNS counterparts (i.e., astrocytes, microglia, and oligodendrocytes). These responses initially activate monoamine synthesis—but under chronic stress, resources that support this process diminish, and monoamine precursors are converted to neurotoxic intermediates that further promote pro-inflammatory cytokine production. This leads to an increase in glutamate release from neurons and astrocytes, reduced glutamate reuptake by astrocytes, enhanced 5-HT transporter gene expression and 5-HT reuptake, and reduced BDNF (Miller & Raison, 2016; Tilleux & Hermans, 2007). PTSD-related deficits in glucocorticoid signaling or GABA-ergic neurosteroid synthesis (Balan, Beattie, O'Buckley, Aurelian, & Morrow, 2019) may contribute to the persistence of such a state.

Potential treatments that may reduce inflammation or its impact in PTSD include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, SSRIs or antidepressants that increase catecholamine levels (e.g., Gałecki, Mossakowska-Wójcik, & Talarowska, 2018), Allo (Balan et al., 2019), endocannabinoids and cannabinoids (Hill, Campolongo, Yehuda, & Patel, 2017), and oxytocin (Clodi et al., 2008). Ketamine-like agents may reduce the negative impact of high glutamate levels associated with inflammation (Walker et al., 2013). The antibiotic minocycline, which has anti-inflammatory, antioxidant, antiapoptotic and neuroprotective effects, while modulating glutamate and monoamine neurotransmission, also might be considered in treating PTSD-related inflammatory states (Soczynska et al., 2017).

SUMMARY

This chapter provides a library of findings and their preliminary clustering into meaningful propositions regarding mechanisms underlying PTSD risk, severity, and recovery. We have chosen a systems approach, covering each domain within its primary physiological context and pointing at times to interactions with other subsystems involved in the pathophysiology of PTSD. Indeed, the didactic separation of the subsystems presented does not exist in reality; cross-system interaction is the rule and "all of the above" happens together in one person continuously interacting with physical, interpersonal, and group environments.

Investigators attempting to understand the biology of PTSD are therefore back-engineering a set of complex, maladaptive biopsychosocial responses (i.e., PTSD symptoms) from their behavioral expression to their constituent components, hoping to find nodal intersections to which preventive or therapeutic interventions can be targeted. To use a musical analogy, we are trying to retrieve and document the scores of distinct instruments within a Mahler symphony fortissimo and uncover how individual instruments might look—while having a much less than optimal understanding of the rules that govern their merged effects (e.g., pitch, volume, keys, harmonies, tempo, rhythm, and start/stop signals).

As data science capabilities dramatically improve, however, some researchers believe—or hope—that the power of machine learning will offer new discoveries (e.g.,

Galatzer-Levy, Ma, Statnikov, Yehuda, & Shalev, 2017) and better integration. Others are still betting on theory-driven human capacities for data-informed pattern recognition and actionable generalizations. In any event, moving from case identification (e.g., PTSD vs. healthy) to risk likelihood data analytic models is likely to help the field, as such models better consider co-occurring factors related to severity (e.g., Shalev et al., 2019), clinical trajectories, and unique associations at the individual and subpopulation level among biological factors in the chain of causality. Thus, we might move from exploring whether a suspected risk factor X predicts group membership to exploring the extent and circumstances under which factor X incrementally changes the likelihood of an outcome. A better way to package the evidence herein presented then might be to introduce a model adjudicating the relative distance of each translational layer of findings (genetic, epigenetic, proteomic, physiological, behavioral) to an outcome, such as PTSD, MDD, substance use, or other trauma-related conditions.

Meanwhile, clinicians and patients continue to be eager to anchor their understanding of PTSD and hope for prevention and cures based on new scientific insights, discoveries, and innovations. For all stakeholders though, the hard-won evidence that this chapter outlines and strives to integrate and contextualize is the raw material necessary for success.

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CHAPTER 11

Genetics of PTSD

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Research on the genetic factors of posttraumatic stress disorder (PTSD) has grown rapidly. This chapter provides an overview of twin, molecular genetic, epigenetic, and gene expression studies of PTSD, as well as novel statistical genetics techniques for molecular data. Early research observed the intergenerational transmission of PTSD, which gave way to twin studies allowing the estimation of PTSD heritability and subsequently molecular efforts. Early molecular approaches heavily utilized candidate gene studies. More recently, the field has shifted to focus on genome-wide association studies (GWAS; for a review, see Daskalakis, Rijal, King, Huckins, & Ressler, 2018; Nievergelt et al., 2019) and has progressed toward discerning epigenetic markers and their role in PTSD (Uddin et al., 2010). The research we will review here now relies more on statistical models and new technology for investigating the genomic factors of trauma exposure and PTSD, their process, implications, and consequences.

FAMILY STUDIES

This line of research intends to determine if a phenotype "runs in families" and if the offspring of parents with the phenotype exhibit a higher likelihood to express it compared to offspring of parents without it. Early PTSD work on family studies focused on survivors of severe traumatic events where parents and their children experienced the same event (e.g., the Holocaust; Yehuda, Schmeidlet, Wainberg, Binder-Brynes, & Duvdevani, 1998). Evidence was mixed, and methodological differences and limitations (e.g., small sample sizes, trauma exposure and type) made it difficult to determine the reasons for the discrepancies. It was also unknown whether conclusions could generalize to more common events in civilians or in families with parents and their children discordant for shared traumatic events. More recent studies have found that

indeed the offspring of mothers with PTSD are at higher risk of experiencing traumatic events, which in turn predicts risk for PTSD (Roberts et al., 2012). Familial factors can contribute to trauma exposure and resulting PTSD symptoms. Specifically, one-third of the variance in PTSD liability is due to familial factors, and approximately one-fifth of this variance overlaps with the familial liability for trauma exposure (Amstadter, Aggen, Knudsen, Reichborn-Kjennerud, & Kendler, 2012). One limitation of family studies is that the variance due to shared genes versus shared environments cannot be parceled out.

TWIN STUDIES

Twin studies can disentangle the genetic and environmental influences on a phenotype. The proportion of the total variance in the phenotype explained by genetic factors (i.e., broad heritability: additive plus dominance genetic effects) and environmental effects (shared and specific) can be calculated comparing the covariance in *monozygotic* (MZ) twin pairs to that of *dizygotic* (DZ) pairs (Neale & Cardon, 1992). MZ twins share 100% of their genes as well as 100% of the shared environment; DZ twins share approximately 50% of their genes and 100% of their environment, under the assumption that twins were reared together. If MZ twins share a higher similarity on a trait than DZ twins, it is assumed that variation in the phenotype is genetically influenced.

Twin studies of PTSD have produced four main findings. First, exposure to traumatic events is influenced by genetic factors. Heritability estimates for trauma exposure in the civilian population are within 38% (Stein, Jang, Taylor, Vernon, & Livesley, 2002), with a range of 35–47% for combat exposure (Eisen, True, Goldberg, Henderson, & Robinette, 1987; Goldberg, True, Eisen, Henderson, & Robinette, 1987). Second, genetic influences explain a substantial proportion of PTSD vulnerability, from approximately 30% in male Vietnam veterans (True et al., 1993) to 72% in young women (Sartor et al., 2011). High levels of exposure to severe traumatic events may amplify the liability for PTSD by increasing the influence of genetic and environmental components (Wolf, Mitchell, Koenen, & Miller, 2014). Third, twin and family studies suggest that the majority of genes that affect risk for PTSD also influence risk for other psychiatric disorders and vice versa. Genetic effects on PTSD appear to be highly shared with depression (Koenen et al., 2007), generalized anxiety disorder and panic disorder (Chantarujikapong et al., 2001), alcohol and drug dependence (Sartor et al., 2011; Xian et al., 2000), and nicotine dependence (Koenen et al., 2005), albeit to a lesser extent. Fourth, bivariate twin studies of PTSD and other constructs found significant overlap. For example, Wolf, Miller, and colleagues (2018) detected that shared genetic factors accounted for approximately 59% of the correlation between PTSD and resilience. In sum, twin studies have laid the foundation for research aimed at identifying specific genetic variants that increase risk for PTSD.

GENETIC ASSOCIATION STUDIES

Molecular approaches seek to identify the underlying biological mechanisms that influence PTSD. Molecular studies of PTSD began with hypothesis-driven approaches, including candidate gene and candidate gene-by-environment (cG × E) studies. Contemporary designs more frequently utilize agnostic approaches (i.e., GWAS), with the

methodological consideration of including trauma-exposed controls to prevent bias in the information from subjects regarding unexpressed genetic liability for PTSD.

Candidate Gene Studies

These studies select genetic variants based on existing theories related to the biological predictors and concomitants of PTSD. Over 100 of such studies have been published (for a review, see Duncan, Cooper, & Shen, 2018). Nevertheless, they had reproducibility challenges and are known to have many limitations such as small sample sizes; limited coverage of genomic regions nominated from incomplete knowledge of the underlying biology of PTSD, which can bias results showing increased rate of false positives and overestimate the effect of the particular gene (Cornelis, Nugent, Amstadter, & Koenen, 2010); and restricted accuracy for differentiating between a focus on promoter or coding regions.

Meta-analyses have been conducted in an attempt to address the limited sample size issue. Two meta-analyses (Gressier et al., 2013; Navarro-Mateu, Escámez, Koenen, Alonso, & Sánchez-Meca, 2013) focused on the polymorphic region *5-HTTLPR* of the gene *SLC6A4* (codes for serotonin transporter protein), finding no association and no direct effects with PTSD. In contrast, researchers detected associations from the gene *ADCYAP1R1,* which encodes for the pituitary adenylate cyclase-activating polypeptide (PACAP) receptor related to the stress response and PTSD (Lind et al., 2017). In another meta-analysis, Bountress and colleagues (2018) did not find support for the brain-derived neurotrophic factor (BDNF) Val66Met variant predicting PTSD.

Researchers have been able to replicate only a minority of cGxE findings, suggesting that many of the interaction effects detected may actually be false positives (Duncan & Keller, 2011). The literature has also been examined via meta-analyses, some of which support the cGxE effects of *FKBP5* on PTSD when interacting with trauma exposure (Hawn et al., 2018). However, cGxE studies and meta-analyses on other genes have been inconclusive or have produced mixed findings (Koenen et al., 2008). Given methodological advances in genotyping and lowering costs, current studies more frequently utilize an agnostic design.

Genome-wide Association Studies

GWAS compare the frequencies of millions of common genetic variants with good coverage of the entire genome. Due to small effect sizes, as well as the number of statistical tests employed, GWAS require large samples for adequate power. A recent review (Daskalakis et al., 2018) reported that over 13 GWAS on PTSD have been published since the first one in 2013 (Logue et al., 2013), finding 15 relevant single-nucleotide polymorphisms (SNPs) related to genes associated with PTSD. Table 11.1 shows the genes mentioned in this chapter, their link to PTSD, their function, and the type of study from which they were identified. Logue and colleagues (2013) used a sample of 295 cases and 196 controls and implicated the *RORA* gene. Results have been successfully replicated (Amstadter et al., 2013). Furthermore, Nievergelt and colleagues (2015) found that the *PRTFDC1* gene (expressing in the brain; see Table 11.1) showed a significant association with PTSD.

Using a diverse GWAS sample, Chen and colleagues (2017) identified one locus (rs2311207) in the European American group associated with the reexperiencing symptoms domain (but not for the avoidance and arousal domains). Although SNP-based

heritability (h^2_{SNP}) had a range of 4.3–8.5%, genetic correlations pointing to their common variation were robust with estimates between 80 and 100%. Estimates of h^2_{SNP} usually rank lower than one of the same phenotypes from twin studies, which take into account genetic factors such as rare and common variants as well as those factors not genotyped for the analysis. Wilker and colleagues (2018), working with a diverse sample, detected a protective association from the rs3852144 marker, where people with higher numbers of G-alleles showed higher resilience to PTSD. Furthermore, Stein and colleagues (2016) noted a particular association of the *ANKRD55* gene associated with increased risk for PTSD in African American subjects. In a GWAS investigating PTSD reexperiencing symptoms using a diverse sample of over 165,000 subjects from the U.S. Million Veteran Program, Gelernter and colleagues (2019) identified in European Americans (however, not in African Americans) three genes (*CAMKV, KANSL1,* and *TCF4*) expressing in brain areas related to PTSD.

Numerous recent studies have confirmed that psychiatric disorders are polygenic and that increasingly large samples are required to reach the power to detect small effects on the phenotype (Logue, Amstadter, et al., 2015; Sullivan, Daly, & O'Donovan, 2012). To achieve adequate power, the Psychiatric Genomics Consortium PTSD workgroup (PGC-PTSD) was formed in 2013. This team combined data from 11 studies for the first data freeze, resulting in a sample of 20,730 participants (Duncan, Ratanatharathorn, et al., 2018). Although the first freeze was not yet powered to detect GWAS significant loci, analyses showed support for shared genetic risk between PTSD and schizophrenia and, to a lower degree, with major depressive and bipolar disorder (MDD; BP). Additionally, this study established evidence for European American females exhibiting higher heritability of PTSD than males (see the following section). At this writing, the PGC-PTSD second data freeze is the largest GWAS of PTSD (Nievergelt et al., 2019), including an ancestry diverse sample of 206,655 subjects (with ~30,000 cases and the remaining as control subjects). Researchers (Nievergelt et al., 2019) estimated an h^2_{SNP} of 10–20% and identified six loci attaining genome-wide significance for PTSD risk. Interestingly, after accounting for the effects of correlated psychiatric traits (which were highest with MDD and schizophrenia), these loci remained particular to PTSD. Including sex-specific and ancestry effects, the loci indicated that five genes (*PARK2, PODXL, SH3RF3, ZDHHC14,* and *HLA-B*; see Table 11.1) may play a crucial role in different mechanisms for PTSD risk (e.g., dopaminergic pathways, cognition and mental abilities, adrenergic receptors, and responses during stress). Large-scale GWAS and expanding computational power have been crucial in providing insights on the architecture of PTSD. Nevertheless, more robust and precise methods that take into account the polygenic nature of PTSD are required in the current stage of gene discovery and association.

Summary

Genetic association studies aimed to uncover the link of putative genes with traits. With few exceptions (see the meta-analytic studies above), findings have been inconsistent from candidate designs, perhaps owing to numerous design limitations (e.g., low sample size, low genetic coverage). GWAS designs have increased the sample size and genomic coverage, uncovering numerous markers (albeit of small influence) linking memory, arousal, reexperiencing symptoms domain, immunity, inflammation, and neural processes in stress response with PTSD (see Table 11.1), and their shared risk with other disorders.

NOVEL STATISTICAL GENETIC TECHNIQUES FOR GWAS

Given the increase in recent GWAS, novel techniques have been developed and applied in order to expand power, handle type I and II errors, and to find polygenic effects that may have gone undetected due to nonsignificant results from individual variants.

Genome-wide Complex Trait Analysis

Genome-wide complex trait analysis (GCTA) utilizes a genetic relatedness matrix and provides estimates of h^2_{SNP} in GWAS samples of unrelated subjects (Yang, Lee, Goddard, & Visscher, 2011). GCTA also allows for calculation of the overlapping genetic variance (i.e., genetic correlation) between two phenotypes in its bivariate extension. Previous individual cohorts have utilized GCTA techniques to investigate risk in PTSD (Melroy-Greif, Wilhelmsen, Yehuda, & Ehlers, 2017; Stein et al., 2016) and found inconclusive evidence for h^2_{SNP} likely due to small sample size. In contrast, using the PGC-PTSD Freeze 1 (N = 20,070), Duncan, Ratanatharathorn, and colleagues (2018), based on GCTA, found a significant h^2_{SNP} estimate of 12% for males and females. Nievergelt and colleagues (2019) also applied GCTA to the PGC-PTSD Freeze 2 and estimated an h^2_{SNP} across ancestries within the range of 10–20%. This sample includes a higher proportion of African ancestry individuals (10% compared to 3% in prior analyses), with results showing h^2_{SNP} similar to those of European ancestry and the overall sample. Results also remained comparable across sex, with a stable trend of females showing significantly higher h^2_{SNP} (10%) compared to males (1%) in the European and African ancestry groups. Estimates of h^2_{SNP} between males and females may vary due to environmental factors. Dissimilarities in trauma exposure severity, type, and symptoms relying on sex-based biological features may be driving the distinction of their h^2_{SNP}. Females might be more at risk for experiencing interpersonal trauma than males (e.g., partner or sexual violence; Benjet et al., 2016), whose liability for traumatic exposure reveals higher frequency of accidental, witnessing, and nonsexual events (Tolin & Foa, 2006).

Linkage Disequilibrium Score Regression

Linkage disequilibrium score regression (LDSC) can estimate h^2_{SNP} and investigate the genetic structure of complex traits. This approach uses SNP summary statistics from GWAS regressed on their own linkage disequilibrium (LD) scores (the sum of the squared correlation estimates between the SNPs), whereas GCTA uses individual-level genotypic data. LDSC requires less computation time and resources and can be implemented to assess the genetic composition and associations of complex traits (Ni et al., 2018). However, using several datasets in LDSC analyses could lead to increased standard error (*SE*) compared to GCTA results. If estimates differ using both methods, it is recommended that reliance be placed on the approach with the lowest SE. Duncan, Ratanatharathorn, and colleagues (2018) calculated the average h^2_{SNP} of PTSD for males and females at 15% (*LDSC* = 0.18, *SE* = 0.06, *GCTA* = 0.12, *SE* = 0.05) utilizing both GCTA and LDSC methods, with an average for females of 29% (*LDSC* = 0.36, *SE* = 0.12; *GCTA* = 0.21, *SE* = 0.09) and for males of 7% (*LDSC* = 0.05, *SE = 0.13; GCTA* = 0.08, *SE* = 0.1). Nievergelt and colleagues (2019) also applied both methods to calculate overall h^2_{SNP} (10–20%), with GCTA estimates similar to those from LDSC, particularly

for those of European ancestry with the exception of males from the PGC sample not showing significant h^2_{SNP} estimates (0.01–0.03, $p > .15$). LDSC can be applied to examine the genetic correlation (r_G) between traits using independent GWAS samples. Analyses of the Freeze 1 have found significant r_G with physical health outcomes, such as coronary artery disease, obesity, and metabolic risk (Sumner et al., 2017), and psychiatric traits, including schizophrenia and bipolar disorder (Duncan, Ratanatharathorn, et al., 2018). Results from Freeze 2 (Nievergelt et al., 2019) show that PTSD is significantly correlated with 21 distinctive traits/phenotypes, for example, negatively with education and well-being and positively with schizophrenia, neuroticism, coronary heart disease, smoking behavior, depressive symptoms ($r_G = 0.80$), and MDD ($r_G = 0.62$).

Polygenic Risk Scores

Polygenic risk scores (PRS) enable evaluation of whether additive genetic risk aggregated across numerous genomic loci are associated with a specific trait. For estimating these statistics, the weighted sum of scores is calculated based on the effect size of the markers from individual-level data. Typically, not all the selected markers achieve genome-wide significance from GWAS; nevertheless, their combined effects are presumed to influence the trait. For instance, using PRS, Nievergelt and colleagues (2018) demonstrated the presence of a consistent rise in odds for PTSD through PRS quintiles, with men from the U.K. Biobank in the highest quintile exhibiting 40% more odds than their peers in the reference quintile for developing PTSD. PRS indicate that the genetic risk for PTSD intersects with those for MDD and bipolar disorder, with more robust support for shared genetic liability for PTSD and schizophrenia (Duncan, Ratanatharathorn, et al., 2018). Furthermore, PRS can predict PTSD liability from that of other psychiatric disorders, highlighting their genetic overlap as polygenic traits (Lori et al., 2019; Misganaw et al., 2019).

Mendelian Randomization

Mendelian randomization (MR) can be used to evaluate the causal effects of associations between liability factors and phenotypes based on genetic variation (Emdin, Khera, & Kathiresan, 2017). Under MR, the variants are assumed to be stochastically assorted and distributed, and free of confounders. The random assortment of alleles allows for a natural experiment from the population. Polimanti and colleagues (2017) assessed the causal relationship between PTSD and body mass index only in females. Their results point to a negative association between PTSD and genetically determined female body configuration based on SNPs linked to anthropometric attributes (e.g., waist circumference adjusted for body mass index [BMI]). Another study indicated that traits associated with cognitive skills, specifically educational attainment, exert causal influences on PTSD liability via risk factors linked to economic status, with no evidence of reverse causation (Polimanti et al., 2018).

Genomic Structural Equation Modeling

Genomic structural equation modeling (genomic SEM) allows one to model the multivariate genetic configuration of several traits that share genetic correlations and

liability, employing their genetic covariance structure based on GWAS summary statistics. Genomic SEM is computationally efficient and enables assessing the genetic overlap in the traits as well as their degree of heterogeneity at the SNP level. Using this method, several groups found consistent results of trait overlap (PTSD with MDD, anxiety, attention-deficit/hyperactivity and autism spectrum disorder; Rao et al., 2019); common factors of PTSD with schizophrenia and MDD, PTSD-specific loci (Grotzinger et al., 2018); as well as PTSD and MDD loading on a common internalizing factor (Luningham, Poore, Yang, & Waldman, 2018).

Summary

Novel statistical techniques using GWAS data have demonstrated: SNP-based heritability of PTSD h^2_{SNP} (10–20%), genetic correlations between PTSD and related phenotypes (e.g., depressive symptoms, $r_G = 0.80$; MDD, $r_G = 0.62$); the power of additive risk of the alleles via PRS for within-trait and cross-trait prediction; and putative causal variants using MR. These methods prioritize computationally efficient process and optimization to offer overall estimates of polygenic traits beyond association statistics.

EPIGENETIC STUDIES

Epigenetic studies focus on associations with a phenotype that are produced beyond DNA sequences. Epigenetic changes can trigger modifications along many metabolic processes (mainly at transcription) that may influence observable traits. The environment and other factors (e.g., aging, disorders, illness) may also modify genetic effects through molecular processes. DNA methylation (DNAm) is one of the major mechanisms of epigenetic regulation of genetic functions. It occurs predominantly when methyl groups are coupled to cytosine residues when cytosine and guanine are separated by a phosphate (a CpG site; Bernstein, Meissner, & Lander, 2007). DNAm involves regulation of DNA accessibility, which in turn alters the transcriptional activity of the surrounding loci. Typically, increased methylation in specific gene regions (e.g., promoter) is associated with reduced transcriptional activity and, therefore, less gene expression. Similar to the trajectory of previous molecular studies, DNAm studies on PTSD were first conducted from a candidate gene methylation (cDNAm) design, and now agnostic epigenome-wide association studies (EWAS) are growing in popularity.

cDNAm Studies

cDNAm studies examine differential methylation status at specific CpG sites. Differential methylation in PTSD has been investigated in more than 22 cDNAm studies conducted to date (see review by Zannas, Provencal, & Binder, 2015). Previous work by several groups (e.g., Alexander et al., 2018; McGowan et al., 2009; Mehta et al., 2013; Philibert et al., 2008; Romens, McDonald, Svaren, & Pollak, 2015) suggest a relation between an environmental exposure (e.g., childhood abuse) and differential methylation in genes (*SLC6A4, NR3C1, FKBP5*) linked to pathways relevant to PTSD. Studies under this design also have power limitations related to small sample sizes, inconsistent coverage of CpG sites hindering replication efforts, issues with population stratification, and precision in selection of genes associated with the pathophysiology of PTSD.

Epigenome-wide Association Studies

Much like GWAS, EWAS use agnostic designs investigating upward of 850,000 DNAm markers across the genome. Although EWAS face similar power challenges than GWAS, relatively smaller sample sizes can achieve enough power to identify epigenetic associations (Klengel et al., 2013). Since 2010, EWAS have been consistently utilized to assess epigenetic variation in PTSD, with 11 studies to date detecting important CpG sites related to the disorder (see Table 11.1). Of those studies, Uddin and colleagues (2010) found that exposure to traumatic events can alter expression of genes linked to dysregulation of immune response, stress and physiological alterations in startle response in persons with PTSD. Hammamieh and colleagues (2017) supported the relevance of DNAm related to immune dysregulation and found epigenetic changes in pathways related to endocrine alterations, learning, and memory. Evidence also suggests that stressful experiences can modify DNAm in pathways related to inflammation in persons with PTSD (Smith et al., 2011). The range of epigenetic changes is considerably higher for individuals with PTSD exposed to traumatic events during childhood, as opposed to those with PTSD without history of childhood trauma (Mehta et al., 2013), and is moderated by changes (in the *ADCYAP1R1* gene) associated with stress response (Uddin et al., 2013). In a longitudinal study of male U.S. Marines, Rutten and colleagues (2018) identified a negative relation of within-subject decrease of DNAm in genes *RNF39, ZFP57,* and *HIST1H2APS2* with PTSD symptoms. With a sample of 473 World Trade responders, Kuan, Waszczuk, Kotov, Marsit, and colleagues (2017) investigated epigenetic changes related to PTSD and MDD. No epigenome-wide significant differences were found; however, several independently significant CpG sites linked to PTSD influencing stress response, neural signaling, synaptic plasticity, and inflammation were detected. Another group found differential methylation in those with PTSD in genes associated with neurological changes (*DOCK2* gene; Mehta et al., 2017).

Several investigators formed a PGC-PTSD epigenetics working group (Ratanatharathorn et al., 2017) aimed at increasing power, particularly by expanding the sample size in EWAS and establishing standards of quality control (QC) and methods to handle potential rise of type I error and population stratification (significant differences in allele frequencies can introduce biased estimates). Using a sample of 1,147 individuals, Ratanatharathorn and colleagues (2017) tested the QC procedures and two analytical pipelines that successfully controlled for genomic inflation and deflation over another standard technique (i.e., functional normalization), suggesting that EWAS with this sample size can be sufficiently powered. From a civilian and military sample (N = 1,896) the PGC-PTSD EWAS workgroup analyzed DNAm microarrays and found that, although with diminished significance when controlling for smoking, the main four CpG sites were in the *AHRR* gene and associated with decreased DNA methylation in PTSD (Ratanatharathorn et al., 2019; Smith et al., 2020). Additionally, Uddin and colleagues (2018) detected two differentially methylated CpG sites significantly linked to present PTSD (*NRG1,* cg23637605; *HGS,* cg19577098).

Novel Technique for EWAS: DNAm Age

This method allows calculation of the DNAm age of different cell types and tissues by estimating the effect of a molecular biomarker for aging in the methylome compared to a standard molecular clock (Horvath, 2013). In a sample of 281 veterans, Wolf

and colleagues (2016) found support for an association of increased cellular aging and PTSD severity, particularly linked to decline of neural integrity of the corpus callosum and linked to reduced working memory performance. This group also demonstrated that PTSD symptoms of hyperarousal (Wolf, Logue, et al., 2018), exposure to traumatic events during childhood, and PTSD severity (largest to date using this method, N = 2186; Wolf, Maniates, et al., 2018) were significantly associated with faster epigenetic aging. DNAm age can help to elucidate the implications of trauma and PTSD consequences for biological systems related to increased decline in cellular and overall health.

Summary

Epigenetic changes can influence PTSD risk. EWAS use an agnostic approach and were preceded by candidate DNAm studies, with similar limitations (e.g., small sample sizes, reduced coverage) as candidate gene studies. EWAS studies have noted alterations in DNAm that are linked to immune dysregulation, changes in learning, memory and endocrine pathways, as well as neural integrity and decline in cellular health from DNAm age results in PTSD.

GENE EXPRESSION STUDIES

Gene expression studies are crucial in discerning the molecular impacts influencing PTSD. Gene expression is the process of synthesizing proteins that regulate cells throughout an organism (Strachan & Read, 2011). Changes in gene expression at different stages of transcription (e.g., different splicing patterns, transcription factors), mRNA processes, translation, or protein phases, can alter function in tissues, systems, and overall health and can contribute to the manifestation of phenotypes.

Candidate-Gene Expression Studies

Similar to other early molecular work on PTSD, research in gene expression has focused on candidate gene approaches to distinguish those with PTSD versus those without. The majority of these studies have assessed, for example, RNA derived from either peripheral blood mononuclear cells (PBMCs) or whole blood. Whole blood-derived differential gene expression among PTSD-affected and -unaffected individuals (who had exposure to the 9/11 attack) was detected in 16 distinct genes, several of which are involved in signal transduction, brain and immune cell function, and hypothalamic pituitary–adrenal axis (HPA) axis activity (Yehuda et al., 2009). Although several genes in this study had previously been linked to PTSD and/or stress-related outcomes (e.g., *FKBP5*; Binder et al., 2008; MHC Class II, Chauhan, Leach, Kunz, Bloom, & Miesfeld, 2003), *MAN2C1* gene, implicated in immune response and expressed in the thyroid (Kent et al., 2002), had the largest difference in expression as well as in DNAm (Uddin et al., 2011). Furthermore, other genes were linked to the HPA axis function (*FKBP5, ADCYAP1*; Kuan, Waszczuk, Kotov, Clouston, et al., 2017; Ressler et al., 2011; Yehuda et al., 2009), memory processes (Logue, Smith, et al., 2015), inflammation (*TNFRSF10B, IL10RB, IL4R, NF-κB, CREB/ATF*; Hollifield, Moore, & Yount, 2013; O'Donovan et al., 2011), and cell processes (*SOD1, BBC3, CASP2*; Kuan, Waszczuk, Kotov, Marsit, et al., 2017).

Genome-Wide Expression Studies

More than nine studies have assessed differential expression among trauma and PTSD cases and controls using agnostic genome-wide analysis. Results suggest significant differences between those with and without PTSD on genes associated with toxicity levels in cells (e.g., *SOD1*; Tylee et al., 2015), fear response and memory (e.g., *CHRNA4, DSCAM*; Bountress et al., under review; Logue, Smith, et al., 2015), signal transduction (e.g., *STAT5B*; Sarapas et al., 2011; Tylee et al., 2015; Yehuda et al., 2009), and HPA axis functioning (e.g., *FKBP5*; Kuan, Waszczuk, Kotov, Clouston, et al., 2017; Sarapas et al., 2011; see Table 11.1). The PGC-PTSD gene expression workgroup aims to develop studies with large samples (~5,000) to confirm and advance previous research in this area (Nievergelt et al., 2018). Studies of gene expression on PTSD have focused on noninvasive peripheral blood samples, most of the times with reduced power. In the future, such studies will need replication with brain tissue. Nevertheless, transcripts related to immunity and wound healing have been associated with biological processes in PTSD (Nievergelt et al., 2018). Further research is needed to assess studies with larger samples, including more PTSD biological pathways, as well as to integrate statistical methods that can facilitate identifying differentially expressed genes linked to PTSD risk.

Novel Techniques for Gene Expression

Recent studies are applying novel algorithms, increased computational power, and machine learning to confirm and discover new markers in the pathways that increase PTSD risk. For example, *weighted co-expression correlation network analysis (WGCNA)* can elucidate patterns based on systems biology, correlations, and interactions from several genes covering different microarray samples (Langfelder & Horvath, 2008). Previous studies have found support for increased expression of pro-inflammatory cytokines (Bam et al., 2016), as well as intensified co-expression of enriched genes that contribute functionally to innate immune responses in the liability of PTSD (Breen et al., 2015). More recently, Breen and colleagues (2018) detected evidence of overlapping systems linked to inflammation and to dysregulation in transcription and expression from genes related to immune response across sex and types of trauma.

A second example is *pathway analysis*; this method can evaluate alterations in different biological pathways linked to gene expression from which causal inference can be made. Kuan, Waszczuk, Kotov, Marsit, and colleagues (2017) detected evidence for particular sets of genes acting in tandem and related to biological pathways of stress response, neuronal signaling, and inflammation linked to PTSD; as well as immune cell dysregulation (CD4T, CD8T, B cells, and monocytes) in the PTSD sample (Kuan et al., 2019). A different group (Rusch et al., 2019) reported 10 genes (*C5orf24, RBAK, CREBZF, CD69, PMAIP1, AGL, ZNF644, ANKRD13C, ESCO1,* and *ZCCHC10*) differentially expressed in subjects with elevated intrusion symptoms cluster of PTSD.

Another technique is *transcriptomic imputation (TI)*. TI uses a machine learning approach to match and impute genotypes and gene expression data to genotyped cases and controls to uncover discrepancies in expression. This method supports analyses using large and multiple transcriptome datasets. In a study using PGC-PTSD GWAS data and TI, Huckins and colleagues (2019) found two new genes (*SNRNP35* and *SENP1*) associated with PTSD risk from stress-related processes in the military cohort (see Table 11.1).

TABLE 11.1. Relevant Genes to PTSD from Agnostic Genetic, Epigenetic, and Expression Studies

Type of study	Name of gene	Possible link to PTSD
GWAS	*RORA:* RAR-related orphan receptor A	Protection against stress-induced apoptosis
	PRTFDC1: phosphoribosyl transferase domain containing 1	Expression in the cerebral cortex, amygdala, hippocampus, hypothalamus, spinal cord, and adrenal gland; memory and arousal process
	rs2311207 marker (iv) on gene *RAB27B*	Reexperiencing symptoms domain
	rs3852144 marker (iv), closest gene: *C5orf67*	Protection from aversive memories, emotional memory formation and resilience
	ANKRD55: ankyrin repeat domain 55	Inflammatory and autoimmune disorders in AA
	CAMKV: CaM kinase-like vesicle associated; *KANSL1:* KAT8 regulatory NSL complex subunit 1; *TCF4:* transcription factor 4	Emotional memory and processing, and arousal
	PARK2: parkin RBR E3 ubiquitin protein ligase	Related to dopaminergic pathways in PTSD
	PODXL: podocalyxin-like	Neural development and synapse formation
	SH3RF3: SH3 domain containing ring finger 3	Neurocognition
	ZDHHC14: zinc finger DHHC-type palmitoyltransferase 14	Regulation of adrenergic pathways
	HLA-B: major histocompatibility complex, Class I, B	Immunity and inflammation in stress response
EWAS	*RNF39:* ring finger protein 39; *ZFP57:* zinc finger protein; *HIST1H2APS2* (pg): histone cluster 1 H2A pseudogene 2	Decreased level in methylation and increased symptoms of PTSD
	DOCK2: dedicator of cytokinesis 2	Neurodegeneration and neuroplasticity
	AHRR: aryl-hydrocarbon receptor repressor	Decreased DNA methylation, expressed in the brain (e.g., ACC, hypothalamus, nucleus accumbens)
	NRG1: neuregulin 1; *HGS,* hepatocyte growth factor-regulated tyrosine kinase substrate	Differential methylation, expressed in the brain (e.g., ACC, hypothalamus)
Expression	*SOD1:* superoxide dismutase 1	Toxicity levels in cells
	CHRNA4: cholinergic receptor nicotinic alpha 4 subunit; *DSCAM:* DS cell adhesion molecule	Fear response and memory
	STAT5B: signal transducer and activator of transcription 5B	Regulation of inflammation
	FKBP5: FKBP prolyl isomerase 5	HPA axis functioning

(continued)

TABLE 11.1. *(continued)*

Type of study	Name of gene	Possible link to PTSD
Expression *(continued)*	*C5orf24:* chromosome 5 open reading frame 24; *RBAK:* RB-associated KRAB zinc finger; *CREBZF:* CREB/ATF BZIP transcription factor; *CD69:* CD69 molecule; *PMAIP1:* phorbol-12-myristate-13-acetate-induced protein 1; *AGL:* amylo-alpha-1,6-glucosidase,4-alpha-glucanotransferase; *ZNF644:* zinc finger protein 644; *ANKRD13C:* ankyrin repeat domain 13C; *ESCO1:* establishment of sister chromatid cohesion *N*-acetyltransferase 1; and *ZCCHC10:* zinc finger CCHC-type containing 10	Differential expression linked to elevated intrusion symptoms (e.g., reexperiencing, flashbacks) and physiological immune systems
	SNRNP35: small nuclear ribonucleoprotein U11/U12 subunit 35	Differential expression in blood and stress variability
	SENP1: SUMO-specific peptidase 1	Heart tissue and cardiovascular dysregulation

Note. Unless otherwise specified, the function of all the genes in the table is coding for proteins (others: iv = intron variant; pg = pseudogene).

Summary

Gene expression modifications can alter functions throughout different stages of biological pathways related to PTSD, impacting the health of cells, tissues, and systems. These studies have detected changes in expression patterns linked to memory, stress response and arousal, inflammation, cardiovascular irregularities, and intrusion symptoms domain with PTSD. New methods are establishing maps of overlapping transcriptome systems between phenotypes and causal inference by assessing the temporal sequence of transcription and disparities between controls and those with PTSD.

FUTURE DIRECTIONS

Genetic research in PTSD has evolved substantially over recent decades. Although association studies present limitations, their contribution to finding genetic factors and mechanisms linked to variation in phenotypes is relevant. Ressler and colleagues (2011) examined the *PACAP-PAC1* receptor pathway involved in abnormal stress responses underlying PTSD in females. A single SNP (rs2267735) predicted PTSD diagnosis and symptoms in females only. This SNP was associated with fear discrimination and with *ADCYAP1R1* messenger RNA expression in the human brain. Furthermore, a significant genotype by environmental interaction including rs2267735 was associated with current PTSD only in adults with severe childhood abuse (Uddin et al., 2013). Mercer and colleagues (2016) found that women with the risk genotype (CC) at rs2267735 who also had low levels of estradiol also exhibited lower *ADCYAP1R1* mRNA expression, as opposed to those with nonrisk genotypes (CG or GG) and males with the risk genotype. Given that genotype, methylation, and gene expression differences likely accompany

the development of psychopathologies such as PTSD, research incorporating all three forms of genetic information (from the same participants) is needed.

Advances in statistical methods (e.g., GCTA, LDSC, PRS, DNAm age, WGCNA, path analysis, TI) and computational power optimize time and resources for analysis, expanding the inference ability from genetic studies. Consortia such as the PGC are establishing workgroups using large-scale GWAS data in many complex traits, as well as cross-disorder and multi-omic perspectives (e.g., copy number variants, EWAS, transcriptome-wide studies, and microbiome; Huckins et al., 2019; Logue, Smith, et al., 2015; Maihofer et al., 2019; Ratanatharathorn et al., 2019). Neuroimaging genetics, a relatively new field, has also contributed to genetic research in PTSD by investigating variation on structural and functional features of brain regions of interest. Results from this field have faced comparable limitations present in association studies. To address these limitations, similar to the PGC, the Enhancing NeuroImaging Genetics through Meta-Analysis consortium (ENIGMA; Thompson et al., 2014) was created to conduct large-scale meta-analyses and investigate different factors influencing brain features, which single sites would not be powered to perform. The increasingly large scope of these types of analysis relies on development of integrative methods and application, grants and diverse funding for different career levels, and meaningful interpretation across fields (e.g., molecular and statistical genetics, epigenetics, multi-omics). As with the PGC, ENIGMA, and other groups, the quest for achieving satisfactory statistical power favors large-scale analyses through consortia; naturally, this quest also promotes collaboration among researchers in similar lines of study and across fields.

CONCLUSIONS

Significant advances have been made in the discovery of genetic risk variants for PTSD. The PGC-PTSD group recently published the second meta-analysis of PTSD GWAS, the largest to date. Genetic variants associated with PTSD are promising biomarkers of risk because they remain unchanged throughout life, and DNA can be obtained noninvasively and assayed reliably. Numerous research groups and consortia have analyzed large-scale GWAS data but have also expanded into EWAS and used novel statistical approaches to build upon previous techniques. The application of methods such as GCTA, LDSC, and PRS expands our knowledge of the etiology of disorders by also assessing unrelated individuals, increasing sample size considerably, and further investigating shared risk among traits. As techniques such as WGCNA, TI, pathway, and gene enrichment analyses are applied more widely to the study of complex traits, we can only forecast increased precision in the study of PTSD. Undoubtedly, continued advances in the field will better inform our understanding of PTSD as well as translate into expanding new ways of intervention and prevention.

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CHAPTER 12

What Brain Tissue Can Tell Us
POSTMORTEM BRAIN BANKING AND ANALYSIS OF PTSD MOLECULAR PATHOLOGY

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Molecular investigations on the postmortem tissue of psychiatric disorders have become critical to understanding the genes, pathways, and transcriptomic organization occurring in diseased brain and provides the only avenue available to study brain-specific molecular characterizations *in vivo* (Schmitt, Parlapani, Bauer, Heinsen, & Falkai, 2008). Postmortem studies have been carried out on many psychiatric disorders, including schizophrenia (Ming Li et al., 2016), bipolar disorder (BPD; Hoffman et al., 2019), major depressive disorder (MDD; Duric et al., 2010; LaBonté et al., 2017; Pantazatos et al., 2016), and drug dependence (Farris, Arasappan, Hunicke-Smith, Harris, & Mayfield, 2014; Kapoor et al., 2019), and have led to improved understanding of the structural and molecular pathological underpinnings of these disorders. As it is likely that brain-specific molecular changes account for the majority of pathological changes, postmortem tissue analysis will be indispensable for improving our understanding of the etiology of these diseases.

Postmortem neuropsychiatric research has advanced considerably in the past few years from case control comparisons to complex genomic analyses, including transcriptomic, epigenetic, and proteomic analyses often coupled with neurobiological studies involving neuroimaging techniques and/or pharmacology. Furthermore, increased interest in studying the molecular pathology of psychiatric disorders such as autism and schizophrenia have led to the creation of large consortia (e.g., PsychENCODE [Akbarian et al., 2015]), CommonMind [Hoffman et al., 2019], and BrainSpan [Najafi, Naseri, Zahiri, Totonchi, & Sadeghizadeh, 2019]) that pool resources, tissue, and analytics. These groups are supported by the National Institutes of Health (NIH) and highlight the growing need and expanding interest in postmortem brain tissue analyses. This need has also raised concerns particularly in implementation of standardized tissue characterization as well as employment of larger sample sizes. Developing a steady

source of well-characterized brain tissue is a major challenge in postmortem brain studies.

Recognizing the challenge of continuous postmortem tissue collection, the NIH began the NeuroBioBank that encompasses six biorepositories, with the specific purpose of collecting postmortem brain tissue specimens spanning neurological, neuropsychiatric, and neurodevelopmental diseases and disorders (*www.neurobiobank.nih.gov*). All sites adhere to stringent rules of collection and neuropathological characterization, and the collection now includes over 9,000 cases. In addition to the NIH Brain Bank, there are numerous brain banks in the United States and abroad that are both privately held or academically and/or government funded. Some are disease specific but most include tissue from many different disorders.

A great deal of effort has been devoted to collecting postmortem tissue of developmental neuropsychiatric disorders such as schizophrenia and autism. In addition, there are several well-characterized collections of postmortem tissue for major depression and suicide, alcohol use disorder, and bipolar disorder. Until very recently, there has not been extensive collection of postmortem tissue from cases with posttraumatic stress disorder (PTSD). Under an initiative of the U.S. Department of Veterans of Affairs National Center for Posttraumatic Stress Disorder (NCPTSD), the National PTSD Brain Bank (NPBB) was established with the goal of collecting PTSD postmortem tissue for molecular and cellular characterization to identify biomarkers and potential therapeutic targets for PTSD (Friedman et al., 2017).

Postmortem brain studies are quickly becoming the gold standard for identification of molecular substrates involved in neurological and neuropsychiatric disorders. There is an important need for the development of a PTSD brain collection to better understand the etiology and molecular pathways that contribute to this disease, particularly as most individuals exposed to traumatic events do not develop PTSD symptomology. NCPTSD, a center of excellence within the U.S. Department of Veterans Affairs (VA), has formed a centralized collection of PTSD postmortem tissue from centers from around the country. This chapter discusses the organization and practices of the NPBB and its role in PTSD brain collection and neuropathological analyses. We then explore how postmortem brain tissue aids in the identification of the molecular processes of diseased tissue and how this data can be extended to identify relevant biomarkers and potential therapeutic targets.

BRAIN BANK ORGANIZATION AND COLLECTION

The NCPTSD is a consortium of seven linked divisions covering areas relevant to PTSD research, education, and treatment. Specific areas include behavioral science, diagnostic assessment, clinical neuroscience, randomized clinical trials, implementation of evidence-based care, and clinical program evaluation. The NPBB is a six-part consortium with its Executive Division at NCPTSD at the VA Medical Center in White River Junction, Vermont, and its hub physically located at the VA Boston Healthcare System. The Boston site is the primary collection and dispersal hub for PTSD brain tissue being collected from sources, including the Durham, North Carolina/Duke University Brain Bank and the University of Miami Brain Endowment Bank. Additional tissue has been obtained from the University of Pittsburgh and the Lieber Institute for Brain Development. Having the NPBB's hub in Boston permits close collaboration and programmatic linkage with other VA and Boston University brain banks that focus on Alzheimer's

disease, amyotrophic lateral sclerosis (ALS), traumatic brain injury (TBI), encephalitis, and Gulf War illness. Antemortem donors provide informed consent to donate their brains to NPBB while they are still alive, while postmortem donations are acquired through the VA Brain Bank Biorepository (VABBB) collection network, medical examiners, and organ donation organizations after informed consent is received through next of kin.

Many patients with PTSD are also comorbid for other anxiety and mood disorders. PTSD has also been associated with a high risk for suicidal ideation and completed suicide attempts in both civilian and military cohorts (Gradus, 2017). In a recent Danish cohort study, the rate of completed suicide among individuals with PTSD was 13 times the rate for non-PTSD individuals (Gradus et al., 2015). Furthermore, it appears that comorbid PTSD and depression is a stronger predictor of suicidal ideation (Ramsawh et al., 2014) and suicide attempts (Kimbrel, Meyer, DeBeer, Gulliver, & Morissette, 2016) than a PTSD diagnosis alone. This is particularly relevant as 52% of individuals with current PTSD are also comorbid for MDD (Rytwinski, Scur, Feeny, & Youngstrom, 2013) and recent psychiatric, epidemiological, physiological, and genetic studies have revealed both shared and distinct phenotypic signatures in PTSD and MDD. To address this issue, the NPBB has focused its tissue acquisition strategy on obtaining comparison brain tissue from donors with MDD with no diagnosis of comorbid PTSD. This non-PTSD psychiatric control group was chosen to control for quality of tissue, manner of death (suicide vs. nonsuicide), antemortem treatment, and substance abuse/dependence. Furthermore, this comparison also allows for the ability to disentangle the molecular substrates that are common versus those that are unique either in PTSD or in MDD brain tissue.

In addition to PTSD cases, the NPBB collects postmortem human brain samples from healthy nonpsychiatric controls and from people with a history of neuropsychiatric disorders, including MDD, depressive disorder not otherwise specified, alcohol use disorder, anxiety, and bipolar disorder. Because postmortem tissue collection has only begun recently, a large portion of the the NPBB current tissue collection was obtained from postmortem donors through collaboration with the Lieber Institute for Brain Development (LIBD; Mighdoll et al., 2017). To date, the NPBB has acquired 185 hemisected brains from LIBD. There are 69 participants with PTSD (mean age, 42.6 ± 14.1 years, 32 females; Table 12.1), 48 matched neurotypical controls (mean age, 46.7 ± 15.2 years, 13 females), and 48 MDD cases (mean age, 44.0 ± 14.1 years, 19 females). There are no significant differences between the PTSD, MDD, and control samples in age, postmortem interval (PMI), or tissue pH.

TABLE 12.1. PTSD Postmortem Brain Collection Demographics

	All cases (n = 67)	Combat PTSD (n = 18)	Domestic PTSD (n = 49)
Age at death (years)	42.6 ± 14.1	47.1 ± 17.8	41 ± 12.2
Sex (% male)	52.20%	100%	34.70%
Race (% White)	83.60%	77.80%	85.70%
Manner of death (% suicide)	17.90%	16.70%	18.40%
% Drug-related death	64.20%	39%	61.20%
% Comorbid substance use disorder	73.10%	66.70%	75.50%
% Comorbid depression	82.10%	55.60%	91.8%

NEUROPATHOLOGICAL CHARACTERIZATION OF POSTMORTEM BRAIN TISSUE

When donor death occurs, brains are collected at autopsy. A 34-item screening is completed with next of kin on the day of collection (Isometsä, 2001; Spitzer, Williams, Gibbon, & First, 1992). This information includes demographic data, neurological, medical and psychiatric information, as well as smoking status at time of death (Brent et al., 1993; Deep-Soboslay et al., 2005). All cases are grouped by type of trauma (physical and/or sexual) and screened for military service, including combat exposure.

Comprehensive toxicology and pharmacology screens are employed on every case. Over-the-counter drugs, ethanol and volatiles, cocaine and its metabolites, opiates (including prescription), benzodiazepines, and phenycyclidine levels are measured. Prescription medication relevant to diagnosis is also screened and includes antidepressants, antipsychotics, and mood-stabilizing agents. Cannabinoids, their metabolites, nicotine, and cotinine are also screened for (Mighdoll et al., 2017).

All brain tissue undergoes physical examination by a board-certified neuropathologist at both the macroscopic and microscopic level. All tissue is screened for confounding neuropathologies, including amyloid plaques, Lewy bodies (Parkinson's disease and dementia with Lewy bodies), and transactive response DNA binding protein-43 (TDP-43) (ALS, frontotemporal dementia, and limbic predominant age-related TDP-43 encephalopathy). All cases are also evaluated at a gross (macroscopic) level to detect evidence of atrophy, trauma, or infarction. Importantly, cases were excluded if massive trauma occurred (from head injury) that severely damaged the tissue, if the tissue was damaged from a stroke involving a large portion of the brain, if the decedent was on a respirator for an extended period of time, if the donor had brain cancer, or if the donor had a history of HIV, AIDS, COVID-19, or other communicable disease.

PMI, along with the RNA integrity number (RIN) and tissue pH, is a widely accepted parameter for determining tissue quality for molecular assays of postmortem tissue (Schroeder et al., 2006; Walker et al., 2016). PMI is calculated from the time the subject is pronounced dead by a medical examiner until brain freezing by the collection agency. This time takes into account length of storage and time to dissect brain tissue. While there is considerable debate about what constitutes an acceptable PMI, most studies suggest that optimal RNA-sequencing results are obtained from tissue with a PMI of 36 hours or less (White et al., 2018). It is important to consider that most bodies are refrigerated shortly after death, and an extended PMI in refrigerated tissue may provide high-quality tissue for molecular analysis. Conversly, tissue that has been left at room temperature or at an elevated temperature may undergo a significant degree of postmortem autolysis. On average, NPBB PMIs were 29.1 ± 9.1 hours for PTSD cohort, 27.8 ± 9.0 hours for MDD cohort, and 30.2 9.3 hours for the neurotypical controls. RIN and pH are routinely measured as well and are included in the case file. At the time of dissection, brain weight, pH, and freezing time are also noted, so they can be included in downstream molecular analyses and are used as a quality control check. Gross pathology of each brain is recorded during dissection, and tissue is then frozen in a mixture of dry ice and methyl butane (Mighdoll et al., 2017) or on aluminum plates on a bed of dry ice.

Modern neuropathology for the diagnosis of neurodegenerative disease consists of a gross evaluation of the brain followed by a histologic workup of the tissue. Neurodegenerative diseases are characterized by a stereotyped pathology and regional involvement of the brain and/or spinal cord. Although clinical diagnoses often predict the underlying pathology, there are discrepancies in 10–40% of subjects, depending on

the syndrome (Brenowitz et al., 2017; Perry et al., 2017). For this reason, a neuropathological workup is necessary for clinical correlation, and in some neuropathological conditions like chronic traumatic encephalopathy, the diagnosis can only be made after death.

At present, there is no neuropathological signature associated with PTSD using the existing toolbox of diagnostic stains. The NPBB's goal is to develop biomarkers that can distinguish tissue from those with PTSD from those without. Those with PTSD carry an increased risk of dementia (Yaffe et al., 2010). To distinguish any novel neuropathology associated specifically with PTSD, we must first characterize any comorbid pathology that is present in these cases. All cases in the NPBB are evaluated with an extensive neuropathological exam that includes 22 distinct regions and uses special stains for phosphorylated *tau,* amyloid beta, alpha synuclein, and TDP-43 to classify and grade pathologies present in the tissue. This workup also includes Luxol fast blue (LFB), which highlights myelin, and hematoxylin/eosin, which highlights cell nuclei as well as specific cell types such as neurons and reactive astrocytes. Additional stains are sometimes employed when specific neurodegenerations are suspected, such as glial fibrillary acidic protein (GFAP) for reactive astrocytosis and p62 to detect specific inclusions associated with ALS. To maintain diagnostic consistency with other neuropathologists, a silver stain is used for grading Alzheimer's-type pathology. All cases are scored by Braak and Braak for NFTs (0–VI scale; Braak, Alafuzoff, Arzberger, Kretzschmar, & Del Tredici, 2006; Braak & Braak, 1991), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scale for plaques (0–3; Mirra et al., 1991), Thal phase of Aβ plaque accumulation (0–5; Thal, Rüb, Orantes, & Braak, 2002), cerebral amyloid angiopathy severity and type (0–3, intracortical and leptomeningeal), and Lewy body disease type (olfactory, brainstem, transitional, neocortical, and amygdala-predominant; Montine et al., 2012). The presence of TDP-43 inclusions is assessed in multiple regions, including the spinal cord, medial temporal lobe, medulla, and frontal cortex. For cases with motor neuron disease, the TDP-43 stage is determined using the criteria of Brettschneider and colleagues (2013).

The diagnostic neuropathological exam will identify most known neuropathologies, which generally involve misfolded aggregates of protein. Detection of PTSD will require translating the macroscopic changes observed with imaging techniques into microscopic correlates. Imaging studies of individuals with PTSD have demonstrated changes in cortical thickness (Wrocklage et al., 2017) and amygdala size (Morey et al., 2012). Future histochemical studies will need to correlate macroscopic structural changes with microscopic alterations such as variation in synaptic density, neuronal loss, and white matter integrity.

BEST PRACTICES OF BRAIN BANK DIAGNOSTIC PROCEDURES, TISSUE PROCESSING, AND TISSUES DISSEMINATION

Diagnostic Protocols

The best prepared tissue in the world has limited usefulness in research without confidence in the donor's psychiatric diagnosis. In the case of *antemortem donors* who enroll in NPBB before death, the following antemortem assessment protocol (AAP) is followed. After obtaining informed consent, donors are assessed via telephone with state-of-the-art structured clinical diagnostic interviews (e.g., Clinician Administered PTSD Scale [CAPS], Mini International Neuropsychiatric Interview [MINI]), and a brief cognitive

screening (Telephone Interview of Cognitive Status—Modified [TICSm]). Demographic factors, medical history, social history, lifestyle factors, and functional achievements are obtained via mail-based surveys. Finally, a thorough review is made of the medical record. This assessment determines current versus lifetime PTSD diagnosis, along with other psychiatric comorbidities such as major depressive disorder. Annual follow-up assessments are conducted to update health information and track PTSD symptomatology (PTSD Checklist) and cognitive function (TICSm). The AAP utilizes a standardized verification procedure to confirm and integrate multiple sources of enrollee information to determine a current and/or lifetime PTSD diagnosis for enrollees. The final step is determining a Diagnosis Confidence Index for PTSD diagnoses, which ranges from 1 (PTSD unlikely) to 5 (PTSD definite).

A much bigger challenge is postmortem diagnostic assessment. Next of kin may not be aware of important subjective PTSD symptoms because the deceased donor never discussed them. NPBB's postmortem diagnostic assessment protocol (PAP) (1) provides a standardized approach for a comprehensive psychiatric and medical record review; (2) tracks and registers the range of previously documented clinical diagnoses, behaviors, and symptoms as well as psychosocial functioning; (3) queries for lifetime history of exposure to potentially traumatic stressors; (4) catalogs results of psychological assessment reports and medical and neurological testing; and (5) provides corroboration of medical record information via interviews with next of kin and/or health care providers familiar with the donor's life history. Finally, as with the AAP, diagnoses determined via the PAP are given a Diagnosis Confidence Index ranging from 1 (PTSD unlikely) to 5 (PTSD definite).

Although there are always diagnostic challenges for any brain bank enrolling postmortem donors, there are unique challenges for PTSD. Individuals with PTSD are especially reluctant to discuss their symptoms with anyone, since such discussions often retrigger painful traumatic memories. Furthermore, next of kin may be unaware of the deceased's nonbehavioral PTSD symptoms because of their subjective nature, reluctance to discuss them because of PTSD avoidance symptoms, and reluctance to acknowledge psychiatric symptoms because of the stigma often associated with such disclosures. These problems can be offset to a great extent when hospital records can be obtained that will enhance diagnostic accuracy.

Peer Review of Research Proposals

When there is a request for brain tissue, NPBB's Tissue Access Committee (TAC) reviews the scientific merit of each proposal, the investigator's productivity, institutional resources, federal/other funding, and the nature/magnitude of the tissue request. Since many investigators request amygdala tissue, which is a very small nucleus, the TAC must balance available tissue inventory with the quality and importance of the request. Furthermore, there may be tissue requests which duplicate investigations that have already been initiated (such as RNA sequencing of key brain nuclei that mediate or moderate PTSD symptoms). Establishment of a data biorepository is one way to approach this matter (see below). Once approved, requested brain fixed and/or frozen tissue is disbursed to approved investigators.

Among the many principles and regulations for operation of brain banks, it is important to have a code of conduct that governs the many complex steps needed for successful operations. With regard to tissue disbursement, a number of documents are needed, such as tissue application forms, material transfer agreements, confidentiality

agreements, and personal data protection measures (Deep-Soboslay et al., 2011; Kliouеva et al., 2015).

Maintenance of a Confidential Data Biorepository

Confidentiality and data security are essential. Privacy must be maintained regarding all collected data. Since NPBB is located within VA, the VA's firewall and safeguards for confidentiality provide an extra layer of protection for any data generated from tissue donations to NPBB (Amarasinghe et al., 2013; Ravid & Ikemoto, 2012; Sheedy et al., 2008).

All raw data derived from research on brain tissue that NPBB has banked and disbursed to investigators is archived in a data biorepository before it can be shared with authorized investigators. In this way, authorized investigators requesting NPBB tissue for a research project that has already been completed may be eligible to receive de-identified data from the data biorepository rather than precious brain tissue. NPBB's data meets VA's stringent requirements for privacy and data security. NPBB is part of that process and will utilize cloud technology when it becomes available.

Strict Adherence to Ethical Standards

A number of important ethical issues and challenges are associated with operating a brain bank. First, given the sensitivity and altruism involved in making a donation to a brain bank, a thorough and rigorous informed consent process must be provided for next of kin who are considering the donation of a loved one's brain tissue in the immediate aftermath of their loss. (In some jurisdictions, next of kin must provide consent even if their loved one had previously provided informed consent.) Similarly, donors who enroll in the NPBB and consent to assessment and eventual donation of their brain tissue must involve their next of kin in informed discussions about their decision because families need to know, before death, that their loved one's brain will be used for scientific research (as opposed to organ transplant). Whether it is an antemortem or postmortem brain donation, donors and families alike have an opportunity to adequately review and understand (usually with the help of NPBB staff as well as an informational brochure) the research purposes and organization of the brain bank. Living enrollees and their families must also understand that they can withdraw consent at any time. As antemortem donors may be enrolled years before their death, there is annual, longitudinal follow-up to allow for up-to-date medical assessment over time and to ensure that the NPBB is notified at the time of donor death. This requires a balance of tactfulness and persistence that upholds ethical standards and respect for the dignity and autonomy of enrollees and their families, yet allows for timely collection of data and tissue. To the extent that enrollment may be sought by or offered to elderly and/or medically ill persons, care must be taken to insure that potential donors are competent to provide informed consent. It is impressed upon donors and their families that any data generated from their family member's tissue are protected by privacy and confidentiality safeguards; this is an increasing concern for next of kin due to the development of techniques for postmortem genetic analyses that may have privacy implications for living relatives (Amarasinghe et al., 2013; Benes, 2005; Schmitt et al., 2007). Finally, to the extent that the NPBB receives brain tissue from other existing collections or brain banks, the NPBB must take appropriate measures to ensure that this tissue was also obtained under institutional review board-approved protocols,

with appropriate safeguards to insure informed consent from donors and appropriate privacy safeguards.

USING MULTIDIMENSIONAL GENOMIC DATA TO UNDERSTAND THE MOLECULAR PATHOLOGY OF PTSD

Psychiatric disorders such as PTSD and depression are devastating illnesses, with high personal and societal costs and limited treatment options. Therefore, to understand the disease etiology, it is necessary to perform comprehensive analyses of the gene expression, epigenetic modification, and genomic patterns across brain regions and cell types in both diseased and control tissue.

Unfortunately, human brain tissue is difficult to study for many reasons. As indicated earlier in the chapter, it is often difficult to obtain high-quality postmortem human brain tissue (made significantly more difficult when confined to particular disorders). The lack of sufficient sample size needed to overcome individual or cohort variability also presents challenges. These issues are further exacerbated by molecular and cellular differences in regional brain structures (Darmanis et al., 2015; Johnson et al., 2015; Kang et al., 2011; Miller et al., 2014). Even within discrete regions of the brain, there are numerous cell types that are molecularly and morphologically distinct from one another. Recent advances in single-cell transcriptomic technologies are beginning to address these issues and are discussed below.

The current genomic studies being conducted by the NPBB are focused on PTSD and MDD. Our investigations into these disorders will prioritize brain regions and cell types that previous studies suggest contribute to these disorders. Three regions implicated by clinical and preclinical studies are the amygdala, hippocampus, and prefrontal cortex (Haubensak et al., 2010; LeDoux, Iwata, Cicchetti, & Reis, 1988; Pape & Paré, 2010; Wilensky, Schafe, Kristensen, & LeDoux, 2006). Discrete subregions of the prefrontal cortex include the dorsolateral prefrontal cortex (dlPFC, Brodmann's area [BA] 9/49), dorsal anterior cingulate cortex (dACC, BA 24), subgenual anterior cingulate (sgACC, BA 25), and the medial orbitofrontal cortex (OFC, BA 11). Other subregions of interest include the central amygdala (CeA) and basolateral amygdala (BLA) and in the hippocampus (CA subregions, dentate gyrus, and subiculum; Girgenti & Duman, 2018). Currently, the prevailing (simplified) model of of PTSD pathophysiology is that inhibition of the PFC leads to hyperactivation of the amygdala and reduced functioning of the hippocampus, thereby causing exaggerated fear responsiveness (Milad & Quirk, 2002; Quirk, Russo, Barron, & Lebron, 2000). Therefore, these three regions have been prioritized for study because they are associated with confirmed alterations in PTSD and known intermediate phenotypes such as volumetric and activity changes, reductions in gray and white matter density, and stress-induced memory disturbances (Nees, Witt, & Flor, 2018).

The NPBB has begun by performing whole-tissue transcriptomic studies (Figure 12.1). The advent of massively parallel RNA sequencing has greatly advanced our understanding of the molecular determinants of many neuropsychiatric disorders (Gandal et al., 2018; Kohen, Dobra, Tracy, & Haugen, 2014; LaBonté et al., 2017; Wang et al., 2018).

RNA-seq uses next-generation sequencing technology to profile the transcriptome of many types of tissues and samples. Briefly, mRNA is extracted, and complementary DNA is generated into libraries with specialized sequence adapters attached to the 3′ and 5′ ends of the strand for attachment to a lawn where sequencing occurs. Fluorescently

labeled nucleic acids are added in the sequence-specific manner to a strand of cDNA and imaged to generate a complementary "read" of the mRNA. The results of this sequencing allow for unprecedented analysis of not only what is expressed but also how it is expressed; alternative splicing events, exonic SNP identification, and novel transcript detection data are all available by RNA-seq (Wang, Gerstein, & Snyder, 2009).

To date, transcriptomic studies of PTSD postmortem tissue have been limited. These studies have either been single-candidate gene studies or had relatively small numbers of samples. NPBB's first PTSD postmortem study identified upregulation of the protein *P11* in the dlPFC (Zhang et al., 2008). *P11* is involved in a variety of cellular functions, including cell proliferation, and is reported to be regulated in major depressive disorder (Svenningsson, Kim, Warner-Schmidt, Oh, & Greengard, 2013). NPBB's first pilot study (N = 5) using whole-genome microarray analysis showed significant regulation of over 250 transcripts in the PTSD dlPFC (Licznerski et al., 2015). This study identified the serum/glucocorticoid regulated kinase 1 (*SGK1*) as downregulated in PTSD cortex. Rodent models of PTSD revealed that *SGK1* inhibition caused higher levels of freezing in contextual memory recall of animals exposed to fear conditioning and decreased spine density of medial PFC, leading to decreased amplitude and frequency of spontaneous mini-excitatory postsynaptic currents. These findings point to a role for *SGK1* in the functional changes of PTSD brain.

Recently, an NPBB intramural research group reported the first large-powered transcriptomic study of PTSD brain (Girgenti et al., 2021). RNA-seq was used to characterize the differentially expressed genes (DEGs) of four PFC subregions (dlPFC, BA

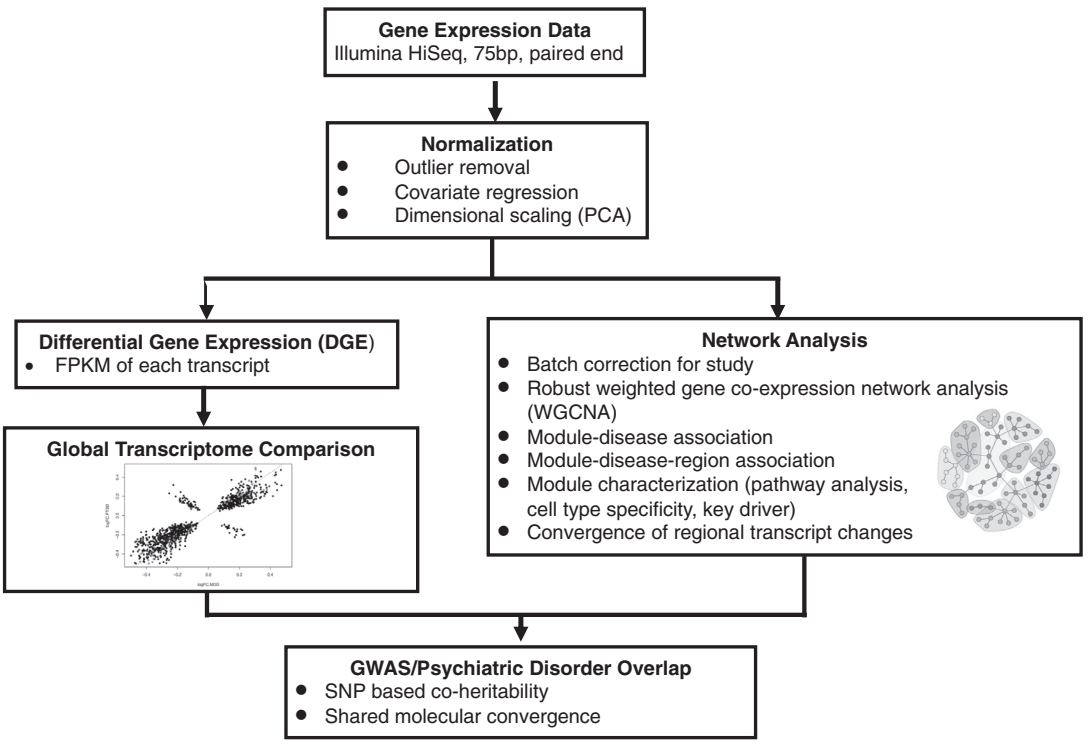

FIGURE 12.1. Flow chart of PTSD transcriptome analysis pipeline.

9/46), medial OFC (BA 11), dACC (BA 24), and subgenual prefrontal cortex (sgPFC, BA 25) from postmortem tissue of subjects diagnosed with PTSD, a matched non-PTSD psychiatric control (MDD) and matched neurotypical controls. For each brain region, we examined 52 PTSD subjects (26 males, 26 females), 45 MDD (18 females, 27 males), and 46 controls (20 females, 26 males). We identified marked sexual dimorphism in the transcriptomic organization of the PTSD PFC. We integrated genotype data from the largest PTSD genome-wide association study (GWAS) (N = 186,689; Stein, Jang, Taylor, Vernon, & Livesley, 2019) with genotype-tissue expression (GTEx) data (GTEx Consortium, 2015) for human prefrontal cortex eQTLs to perform the first transcriptomewide association study (TWAS) of PTSD. Seven cortical TWAS hits were also identified as significant DEGs, including the interneuron, key driver *ELFN1*.

While whole-tissue RNA-seq has been successful in identifying many of the molecular determinants of psychiatric disorders, the shear number of different cell types in the human brain makes interpretation of this data difficult. Single-cell capture methods, including fluorescent-activated cell sorting and laser capture microdissection, are limited in that they require a priori knowledge of the cell types harboring biologically meaningful molecular signals. Single-nuclei RNA-sequencing (snRNA-seq) has emerged as the definitive method for single-cell molecular studies (Lake et al., 2018). Briefly, snRNA-seq combines microfluidics and next-generation sequencing to allow single-cell interrogation of the transcriptome. Sequencing is performed on the nuclei of cells because of technical difficulties in isolating intact whole cells from frozen brain tissue. It should be noted that there is high concordance between the transcriptome of the cytoplasm and nucleus, providing validation for the snRNA-seq approach (Lake et al., 2018). This technically complex assay has been applied to several neurological (Mathys et al., 2019) and developmental disorders (Mingfeng Li et al., 2018; Zhu et al., 2018) and has become extremely informative in postmortem molecular studies.

According to some estimates, the human genome contains 400,000 enhancer and 70,000 gene promoter regions (ENCODE Project Consortium, 2012). Control of these regulator regions involves several substrate modifications, including DNA methylation and histone posttranslational modifications (Cedar & Bergman, 2009). Since methylation determines which part of the gene is expressed or suppressed, individual differences in methylation of the same gene can account for differences in how that gene is expressed (see Girgenti, Chapter 12, this volume, on PTSD-related genetic research). Methylation of DNA, at CpG and non-CpG dinucleotides, can be assayed by SNP microarray to obtain genome-wide DNA methylation profiles of PTSD and neurotypical control cases, adding an epigenomic layer to the consortium's efforts. This technology uses bisulfite conversion of DNA to find C-to-T changes at defined genomic positions (representing 99% of RefSeq genes and 95% of CpG Islands).

Mass spectrometry-based proteomics is becoming a popular technology in the field in molecular genomics. It allows for systematic study of the proteins expressed in a biological system at a given time and condition and is suitable for identifying and quantifying proteins and protein modifications across numerous types of samples. Several studies have used proteomic approaches to discover molecular determinants of neuropsychiatric diseases, including schizophrenia (Martins-de-Souza et al., 2009; Saia-Cereda et al., 2015), MDD (Martins-de-Souza et al., 2012; Stelzhammer et al., 2014), and BPD (Gottschalk, Wesseling, Guest, & Bahn, 2015).

The NPBB is developing a novel strategy for protein identification and quantification in postmortem brain tissue. Previously, we used standard methods of protein isolation and digestion before tandem mass spectrometry to identify proteomic changes in

sgPFC of PTSD patients. While we were able to identify numerous changes in the PTSD transcriptome of tissue isolated from identical samples, we were unable to identify any changes to the proteome despite being able to detect expression of over 3,000 different proteins. When mRNA transcript changes are overlayed with protein abundances from mass spectrometry, we find that the median expression of genes significantly changed by mRNA is much lower than the median expression of detected proteins (Figure 12.2). This suggests that our current system is not sensitive enough to detect significant changes of lower abundance proteins. It is likely that many important proteomic changes are occurring at the level of low-abundance proteins, and so our focus is on developing technologies to identify these changes (Sandberg, Branca, Lehtiö, & Forshed, 2014). We are developing the first tandem mass tag (TMT) system for labeling and quantifiying postmortem brain proteins by mass spectrometry. The TMT labeling approach is similar to other peptide isotope techniques, but it has several distinct advantages (Ren et al., 2016; Thompson et al., 2003). Pairs of TMT peptides are chemically identical and have the same overall mass allowing them to comigrate in chromatographic separations. This acts as a more precise internal standard allowing for more accurate quantification.

Utilizing proteomics and transcriptomic data will allow for the identification and examination of pathways that are differentially regulated in PTSD by combining genetic, epigenetic, transcriptomic, and proteomic levels of analysis. One of the primary goals of the NPBB is to develop a PTSD postmortem multi-omics dataset to identify global mechanisms relevant to PTSD. The brain bank is now large enough to provide sufficient statistical power to reliably detect different types of genomic elements active in PTSD brain. DNA variation datasets will be integrated with datasets of transcript abundance datasets (eQTL), protein expression (pQTL) and methylation status (epiQTL; Figure 12.3). Confounding factors, including age, sex, and technical

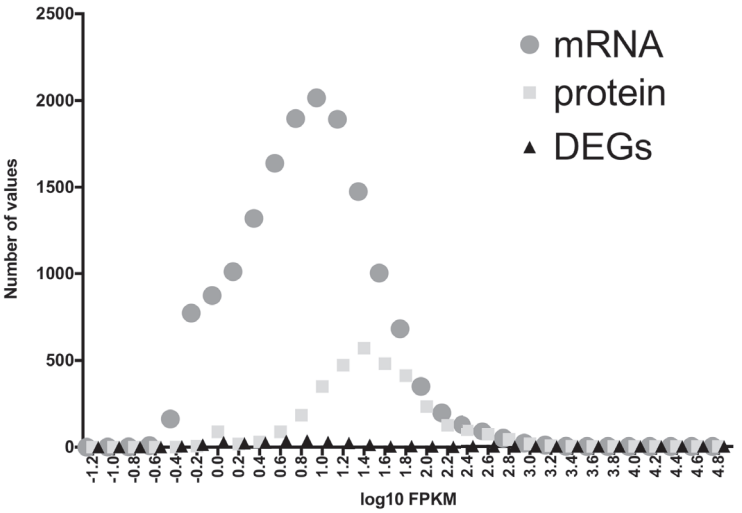

FIGURE 12.2. Distribution of mRNA and protein levels in human subgenual anterior cingulate. Histogram shows the number of transcripts and proteins identified. Significantly regulated mRNA (DEGs) is plotted in white. The median expression of genes significantly changed (DEGs) is lower than the median of detected proteins.

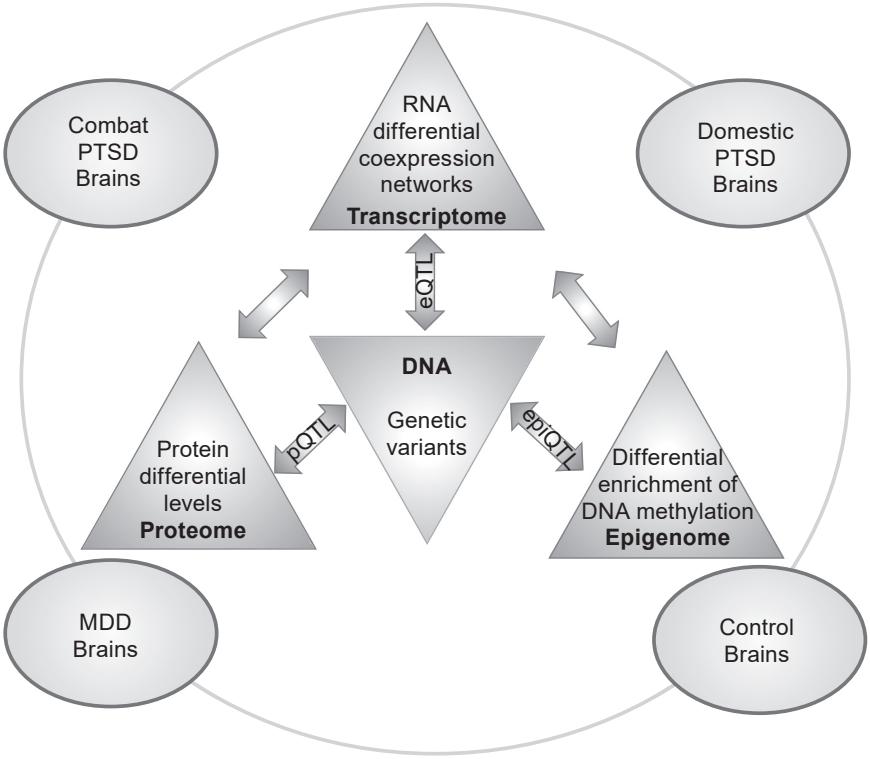

FIGURE 12.3. Overview of the NPBB molecular studies showing a schematic of the proposed data and analyses. The genomic data will be generated from bulk tissues and sorted nuclei. For each data type, brain region, cell type, sex-specific, and disease-related differences will be identified. Data modalities will be integrated to identify global mechanisms relevant to PTSD. Bidirectional flow between genetic information and functional data define eQTLS, epiQTLs, and pQTLs, which in turn will assist in prioritizing gene targets.

covariates, can be taken into account and corrected for. This will allow for comparison with already existing datasets from human PTSD studies, such as the PGC-PTSD consortium (Duncan et al., 2018), the Million Veteran Program (Gaziano et al., 2016; Gelernter et al., 2019), and predicted biomarkers identified in peripheral tissue (Passos et al., 2015). This method takes an integrated approach, modeling transcriptomic, genetic, methylomic and proteomic data.

TRANSLATIONAL APPLICATIONS AND NOVEL THERAPEUTICS

PTSD is among the most likely of psychiatric disorders to be understood from the perspective of environmental influences interacting with genetic vulnerability. Diagnosis requires identification of a prior, specific, highly traumatizing, fear-evoking experience. Risk heritability of PTSD is estimated to be between 30 and 40% after trauma (Koenen et al., 2003, 2005; Stein et al., 2002; True et al., 1993; Xian et al., 2000). One of the best current treatments is exposure-based cognitive-behavioral therapy, which

is thought to act through the fear circuitry of the brain. The only FDA-approved treatments are two classes of antidepressants: SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors) and specific psychotherapies (McAllister, 2009; Mellman & Lydiard, 2008; Strawn, Keeshin, DelBello, Geracioti, & Putnam, 2010).

A promising route for discovery of novel therapeutic agents for PTSD is multi-omic characterization for postmortem brain tissue from affected individuals. Integration of neuropathological, transcriptomic, proteomic, and neurochemical expression data on the same set of brain tissues will likely reveal disease-related targets. These datasets, coupled with genome-wide genetic studies (which by necessity require larger sample sizes), would likely reveal the strongest therapeutic targets possible.

Recently, there has been increasing interest in the computational analysis of drug perturbation datasets (Musa et al., 2018). Large-scale perturbation datasets such as Connectivity Map (CMap; Lamb et al., 2006; Subramanian et al., 2017) or Library of Integrated Network based Cellular Signatures (LINCS; Vidović, Koleti, & Schürer, 2014) combine single-target pharmacology with whole-genome transcriptomics to provide enormous databases of drug–gene interactions that can be mined for genes identified in genomic studies. These databases can be used to determine if there are interactions between candidate genes and available drug treatments and could indicate novel drug strategies. For example, Stein and colleagues (2021) identified *PLEKHM1* as a high-confidence target meeting genome-wide significance in the largest PTSD GWAS. Drug-repositioning analysis with CMap identified several classes of drugs sharing biological effects with *PLEKHM1,* including dopamine receptor antagonists, acetylcholine receptor antagonists, and angiotensin receptor antagonists. It is likely that even more suitable targets will be discovered by identifying GWAS hits that overlap with transcriptomic or proteomic targets changing in PTSD.

SUMMARY

The most compelling reason for establishing a PTSD postmortem brain bank is to elucidate the molecular biology of the disorder in the hopes that this information will lead to novel targets for treatment. The collection of the NPBB is ongoing and is expected to increase in the future. In the face of increasing civilian and military trauma, there is a critical need for a more mechanistic understanding of the neural circuitry underlying PTSD. In so far as this problem exists, brain-specific molecular changes can only be measured in postmortem human brain. In this chapter, we have discussed a multi-omic approach to understanding the molecular determinants of PTSD, the main outcome of which will be a predictive model of genetic, epigenetic, transcriptomic, and proteomic profiles of brains from PTSD cases versus controls. The creation of a PTSD brain bank coupled with this model will allow an understanding of brain-specific molecular profiles and identification of targets relevant for PTSD therapy.

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CHAPTER 13

Gender Issues in PTSD

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Effective research and treatment of posttraumatic stress disorder (PTSD) requires attention to gender issues regarding trauma exposure, traumatic stress reactions, and treatment of PTSD. Men and women differ markedly in the patterns of exposure to traumatic stressors, and the prevalence of PTSD among women is at least twofold that of men, across a wide range of populations and nationalities (Seedat et al., 2009; Shalev et al., 2019). The phenotypic expression of PTSD is reliably similar across men and women, as is treatment effectiveness. DSM-5 (American Psychiatric Association, 2013) is the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* to specifically address gender issues in PTSD. Across the continuum of care, awareness of the potential impacts of gender is integral to detection, diagnosis, prevention, and treatment. In this chapter, we synthesize widely held conceptual perspectives on sex and gender with the extant traumatic stress literature, while suggesting possible explanations for the observed effects of gender. We also point to specific directions for future research that will focus on important unanswered questions on the role of gender in the development and treatment of PTSD.

PERSPECTIVES ON SEX AND GENDER

The term *sex* refers to the biological signs of male or female, such as reproductive organs, chromosomes, and hormones. Accordingly, we use this term to refer only to specific sex-linked biological processes. The term *gender* refers to socially defined roles, traits, and entitlements ascribed to masculinity and femininity in a given community or culture. An individual's experience or expression of their gender may be more or less consistent with social norms for behavior that is expected or valued by gender. Within this chapter, we will use the term *gender* to refer broadly to the expression of sex-linked biological variables when moderated by social context, as well as gender-linked variation in individual psychological differences. Although the vast majority

of research treats both sex and gender as binary constructs (i.e., male/female, man/woman), research into sexual expression at the cellular level (Ainsworth, 2015) and the distribution of gender-normative psychological traits (Carothers & Reis, 2013) indicate a broader spectrum of possibilities.

Gender may have more utility when viewed as a social determinant of health, a proxy for multiple interacting biological, psychological, and cultural processes. Though biological sex may influence PTSD risk via genetic vulnerabilities (Duncan et al., 2017) or neurobiological pathways (Pineles et al., 2017), these factors are moderated by social-environmental effects. For example, culture moderates gender differences in the incidence of PTSD following disaster. In one study of PTSD symptoms following two very similar hurricanes in the United States (sample limited to non-Hispanic Americans) and Mexico, investigators found expected sex differences in PTSD, but more pronounced gender differences among participants from Mexico, representing a culture with more traditional gender roles, as compared to the United States, a culture with relatively more egalitarian roles (Norris, Perilla, Ibañez, & Murphy, 2001). Other social influences are more apparent when disaggregated by gender. For example, research documents a mental health "paradox" of similar rates of mental health conditions among Black and White Americans, despite differences in stressor exposure and socioeconomic status (Gibbs et al., 2012). Gendered models reveal an exception: a higher prevalence of lifetime PTSD among Black women as compared to White women (Erving, Thomas, & Frazier, 2019). The most informative explanations for sex and gender differences observed in quantitative research point to multiple, intersectional social processes. As a field, we must endeavor to capture the conceptual complexity associated with sex and gender within methodologically rigorous conceptual and statistical approaches. However, we must retain the important perspective that most responses to overwhelming traumatic stress represent universal human reactions.

CURRENT STATE OF THE ART

Gender and the Prevalence of Traumatic Events

The experience of trauma is widespread, and most trauma-exposed individuals are resilient to these experiences. In the United States, about 70% of the population has experienced at least one event consistent with the DSM-5 trauma criterion (criterion A) at some point in their lives (Goldstein et al., 2016), with similar proportions among men and women (Lehavot, Katon, Chen, Fortney, & Simpson, 2018). The similarity in DSM-5 trauma exposure for men and women found in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Goldstein et al., 2016) is consistent with some epidemiological estimates for DSM-IV trauma exposure (Blanco et al., 2018), but contrasts with other prior research using DSM-III-R and DSM-IV criteria (Tolin & Foa, 2006) that find a higher prevalence of trauma exposure among men. Some researchers have hypothesized that enhancements to the scope and specificity of trauma exposure items in modern epidemiological assessment instruments (e.g., specific queries for intimate partner violence, distinct from physical assault items) have led to more precise exposure estimates and attenuated gender differences (Mills et al., 2011; Peirce, Burke, Stoller, Neufeld, & Brooner, 2009).

Gender differences in the types of traumatic events experienced by women and men account for some, but not all, of women's increased risk for PTSD. Men are more likely to experience war-related events, accidental injury, serious illness, physical assault/

mugging, and terror attacks, and to witness injury, whereas women are more likely to experience all forms of childhood maltreatment, sexual assault/rape, intimate partner violence (IPV), kidnapping, and stalking (Blanco et al., 2018). Patterns of exposure influence the prevalence of PTSD because some traumatic events confer a higher risk for PTSD than do others. Worldwide DSM-IV data indicate that approximately 4% of individuals who experience any type of traumatic event will develop PTSD in response to that event, but the proportions differ across events (Liu et al., 2017). DSM-5 data from U.S. populations suggest a higher prevalence of PTSD among trauma-exposed individuals, at 9–10%, with similar heterogeneity in risk for PTSD across events (Goldstein et al., 2016; Kilpatrick et al., 2013). Across all populations and PTSD definitions, rape and sexual assault pose the highest risk for PTSD. Other events more common among women are linked to a higher-than-average risk for PTSD, including child physical abuse, kidnapping, and stalking. Although risk for PTSD following physical assault is relatively low, women are more likely to be assaulted by an intimate partner (Blanco et al., 2018), which poses a substantially higher risk for PTSD. Risk profiles for events more common to men are mixed: There is a higher-than-average prevalence of PTSD in response to torture, witnessing of atrocities, and accidents, and combat exposure (in the United States), but lower-than-average risk in response to injury, witnessing of death or serious injury, and mugging (Goldstein et al., 2016; Liu et al., 2017).

The frequency and timing of trauma exposure also contribute to women's greater PTSD risk, highlighting the importance of gendered exposure to childhood trauma, sexual violence, and repeated trauma exposures. Prior exposure to physical and sexual violence is associated with increased vulnerability to both subsequent trauma exposure (Benjet et al., 2016) and PTSD following subsequent trauma (Liu et al., 2017), which may exacerbate women's risk. Repeated, chronic exposure to violence and assault are associated with increased risk for PTSD (Liu et al., 2017), and the forms of violence more common among women (childhood abuse, partner violence) tend to be repeated, chronic forms of violence (Benjet et al., 2016; Goldstein et al., 2016).

Furthermore, chronic forms of trauma exposure create a "traumatic context" (Kaysen, Resick, & Wise, 2003) of fear, threat, and adversity, which also impact PTSD risk. For example, combat exposure is associated with war-zone stressors, including environmental characteristics such as quality or scarcity of basic resources, difficult living conditions, and pressure or constraints in performing duties (Fox et al., 2015; Sternke et al., 2017). Some aspects of war-zone stress differ among men and women, notably, the frequency of gender discrimination and harassment, which exert gender-linked risks for PTSD (Smith et al., 2017; Street, Gradus, Giasson, Vogt, & Resick, 2013). Traumatic contexts are also associated with higher prevalence rates of interpersonal violence. Rates of childhood abuse and IPV escalate in the wake of major natural disasters (Schumacher et al., 2010) and in high-crime environments (Finkelhor, Ormrod, Turner, & Hamby, 2005). Sexual trauma in the military is linked to service in combat zones (Barth et al., 2016), where the traumatic context potentiates the impact of direct exposure to traumatic events (Cobb et al., 2014). Finally, women's increased risk for physical and sexual abuse during childhood may be particularly important: These events cluster with other childhood adversities that enhance risk for poor adult mental health, erode existing social resources, and impede development of new resources (Barboza, 2018). These adversities also increase risk for subsequent trauma exposure as well as the risk for PTSD following subsequent trauma (Kessler et al., 2018).

Promising approaches to accounting for the interplay of qualitative and quantitative characteristics of trauma exposure are emerging, such as person-centered approaches

that group individuals into qualitatively different subtypes of trauma exposure. Using this approach, a study of North American adults found three classes of exposure: a low-exposure group (primarily vicarious trauma and accidents), a moderate-exposure group characterized by witnessing violence and being threatened with a weapon, and a high-exposure group characterized by a high prevalence of interpersonal violence experiences and a high number of exposures (Sullivan, Contractor, Gerber, & Neumann, 2017). This high-exposure group was significantly overrepresented among women and was associated with higher DSM-5 PTSD symptoms scores as compared to the other classes. Similar methods that can quantify the severity of trauma exposure into parsimonious but clinically meaningful ontologies will further advance efforts to identify gender-linked risk.

The Role of Social Context

Environmental characteristics may function as risk factors for both trauma exposure and PTSD. Supportive social networks can buffer the impacts of traumatic stress (Vogt, Erbes, & Polusny, 2017); social capital, a term that refers to area attributes of social support, social resources, and connectedness in the environment, functions similarly as a contextual risk factor. Lower social capital is associated with an increased past-year incidence of interpersonal violence among women but not men (Ahnlund, Andersson, Snellman, Sundström, & Henner, 2020). Higher levels of social capital are associated with a decreased risk for PTSD (Monson, Paquet, Daniel, Brunet, & Caron, 2016) and remission from PTSD (Ahnlund et al., 2020). Similarly, the incidence of interpersonal violence is greater in contexts characterized by lower socioeconomic status and neighborhood disorder (Gracia, López-Quílez, Marco, Lladosa, & Lila, 2015; Krieger et al., 2017), as is the risk for PTSD (Monson et al., 2016). Furthermore, these associations appear to be significantly stronger among women as compared to men (Butcher, Galanek, Kretschmar, & Flannery, 2015).

The effects of social capital are not always protective. However, cohesive communities can maintain social norms that have negative health effects or that affect individuals differently across the community (Villalonga-Olives & Kawachi, 2017). For example, the risk of sexual assault among adolescents is a function of individual risk and the risks in the close social network (Shakya, Fariss, Ojeda, Raj, & Reed, 2017). Culturally defined gender roles and expectations influence women's status relative to men, impacting social capital. Social contexts with norms that support stricter gender roles show increased rates of child abuse, intimate partner violence, and sexual violence (Wilkins, Myers, Kuehl, Bauman, & Hertz, 2018). The prevalence of past-year PTSD in the United States varies with state-level reproductive rights (an indicator of gender equality), with a higher prevalence of PTSD in contexts of greater inequality (McLaughlin, Xuan, Subramanian, & Koenen, 2011).

Women are more often victims of interpersonal violent crimes associated with negative or stigmatizing social responses, such as sexual assault. Resulting social stigma can erode posttrauma social support and well-being (Ullman & Peter-Hagene, 2016). Studies of interpersonal violence suggest that the effects of negative social responses on PTSD may be more pronounced among women and particularly Black/African American women and lesbian or bisexual women (Dworkin, Brill, & Ullman, 2019). However, social stigma in response to sexual assault may be particularly pronounced among men, in part due to the violation of cultural norms regarding the male gender role (Turchik et al., 2013).

Nonconformity to gender roles and gendered expectations may be a salient aspect of social contextual influence, though few studies have formally tested hypotheses regarding community-level gender norms and individual gender expression. Yet interpersonal violence is often so inextricably tied to gendered inequalities and gender behaviors that these forms of trauma exposure are commonly referred to as *gender-based violence* (Wirtz, Poteat, Malik, & Glass, 2020). Among both men and women, higher degrees of childhood gender nonconformity are associated with greater risk for PTSD in young adulthood (Roberts, Rosario, Corliss, Koenen, & Austin, 2012a). This relationship is partially mediated by the higher prevalence of childhood sexual and psychological abuse associated with gender nonconformity, where the effects on sexual abuse are stronger among men as compared to women. The impact of gender nonconformity may be especially relevant in understanding the elevated incidence of PTSD among individuals with minority sexual orientations, as strong associations between minority sexual orientation and childhood gender nonconformity have been observed for both men and women in U.S. and Australian epidemiological samples (Dunne, Bailey, Kirk, & Martin, 2000; Roberts et al., 2012a). Among U.S. young adults, there is a twofold risk for PTSD among lesbian and gay individuals relative to heterosexual individuals (Roberts, Austin, Corliss, Vanermorris, & Koenen, 2010), which we note is similar in magnitude to women's greater risk for PTSD relative to men. The elevated risk for PTSD among lesbian and gay individuals is partially mediated by increased exposure to childhood abuse, which in turn is influenced by higher levels of childhood gender nonconformity (Roberts, Rosario, Corliss, Koenen, & Austin, 2012b).

Assessment and Diagnosis

A nuanced understanding of the intersection of gender and trauma is critical to a successful gender-informed approach to assessment and diagnosis. Appreciation of the gendered patterns in trauma exposures and conditional risk for PTSD is important, yet we caution against overpathologizing women based on exposure to sexual or interpersonal violence, as well as minimizing such experiences among men. Sensitivity to sexual and gender identities is also an important aspect of assessment, as sexual and interpersonal violence are also overrepresented among sexual and gender minorities (Roberts et al., 2012a). Research supports the acceptability of asking about identities and preferences in a manner that decouples sex assigned at birth from broader aspects of gender identity (Cahill et al., 2014). Examples (GenIUSS Group, 2014; Grasso et al., 2019) are illustrated in Figure 13.1. Norms regarding the frequency and appropriateness of terms can vary based on regional or generational preferences, or the characteristics and experiences of the assessment population. Specific terms (e.g., two-spirit identity, asexual sexual orientation) can be incorporated into assessments as needed to enhance sensitivity and information value.

Assessment language that is clear, specific, nonstigmatizing, and gender-inclusive is essential. Many years of research document the pitfalls of vague and open-ended queries (e.g., "Has anything bad ever happened to you?") and use of language that victims may not use to label their own experiences (e.g., "Have you ever been raped?) may lead to inaccurate screening of trauma exposure. In contrast, using neutral, behaviorally worded, and specific language (e.g., "Have you ever been touched sexually against your will or without your consent?"; " Have you ever been forced or pressured to have sex?") is likely to lead to more accurate identification of trauma history (Koss, 1985; National Research Council, 2014). We also suggest attention to gender-inclusive phrasing (e.g.,

What is your current gender identity?

☐ Female
☐ Male
☐ Nonbinary/third gender/queer/++
☐ Intersex
☐ Prefer to self-describe _____
☐ Prefer not to say

Pronoun use:

☐ He/His
☐ She/Hers
☐ They/Ours
☐ Other _____

Do you identify as transgender?

☐ Yes ☐ No ☐ Prefer not to say

Do you think of yourself as . . . ?

☐ Straight/heterosexual
☐ Gay or lesbian
☐ Queer
☐ Bisexual
☐ Prefer to self-describe _____
☐ Prefer not to say

FIGURE 13.1. Example of a brief assessment of gender identity and sexual identity.

"I ask all of my patients these questions, because these experiences are unfortunately very common. . . ."). Studies that assess PTSD must strike a difficult balance assessing trauma exposure between the brevity required by large-scale survey research versus sufficient specificity to produce accurate, unbiased prevalence estimates (National Research Council, 2014).

These adaptations to assessment language will often increase the specificity of trauma exposure assessment, which yields substantially higher reports of trauma exposure as compared to a general open-ended query and enhances the accuracy of assessment. For example, when the broad, single-item trauma probe used in the Structured Clinical Interview for DSM-IV (SCID) PTSD assessment (First & Gibbon, 2004) was compared to the Traumatic Life Events Questionnaire (Kubany et al., 2000), a list of 23 behaviorally descriptive traumatic events, use of the behaviorally specific list identified a greater number of traumatic events and a higher rate of trauma exposure, allowing better ascertainment of PTSD cases (Peirce et al., 2009). The increased detection of trauma exposure and PTSD was greater for women as compared to men. Similarly, in changes from the 1997 to 2007 Australian National Surveys of Mental Health and Wellbeing, the number of discrete types of traumatic events queried increased from 11 to 29 events. The resulting population estimates of trauma exposure increased by 18%,

with increases significantly greater for women as compared to men (Mills et al., 2011). Taken together, these findings suggest that enumeration of potentially traumatic events with less specificity may underestimate the prevalence of trauma exposure, especially among women. Comprehensive assessments, such as the Life Events Checklist (Gray, Litz, Hsu, & Lombardo, 2004) or the Life Stressor Checklist (McHugo et al., 2005) where a wide range of potential traumatic events are queried using behaviorally specific language, may ensure accuracy of estimates of trauma exposure and PTSD and potentially reduce gender bias.

Finally, assessment of the magnitude and complexity of a traumatic event are needed, including efforts to understand the individual's perception of the event's controllability and broader social meaning. For example, physical assault perpetrated by strangers is more common among men, while physical assault in the form of repeated exposure to intimate partner violence is more common in women (Blanco et al., 2018). While both events are traumatic, the contextual features of the latter (i.e., severity, chronicity and proximity to the perpetrator) likely magnify the risk for PTSD. Similarly, sexual minority men may report adolescent sexual experiences with older same-sex partners that are experienced as consensual, where the distinction from coercive sexual experiences must be informed by consideration of contextual aspects of the experience and the individual's appraisal of the experience (Arreola, Neilands, Pollack, Paul, & Catania, 2008; Carballo-Diéguez, Balan, Dolezal, & Mello, 2012).

Accurate diagnosis of PTSD rests on the assumption that symptom criteria and assessment instruments reflect the PTSD construct equally well for men and women. Conversely, if some symptoms are more strongly associated with the PTSD diagnosis in either women or men, this could suggest gender bias in the PTSD construct. There is good empirical support for the DSM-5 model of PTSD as well as a "hybrid" model blending transdiagnostic dimensions of positive–negative valence and internalizing–externalizing behaviors (Armour et al., 2015; Carragher et al., 2016; Silverstein, Dieujuste, Kramer, Lee, & Weathers, 2018). These models generally fit the PTSD symptoms of men and women equally well, suggesting few phenotypic differences in the expression of PTSD (Cao, Wang, Cao, Zhang, & Elhai, 2017; Carragher et al., 2016; Murphy, Elklit, Chen, Ghazali, & Shevlin, 2018). The dissociative subtype of DSM-5 PTSD, characterized by symptoms of derealization and depersonalization, does not show pronounced gender differences in prevalence (Hansen, Ross, & Armour, 2017; Wolf et al., 2017).

Treatment

Psychotherapeutic Treatments

Trauma-focused psychotherapies (TFPs)—for example, prolonged exposure (PE), cognitive processing therapy (CPT), and eye movement desensitization and reprocessing (EMDR)—have long been identified as among the most efficacious psychotherapeutic treatments for PTSD for both women and men. These individual psychotherapies are recommended as first-line treatments by most practice guidelines (American Psychological Association, 2017; Department of Veterans Affairs & Department of Defense [VA/DoD], 2017; International Society for Traumatic Stress Studies, 2019).

Meta-analyses suggest that these psychotherapies are more effective for women as compared to men, though the magnitude of these differences is not large. An analysis of 48 randomized clinical trials of trauma-focused treatment composed mostly of trauma-focused cognitive-behavioral treatments such as PE and CPT revealed that reductions

in clinician-rated symptom severity were larger for women relative to men, with large versus moderate effects at posttreatment (standardized mean difference [95% confidence interval] = –1.05 [–1.31, –0.78] vs. –0.64 [–0.94, –0.35]), and moderate versus small effects at follow-up (–0.46 [–0.88, –0.30] vs. –0.19 [–0.36, –0.01]) (Wade et al., 2016). These effect sizes can be viewed in terms of the probability of treatment benefit (Faraone, 2008) and would suggest that women have an approximately 78% chance of benefit from TFPs for PTSD, whereas men have approximately a 68% chance of benefit (Kimerling, Allen, & Duncan, 2018).

Examining the subset of trials that included both women and men allows for analyses to directly examine whether gender moderates treatment outcomes. This subset of studies demonstrated similar results: There were greater pre- to posttreatment reductions in trauma symptom severity for women than for men (mean difference [96% confidence interval] = 11.53 [1.82, 21.24]; $z = 2.33$, $p = .02$), where the magnitude of this change is just above what is considered minimally significant change (Schnurr et al., 2007). Meta-analyses of group-based trauma-focused cognitive-behavioral therapies (TF-CBTs) for PTSD have found similar gender differences in treatment benefit, with greater reductions in symptom severity from pre- to posttreatment among women as compared to men (Schwartze, Barkowski, Strauss, Knaevelsrud, & Rosendahl, 2019; Sloan et al., 2013).

The gender-related factors that act as the mechanisms for these treatment effects are not yet understood. Because trauma exposure patterns differ by gender, it can be difficult to discriminate the extent to which these effects may be due to some forms of exposure being more refractory to treatment than others. The two questions are actually similar comparisons because women are more frequently treated for interpersonal violence and studies of men are more commonly focused on combat-related trauma exposure. Other meta-analyses have not found significant differences in treatment effectiveness based on type of trauma or comparison of military or veteran populations to civilian populations (Haagen, Smid, Knipscheer, & Kleber, 2015; Kline, Cooper, Rytwinksi, & Feeny, 2018). Similarly, a meta-analysis of PE did not find differences in effectiveness by trauma type (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010). Studies of CPT have compared effects by gender in studies of sexual assault survivors and have found similar treatment effects (Galovski, Blain, Chappuis, & Fletcher, 2013). In summary, the literature does not suggest pronounced differences in treatment effectiveness as a function of trauma type or military service, but patient-treatment matching is a burgeoning area of treatment research.

In practice, several gender differences in treatment access and retention have been observed, but similar to the treatment effectiveness literature, these differences are not substantial. In the United States, only a little more than half (59.4%) of the individuals who ever experience PTSD seek treatment (Goldstein et al., 2016). Epidemiological literature suggests that women are more likely to seek treatment (60.4% vs. 52.3%) as compared to men and are somewhat more likely (55.1% vs. 48.2%) to seek psychotherapy (Lehavot et al., 2018). This finding has also been documented in large observational studies of VA treatment for PTSD where 52.3% of women but only 40% of men initiated psychotherapy (Valenstein-Mah et al., 2019). In this study, retention in psychotherapy was low, but somewhat higher among women as compared to men (17.7% vs. 10.8%), where negative beliefs about psychotherapy were a factor in premature treatment termination among male, but not female, veterans (Valenstein-Mah et al., 2019).

Recognition that symptoms highly comorbid with PTSD can impair functioning has led to investigations into focused psychotherapies that can augment or follow evidence-based trauma-focused cognitive-behavioral therapies (TF-CBTs; Gutner, Pedersen, & Drummond, 2018). Though (female) sex and gender have been identified as salient risk factors for sleep disturbances in the general population (O'Hayon & Shapiro, 2000), among patients with PTSD, sleep disturbances are universally common in men and women (Kobayashi, Cowdin, & Mellman, 2012). Cognitive-behavioral therapy for insomnia (CBT-I) is the gold-standard psychotherapeutic treatment for insomnia, effective in men and women alike, and can be used as stand-alone intervention or augmentation therapy conjointly with TF-CBT (Colvonen et al., 2018). We note, however, that more research is needed regarding women's sleep difficulties associated with critical reproductive periods such as pregnancy and menopause (Nowakowski & Meers, 2019), and their impact on PTSD risk and symptom severity.

Psychopharmacological Treatments

Treatment guidelines recommend several selective serotonin reuptake inhibitors (SSRIs) and the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine (recommended in the VA/DoD guidelines) as the most effective pharmacological agents to treat PTSD (Hamblen et al., 2019). A meta-analysis found insufficient evidence for gender differences in the effectiveness of these medications for PTSD (Forman-Hoffman et al., 2018), as few studies have reported sex/gender differences. There is some evidence for gender differences in adverse drug reactions. Surveillance data from the Netherlands indicates gender differences in reactions to SSRI medications, where men are more likely to report reactions such as aggression, suicide, and sexual dysfunction, and women are more likely to report reactions such as hair loss, weight gain, and gastrointestinal (nausea, dry mouth) and nervous (dizziness, tremor, vision problems) system symptoms (de Vries et al., 2019).

In the U.S. population, about 1 in 8 individuals report antidepressant medication use in the past month, with women and girls twice as likely to use as boys and men (Pratt, Brody, & Gu, 2017). Similar elevated rates for antidepressant use among girls and women are documented in European countries (Gomez-Lumbreras et al., 2019). Higher rates of psychotropic medications among women may be due to the higher prevalence of depressive and anxiety disorders in women relative to men. Data from the Veterans Health Administration (VHA) users suggest this may be true, in part: Gender differences in comorbidity patterns explained some, but not all, of the increased likelihood of SSRI/SNRI prescriptions among women diagnosed with PTSD relative to men (Bernardy et al., 2013). Women's greater propensity to receive medication for insomnia may underlie at least part of this effect, though the extent to which women with PTSD are more likely to experience sleep disturbance is unclear (Bernardy & Friedman, 2016; Milanak et al., 2019).

Fewer gender differences are observed among PTSD populations, however. Nearly one-third of individuals with lifetime PTSD report a history of pharmacological treatment, with similar rates among men and women (Lehavot et al., 2018). Data from VHA users suggest some gender differences in the management of PTSD. Across medication treatment episodes for PTSD, women are more likely to be prescribed topiramate relative to men, whereas men are more likely to receive paroxetine, fluoxetine, sertraline, or venlafaxine relative to women (Shiner et al., 2018). Notably, individuals who had

experienced military sexual trauma were also significantly overrepresented among those receiving topiramate, though topiramate represented a relatively small proportion of medication episodes. There were no differences in medication effectiveness, with less than 20% of individuals in any medication group achieving remission.

Prescribing SSRIs and SNRIs to women with PTSD who are pregnant or of childbearing age requires a careful assessment of the risks and benefits to the woman, her unborn child, and, in the case of women who are breastfeeding, to their newborn. Clinicians must not only consider potential teratogenic effects of these medications but balance this with the risks associated with untreated PTSD. SSRI use during pregnancy is linked to increased risk of preterm birth (Eke, Saccone, & Berghella, 2016). However, PTSD also has been associated with increased risk of preterm birth, even when effects are adjusted for SSRI use (Shaw et al., 2014; Yonkers et al., 2014), possibly due to increased risks for gestational diabetes and preeclampsia (Shaw et al., 2017). We caution readers that there is not yet data comparing risks associated with SSRIs to risks associated with either untreated or psychotherapy-treated PTSD. While there is some evidence to suggest increased rates of cardiac malformations among newborns exposed to SSRIs in utero (Ornoy & Koren, 2019), due to the difficulties of disentangling the effects of untreated depression or PTSD, these data do not meet the definition for teratogenic effects. Increased risk for poor neonatal adaptation and pulmonary hypertension has also been documented, but the risk is small and may not exceed the risk associated with untreated PTSD or comorbid depression (Fischer Fumeaux et al., 2019). Given these concerns, psychotherapy will often be a more effective treatment for PTSD and is a safer treatment option during pregnancy and breastfeeding. However, for women on a course of SSRI/SNRI treatment who are experiencing clinical benefit, continuation during pregnancy should be weighed against the risks for both mother and child associated with symptoms of PTSD and comorbid conditions.

CHALLENGES FOR THE FUTURE

Recent guidelines from the U.S. National Institutes of Health that require research designs to include sex-based comparisons have potential to better elucidate gender issues in PTSD. The policy has been associated with an increased number of studies addressing sex and gender comparisons, as well as a change in attitudes of scientists toward appreciating the value of gender differences in research across a wide range of clinical conditions (Woitowich & Woodruff, 2019).

The pronounced gender differences in the prevalence of PTSD are associated with gender differences in traumatic event type, chronicity, and age at exposure. The social context of exposure appears to influence risk for PTSD to a greater extent among women as compared to men. If we consider gender to be a proxy variable for multilevel interactions (Kimerling et al., 2018), these social and contextual factors may serve as pathways for gender-linked risk. Models of PTSD risk that ignore context may be vulnerable to an omitted variable bias, yielding inflated estimates for proxy variables such as gender due to unmeasured contextual variables associated with both exposure and PTSD. More epidemiological research that accounts for the effects of social context may help explain gender differences.

Though differences in trauma exposure and social context do not appear to completely account for gender differences in prevalence, there is little evidence for mechanisms that suggest an excess vulnerability to traumatic stress among women. However,

emerging research with potential to shed light on this issue are genome-wide association studies of PTSD (see Girgenti et al., Chapter 12, this volume). These studies have identified the greater heritability of PTSD among women as compared to men, consistent across European and African ancestries, though samples with civilian men appear to find higher heritability estimates for men as compared to samples of veteran men (Duncan et al., 2017; Nievergelt et al., 2019). Among women, genetic risk for PTSD has been linked to younger age at first childbirth (Nievergelt et al., 2019; Polimanti et al., 2017). Shared genetic vulnerability was found for PTSD with depression and schizophrenia, as well as genes that regulate dopaminergic and immune systems (Duncan et al., 2017; Nievergelt et al., 2019). These sex differences in the strength of genetic associations could stem from sex-linked biological factors; these studies have pointed to the potential roles of physiological regulatory systems such as dopaminergic systems and immune pathways that are consistent with physiological hypotheses regarding gender differences in PTSD risk (Pineles et al., 2017).

Research finds more commonalities than differences across gender with respect to the construct of PTSD. Individual TFP is the most effective treatment for PTSD for both men and women, and gender differences in favor of women are small. Pharmacotherapy for PTSD appears to be equally effective for men and women, but pharmacotherapy with pregnant and breastfeeding women requires careful individualized assessment of the risk and benefits posed by medications. Extant research suggests some gender differences with respect to the pharmacological management of PTSD, and more research is needed to investigate gender differences in receipt of guideline concordant care for PTSD.

Finally, it is important to note that investigations of gender issues in PTSD can improve assessment and treatment of both men and women. Investigations of gender issues yield a more comprehensive understanding of trauma severity, the range of traumatic stress reactions, and the influence of social context on the response to trauma. For example, research on sexual harassment and sexual assault as components of warzone trauma emerged from research on women veterans and PTSD. Recognizing these factors as important aspects of both men's and women's military trauma might result in better treatment for both men and women with PTSD.

Research on men's gender issues in trauma exposure has illuminated the need for research on the role of multiple traumas, as well as research on traumatic events that occur less frequently among men, such as sexual assault and childhood trauma. As research on gender continues to develop beyond sex-based comparisons and incorporates the qualitative aspects of trauma, the context in which trauma occurs, and the social roles and experiences that influence the risk for and outcome of traumatic stressors, these results enhance our capacity to address PTSD as it occurs in individual patients and in communities.

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CHAPTER 14

A Developmental Perspective on Childhood Traumatic Stress

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Baby birds, according to experts, are biologically programmed for their own particular song (Katsis et al., 2018). The song, however, only develops according to this design with modeling, coaching, and support from parents or other adult birds in the species. In the absence of guidance from an adult "song tutor," a song will develop, but it will have a different sound than that of the other birds in the species, and it will not provide the bird with the crucial environmental adaptations the song is designed to facilitate, such as establishing territory and community, and attracting a mate.

These ornithological observations provide significant parallels to key issues in human development. Children raised in isolation, or without the requisite adult nurturing and support, will likely grow to be adults but will not resemble other adults in language or behavior. They will not have received the environmental factors necessary to facilitate ideal and adaptive social and biological development—to create and refine their "song."

The role of environmental influences on human neurodevelopment is well documented. According to Perry (2001, p.4), "the developing brain organizes in response to the pattern, intensity and nature of sensory, perceptual, and affective experience of events during childhood." Human neurodevelopment follows a specific biological course from the development of more primitive to more complex structures (Nelson & Bloom, 1997) during periods of developmental sensitivity (Bateson, 1979). This course is shown to be sensitive to environmental influences by means of the process known as *neuroplasticity* (Singer, 1995). In addition to the occurrence of key neurobiological processes such as myelination, synaptogenesis, and the growth and articulation of brain structures (Perry, 2001), processes crucial to the neurotypical development of the person's sense of self also occur during early childhood, including processes such as attachment, planning and reasoning, impulse control, empathy, self-soothing, and the integration of a sense of self-concept.

When a traumatic event happens to an adult, assuming that the adult has followed a typical developmental path, the event is experienced through the lens of a person who has presumably achieved developmental milestones, whose brain is fully developed, who has internalized adequate coping resources, who has an adequate support system, and who has consolidated a sense of "personhood." When a traumatic event happens to a child, however, not only does that child lack the benefits these processes provide, but these processes may become interrupted or altered, or they may never occur at all.

Although negative events have happened to children for as long as humans have existed, the organized study of the impact of such events did not emerge until roughly the middle of the 20th century. Until that time, the prevailing thinking was that children's reactions to traumatic events were transient (Vogel & Vernberg, 1993) and that the coping of youth who underwent stressful, overwhelming events depended on the way their parents responded (Terr, 1990), rather than recognizing that children have unique and complex reactions of their own, with profound implications for subsequent development and functioning. Terr's landmark study in 1976 of 23 children between ages 5 and 14, who were kidnapped and imprisoned in darkened vans, then buried underground for a total of 27 hours before being reunited with their families, was the first scientific study to examine the impact of a traumatic event on multiple domains of functioning in a group of children. Terr's finding, contrary to the prevailing thinking of the time, was that every one of the children interviewed evidenced symptoms of posttraumatic stress, including reexperiencing, avoidance, and arousal. She noted that while many of these symptoms paralleled those of adult posttraumatic stress, the manner in which these patterns of responding manifested was specific to the developmental level of the person. For example, the reexperiencing symptoms of these children were often seen through behavioral reenactments, including stereotyped, repetitive play involving themes related to the kidnapping (Terr, 1981).

Due to the groundbreaking work of Terr and others, we now have a much broader understanding of the role of negative environmental experiences in child development. This chapter summarizes the literature on the impact of traumatic events on child development that has emerged over the last 35 or so years. This review takes into account the distinction, pointed out by Terr and others, between a single occurrence of an unexpected, negative event, and the ongoing, chronic repetitive occurrence of adverse events. We examine what is currently known about the implications of such events, considering a variety of factors, including emotional and behavioral regulation, consciousness, sensory processing, attachment, social/interpersonal skills, empathy, academic functioning, and physical health. We also consider the implications of these findings for public health and welfare, and identify areas in which the literature is lacking, providing suggestions for future study.

PREVALENCE OF TRAUMATIC STRESS DURING CHILDHOOD

Children are at particularly high risk of being exposed to traumatic events (Gunaratnam & Alisic, 2017). In one study, statistics documented that approximately 56% of victims of abuse were under the age of 7 (U.S. Department of Health and Human Services, 2017). When a broader range of stressful events is included, such as parental divorce or bullying, research indicates anywhere between 78 and 95% of adolescents have experienced at east one adverse childhood experience (Gunaratnam & Alisic, 2017).

The percentage of children who develop posttraumatic stress disorder (PTSD) following a traumatic event is significantly higher than the percentage of adults who develop PTSD (Perry, 2000; Gabbay, Oatis, Silva, & Hirsch, 2004; see Copeland & McGinnis, Chapter 5, this volume). Findings indicate that posttraumatic symptoms in young children are not a normative reaction that they outgrow. Rather, if left untreated, PTSD in childhood appears to follow a chronic and unremitting course (Karsberg & Elklit, 2012) and can have even more detrimental effects on developmental trajectories than trauma occurring later in life (Cohen, Mannarino, & Deblinger, 2006). A meta-analysis showed a 16% prevalence of PTSD in youth exposed to traumatic events (Alisic et al., 2014). Another study reported 25% of youth exposed to interpersonal trauma developed PTSD compared to 10% of youth exposed to other types of traumatic events (Kolaitis, 2017). A recent review of 42 studies on refugee children suggests the rates of PTSD among refugee children have ranged from 40 to 63% (Reavell & Fazil, 2017).

NEUROBIOLOGICAL AND COGNITIVE IMPACT

We are only beginning to understand the substantial impact of trauma exposure on children. Current research has documented that exposure to traumatic events in childhood may be more detrimental than trauma experienced by adults because of the interaction between such events and the ongoing process of psychological and neurodevelopment in children (Karsberg & Elklit, 2012).

Young children's neurophysiological regulation systems (especially from birth to age 2) undergo rapid development and reorganization that are heavily influenced by environmental factors (Carpenter & Stacks, 2009). The reorganization that occurs during this period may become permanent and influence subsequent development, even after environmental conditions change (Pechtel & Pizzagalli, 2011). Exposure to a traumatic event combined with a poor-quality parent–child relationship during this sensitive period can have especially detrimental consequences (Cicchetti & Lynch, 1995). Early adverse experiences produce lasting effects on an organism's stress responses and brain structures (Crowe & Blair, 2008; Teicher & Samson, 2016).

The profound impact of traumatic experiences on a child's emotional, behavioral, cognitive, social, and physical functioning is due to the strong negative impact of adverse events on the developing brain (De Bellis, Keshavan, et al., 1999). When a child's experience is chaotic or when sensory patterns are not consistent and predictable during critical periods of development, the organizing systems in the brain reflect this and organize in ways that result in dysregulation (Perry, 2000).

It is adaptive for a child growing up in a violent or chaotic environment to be hypersensitive and hypervigilant, and to remain in a persistent stress response state. The child who grows up in the context of chronic traumatic experiences learns to anticipate recurring and unremitting pain and fear. The more intense and prolonged the traumatic event, the more likely there will be changes in the neural system (Perry & Pollard, 1998).

These neural changes in response to environmental stressors provide the biological mechanism through which states become traits. What was an adaptive coping strategy in response to a temporal event becomes a hardwired way of being in the world, often with less than optimal outcomes. Traumatic reminders can renew the child's negative emotions and further handicap development (Pynoos et al., 2009). Studies indicate that the more chronic the trauma, the higher the degree of developmental dysfunction to the hypothalamus–pituitary–adrenal (HPA) system, and the less the system is able to recover under improved conditions (Gunnar & Cheatham, 2003).

Affected areas of the brain and hormonal systems are those associated with regulation of emotions, impulse control, problem solving and reasoning, and judgment (amygdala, medial prefrontal cortex, dopamine system, adrenergic system, HPA axis, hippocampus, corpus callosum, serotonin system, and endogenous opiate system; De Bellis, Keshavan, Shiflett, et al., 2002; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Whereas adults with symptoms of PTSD show lower levels of basal cortisol activity and elevated adrenocorticotropic hormone in response to stress, children display elevated cortisol levels (Tarullo & Gunnar, 2006). It is hypothesized that this difference reflects long-term adaptation to trauma (Gunnar & Vasquez, 2001).

Anatomical differences have been found in children's brain structures following trauma, and differences are generally associated with earlier age of trauma, greater severity, and chronicity (De Bellis, Baum, et al., 1999). De Bellis, Baum, and colleagues (1999) found that children and adolescents diagnosed with PTSD had significantly smaller intracranial and cerebral volume than matched controls. Preliminary research with children ages 7–13 years revealed that PTSD symptoms and cortisol levels were associated with hippocampal reduction over a 12- to 18-month period (Carrion, Weems, & Reiss, 2007).

A variety of intellectual and academic impairments have been consistently reported in abused children (Hart & Rubia, 2012). Children raised in neglectful or abusive environments spend a majority of their time in a low-level state of fear and consistently focus on nonverbal rather than verbal cues. Research demonstrates a negative correlation between Verbal IQ and severity of abuse (Carrey, Butter, Persinger, & Bialik, 1995). Posttraumatic reactions have included lower IQ and reading achievement (Delany-Black et al., 2002), a prominent verbal–performance split on the Wechsler Intelligence Scale for Children (Perry, 2000), and delayed language and poorer performance in school (Shonk & Cicchetti, 2001). Furthermore, children diagnosed with PTSD have significant impairments in attention, abstract reasoning, and executive functioning compared to healthy controls (Beers & De Bellis, 2002). In a twin study, exposure to domestic violence accounted for 4% of the variance in IQ and was associated with a lower IQ of about 8 points (Koenen, Moffitt, Caspi, Taylor, & Purcell, 2003). Results from a prospective study examining the impact of early maltreatment and violence suggest that there are significant and enduring effects on cognitive development (Enlow, Egeland, Blood, Wright, & Wright, 2012). It is hypothesized that posttraumatic reactions can impact cognitive functioning through stress pathways (Pechtel & Pizzagalli, 2011). In fact, extreme stress reactions following traumatic exposure have been associated with lasting changes in the secretion and metabolism of various hormones and neurotransmitters (specifically, dopamine and norepinephrine; De Bellis, 2001). PTSD symptoms may contribute to cognitive deficits by impeding the child's ability to engage with the environment effectively and acquire new skills (Veltman & Browne, 2001). Other studies have shown lower IQ in children to be a risk factor for the development of PTSD (Koenen, Moffitt, Poulton, Martin, & Caspi, 2007). Thus, it is clear that the relationship between trauma symptomology, cognitive functioning, and brain development is complex and multidirectional.

EMOTIONAL AND BEHAVIORAL IMPLICATIONS

The developmental consequences of posttraumatic reactions can lead to failures in emotional and behavioral regulation, as well as cognitive consequences (Hart & Rubia, 2012). Traumatic experiences affect children's sense of personal safety and predictability

(Groves, Zuckerman, Marans, & Cohen, 1993). Children struggling with these kinds of fears are often unable to face and achieve other normal developmental milestones and may fall behind in their emotional, social, and cognitive development (Osofsky, 1999). In fact, decreased capacity for emotional regulation is one of the most significant adverse effects of early exposure to trauma (Cheasty, Claire, & Collins, 2002). Early traumatic experiences disrupt the attainment of emotion regulation and interpersonal skills (Cloitre, Miranda, Stovall-McClough, & Han, 2005).

While there is variability in response following trauma exposure, studies have found increased rates of internalizing and externalizing disorders in children and adolescents who have experienced trauma (for a review, see Teicher & Samson, 2016). Trauma-related symptoms have been associated with increased risk for psychiatric disorders in preschool-age children (Briggs-Gowan, Carter, & Ford, 2012) and older children (Carter et al., 2010). While the research on children under 5 years old is limited, the evidence suggests that early childhood exposure to trauma is also associated with increased emotional problems and disruptive behavior (Briggs-Gowan et al., 2010; Mongillo, Briggs-Gowan, Ford, & Carter, 2009). A longitudinal epidemiological study of children and young adolescents exposed to traumatic events demonstrated an increased risk of PTSD, anxiety disorders, depression, and disruptive behavior disorders (Copeland, Keeler, Angold, & Costello, 2007).

Additional studies indicate a significant association between childhood traumatic events and the onset of psychiatric disorders (Green et al., 2010). A number of studies have shown that exposure to violence and abuse are unique antecedents of severe psychopathology, independent of other risk factors (Kitzmann, Gaylord, Holt, & Kenny, 2003; Knickerbocker, Heyman, Slep, Jouriles, & McDonald, 2007). The failure to regulate behavior and emotions can lead to externalizing and internalizing symptoms that have long-term negative sequelae and continue into adulthood (see De Bellis, 1997, for review). The residual emotional, behavioral, cognitive, and social sequelae associated with childhood trauma can persist and contribute to a range of other problems throughout life (Fergusson & Horwood, 1998), including attachment problems (Bell & Belicki, 1998), eating disorders (Rorty & Yager, 1996), depression (Winje & Ulvik, 1998), suicidal behavior (Molnar, Shade, Kral, Booth, & Watters, 1998), anxiety (Fergusson & Horwood, 1998), alcoholism (Epstein, Saunders, Kilpatrick, & Resnick, 1998), violent behavior (O'Keefe, 1995), mood disorders (Kaufman, 1991), and physical health issues (Maschi, Baer, Morrissey, & Moreno, 2013; Mock & Arai, 2010). These poor outcomes may be mediated through the developmental consequences of trauma. Specifically, deprivation and trauma are associated with dysregulation of the biological stress response and emotion regulation systems, which in turn lead to abnormal infant behavior and subsequent issues in childhood and adulthood (De Bellis, Keshavan, et al., 1999).

THE PARENT–CHILD RELATIONSHIP

Human infants are biologically programmed to emit signals designed to elicit caretaking behavior from adult caregivers. The infant communicates basic needs such as "I'm hungry; feed me," "I'm wet; change me," or "I'm vulnerable and need affection; cuddle and nurture me." When this system works well, these communications are delivered effectively, and adult caregivers respond to and meet these needs. These repeated experiences are eventually internalized by children, who develop the ability to provide these functions for themselves. This is the process by which humans transition from mutual

regulation to self-regulation, and develop secure patterns of attachment. It is when this paradigm fails to work, due to a malfunction on one or both sides of the dyad, that developmental difficulties can occur. It is therefore evident that the impact of trauma in young children must be considered within the context of the parent–child relationship.

Applying this concept to the "fight–flight–freeze" paradigm of responding to trauma, it is evident that infants or very young children who, in most situations, are unable to fight or to flee from a negative event are therefore dependent on caregivers to provide these functions for them. If caregivers are unable to fulfill this role because they are unavailable, or because they are also impacted by the negative event, such that their own ability to help and protect the child is compromised, or, as is too often the case, the negative event takes place at the hand of the caregiver, serious problems can occur. If the threat persists, the only coping strategy left is for the infant or young child to dissociatively "freeze," which can manifest as disengagement, inward focus, avoidance, numbing, daydreaming, fantasy, derealization, depersonalization, and, in extreme cases, catatonic reactions (Perry, 2001).

An interpersonal trauma, such as maltreatment and abuse, often involves children losing trust in adults—both the perpetrator and the parent or caregiver who failed to adequately protect them. Thus, one of the effects of the trauma is a disruption in children's ability to form relationships and attachments. Since forming an attachment with the primary caregiver is one of the key developmental tasks of infancy (Lieberman, 2004), when the perpetrator is a parent or caregiver, this clearly has significant negative consequences for the development of interpersonal functioning. When young children are exposed to interpersonal trauma, the development of attachment with their primary caregiver may be disrupted (Myers & Wells, 2015; Pat-Horenczyk et al., 2017). Freyd (1996, p. 17) refers to this paradigm as "betrayal trauma" and defines this concept as "a betrayal of trust that produces conflict between external reality and a necessary system of social dependence" (see DePrince et al., Chapter 8, this volume). This theory postulates the occurrence in such situations of "psychogenic amnesia" for parental maltreatment, which occurs as a means of coping and survival. An attachment figure who is consistent and available to the child during times of stress can buffer a child's response to a traumatic event, whereas a parent who is unavailable or frightening can exacerbate the child's fears (Gunnar & Quevedo, 2007). Children with insecure or disorganized attachments are at greater risk for negative outcomes following trauma. They are less likely to engage in emotionally supportive relationships that help them to process and cope with the overwhelming emotional experience (Lieberman, 2004).

Research has consistently shown significant associations between caregiver functioning and child functioning after a traumatic event (Scheeringa, Zeanah, & Cohen, 2001). Children's ability to cope with a traumatic event and accurately process it is influenced by their parents' reaction to the event (Swenson et al., 1996). Parents may become impaired in their ability to detect and respond effectively to their children's needs (Sheridan & Nelson, 2009) and distress. Overprotective parents may influence their children's exposure to traumatic reminders and impede habituation to the event (Nugent, Ostrowski, Christopher, & Delahanty, 2007). Furthermore, children often evaluate parental distress as a measure of the severity of a situation, and may model their parents' fear response or coping style (Linares et al., 2001).

Swenson and colleagues (1996) found that the longevity of children's emotional and behavioral symptoms was significantly related to the mother's level of distress, maternal psychiatric symptoms, property loss, and other family stress following the traumatic event. It is also possible that the child's response to a traumatic event contributes to

parental distress and affects parenting practices (i.e., becoming more overprotective, allowing avoidance, insisting on being near the child at all times, or spoiling the child). These changes in parenting practices may further exacerbate behavioral and emotional difficulties in the child. It can also contribute to the child's belief that the world is an unsafe place (Scheeringa & Zeanah, 2008).

DEVELOPMENTAL DIFFERENCES

Traumatized children exhibit a wide range of psychological problems, including disruptions in daily functioning (Galante & Foa, 1986), PTSD, anxiety, depression, and disruptions in sleep patterns (Houlihan, Ries, Polusny, & Hanson, 2008). Children process stressful events differently than do adults and respond according to their developmental level (Anthony, 1991). Developmental differences affect children's ability to understand the nature of traumatic experiences and their role in the event (Vogel & Vernberg, 1993). In general, reactions to traumatic events are evidenced in somatic, cognitive, emotional, and behavioral symptoms in children and adolescents; however, the specific presentation varies by developmental level and capacity. Thus, children of all ages have the developmental capacities to experience adverse effects after traumatic experiences, with unique developmental differences in the manifestation of trauma symptoms.

Birth through Preschool Age

Infants to preschool-age children are inclined to process the world on a sensory level (Piaget, 1960) and are therefore vulnerable to sensory overload and less able to buffer traumatic stimuli in their environment. Furthermore, because they have limited ability to verbalize fears, they may reenact the trauma in their play or behavior as a way of processing the experience (Deering, 2000). Although data on trauma symptoms in very young children are limited, one cross-sectional study found significant associations between stressful events and trauma symptoms in children ages 18–36 months (Briggs-Gowan et al., 2010).

While the research on preschoolers' reactions to traumatic events is sparse, the limited findings suggest that preschool children show less psychological distress and fewer cognitive problems than do older children (Salmon & Bryant, 2002). Somatic complaints include sleep disturbances (recurring nightmares, sleepwalking, refusal to sleep alone), dizziness, and eating problems. Cognitive problems may include magical explanations for the event, repeated retelling, and recurrent memories of the trauma. Preschool children show increased emotional difficulties, including tearfulness, excessive clinginess, temper outbursts, irritability, separation anxiety, stranger anxiety, and specific and generalized fears (Baggerly & Exum, 2008; Corrarino, 2008). Preschool children often present with increased separation anxiety and new fears without obvious links to the event (e.g., fear of toileting or fear of the dark; Scheeringa, Zeanah, Myers, & Putnam, 2003). Behavioral consequences often manifest as anxious behavior (skin picking and finger biting), reenactment in play, temper tantrums, hyperactivity, and regression in skills (including enuresis, thumb sucking, and loss of previously acquired language; Baggerly & Exum, 2008; Corrarino, 2008). Traumatic events typically cause young children to experience increased feelings of vulnerability and heightened dependency and reassurance seeking (Anthony, 1991). A specification of the presentation of

PTSD symptoms in children 6 years and younger is included in the DSM-5, as the preschool subtype, based partially on the work of Scheeringa, Zeanah, and Cohen (2011). This specification includes lower symptom thresholds to account for the lower rates of PTSD diagnosed in this age group, which have been attributed to the differential presentation of symptomology in preschoolers, as well as the lower capacity for accurate verbal expression and capacity for abstract thinking.

School Age

School-age children are more able to use logic to understand events and are therefore capable of grasping the seriousness of a traumatic event, of remembering it more vividly, and of understanding the impact on themselves and their families (Conway, Bernardo, & Tontala, 1990). In general, research suggests that school-age children show more overall psychological distress and PTSD symptoms than preschool children, but less than adolescents. Common somatic complaints include sleep disturbances (difficulty going to sleep and sleeping well), physical complaints (muscle aches, headaches, diarrhea), and loss of energy (Zubenko, 2002). Cognitive reactions in children may result in a decline in school performance (Gurwitch et al., 2004). Cognitive problems can include distractibility, poor concentration, problems with reading, and declining grades (Brown, 2005). In addition, school-age children also show emotional and behavioral reactions to traumatic events, including anger, denial, feelings of guilt, helplessness, anhedonia, mood lability, depression, self-blame, tearfulness, and specific and generalized fears. They may also display increased startle response, aggressive behavior, hyperactivity, hypervigilance, problems with peer relationships, repetitive trauma-related play, and emotional withdrawal (Dogan-Ates, 2010).

Adolescence

Adolescents are typically considered "adult-like" in their reactions to traumatic events because of their more sophisticated cognitive style and ability to understand the meaning of events (Pynoos & Eth, 1985). Adolescence is marked by an increased ability to use abstract thought and imagine the complexities of an event (Piaget, 1960). Adolescents dealing with traumatic events tend to rely on their more intact defense systems, formed throughout childhood, to modulate their reactions (Conway et al., 1990).

Adolescent PTSD differs from the adult presentation, and symptom expression varies greatly (Herringa, 2017). Adolescents tend to show heightened stress sensitivity of the developing neural systems and delayed expression of the full effect of the trauma, when compared to adults (Herringa, 2017). A recent study shows that symptoms related to intrusion, avoidance, negative affect, anhedonia, externalizing behavior, anxiety, and depression best characterize PTSD in teenagers (Cao, Wang, Cao, Zhang, & Elhai, 2017). Adolescents also commonly experience somatic symptoms, including eating disturbances, loss of energy, insomnia, and physical complaints (headaches, stomachaches; Dogan-Ates, 2010). Some younger adolescents may regress into use of previous childhood coping mechanisms and present with symptoms such as nocturnal enuresis, separation anxiety, and temper outbursts (Shelby & Tredinnick, 1995). Cognitive symptoms, such as poor attention and concentration, declining school performance, memory problems, and recurrent thoughts, are common reactions. Adolescents also show some brain abnormalities, like reduced ventromedial prefrontal cortex volume and impaired recruitment of prefrontal cortex, but not the reduced hippocampal volume

and hyperactivity of the amygdala and insula, as is often found in adults with PTSD (Herringa, 2017; see Averill et al., Chapter 9, this volume, on altered neurocircuitry on PTSD). Adolescents may exhibit negative expectations of the future and changes in attitudes about career and future goals (Barnard, Morland, & Nagy, 1999). Adolescents may also display lack of affection, oppositional behavior, and risk-taking or antisocial behavior (i.e., substance use, sexual activity, truancy; Gaffney, 2006). Involvement in life-threatening and risky behavior can negatively affect peer relationships and lead to rejection or decreased social support (Pynoos, Steinberg, & Wraith, 1995). Teenagers who do not regress or act out may pretend they do not have increased needs related to traumatic exposure, or they may take on a caregiving role for their parents (Conway et al., 1990).

ASSESSMENT AND DIAGNOSIS

Concerns have been raised that assessment measures for childhood trauma are not developmentally sensitive and do not take into account the ways in which trauma symptoms manifest differently in children. Similar concerns have been raised that diagnostic criteria for PTSD may not have been the best way of conceptualizing traumatic reactions in children, particularly those who have experienced chronic, ongoing trauma. (These concerns and a full discussion of assessment and screening measures for trauma in children are addressed in Briggs et al., Chapter 17, this volume.)

The significant lack of developmental differentiation regarding expression of PTSD in DSM-IV is acknowledged in DSM-5 by including diagnostic criteria for children 6 years and younger (e.g., the preschool subtype; see Friedman et al., Chapter 2, this volume). Although the inclusion of criteria for children 6 years and younger represents an advancement from DSM-IV criteria, further specificity appears warranted.

One such approach, developmental trauma disorder (DTD), has been proposed as a more integrative, clinical framework to better assess and classify children's complex dysregulation in the wake of chronic traumatic events and disrupted attachment (D'Andrea, Ford, Stolbach, Spinazzola, & van der Kolk, 2012). A study comparing multifactor analyses of both DTD and PTSD revealed that "although childhood PTSD and DTD share several traumatic antecedents, DTD may be uniquely associated with pervasive exposure to violent environments and impaired caregiving" (Spinazolla, van der Kolk, & Ford, 2018, p. 1). These initial findings, while intriguing, require further study since more evidence will be needed before DTD is accepted as a DSM diagnosis.

THE ROLE OF THE SOCIAL ENVIRONMENT

Bronfenbrenner's (1979) social-ecological model of human development describes multiple layers of a child's social ecology, pointing to important roles played by larger institutions and cultural contexts in shaping a child's development, in addition to the role of the immediate family system. Each level of the social ecology plays a key role in some aspect of healthy child development. Bronfenbrenner's model provides a way to understand how children are influenced by, and influence, their world throughout development. There are ongoing transactions between the levels of this social environment/social ecology that shape all aspects of development and highlight ways in which healthy development is either promoted or inhibited.

While many have written about the role of the family in childhood trauma, little systematic work is available to evaluate the role of the child's overall social ecology or "system of care." It is therefore crucial to achieve through future research a more robust understanding of the role that familial, social, and political structures play in risk factors, protective factors, and recovery from traumatic experiences.

PUBLIC HEALTH AND WELFARE

The impact of childhood trauma has significant implications for public medical and mental health systems (Felitti et al., 1998), as well as for the systems with which many traumatized youth are regularly involved, namely, the child welfare and juvenile justice systems. Children and families involved with the child welfare system have almost by definition experienced trauma, both because of the maltreatment that brings them into contact with the system and the invasive nature of system involvement itself. National data consistently show that neglect is the most common reason for involvement in the system; in 2017, 74.9% of children subjected to a child protective investigation had experienced neglect, followed by 18.3% who had experienced physical abuse, 8.6% who had experienced sexual abuse, 5.7% who had experienced psychological maltreatment, and 2.2% who experienced medical neglect (Child Welfare Information Gateway, 2018). Since reports indicate that many children were exposed to more than one type of maltreatment, these numbers add to more than 100%. This differential exposure of children within the child welfare system to maltreatment parallels the most recent national prevalence data on all children and adolescents who have experienced abuse or neglect (Sedlak et al., 2010).

During fiscal year 2017, there were 2,402,827 children screened in referrals of child abuse and neglect nationally, with 442,893 children in out-of-home care (Child Welfare Information Gateway, 2018). Approximately one-fourth of these children were placed with family members; half were in nonrelative foster homes; and the remainder were in residential programs, institutions, preadoptive homes, or other settings.

Multiple challenges are involved in considering how best to help the child welfare system work more effectively for traumatized children. Providing quality care for such children requires successfully addressing three difficult realities: (1) clinical and practical needs; (2) organizational needs, including factors such as financial and regulatory issues; and (3) human services workers' needs. Until these needs are met, children with abuse or neglect histories who are placed into the child welfare system will continue to be underserved and cared for inadequately. There is therefore an important need to create trauma-informed systems within child welfare and juvenile justice settings that train all staff to understand the impact of trauma and the needs of traumatized youth and families; integrate trauma-specific interventions into practice; and address the need to help those who work in such systems to avoid vicarious traumatization.

IMPLICATIONS FOR TREATMENT

Many interventions now exist for youth who have experienced trauma, including manualized cognitive-behavioral interventions designed to help youth and their families learn to manage symptoms of posttraumatic stress (Cohen et al., 2006) via exposure and response prevention techniques. The most commonly used intervention for youth,

trauma-focused cognitive-behavioral therapy (TF-CBT), is well supported via multiple published studies f controlled trials. A review of meta-analytic studies of TF-CBT shows consistently positive outcomes regarding reduction of PTSD synmptoms (deArellano et al., 2014). For a full review of psychosocial interventions for traumatized children, please refer to Cohen and Mannarino, Chapter 20, this volume.

While many controlled studies demonstrate the efficacy of such approaches, there is an increasing consensus that many of the interventions with demonstrated efficacy or effectiveness in clinical trials have not had a widespread impact on typical clinical practice and therefore have had limited ability to improve the lives of the children and families at highest need (Beidas, Marcus et al., 2015; Saxe & Acri, 2017;).

This suggests that efficacy alone is not sufficient. Emphasis needs to be placed on ensuring that effective interventions reach those who need them the most. Several studies of a systemic intervention designed to include all members of a youth's social ecology have indicated promising results in terms of improved functioning of the youth and the youth's family and larger system of care (Murphy, Anderson, Redd, & Malm, 2017). It would therefore appear that there is a need for interventions that integrate self-regulation and response prevention techniques, as well as a method for assessing the stability of the larger social context, including how to help the ecology become more stable and better able to support the child. The need is for a methodological shift that focuses on not only symptom reduction but also the way in which interventions are delivered and the impact they have in real-world settings. (See Stirman, Chapter 32, this volume, on implementation of effective treatments.)

The findings summarized in this chapter have profound implications for the effective treatment of children who have experienced traumatic events. Developmental considerations are crucial to take into account. For example, based on the work of our team in child welfare settings, it is necessary to consider questions such as the following:

- What type of attachment patterns might develop for a child whose mother has a depressive disorder and is often isolated in her bedroom, whose father is alcoholic and intermittently violent, and whose brother is in a gang?
- What is the impact on the sense of identity of a 13-year-old child to have a father in prison, after witnessing that father beat his mother and brother?
- How do these experiences and their influence on attachment and identity formation affect that child's ability to regulate emotion, to develop peer relationships, and to function academically?

These are the types of questions that must inform the development of treatment models for such children and adolescents. Effective treatments must therefore be specific to the developmental needs of the child and address all levels of the social environment, including the youth, the family, and other important members of that youth's social ecology. These interventions must be studied for their practical use and efficacy in real-world settings.

DISCUSSION AND RECOMMENDATIONS

The field of child and adolescent psychology and psychiatry has come a long way since the 1970s. The U.S. government's creation of the National Child Traumatic Stress Network in 2001, which indicates recognition of childhood trauma as an epidemic with

wide-reaching implications for individuals and society, has allowed important collaborations, funded crucial research, and developed and disseminated assessment and treatment models throughout the United States and beyond.

Much important work, however, remains to be done. We need to reach the point where all child-serving systems, including medical, mental health, child welfare, juvenile justice, and educational systems, become aware of and sensitive to the needs of traumatized youth and families, and are able to meet these needs consistently and effectively. This work is beginning to be recognized by professional organizations. For example, the American Academy of Child and Adolescent Psychiatry (AACAP) issued practice parameters for treating child and adolescent trauma, including specific recommendations that urge all professionals who assess youth, including pediatricians, child psychologists, and psychiatrists, to screen for traumatic events, even if that is not the reason for the assessment. It was also urged that trauma-focused psychotherapies be considered first-line treatment (AACAP Official Action; Cohen et al., 2010). Unless and until all professional organizations take similar action, we continue to face an uphill battle with profound implications. It is crucial that child-serving individuals and entities recognize the factors that contribute to adverse childhood experiences and begin to build systems and supports that will prevent such experiences from occurring and will provide early detection and intervention across all levels of the social ecology.

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CHAPTER 15

Trauma and PTSD in Older Adults

Joan M. Cook and Vanessa Simiola

Psychological trauma and its consequences, including posttraumatic stress disorder (PTSD), have received less scientific study in older adults (65 years of age or older) than in younger persons. More recently, however, the research on trauma in older populations has begun to increase. Our goals in this chapter are to outline the scope and nature of aging populations in industrialized countries; to summarize the epidemiology of trauma and PTSD in older adults; to review current evidence concerning psychological and pharmacological treatments applied to older patients; to discuss methodological challenges related to the study of older populations; and to highlight potential opportunities for future investigation.

Most of the extant literature has focused on male veterans or former prisoners of war, White persons, and those from the United States. There have been several recent reports from longitudinal investigations using representative samples of veterans regarding traumatic exposure and subsequent effects on health and functioning that are important and worth noting. There has also been further documentation of the significant association between PTSD and dementia as well as accelerated aging in late life. Elder abuse has been identified as an important global health care issue, and some progress has been made in terms of psychological treatment of older adult trauma survivors. Here, we focus primarily on PTSD because it is the most studied outcome associated with exposure to potentially traumatic events. This chapter updates and expands coverage of topics in the previous editions of this volume (Cook & Niederehe, 2007; Cook, Spiro, & Kaloupek, 2014), but it does not address previous material on the course and phenomenology of PTSD, late-life developmental tasks, and normal aging concerns that may be of interest to the reader. This chapter represents both longitudinal work on people who were traumatized in young adulthood and information about older adults who are exposed to traumatic events in late adulthood.

The global aging of the population is expected to have numerous implications for health care and other social services for older adults. History of trauma exposure may influence the mental and physical health of aging adults, particularly if it is undetected.

Older adults may not be aware of the potential consequences exposure to trauma can have on their health and therefore may not disclose this information unless specifically asked about it. Physicians and other health professionals may not be trained to assess trauma histories, leading to potential ruptures in older adults' physical and emotional treatment and recovery, such as inaccurate diagnoses and inappropriate administration of psychotherapy, pharmacotherapy, and other interventions.

EPIDEMIOLOGY OF TRAUMA AND PTSD IN OLD AGE

Until the past decade, most epidemiological studies examining the prevalence and impact of traumatic experiences and PTSD either excluded older adults or did not recruit sufficient numbers to examine late-life age effects. In addition, the scientific value of the studies reviewed was limited by focus on a single event type (e.g., combat, natural disaster), reliance on nonrandom or convenience samples, and/or relegation of all adults age 65 and older to one broad category despite potentially meaningful differences tied to cohort experiences and developmental factors. Epidemiological investigations conducted over the past 10 years have strengthened, including older adults in adequate numbers as well as improved measurement, sampling, and analytic methods (e.g., Creamer & Parslow, 2008; de Vries & Olff, 2009; Pietrzak, Goldstein, Southwick, & Grant, 2012; Spitzer et al., 2008).

The evidence on PTSD rates in older age remains variable and open to interpretation, despite these notable improvements. General population surveys in 24 countries across six continents found that over 70% of adults are exposed to a potentially traumatic event at some point in their lives (Benjet et al., 2016). Compared to younger age cohorts, participants age 65 and older had higher odds of exposure to collective violence but lower odds of interpersonal violence, sexual violence, accidents/injuries, and mugging.

One of the largest epidemiological investigations in the United States (the National Comorbidity Survey) found that lifetime prevalence of PTSD among individuals age 60 and older was only 2.5%, a rate significantly lower than that in other adult age groups in the same study (Kessler et al., 2005). Indeed, individuals over age 60 were five to six times less likely to have had a PTSD diagnosis at any time compared to younger adults. In contrast, another large epidemiological study in the United States, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Pietrzak et al., 2012), estimated a 6.5% prevalence for PTSD in persons age 60 and older, which is only somewhat lower than the typical 8–10% prevalence for adults (Kessler et al., 2005). In a more recent update of the NESARC epidemiological investigation, Goldstein and colleagues (2016) found lower rates of lifetime PTSD among individuals 65 and over (3.2%), compared to the earlier investigation by Pietrzak and associates (2012). Differences may be explained in part by Goldstein and colleagues' use of the more stringent criteria for PTSD in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013) compared to those of DSM-IV (APA, 1994) criteria used in the earlier investigation.

Other epidemiological investigations of community-dwelling adults outside the United States show either lower prevalence of PTSD with age (Creamer & Parslow, 2008; de Vries & Olff, 2009) or no differences in prevalence among young, middle-aged, and older adults (Spitzer et al., 2008). One concern is that evidence of age-related differences may in part reflect a form of survivor bias tied to sampling relatively healthy older adults or to the related possibility that those with PTSD in midlife are less likely

to survive into later adulthood. In addition, lower prevalence rates of PTSD in older adults may be influenced by a number of currently unaccounted for factors, including the tendency of older adults to express psychological difficulties as somatic complaints and generational reluctance to admit psychological difficulties due to perceived stigma (see Thorp et al., 2011, for further discussion). Indeed, it has been suggested that PTSD diagnostic thresholds should be lowered (for a review, see Cook & O'Donnell, 2005), as they have been for preschool children (see Friedman et al., Chapter 2, this volume, on DSM-5 criteria).

Although the prevalence of full PTSD appears to be relatively low, some evidence suggests that older adults may have clinically important PTSD symptoms. Subthreshold PTSD (wherein all but one or two criteria are present) appears to be a prevalent and clinically significant problem in the older adult population. For example, Pietrzak and colleagues (2012) reported that the rate for subthreshold/partial PTSD was 3.6%.

Experiences identified by older adults as potentially traumatic are relatively consistent. Although no longer considered a criterion A event in DSM-5 (APA, 2013), previous investigations using earlier iterations of the DSM criterion frequently identified unexpected death or serious illness/injury to someone close and their own serious illness as the worst stressful events (e.g., Breslau, Peterson, Schultz, & Lucia, 2004; Spitzer et al., 2008). In a large, relatively comprehensive assessment of potentially traumatic events in older adults, Pietrzak and colleagues (2012) found that respondents who met criteria for full PTSD most frequently reported sexual assault or intimate partner violence as their most distressing event. The next most frequent distressing event category noted by respondents with full or partial PTSD was unexpected death and serious illness or injury of a close person.

POPULATIONS STUDIED

The current knowledge base would benefit from more research on traumatized older adults from non-industrialized countries, as well as those in North America from diverse backgrounds, including ethnic and racial minorities, women, and those with cognitive impairments. Much of the extant literature has focused on male veterans or former prisoners of war, Whites, and people from the United States. The next largest literature is on older adults who experienced natural or human-made disasters later in life. In contrast, relatively little research on trauma in aging populations has been conducted with ethnic and racial minorities or with traumatic exposure involving interpersonal violence or criminal victimization.

Combat Veterans and Former Prisoners of War

Data from several longitudinal investigations of veterans shed light on trauma and aging-related issues. Perhaps the most important finding on the impact of war trauma in older veterans comes from a 50-year longitudinal investigation of male college students who served in World War II (Lee et al., 1995). Members of the Harvard University classes of 1939–1940 were studied extensively before and immediately after serving overseas, then biennially for 50 years or until death. Over half of the men who experienced heavy combat were chronically ill or dead by age 65, suggesting a striking linkage between the adversity of war and early mortality.

The Veterans Affairs' Normative Aging Study (Bosse, Ekerdt, & Silbert, 1984) was one of the first large, longitudinal studies of community-residing male veterans, and it

continues to be a solid source of information on trauma and PTSD in older former military men. This study began in the 1960s. Every 3 years, male participants receive health examinations and periodically are sent surveys. The sample is largely White and middle class and was initially selected for participation for good physical health. Schnurr, Spiro, Vielhauer, Findler, and Hamblen (2002) provided diagnostic information based on clinician-rated interviews using the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) in the Normative Aging Study sample. The study found that trauma exposure was highly prevalent, but many subjects were asymptomatic. This dataset has also provided important information about the effects of trauma and PTSD on physical health (e.g., Schnurr, Spiro, & Paris, 2000; see Schnurr et al., Chapter 25, this volume).

Recent data from the Normative Aging Study demonstrated that noncombat veterans showed little change in their depressive and anxious symptoms as they aged, whereas combat veterans showed higher levels of symptoms in midlife, decreasing until their mid-60s, and then increasing again in their 70s and 80s (Lee, Aldwin, Choun, & Spiro, 2019). This steeper increase in mental health symptoms during later life in combat veterans indicates that combat exposure likely alters the relationship between age and psychological symptoms.

The Vietnam Era Twin Study of Aging examined environmental and genetic risk and protective factors on cognitive and brain aging beginning in midlife in a community dwelling cohort of 5,574 Vietnam-era veterans. Using data from this study, Goldberg and colleagues (2014) identified disparities among older veterans with and without PTSD and those who were exposed to combat. Specifically, combat-exposed veterans and veterans with PTSD were found to have poorer health functioning and higher rates of disability. Furthermore, in another investigation of this cohort, Franz, Lyons, and Kremen (2018) found that PTSD predicted hippocampal atrophy and smaller amygdala volume, which were associated with poorer psychological and physical health outcomes in later life. These findings demonstrate the potential sequalae of PTSD on stress neurocircuitry among aging populations.

One of the most significant contributions to the study of adult development was the National Vietnam Veterans Readjustment Study (NVVRS; Kulka et al., 1990), and its more recent 25-year follow-up, the National Vietnam Veterans Longitudinal Study (NVVLS; Marmar et al., 2015). In response to a congressional mandate in the early 1980s to obtain detailed information about the psychological impacts of war, the NVVRS demonstrated that a significant number of Vietnam veterans were experiencing PTSD and other life stressors such as marital problems and work-related stress. Over the 25-year follow-up, PTSD symptoms remained relatively stable, with 16% of combat-exposed veteran reporting an increase in PTSD symptoms and only 7.6% reporting a decrease. Using NVVLS data, Steenkamp and colleagues (2017) identified predictors of current PTSD as well as changes in PTSD symptoms over the 25-year period. African American race, lower educational attainment, low social support, and past year stress were all predictors of current PTSD. In addition to these, younger age at entry to Vietnam and greater combat exposure predicted symptom exacerbation. Information gathered through this impressive dataset can be used to guide targeted interventions for aging veterans as well as to guide treatment development for veterans returning from war today.

In a sample of 2,025 veterans age 60 and over from another longitudinal investigation, the National Health and Resilience in Veterans Study (NHRVS), Pietrzak and Cook (2013) examined the prevalence and determinants of psychological resilience. Veterans were grouped into three categories based on their number of lifetime traumas and current psychological distress: Control (low number of lifetime traumas, low

current distress), Resilient (high number of lifeline traumas, low current distress), and Distressed (high number of lifetime traumas, high current distress). Compared to the Distressed group, the Resilient group demonstrated higher emotional stability, social connectedness (i.e., secure attachment style, social support), protective psychosocial characteristics (e.g., community integration, purpose in life), and positive perceptions of their military experience's effect on their life.

The existence of a late-life phenomenon termed *late-onset stress symptomatology* (LOSS; Davison et al., 2006; King, King, Vickers, Davison, & Spiro, 2007) was proposed, which occurs when older combat veterans who have had no recognized trauma-related difficulties with functioning throughout most of their lives first express combat-related stress symptoms and impairment in older adulthood. This phenomenon has more recently been reconceptualized and renamed *later-adulthood trauma reengagement,* or LATR (Davison et al., 2016) to better reflect not just an elevation in symptoms, but the approach toward reworking and life review. Empirical investigation is required to verify this construct, differentiate it from delayed-onset PTSD, and test its applicability to other older adult trauma populations.

Disaster Survivors

This section covers two groups: survivors of natural disasters and survivors of human-induced disasters.

In a recent systematic review, Parker and colleagues (2016) identified six high-quality studies on whether older persons have increased risk of mental health outcomes after exposure to natural disasters, such as cyclones, hurricanes, floods, earthquakes, and tsunamis, for a random effects meta-analysis. Although older adults were not at increased risk for depression or other anxiety symptoms, they were 2.11 times more likely to experience PTSD symptoms and 1.73 times more likely to develop adjustment disorder when exposed to natural disasters when compared with younger adults. The samples that were featured in these studies were from five countries, including two high-income (Australia and Taiwan), one upper-middle-income (China) and two lower-middle-income (India and Indonesia) countries.

These findings are in contrast with data from a quantitative review of mental health in a broad range of disaster survivors, which reported differential negative risks associated with older age in only 2 of 17 distinct samples that included older adults (Norris et al., 2002). On the contrary, 15 of the 17 samples indicated that the mental health effects of disasters declined with age. However, a critical examination of the 17 distinct samples from that review indicate that most of these studies include primarily or solely community-dwelling, noninstitutionalized individuals (Cook & Elmore, 2009). Thus, the least healthy and potentially most at-risk older adults were excluded (i.e., those with, physical, emotional, or cognitive impairment; the homebound; and long-term care residents).

In general, due to physical changes and life circumstances, some older adults may be more vulnerable to adjustment disorder and PTSD following disasters, in part because of increased pain, injury or bereavement. They may be less likely to receive advanced warnings or evacuate (Powell, Plouffe, & Gorr, 2009). Since many older individuals are on fixed incomes and are unable to increase earnings to address unexpected post disaster expenses, they may also have a harder time reestablishing residence and routine (Acierno et al., 2006).

Hurricane Katrina is one recent U.S. disaster that shows how older adults are particularly vulnerable, particularly to dying. Older adults of New Orleans had the highest

mortality rates during and immediately following Hurricane Katrina, which struck in New Orleans in 2005. The high mortality rates were related to a variety of factors, including lack of evacuation facilities, injuries prohibiting evacuation, impoverished living conditions, and social isolation (Gibson, 2006). Despite showing higher mortality rates, research on those who survived the devastating effects of Hurricane Katrina demonstrated that older adults' previous life experiences may result in more positive coping following disaster compared to younger generations. Specifically, Adams and colleagues (2011) interviewed adult survivors (age 40–98) several times over a 3- to 4-year period, beginning 2 years after the hurricane. Older adult survivors ranging in age from 65 to 98 were more likely to report "making the best" of the challenges they faced, whereas younger generations reported more difficulty managing responsibilities (e.g., generating income, rebuilding, caretaking), resulting in sharper declines in mental health, and thus they were unable to increase earnings to address unexpected post-disaster expenses.

Ethnic and Racial Minorities

The limited information on the experience of trauma and its treatment in cross-culturally diverse older adults comes primarily from refugee or immigrant populations or from comparisons of White and Black Americans. In a paper that included data from two large national household surveys of English-speaking, noninstitutionalized adults age 18 and over, risk of developing PTSD was elevated throughout the lifespan for American Blacks and Caribbean Blacks, while it decreased after young adulthood for non-Hispanic Whites (Himle, Baser, Taylor, Campbell, & Jackson, 2009). The authors hypothesize that increased vulnerability for PTSD in these groups was due to higher exposure to trauma and the continuing impact of race-related discrimination and stress.

A few small studies have been conducted on African American older adult female survivors. For example, older African American women with histories of interpersonal violence who were identified through ambulatory clinics of a large public hospital had worse physical and mental health status than those who had little or no family violence exposure (Paranjape, Sprauve-Holmes, Gaughan, & Kaslow, 2009). Focus groups with 30 of these women identified individual, dyadic, and community-level variables that might influence the risk of family violence in this population. Key among them were poor physical health, violence in the surrounding neighborhood, and generational differences in values (e.g., related to prioritizing the needs of others over one's own). Relatedly, 23 African American women, mean age 60, living in a mixed-age public high-rise community in an urban setting discussed how interpersonal traumas impacted their current life, including challenges associated with aging (Bowland, 2015). Many of the women talked about the environmental characteristics of the high-rise buildings (e.g., long, dark hallways; slow elevators) that increased their hyperarousal symptoms. For them, the idea of recovery from trauma seemed out of reach as there were so many complicated safety issues in their present living situations.

Elder Mistreatment

Elder mistreatment is a pervasive and growing public health problem in both community and residential settings. There are generally five types of elder abuse: physical abuse, psychological or verbal abuse, sexual abuse, financial exploitation, and neglect,

or the failure of a designated caregiver to meet the needs of a dependent older person (Pillemer, Burnes, Riffin, & Lacks, 2016). Until recently, most evidence on maltreatment of older adults was derived from surveys of professionals or highly selected samples, such as those identified as the result of reports to Adult Protective Services. However, numerous methodologically sound investigations, including the use of representative samples, have now been conducted. For example, a study of almost 6,000 older adults examined the prevalence of emotional, physical, sexual, and financial maltreatment or neglect (Acierno et al., 2010). More than one older adult in 10 (11.4%) reported some type of past-year maltreatment, with prevalence of 4.6% for emotional abuse, 1.6% for physical abuse, 0.6% for sexual abuse, 5.2% for financial abuse, and 5.1% for potential neglect. In the second wave of this study, Hernandez-Tejada, Frook, Steedley, Watkins, and Acierno (2020) reported that only low household income was associated with increased psychopathology among older adult abuse victims, and only low household income and unemployment were associated with poor self-rated health. It may be that those with limited financial resources must rely on others to a relatively large extent.

Although a few thousand papers address elder maltreatment, relatively few have been intervention studies. In a systematic review of scientifically sound studies designed to prevent or stop elder maltreatment, Ayalon, Lev, Green, and Nevo (2016) identified two interventions designed to improve the ability of professionals to detect or stop elder maltreatment; three interventions that targeted older adults who experienced elder maltreatment; and 19 that targeted family and paid caregivers who maltreated older adults, including use of physical restraints in institutions. Sadly, despite efforts, there remains limited empirical evidence for evidence-based interventions that prevent mistreatment and assist older adults post abuse (Moore & Browne, 2017). Given the prevalence and negative effects of elder abuse, health care systems, social welfare agencies, policymakers, and the public must work together to combat this problem.

Older Women

The research on older adult women who have experienced trauma is relatively sparse compared to research on their male counterparts. Much of the research to date has focused on veterans or survivors of interpersonal violence. Recently, several key papers have been written on these populations. For example, the Health of Vietnam-Era Women's Study is a retrospective study of women who served in Vietnam, women who served in other countries near overseas, and nondeployed women. Many were nurses. Accounting for wartime location, Magruder and colleagues (2015) examined the impacts of potentially traumatic events experienced during wartime to determine the rates of PTSD in this population. Wartime potentially traumatic events included (1) physical, sexual, and verbal harassment; (2) compulsory pressure to perform their job functions while under enemy fire; and (3) unwanted sexual experiences that involved use of threat or force. Lifetime prevalence of PTSD was highest among women who served in Vietnam (20.1%), followed by nondeployed women (14.1%), and was lowest amongst women stationed around, but not in, Vietnam (11.5%). Strikingly, the prevalence of lifetime PTSD for the women stationed in Vietnam and the nondeployed cohort is higher than what has been documented in women of comparable age in the general population (Magruder et al., 2015). Not only were risks of PTSD higher, but in an investigation of mortality in this population, Kang and colleagues (2014) found that nurses stationed in Vietnam had a twofold higher risk for pancreatic cancer death and nearly a fivefold higher risk of brain cancer death when compared with nondeployed nurses.

The authors speculate this may be due to some aspect of the military nursing environment (i.e., smoking, herbicide and pesticide exposure) in Vietnam that could be associated with higher cancer risk, though no one specific factor was identified in this study.

For older women who experience interpersonal violence, there is limited public awareness, and fewer services are available that are specifically designed for their needs than there are for younger and middle-aged survivors of this type of trauma. A recent systematic review that focused on older women with lifetime experience of interpersonal violence (Cook, Dinnen, & O'Donnell, 2011) found that they have greater psychological difficulties than older women who do not have these experiences. In fact, one out of seven older women in a large nationally representative sample reported a history of physical or sexual assault, or both (Cook, Pilver, Dinnen, Schnurr, & Hoff, 2013). Those who reported this type of traumatic history were generally more likely to meet criteria for past-year and lifetime PTSD, depression, or anxiety than those without such a history. Similarly, in older women from a national probability sample of adults between the ages of 57 and 85, 7% reported adult rape, with an average of 36 years since the rape had occurred (Sachs-Ericsson et al., 2014). Compared to findings observed in younger women, older women who had been raped had lower self-esteem and lower psychological and physical health functioning.

METHODOLOGICAL CONSIDERATIONS

There are numerous methodological challenges for mental health research on older traumatized individuals. These include cognitive, sensory, and functional impairments that may affect the experience, impact, or reporting of trauma-related symptoms, as well as unfamiliarity with or reluctance to engage in discussion of mental health issues. Thorp, Sones, and Cook (2011) provide general guidance for conducting psychological assessment with older adults, as well as specific recommendations for conducting PTSD-related assessment with older trauma survivors. The potential issues are numerous and include differences among age cohorts in the expression of psychiatric symptoms, the importance of recognizing the potential impact of social desirability on reporting, and the need for large, bold fonts in written materials to increase readability and minimize frustration. PTSD-specific issues include the challenge of systematically assessing exposure to potential traumatic events across an extended lifetime, the need for specific behaviorally anchored questions, and the benefits of using more than one method of assessment (e.g., self-report, observation, caregiver report, structured interviews), particularly for respondents with cognitive or sensory impairments. Thorp and colleagues provide a useful summary of PTSD measures with established psychometrics applicable to older adults.

CURRENT STATE OF THE ART

Treatment

Psychotherapy

Although numerous randomized controlled trials of psychotherapy for adults with PTSD have been conducted, most either do not include adults 65 of age and over or do not have sufficient numbers to examine age effects. A systematic review of the

psychotherapy literature for PTSD showed that there were 13 case studies and 7 treatment outcome studies that had at least 50% of participants over age 55 (Dinnen, Simiola, & Cook, 2015). As authors of that systematic review, we had intended to examine the literature on those aged 65 and older. However, had we chosen that higher age cutoff, we would have only had 12 case studies and no treatment outcome studies.

Of the case studies included in the published review, all but two stated that older adults reported a significant reduction in PTSD symptoms. However, the treatment outcome studies had mixed results. Interestingly, most of these studies had relatively weak methodological design with no randomization, lack of comparison conditions, small sample sizes, and nonuse of full protocols of evidence-based trauma-focused therapies. Additional studies of psychotherapy for older adults with PTSD are warranted, particularly those that focus on those aged 65 and over.

Since the systematic review was published, there have been few reports of psychotherapy for older trauma survivors. Most recently, Thorp and colleagues (2019) reported on the first randomized controlled trial of prolonged exposure (PE; Foa, Hembree, & Rothbaum, 2007) for older adults with PTSD—namely, U.S combat veterans over the age of 60 with military-related PTSD. In that study, veterans who received PE and those who were treated with relaxation therapy had significant declines in clinician-rated PTSD symptoms, but groups did not differ at posttreatment or follow-up. However, the PE group had greater improvement than the relaxation group at posttreatment in self-reported PTSD symptoms, although the improvement was not sustained. Of the older adults who received PE, over one-third had clinically significant reductions in PTSD symptoms, while approximately 75% still met the criteria for PTSD. Since many of the veterans in the Thorp and colleagues (2019) study continued to experience distress after completion of PE, additional advances to improve the efficacy of the treatment with older adults may be needed.

There may be some concern regarding the use of exposure techniques with older adults in part because of potential physiological arousal in those with heart conditions. However, those who advocate the use of exposure with older trauma survivors view emotion-based physiological arousal as a tolerably unpleasant but safe aspect of the approach (Thorp et al., 2011). There is empirical evidence for the safety and tolerability of exposure therapy in older adults for other disorders (Jayasinghe et al., 2017). In addition, of the case studies of exposure therapy with older adults with PTSD, none reported long-term adverse effects despite inclusion of older adults with comorbid conditions such as heart disease, dementia, depression, and panic disorder (Dinnen et al., 2013). However, two studies that were reviewed did note an increase in symptoms prior to improvement (Russo, Hersen, & van Hasselt, 2001; Yoder, Tuerk, & Acierno, 2010), as has been observed in younger adults. It is important to proceed with appropriate caution and to monitor those for whom high arousal might be a risk, such as those with serious cardiac or respiratory problems.

Therapeutic interventions for PTSD can be similar for older and younger adults with respect to education about symptoms, enhancement of social support, and teaching coping skills to manage symptoms, but additional unique considerations apply for older adults. This is the reason that guidelines for psychological practice with older adults (American Psychological Association, 2014) advise clinicians to gain knowledge of theory and research on aging, including the social and psychological dynamics of the aging process, biological and health-related aspects of aging, and common issues related to cognitive changes and problems in daily living (e.g., ability to function independently). It is important to be able to distinguish between the aging per se and the

increasing impairments and diseases that occur with advancing age. A greater need to appreciate maturational and cohort differences, to understand the impact of chronic disease and pain, to recognize behavioral signs of negative medication effects, and to assess factors that influence adherence to both treatment and rehabilitation regimens is warranted.

Such knowledge may lead to modification of treatment techniques. For example, provision of mental health treatment to older individuals often occurs at a slower pace due to possible sensory problems and slowed learning rates. Repetition can be very important in the learning process to assist older patients in encoding and retaining information. And, in general, flexibility is necessary with respect to scheduling, location, and the role of the person as an active collaborator in care. It may be crucial to engage the care provider in the treatment process when an older adult has become dependent on formal or informal care. One successful example of the use of modifications was a case study of a Vietnam veteran with dementia who completed PE (Duax, Waldron-Perrine, Rauch, & Adams, 2012). To circumvent reading and writing challenges, the patient's wife was asked to read the handouts out loud to her husband. Furthermore, to facilitate learning, phrases commonly used in the treatment such as "imaginal" and *in vivo* were renamed "memory." With the assistance of his wife, the veteran was able to complete 14 sessions of PE, which resulted in significant reductions in depression and PTSD symptoms.

PTSD in older adults is an important target, but it also may be a comorbidity that interferes with the treatment of other disorders. For example, comorbid PTSD or panic was examined for its effect in relation to outcome for depression treatment in older adults in primary care (Hegel et al., 2005). Depressed patients with PTSD were more likely to have a history of multiple depressive episodes, more chronic medical conditions, more severe health-related impairment, and lower quality of life than those without PTSD. Treatment response for depression was slower for those with comorbid PTSD, averaging 12 months, compared to 3 months for other groups. When primary care practitioners and mental health specialists worked collaboratively, those with depression without comorbidity also improved faster, and treatment gains were maintained longer for older adults. Thus, it appears that older adult trauma survivors with comorbid PTSD and depression may need more intense treatment or longer follow-up.

Pharmacotherapy

The recommended first-line pharmaceutical treatments for PTSD in the general adult population are selective serotonin reuptake inhibitors (SSRIs), particularly sertraline and paroxetine and fluoxetine and one selective serotonin and norepinephrine reuptake inhibitor, venlafaxine (American Psychological Association, 2017; see Davis et al., Chapter 23, this volume, on pharmacotherapy for PTSD). However, most of these studies do not include older adults or have not examined aging as a factor in safety or effectiveness.

Recent studies have shown promising results related to the trends in pharmacological interventions for older adult veterans. For example, Bernardy, Lund, Alexander, and Friedman (2014) found that polysedative prescribing of benzodiazepines, hypnotics, atypical antipsychotics, opioids, and muscle relaxants were all lower among older compared to younger veterans. Hawkins, Malte, Grossbard, and Saxon (2015) examined concurrent prescribing of opioids and benzodiazepines in veterans with PTSD and found significant increases in concurrent long-term use of these drugs in all age groups

except for women age 65 and over. Furthermore, Semla and colleagues (2017) found that second-generation antipsychotic prescribing declined from 13.2 to 8.9% and from 7.0 to 5.1% for older adult veterans with PTSD with and without dementia, respectively. These findings are encouraging, given that older adults are more susceptible to falls and to adverse reactions to medications, and typically they have more complex medication routines.

There are several important issues to consider in the pharmacological treatment of mental health disorders in older adults. First, age-related biological changes may complicate the application of psychotropics to this population. Specifically, older adults are susceptible to side effects in part because the rate at which the body metabolizes medications slows with age. This metabolic slowing results in medications remaining active for long periods of time. In addition, the old-old (those age 85 and older) and those with comorbid medical conditions that further reduce metabolic efficiency are more susceptible to building up toxic drug levels in the blood and may experience intolerance or adverse reactions at lower dosages than would be typical in younger adults. Second, older adults are more likely to be taking more than one medication, thereby increasing the possibility of drug interactions. This may reduce the effectiveness of PTSD medication and/or increase the likelihood of adverse side effects. Because polypharmacy is common in older adults, best practices for pharmacotherapy in older trauma survivors with PTSD include consideration of the side effect profiles of various medications, starting with low dosages, titrating the dosage slowly and cautiously, and adjusting one medication at a time, so that potential reactions can be isolated and corrected (e.g., "start low and go slow").

Special Needs and Concerns

Two timely areas of special concern are (1) the relationship among trauma, PTSD, and cognitive impairment in later life and (2) the impact of trauma and PTSD on the biology of older adult trauma survivors, including possible effects of accelerated aging. First, recent studies have examined the relationship between PTSD and dementia or accelerated aging. For example, five retrospective cohort studies based on VA administrative data found a significant association between PTSD and a later diagnosis of dementia in veterans (Rafferty, Cawkill, Stevelink, Greenberg, & Greenberg, 2018). This supports the assertion that veterans with PTSD are at a significantly greater risk of developing dementia. Mawanda, Wallace, McCoy, and Abrams (2017) found that PTSD was associated with increased risk of dementia, but the risk was increased even more among veterans taking SSRIs, novel antidepressants, and atypical antipsychotics. Although it is not clear if the medication or the underlying diagnosis for which the medication is being prescribed is mediating the relationship between dementia and PTSD, these results suggest that more research is needed.

Several large studies in civilian populations have recently been conducted. Using a dataset from Taiwan, Wang and colleagues (2016) examined the incidence of PTSD and dementia. In this study, adults age 45 and over with a diagnosis of PTSD had a 4.37-fold higher risk of dementia compared to matched controls, even after accounting for demographic variables and medical and psychiatric diagnoses. In another investigation that used 13 years of prospective data in a large integrated health care system in northern California, Flatt, Gilsanz, Quesenberry, Albers, and Whitmer (2018) examined the association between PTSD and dementia in men and women 60 years of age and older. Electronic medical record data from 499,844 members was extracted

to determine dementia and PTSD diagnoses between 1996 through 2001 from both inpatient and outpatient settings. Older adults with PTSD had a 73% increase in risk of dementia compared to those without a PTSD diagnosis. Differences in gender were also noted as men with PTSD had a 100% increased risk of dementia, whereas women had a 60% increase. Furthermore, a significant three-way interaction emerged between depression, PTSD, and sex. In men, PTSD, depression, or PTSD plus depression were all associated with increased risk. In women, only depression or PTSD plus depression were associated with increased risk, meaning that for women, PTSD alone was not related to dementia.

Stress Hormones

The past decade has generated much research on the neurobiology of PTSD, although little of it has involved older adult trauma survivors. For example, drawing upon data from the Longitudinal Aging Study of Amsterdam, Gerritsen and colleagues (2010) examined the differential relationship between early- and late-life adverse events and diurnal salivary cortisol in older adults. The sample included 1,055 adults ages 63–93. Those who had experienced late-life adverse events had higher morning cortisol levels and a more variable diurnal pattern than those who had experienced early-life adverse events. The results suggest a differential association between adverse events and hypothalamic–pituitary–adrenal axis regulation in older adults, based on event timing during the lifespan. The most prominent implication of this study seems to be that differential PTSD risks may be associated with early-life versus later life adversity.

Wolf and Schnurr (2016) provided a review of the literature showing that PTSD is associated with cardiometabolic conditions, including metabolic syndrome, which may be caused by underlying cellular aging related to the psychological and biological stress of PTSD symptoms and related determinants. Research on DNA methylation, also by Wolf, Logue, and colleagues (2016), suggests that PTSD is associated with accelerated aging as well as poor performance on executive functioning and memory. Other areas of neurocognitive functioning have also been impacted by trauma exposure. For example, Karstens and colleagues (2017) found that trauma, independent and regardless of depression, was negatively associated with verbal learning and memory performance. Collectively, these findings suggest that older adults who are experiencing memory difficulties and other neurocognitive decline should be screened for trauma to ensure comprehensive evaluation of all potential contributing factors.

CHALLENGES FOR THE FUTURE

Knowledge in the geriatric trauma field is far from complete. More information is needed regarding the nature and course of trauma-related symptom expression with aging. This, in turn, requires development of assessment techniques to capture the key psychosocial and behavioral responses. In general, research on older adult trauma survivors would benefit from inclusion or focus on more diverse samples, including those with a broader range of traumatic events and varying ethnicity and socioeconomic levels, the oldest old (85+), and those who are cognitively impaired.

Older adulthood encompasses at least a 30-year age range; differences within this range can be quite substantial. Within this span are age bands that might be labeled young-old (65–74 years), middle-old (75–84 years), and old-old (85 years and older),

each of which has rather distinct life experiences. For instance, those currently in the old-old category lived through the Great Depression and World War II as teenagers or young adults, whereas the young-old experienced the prosperous post–World War II period at a comparable developmental stage of their lives. In addition, these subpopulations of older adults are likely to be differentiated in terms of health status and life functioning. These considerations may shape their treatment-seeking clinical presentation and approach to trauma-related treatment. Thus, more fine-grained analyses (even if they are exploratory) on young-old, middle-old, and old-old are necessary to advance understanding of trauma and aging.

Most empirical investigations of older adult trauma survivors are cross-sectional and retrospective, and few longitudinal studies have followed young or middle-aged adult trauma survivors into older adulthood. The limited information that is available on the longitudinal course of PTSD has been primarily based on combat veterans and former prisoners of war.

It is not clear whether individuals who develop PTSD as children or adults experience different trajectories as they age. Factors that mediate the relationships between traumatic experiences and development of PTSD in late life, or that influence the ebb and flow of symptoms over the life course, are not yet known. Clinical lore suggests that the occurrence or reactivation of traumatic stress symptoms may be due in part to aging-related life events: for example, illness; decrements in cognitive or functional status; bereavement; and changes in occupational, social, and familial roles. Additionally, aging is often tied to loss of control or increased vulnerability in late life. These changes and losses can elicit traumatic memories of death, physical injury, and lack of control.

Like younger adults, older adults may present to a mental health provider with limited awareness that their current difficulty is related to past traumatic experiences. Older adults may present with somatic complaints or other clinical needs that make it easy to miss the connections to trauma if suitable assessment is not undertaken. Even when mental health issues such as depression or anxiety are identified, patients and providers may not recognize or focus on potential links to trauma. One of the first tasks for scientifically informed practitioners is to assess their older patients for traumatic exposure and its effects. Such screening is particularly important for high-risk groups that likely have experienced trauma, whether in the remote past (e.g., veterans, survivors of childhood maltreatment) or more recently (e.g., those identified in rape crisis centers or older adult abuse contexts).

More methodologically rigorous research on mental health treatment for PTSD in older adults is needed, with sufficient numbers of older adults, randomization, and credible comparison conditions. Efficacy trials are needed to determine optimal methods of intervention and durability of treatment effects for older adults, as well as factors that affect their engagement, adherence, and outcome. Additionally, effectiveness research must evaluate the acceptability and tolerability of these treatments for older adults in the real world, along with their transportability and deliverability across a variety of settings (e.g., including nursing homes).

In conclusion, trauma and its potential deleterious effects, including PTSD, are less well researched in older as opposed to younger adult populations. Although the majority of older adult trauma survivors do not develop PTSD, a significant minority do. Unless treated, older trauma survivors seem to experience a relatively stable course of PTSD across the lifespan, with some waxing and waning of symptoms. PTSD can reappear or worsen later in life.

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PART III

CLINICAL PRACTICE
EVIDENCE-BASED STATE OF THE ART

CHAPTER 16

Assessment of PTSD and Its Comorbidities in Adults

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The original criteria for posttraumatic stress disorder (PTSD) in DSM-III (American Psychiatric Association [APA], 1980) defined "traumatic events" as relatively rare phenomena and PTSD as an uncommon condition in the general population. Research over the past 40 years has challenged these original assumptions, and now, traumatic events and PTSD are widely recognized as affecting millions of individuals worldwide (APA, 2013).

Most epidemiological studies of trauma exposure and PTSD to date have focused on the United States, yet a vast majority of the wars, violence, and natural disasters in the last century occurred in developing countries. Epidemiological studies confirm that trauma exposure does not inevitably lead to the development of PTSD or any other disorder (e.g., depression, substance use disorder). For instance, 68.9% of the U.S. population report past trauma exposure, but the lifetime prevalence of PTSD is estimated to be 6.1–6.8% (Goldstein et al., 2016; Kessler, Chiu, Demler, & Walters, 2005). The most common trajectory of adjustment after trauma exposure is recovery over time (Bonanno, 2004; Santiago et al., 2013). Yet, a distinct minority of those exposed develop PTSD, depression, another anxiety disorder, or a substance use disorder, and among these individuals there is a high rate of comorbidity (Brown, Campbell, et al., 2001).

Assessment of PTSD is a complex task that demands careful attention to the individual's presenting concerns, co-occurring mental and physical health problems, social and occupational functioning, and cultural and other contextual factors that may be related to the expression and course of PTSD symptomology (Dutra, Lee, Marx, & Keane, 2018). Further complication arises from the fact that PTSD is a heterogeneous disorder, characterized by avoidance, fear and anxiety, and varying degrees of accompanying and overlapping internalizing and externalizing symptoms that make differential diagnosis difficult (Weathers, 2017). Given the high degree of comorbidity with

PTSD, these questions provide the impetus for development of new conceptual models with supporting empirical evidence to inform assessment and treatment.

ASSESSMENT OF PTSD

In clinical settings, PTSD is assessed for many different reasons, and the goal of each assessment determines the methods and measures selected by the professional. For example, clinicians may require a diagnostic evaluation that includes differential diagnoses, a functional assessment of home, work, or interpersonal impairment, or other information that might be a target of a treatment intervention or assist in treatment planning. Other practitioners may be involved in forensic work in which diagnostic accuracy is of paramount importance, suggesting the need for assessment tools with proven reliability and validity.

Evidence-Based Assessment of PTSD

With the ongoing movement toward evidence-based health care, there is increased emphasis on the use of evidence-based assessment (EBA) to guide the selection of constructs and measures used in psychological assessment. EBA allows for greater diagnostic consistency in both clinical and research settings and ultimately leads to better treatment outcomes. Thus, there is a growing consensus that it is important to use standardized, objective, and psychometrically sound instruments for diagnostic purposes, with careful consideration of patient factors that might contextualize assessment results (e.g., age, culture, ethnicity, gender, and sexual orientation). Perhaps most importantly, and very relevant to the approach we recommend for the assessment of PTSD, is that clinician judgment is an integral part of the process.

Selection of Assessment Measures

The process of assessing PTSD may consist of a range of different approaches, including clinician-administered structured diagnostic interviews, structured diagnostic interviews to assess its related comorbidities, self-report psychological tests and questionnaires, and psychophysiological measures. In addition to the formal assessment, clinicians may want to review medical records and gather relevant data from multiple informants regarding the patient's behavior and experiences. Multiple informants can be useful when there are concerns about the accuracy of self-report data, which can be undermined by normal forgetting, impaired memory encoding related to the trauma or injury (e.g., traumatic brain injury), or malingering. When faced with different assessment contexts, the assessor should evaluate the quality of the measures when used in similar contexts in the past, or if this information is unavailable, use the psychometric properties of each instrument as a guideline.

Types of Assessment Measures

Structured Diagnostic Interviews

In clinical research settings, the use of structured diagnostic interviews represents both standard and recommended practice; their use in clinical settings is less common, with perhaps the single exception of clinical forensic practice (Keane, Buckley, & Miller,

2003). In general, this may be related to the specialized training needed to master the administration of these interviews, or to time constraints or the cost burden. Nonetheless, evidence-based screening and diagnostic methods are critical to ensure that individuals with PTSD and related disorders are identified and offered effective treatment options. Several well-validated clinical interviews available for the assessment of PTSD are described below.

Structured Clinical Interview for DSM-5 Axis I Disorders–PTSD Module. The Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2016) is a semistructured interview designed to assess a broad range of psychiatric conditions. It contains separate modules corresponding to DSM-5 (APA, 2013) diagnostic criteria, with each module providing the interviewer with specific prompts and follow-up inquiries. Symptoms are rated as present, subthreshold, or absent based on the interviewer's evaluation of the individual's responses. In the PTSD module, respondents are asked to frame symptoms in terms of their worst trauma experience. A diagnosis of PTSD is made following the DSM-5 diagnostic algorithm. The modular structure of the SCID-5 allows clinicians to select modules that correspond with conditions frequently comorbid with PTSD, such as anxiety, mood, and substance use disorders, which may require a different set of treatment interventions.

Further psychometric research is needed to evaluate the validity and reliability of the SCID-5; however, previous versions, including the SCID-PTSD module, are considered psychometrically sound. Regarding previous versions, Keane and colleagues (1998) reported modest estimates for interrater reliability within a 1-week interval for a diagnosis (kappa = 0.66, with diagnostic agreement of 78%). McFall, Smith, Roszell, Tarver, and Malas (1990) reported evidence of convergent validity with other established measures of PTSD (e.g., Mississippi Scale for Combat-Related PTSD, kappa = 0.65 [Keane, Caddell, & Taylor, 1988]; Keane PTSD scale of the Minnesota Multiphasic Personality Inventory [MMPI-PK], kappa = 0.46 [Keane, Malloy, & Fairbank, 1984]). The SCID-PTSD module also yields substantial sensitivity (0.81) and specificity (0.98), and a robust kappa (0.82) when compared to a composite PTSD diagnosis (Kulka, 1988).

Notably, the SCID-5 possesses some important limitations. First, the SCID-5 scoring algorithm permits only a dichotomous rating of PTSD (i.e., present or absent). A second limitation of the SCID-5 is that by assessing symptoms in response to the "worst event" experienced, important information may be lost regarding the impact of other traumatic events. In contrast, the Clinician-Administered PTSD Scale (CAPS) interview (see below) can focus on all events that meet criterion A. It is notable, however, that with any PTSD measure, it can be easy to overlook noncriterion A and yet "high-impact" experiences that may also (1) be targets of intervention, (2) impact susceptibility to future trauma(s), or (3) influence PTSD symptom and/or treatment course over time (Livingston, Berke, Ruben, Matza, & Shipherd, 2019).

Clinician-Administered PTSD Scale. Developed by the National Center for PTSD (Blake et al., 1990), the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018) is considered the "gold-standard" structured interview for the assessment of PTSD (Dutra et al., 2018). The CAPS-5 is a comprehensive structured assessment composed of 30 items that assess all diagnostic criteria for PTSD, including A (exposure), B (reexperiencing), C (avoidance), D (negative alterations in cognition and mood), and E (hyperarousal). For each diagnostic criterion assessed, the frequency and intensity are combined into a single severity score for each item. In addition, the

CAPS-5 also assesses PTSD onset and duration, symptom severity and functional impact, subjective distress, dissociative symptoms, and estimated validity of patients' responses during assessment.

An important feature of the CAPS-5 is its use of a five-point rating scale ranging from 0 = "absent" to 4 = "extreme/incapacitating" to describe symptom levels. These scores can then be aggregated to derive an overall severity score, or binary score, to indicate whether the symptom or disorder is present or absent. For diagnostic purposes, an established scoring rule requires the endorsement of at least one reexperiencing symptom, one avoidance symptom, two hyperarousal symptoms, and two symptoms listed under "negative alterations in cognition and mood" (cf. Weathers, Ruscio, & Keane, 1999). The CAPS promotes uniform administration and scoring through carefully phrased prompt questions and explicit rating anchors with clear behavioral referents. Once trained, clinical interviewers can ask their own follow-up questions and use their clinical judgment in arriving at optimal ratings. Administration of the complete CAPS-5 takes approximately 45 minutes to an hour; however, if only the core symptoms or current symptoms are assessed, administration time can be reduced to about 30 minutes.

Previous versions of the CAPS have shown excellent reliability and validity (Blake et al., 1990), high internal consistency across all items (alpha = 0.85–0.94), and good test–retest reliability (0.77–0.96) for each symptom cluster. Strong convergent validity with the SCID-based PTSD module and the PTSD Symptom Scale Interview have been reported (0.83 and 0.73, respectively). Psychometric research on the updated CAPS-5 demonstrates strong construct and convergent validity with other established self-report PTSD symptom measures (Weathers et al., 2018).

PTSD Symptom Scale Interview. The PTSD Symptom Scale Interview (PSSI) was originally developed by Foa, Riggs, Dancu, and Rothbaum (1993) as a semistructured interview designed to assess both the presence and severity of the 17 PTSD symptoms outlined in DSM-IV for individuals with a known trauma history. The updated PSSI-5 (Foa et al., 2016) is a semistructured clinical interview based on the DSM-5 criteria for PTSD. This version contains 24 items, and each item is assessed with a brief, single question and no probes or follow-up questions. The frequency and intensity of symptoms are combined into a single severity score for each item. According to the authors, combining these two dimensions reflects the fact that some symptoms lend themselves to frequency estimates (e.g., flashbacks), whereas others are better described in terms of intensity (e.g., hypervigilance).

The previous PSSI possessed strong internal consistency, 1-month test–retest reliability of severity score, and very high interrater agreement for a PTSD diagnosis (Foa et al., 1993; Foa & Tolin, 2000). With respect to validity, the PSSI score is correlated with other measures of traumatic stress (e.g., 0.69, Impact of Event Scale [Horowitz, Wilner, & Alvarez, 1979]; 0.67, Rape Aftermath Symptom Test [RAST; Kilpatrick, 1988]) and has demonstrated good diagnostic utility when compared to a SCID PTSD diagnosis (sensitivity = 0.88, specificity = 0.96). There is currently less psychometric data on the PSSI-5; however, one study suggests that the PSSI-5 has strong construct validity, convergent validity with CAPS-5, internal consistency, and test–retest validity (Dutra et al., 2018).

Anxiety Disorders Interview Schedule–Revised. The Anxiety Disorders Interview Schedule (ADIS), originally developed by DiNardo, O'Brien, Barlow, Waddell, and

Blanchard (1983), is a semistructured interview originally designed to assess DSM-III (APA, 1980) criteria for anxiety and affective disorders and initially included a PTSD module. It has now been revised to accommodate DSM-5 criteria (ADIS-5; Brown & Barlow, 2014). The interview takes about 2 hours and provides an assessment of symptom severity and lifetime and current disorders, as well as onset and duration.

Psychometric studies with the ADIS PTSD module provide mixed results. Only fair to moderate agreement between two independent raters for a current PTSD diagnosis was found in community samples recruited from an anxiety disorders clinic (Brown, DiNardo, Lehman, & Campbell, 2001). Additional reliability and validity data on the ADIS-5 are needed to understand its psychometric properties.

PTSD Questionnaires

Self-report measures are generally more time- and cost-efficient than structured interviews. They can be especially valuable when screening for PTSD or in conjunction with structured interviews to provide clinicians with additional information and to track treatment progress over time. For the most part, self-report measures are dimensional indicators of PTSD and reflect symptom severity, but for several of these measures, specific cutoff scores can suggest a diagnosis of PTSD. In selecting an instrument to use, the assessor is encouraged to examine the psychometric data for the instrument in the population with which it will be employed to maximize the accuracy and efficiency of the test (Keane & Barlow, 2002).

Impact of Event Scale–Revised. The Impact of Event Scale—Revised (IES-R; Weiss & Marmar, 1997), designed to measure psychological responses to trauma, is a revision of the original IES (Horowitz et al., 1979). The initial 15-item questionnaire, which focused only on intrusion and avoidance symptoms, was derived from an emotional processing model of traumatic stress. The IES was modified to include items measuring hyperarousal to correspond more closely with DSM-IV diagnostic criteria for PTSD. However, the IES-R does not completely map onto the DSM-IV PTSD criteria and has not been updated since the release of DSM-5.

Mississippi Scale for Combat-Related PTSD. The Mississippi Scale for Combat-Related PTSD (M-PTSD), developed by Keane and colleagues (1988), is a 35-item measure to assess combat-related PTSD symptoms. Respondents are asked to rate, on a five-point Likert scale, the severity of symptoms since the event occurred. After reversing the positively worded items, a total severity score is derived by summing the items (range 35 to 175). A diagnostic cutoff score of 107 was originally established for the measure. The M-PTSD takes 10–15 minutes to administer.

The M-PTSD has excellent psychometric properties. In samples of Vietnam-era veterans (Keane et al., 1988; Orazem, Charney, & Keane, 2006), the M-PTSD yielded high internal consistency (alpha = 0.94–0.96) and 1-week test–retest reliability (0.97). Item–total score correlations ranged from 0.33 to 0.77 (mean = 0.65), with a correlation of 0.83 with the MMPI-PK. These authors also reported substantial sensitivity (0.84–0.93) and specificity (0.83–0.89) against DSM-III criteria. The M-PTSD has demonstrated strong concordance with popular PTSD assessment measures despite changes in PTSD diagnostic criteria and corresponding updates to the PCL and CAPS assessments over the last 30 years (Marmar et al., 2015), and it remains a valuable self-report tool for the assessment of combat-related PTSD.

Keane PTSD Scale of the MMPI-2. Originally derived from the MMPI Form R (Keane et al., 1984), the Keane PTSD Scale (PK) comprises 46 items empirically drawn from the MMPI-2 (Lyons & Keane, 1992). The PK is typically administered as part of the full MMPI-2, but it can be useful as a stand-alone scale. The items are answered in a true–false format; a total score is derived by summing the positive responses that reflect the presence or absence of PTSD. A cutoff score range between 24 and 28 has been proposed, with a suggested cutoff range of 15 to 19 among civilians. Scores greater than 38 may suggest fabrication of symptoms. It takes about 15 minutes to administer the stand-alone version of the PK of the MMPI-2.

Psychometric data on the embedded and stand-alone versions of the PK are excellent. In a veteran sample, Herman, Weathers, Litz, and Keane (1996) reported evidence of strong internal consistency (alpha = 0.95–0.96) for both versions of the PK, and high test–retest reliability coefficients (0.95) for the stand-alone version over 2–3 days. Validity for both versions of the PK was strongly to very strongly correlated with other self-report measures of PTSD, including the M-PTSD (0.81–0.85), the IES (0.65–0.71), the PTSD Checklist (PCL; 0.77–0.83), and the CAPS diagnostic interview based on DSM-IV criteria (0.77–0.80). Additional psychometric data is needed to compare this scale to the updated CAPS based on DSM-5 criteria.

Posttraumatic Stress Diagnostic Scale. The Posttraumatic Stress Diagnostic Scale for DSM-5 (PDS-5; Foa et al., 2016) is a 24-item self-report assessment of PTSD symptoms and symptom severity. The initial items on the PDS-5 inquire about whether individuals have been exposed to potentially traumatic event(s) and then ask them to identify the event that meets the definition of a criterion A trauma. Next, individuals answer a series of 20 items, based on DSM-5 PTSD symptoms, on a five-point scale ranging from "not at all" to "6 or more times a week/severe," and then (unlike the PTSD Checklist discussed below) estimate the time of symptom onset, duration, and associated distress and impairment. The PDS-5 yields a total severity score that largely reflects symptom frequency and a dichotomous PTSD diagnosis, and it can be administered in 10–15 minutes.

The PDS-5 has very high internal consistency (alpha = 0.95), test–retest reliability (r = .90; Foa et al., 2016), and good convergent validity with other self-report and interview-based PTSD assessments, such as the PTSD Checklist (PCL; r = .90), PSSI-5 (r = .85), and PSSI-5 (78% agreement). In addition, the measure has yielded substantial sensitivity (0.89), specificity (0.75), and high levels of diagnostic agreement with a SCID diagnosis (kappa = 0.65, 82% agreement). The updated PDS-5 has demonstrated good discriminant validity with common self-report depression and anxiety measures, such as the Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) and State–Trait Anxiety Inventory (Spielberger, 1983). Based on these data, the authors recommend the PDS as an effective and efficient screening tool for PTSD.

PTSD Checklist for DSM-5. The PTSD Checklist (PCL), also developed at the National Center for PTSD (Weathers, Litz, Herman, Huska, & Keane, 1993), is the most widely used self-report measure of PTSD in both research and clinical contexts (Elhai, Gray, Docherty, Kashdan, & Kose, 2005). The original scale was based on DSM-III-R criteria for PTSD and was subsequently updated to assess DSM-IV and then DSM-5 diagnostic criteria (PCL-5; Weathers, Litz, et al., 2013). The PCL-5 comprises 20 items that correspond directly to the DSM-5 PTSD symptoms, with each item rated on a five-point Likert scale. Diagnostic status can be determined in three ways: (1) following the

DSM-5 algorithm, in which probable PTSD is defined as endorsement of at least one criterion B, one criterion C, two criterion D, and 2 criterion E symptoms, each at a moderate level of distress or greater (cf. Keen, Kutter, Niles, & Krinsley, 2008; Weathers et al., 1993); (2) total severity score at or above a specified cutoff score (31–33; Bovin et al., 2016); and (3) DSM-5 algorithm plus a specified severity cutoff score.

The PCL-5 offers three different formats. The first format includes all 20 items without a criterion A specifier, the second includes a criterion A specifier, and the third includes the Life Events Checklist-5 for extended reporting of a range of criterion A traumas (Weathers, Blake, et al., 2013). The time frame can be adjusted as needed to suit the goals of these assessments (e.g., symptom severity during past week vs. past month). The PCL-5 has been used extensively in both research and clinical settings and takes 5–10 minutes to administer.

The PCL-5 has strong internal consistency (alpha= 0.96), test–retest reliability (r = .84), and convergent and divergent validity (Bovin et al., 2016). Bovin and colleagues (2016) recommend an optimal cutoff score range of 31–33, whereas others recommend 34 and higher as optimal to differentiate individuals with versus without PTSD (Ibrahim, Ertl, Catani, Ismail, & Neuner, 2018). However, clinicians and researchers should still carefully evaluate the specific needs of the assessment (e.g., maximizing sensitivity or specificity) to assist in selecting the appropriate cutoff score. The PCL-5 was not intended for use alone as a diagnostic instrument, so caution should be applied when it is used as the sole measure of PTSD. Although briefer, unlike the PDS-5, the PCL-5 does not assess symptom onset, duration, or interference.

PTSD Screening. Prins and colleagues (2016) recently published a five-item version of the PCL-5 scale, the Primary Care PTSD symptom screen for DSM-5 (PC-PTSD-5), which has been tested and validated for use within primary care settings. When evaluated against the MINI-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), the PC-PTSD-5 demonstrated excellent diagnostic accuracy (area under the curve [AUC] = 0.94); optimal scores to maximize sensitivity and specificity are 3 and 5, respectively (Prins et al., 2016). However, a positive screen on the PC-PTSD-5 does not signify a diagnosis, which would require follow-up assessment and interview using one or more the above-mentioned tools (e.g., CAPS-5).

PSYCHOPHYSIOLOGY IN THE DIAGNOSTIC ASSESSMENT OF PTSD

Establishing a valid diagnosis based on self-report or interview data is greatly influenced by patient characteristics (e.g., motivation, insight; willingness to disclose; memory of the trauma; presence of traumatic brain injury) and the clinician's ability to determine whether self-reported symptoms exceed diagnostic thresholds. Psychophysiological assessment can offer independent corroboration of self-reported symptoms, especially following additions to criterion E in DSM-5. This criterion assesses alterations in arousal and reactivity that are associated with traumatic experiences and are amenable to psychophysiological measurement. However, it should be noted that psychophysiological assessment is not ready for routine diagnostic use, as there are currently no accepted standards by which to use and interpret psychophysiological data; future research and development are needed. Nevertheless, psychophysiological research continues to provide insight into potential biomarkers of PTSD that warrant further investigation.

Physiological measures that are considered relevant to the assessment of PTSD include indices of autonomic activity (i.e., heart rate [HR], HR variability, blood pressure, and electrodermal responses), the overt expression of negative affect and speech quality, which may be collected via audio, and visual recordings of facial muscle activity. When other factors are held constant (e.g., ambient room temperature), skin conductance (SC) responses provide a near-direct measure of general sympathetic activation (e.g., Hauschildt, Peters, Moritz, & Jelinek, 2011). Additional biomarkers include facial muscle activity and voice characteristics, which have been shown to correctly classify individuals with versus without PTSD (Fujiwara, Mizuki, Miki, & Chemtob, 2015; Marmar et al., 2019). Though promising, in order for psychophysiological assessment to become a routine part of any comprehensive PTSD assessment, substantial work needs to be done.

TECHNOLOGICAL ADVANCES IN THE ASSESSMENT OF PTSD

Recent technological advances have the potential to change the landscape of assessment and increase the accuracy and efficiency of PTSD assessment. Several of the new methods of assessment described below have garnered some empirical support but still require considerably more research. As such, the following discussion is intended to update the field about recent advances and potential future directions, but these approaches should not supersede the use of currently established EBA methods or informed clinical judgment.

Computerized-adaptive testing (CAT) methods hold promise in terms of increasing the accuracy and efficiency of self-report PTSD assessment (Eisen et al., 2016). CAT is accomplished by developing computer algorithms that adapt to individuals' responses in real time, delivering the most relevant questions throughout the ensuing assessment to maximize efficiency and derive precise estimates of PTSD severity. The added value of this technology is the streamlining and consolidation of large measures into more tailored versions that maximize diagnostic precision. Another recent advance includes the application of machine learning to assessment. Machine learning is a type of artificial intelligence that allows for "learning" by computers through the use of algorithms that aid prediction. Machine learning uses data to identify patterns and make predictions with minimal human input. This approach has the potential to improve the accuracy of screening, assessment, and monitoring of PTSD (Karstoft, Galatzer-Levy, Statnikov, Li, & Shalev, 2015; Karstoft, Statnikov, Andersen, Madsen, & Galatzer-Levy, 2015).

Self-report assessments, performed via mobile devices, provide an alternative to traditional requirements for paper-and-pencil, in-person completion of questionnaires, and appear to be just as accurate (Price, Kuhn, Hoffman, Ruzek, & Acierno, 2015). This approach provides a convenient and more expedient approach to PTSD assessment (Finkelman et al., 2017) as well as a means of facilitating repeated assessments to track progress over time (e.g., daily diaries and ecological momentary assessment [EMA]). Yet, a drawback of remote data collection is that it may complicate clinicians' ability to follow up on items endorsed in the moment and introduces new concerns regarding data security, privacy, and respondent burden.

Advances in passive data collection via smartphones, tablets, and other mobile devices could enable researchers to discover potential digital phenotypes of PTSD and classify individuals who are at risk of developing or who meet criteria for PTSD. Digital

phenotyping is a method of utilizing multiple sources of passive data such as geolocation, voice (e.g., prosody), call and text log, screen use (typing acceleration vs. deceleration), and website navigation, collected via mobile devices (smartphones, wearable sensors) to quantify individual-level risk and make predictions about disorder onset and course (Bourla, Mouchabac, Hage, & Ferreri, 2018). Digital phenotyping remains a relatively new approach to assessment of psychological disorders, but it offers promise. For example, objective assessment of this kind could circumvent issues inherent with clinician-administered and self-report instruments, particularly as they relate to assessing PTSD onset and course among those with little to no memory of their trauma and/or individuals with traumatic brain injury (TBI). Efforts are currently underway (e.g., *ClinicalTrials.gov:* NCT03788278) to develop phenotypes of PTSD to aid in future prediction and, possibly, diagnosis. Taken together, these remarkable innovations have the potential to change the landscape of PTSD screening, monitoring, and assessment.

PTSD COMORBIDITY

For individuals diagnosed with PTSD, the presence of comorbid disorders is widely observed in community, veteran, and epidemiological studies (Goldstein et al., 2016; Kessler et al., 2005; Kulka et al., 1990; Smith, Goldstein, & Grant, 2016). For example, Brown, Campbell, and colleagues (2001) found that 92% of individuals with a current diagnosis of PTSD also met criteria for another disorder, with the most frequent ones being major depressive disorder (77%), generalized anxiety disorder (38%), and alcohol use disorder (31%). High rates of comorbidity have also been reported in studies of veterans (Smith et al., 2016), with 50–85% of veterans with PTSD simultaneously meeting criteria for another mental health disorder (Kehle et al., 2010; Kulka et al., 1990; Magruder et al., 2005). Traumatic brain injury is also a hallmark injury among returning veterans and is often associated with PTSD (Defense and Veterans Brain Injury Center, 2016).

The Externalizing–Internalizing Model of Psychopathology

One model of psychiatric comorbidity that is useful to our understanding of patterns of PTSD comorbidity, albeit largely predicated on DSM-III and DSM-IV PTSD nosology, proposes that patterns of behavioral disturbance and psychiatric symptoms exhibit a coherent liability along latent dimensions of *externalization* (EXT) and *internalization* (INT). This model suggests that patterns of comorbidity tend to cohere along these dimensions, with alcohol use disorder (AUD) and drug-related disorders and antisocial personality disorder (ASPD) loading on the EXT dimension, characterized by problems in the domain of impulsivity, and unipolar mood and anxiety disorders falling on the INT dimension, defined largely by heightened negative emotionality (Cox, Clara, & Enns, 2002; Krueger, McGue, & Iacono, 2001). Further research implicates genetic factors in the etiology of EXT and INT dimensions (Wolf et al., 2010), and tendencies toward EXT and INT are stable over time (Krueger, Caspi, Moffitt, & Silva, 1998). Thus, one important strength of this model is that it affords consistency in the conceptualization of psychopathology across the lifespan. The EXT–INT model is conceptually consistent with other models of comorbidity, which state that the overlap among broad classes of disorders is due largely to the fact that they emerge from a common diathesis (e.g., Barlow, 2002). Whereas much overlap exists in terms of the predisposing

factors within a given spectrum of psychopathology, the expression of this liability varies considerably as a function of exposure to various environmental factors (e.g., trauma exposure). This concept might also help account for heterogeneity in PTSD and co-occurring mental health disorder symptom presentations, expressions, and course. For example, "externalizers," characterized by elevated anger, aggression, substance use, disconstraint, and emotional lability, have been shown to be more likely to express their posttraumatic distress outwardly through antagonistic interactions (e.g., Miller, Greif, & Smith, 2003). Veterans in this subtype, and for whom data on premilitary characteristics were available, reported elevated rates of premilitary delinquency. This suggests that these characteristics may reflect the influence of externalizing personality traits that were present prior to the trauma.

In contrast, individuals who "internalize" were characterized by tendencies to direct their posttraumatic distress inwardly through self-defeating behaviors, avoidance, and withdrawal. Individuals who internalized were characterized by high rates of comorbid major depression and panic disorder, schizoid and avoidance personality disorder features, and personality profiles defined by combined high negative emotionality and low positive emotionality (Miller et al., 2003). These individuals may lack enthusiasm and interests, feel uninspired and become fatigued more easily, and are prone to experiencing frequent and intense negative emotions. They also have a tendency to be self-effacing and humble, and to report having few friends and preferring solitary activities. Social inhibition, feelings of inadequacy, hypersensitivity to negative evaluation, and trauma-related shame are also common (see also Miller, Fogler, Wolf, Kaloupek, & Keane, 2008).

Taken together, these findings suggest that the EXT–INT model is relevant to understanding the heterogeneity of psychopathology and comorbidity within PTSD, which may be rooted in heritable dispositions. To this end, knowledge of individuals' premorbid characteristics may provide insight into PTSD expression and symptom course, provide clues about potential concerns requiring follow-up assessment (e.g., risk for violence among EXT, depression and isolation among INT), and assist in the conceptualization of effective intervention strategies.

Screening and Assessment of Co-Occurring Disorders

The high prevalence of co-occurring disorders among individuals with PTSD, as well as the high degree of symptom overlap among these conditions, can significantly complicate assessment and treatment efforts (Moshier, Parker-Gilbert, Marx, & Keane, 2018. It is therefore essential to include screening and, as needed, follow-up assessment of common co-occurring disorders to help ensure accurate case conceptualization and correct specification of intervention targets (e.g., PTSD symptoms vs. high-risk substance use or other imminent threats to self or others).

A comprehensive discussion of screening and assessment measures for co-occurring mental health disorders is beyond the current scope; however, we provide a few recommendations below to encourage inclusive screening practices that capture common comorbidities. Among individuals with PTSD, three of the most common co-occurring mental health disorders are generalized anxiety disorder, major depressive disorder, and substance use disorder (Goldstein et al., 2016; Kessler et al., 2005; Kulka et al., 1990; Smith et al., 2016). Accordingly, it is strongly advised that PTSD assessment include additional screening and potentially follow-up assessment anxiety, depression, and substance use.

It is often more practical to lead with brief self-report screening measures prior to conducting structured interviews. There are dozens of validated and reliable substance use measures in the public domain. Several of the most common examples include the Quick Drink Screen (QDS; Sobell et al., 2003). The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993), the Drug Use Disorders Identification Test (DUDIT; Berman, Bergman, Palmstierna, & Schlyter, 2005), and the Drug Abuse Screening Test (DAST; Skinner, 1982). The QDS is a four-item questionnaire used to quantify the frequency and amount of past-month drinking. From this measure, screeners can derive the average number of drinks per day/week; and number of drinking days per week, number of binge drinking days, percentage of "heavy" drinking days per month; and information about their heaviest drinking day in the last 30. The 10-item AUDIT and 11-item DUDIT, on the other hand, quantify frequency of substance use, but also include items related to risk for substance use disorder, including negative consequences incurred as a result of alcohol and drug use in the past year, respectively. The DAST is another common screener that comes in 10-, 20-, and 28-item versions to assess use of illicit drugs in the past year and negative consequences associated with drug use on a binary yes/no scale. For further substance use screening and assessment recommendations, readers are encouraged to review Rohsenow (2018) and McCauley, Killeen, Gros, Brady, and Back (2012).

Three common screening tools for depression include the 21-item Beck Depression Inventory–II (BDI-II); Beck et al., 1996); Depression, Anxiety, and Stress Scale (DASS; 42- and 21-item versions; Antony, Bieling, Cox, Enns, & Swinson, 1998), and the nine-item Patient Health Questionnaire–9 (PHQ-9). Common anxiety specific measures include the 21-item Beck Anxiety Inventory (Beck & Steer, 1993) and State-Trait Anxiety Inventory (Spielberger, 1983). Each of these screeners offers continuous response options and can be summed to derive an overall level of severity, relative to established cut scores, to determine the clinical significance of the patients' current distress. One notable difference is that, unlike the BDI-II and PHQ-9, the DASS depression screener does not include an item to assess suicide risk (e.g., ideation, intent), which is critical to assess as part of any depression screening or diagnostic assessment. In addition to these established anxiety and depression screeners, Dugas, Charette, and Gervais (2018) and Persons, Fresco, and Ernst (2018) provide a listing of additional measures and recommendations for use. Beidas and colleagues (2016) provide further recommendations as well as a comprehensive list of free, accessible, and brief measures that have been validated for numerous other co-occurring conditions, such as borderline personality disorder, mania, and eating disorders.

Positive screens on either of these measures are insufficient to establish a mental health diagnosis; follow-up and ideally structured diagnostic assessment are needed. Structured and semistructured interviews, such as the SCID-5 for anxiety, depression, substance use disorders, and others, are among the strongest assessment tools available (First, Williams, Karg, & Spitzer, 2016). Other interview-based assessments include the Addiction Severity Index for substance use disorders, which is administered over 45–60 minutes and provides both global and specific information about addiction severity (ASI; McLellan et al., 1992); and the ADIS-5 for anxiety and mood disorders (Brown & Barlow, 2014). However, follow-up questions are often needed to assess types of substances used (e.g., heroin vs. fentanyl), routes of administration, risk for harm to self (including suicidal ideation, intent, planning, and previous attempts) and others (e.g., domestic violence, substance use while caring for dependent children), and to tailor structured interviews as needed.

SUMMARY

Assessment of PTSD and its comorbidities continues to garner a great deal of interest across countries and continents. Since the inclusion of PTSD in DSM-III, our understanding of the psychological consequences of exposure to traumatic events has expanded greatly. Conceptual models of PTSD assessment have evolved, psychological tests have been developed, diagnostic interviews have been validated, and subscales of existing tests have been created. The assessment instruments available to evaluate PTSD are comparable to or better than those available for any disorder in the DSM, and multiple instruments are now available that cover the range of clinicians' and researchers' needs. The psychometric data examining the reliability and validity of many of these instruments are excellent.

Our intent in this review has been to provide a heuristic structure that assessors and clinicians might employ when selecting a specific instrument for their purposes. Clearly, the assessment of PTSD in clinical settings focuses on more than the presence, absence, and severity of PTSD. A comprehensive assessment strategy involves gathering information about an individual's family history, life context, beliefs, strengths, weaknesses, support system, and coping abilities, as well as careful assessment of social, interpersonal, and occupational functioning. Instruments that are developed and evaluated on multiple trauma populations, varying genders, and with different racial, ethnic, cultural, and age groups are highly desirable. In order to achieve an optimal examination, the assessor/clinician must also be sensitive to the intensity of the traumatic events, the difficulties many people have in disclosing aspects of traumatic experiences, the recency of the exposure, and the debilitating effects these symptoms have on individuals and their families.

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CHAPTER 17

Assessment of PTSD in Children and Adolescents

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Rates of exposure to violence and traumatic events for children and adolescents are alarmingly high. According to the 2010 American Academy of Child and Adolescent Psychiatry's practice parameters for assessment of posttraumatic stress disorder (PTSD) in youth, more than 25% of children and adolescents will experience a traumatic event before the age of 18. In the United States alone, this amounts to more than 18 million children, with a disproportionate number of those coming from lower socioeconomic status and ethnic/minority backgrounds (DeNavas-Walt, Proctor, & Smith, 2011, 2013; Enlow, Blood, & Egeland, 2013; Merrick, Ford, Ports, & Guinn, 2018). Estimates from nationally representative samples also suggest that many children experience repeated exposure to trauma or multiple types of traumatic events over their lifetime (Copeland, Keeler, Angold, & Costello, 2007; Enlow et al., 2013; Finkelhor, Ormrod, & Turner, 2009; Finkelhor, Shattuck, Turner, Ormrod, & Hamby, 2011; Finkelhor, Turner, Hamby & Ormrod, 2011; Margolin & Vickerman, 2011). The range of potentially traumatic events runs the gamut from child maltreatment and domestic violence to natural disasters, community and school violence, and other events, including sexual assault.

A significant number of children and adolescents exposed to potentially traumatic events develop PTSD, PTSD symptoms, and other common trauma-related sequelae, including depression, anxiety, and behavioral disorders. The growing empirical literature also suggests that exposure to trauma during childhood and adolescence may profoundly derail healthy development and result in myriad psychosocial, biological, behavioral, and cognitive consequences that persist well into adulthood (Anda et al., 2006; Briere, Kaltman, & Green, 2008; Copeland, Wolke, Shanahan, & Costello, 2015; Felitti et al., 1998; Ford, Connor, & Hawke, 2009; Heleniak, McLaughlin, Ormel, & Riese, 2016; Walsh, McLaughlin, Hamilton, & Keys, 2017). Among these, PTSD has been identified as perhaps the most common response. For far too many children, these experiences go unrecognized and untreated, resulting in increased risk for PTSD and a more chronic and debilitating course.

Given the prevalence of trauma exposure among children and adolescents, the potential for PTSD, and the developmental implications of leaving trauma untreated, increased attention has been placed on the assessment and treatment of PTSD in youth (Guterman, Schwartzkopff, & Steil, 2017; Hawkins & Radcliffe, 2006; Hodgdon et al., 2019; Slavich, Stewart, Esposito, Shields, & Auerbach, 2019). Our purpose in this chapter is to provide a comprehensive overview of the assessment of PTSD in children, with a particular focus on some of the challenges associated with assessing PTSD, including relevant developmental considerations, as well as directions for clinicians and researchers pertaining to changes in the overall conceptualization and pediatric specification of PTSD in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013).

PREVALENCE, COURSE, AND CONSEQUENCES OF TRAUMA EXPOSURE

PTSD is one of the more serious and debilitating mental disorders that may occur following trauma exposure. Estimates of PTSD among children and adolescents vary considerably, ranging from approximately 5 to 60% of youth meeting criteria for PTSD in the months following traumatic exposure (Levendosky, Huth-Bocks, Semel, & Shapiro, 2002; Rosellini et al., 2018; Scheeringa, Myers, Putnam, & Zeanah, 2012; Scheeringa, Zeanah, Drell, & Larrieu, 1995). The exact rate depends largely on the particular type of trauma examined (e.g., sexual abuse vs. natural disaster); gender of participants (girls tend to have slightly higher rates); the study population of focus (e.g., clinical vs. community samples); the age of the youth assessed (preschoolers vs. adolescents); and the specific assessment instruments, methods, or developmentally sensitive criteria utilized (see Copeland & McGinnis, Chapter 5, this volume).

Despite variations in prevalence rates, clinicians and researchers generally agree that PTSD symptoms are pretty common following trauma exposure. Although most individuals adapt and recover, it is estimated that, in general, approximately 5–15% of trauma-exposed children and adolescents develop PTSD (Alisic et al., 2014; Landolt, Schnyder, Maier, Schoenbucher, & Mohler-Kuo, 2013; McLaughlin, Koenen, Hill, & Kessler 2013), with many of these individuals experiencing an impairing and unremitting course (Copeland et al., 2015; DeYoung, Kenardy, Cobham, & Kimble, 2012; Le Brocque, Hendrikz, & Kenardy, 2010; Scheeringa, Zeanah, Myers, & Putnam, 2005). These findings are particularly concerning given that trauma during this critical developmental period may result in myriad consequences that may persist well into adulthood—including risky health behaviors (e.g., substance use), physical health conditions (e.g., heart disease), structural and functional impairments in brain functioning, dysregulation of affect and behavior; and learning and cognitive difficulties (Anda et al., 2006; Briere et al., 2001; Felitti et al., 1998; Ford, 2013; Ford et al., 2009; Hambrick, Brawner, Perry, 2019; Marshall, 2016).

Youth with PTSD often experience other comorbid conditions, making it difficult for clinicians to distinguish between overlapping symptoms, particularly anxiety and depressive symptoms. High rates of comorbidity have been documented in youth exposed to a variety of traumas (Cohen & Scheeringa, 2009; Hedtke et al., 2008; Kilpatrick, Saunders, & Smith, 2003; Runyon, Faust, & Orvaschel, 2002). A survey of 1,433 youths revealed that victimization, during a 15-month follow-up period, was significantly related to PTSD symptoms and depression, even after researchers controlled for the symptoms they initially observed (Boney-McCoy & Finkelhor, 1996;

TABLE 17.1. PTSD Assessment and Comorbid Disorders: Examples of Suggested Additional Assessments If Comorbid Disorders Are Suspected

Comorbid disorder	Recommended assessments
Attention-deficit/ hyperactivity and disruptive behavior disorders	• Child Behavior Checklist • Conners ADHD Rating Scale • K-SADS-PL
Substance use and related disorders	• NIDA Drug Use Screening Tool • K-SADS-PL
Mood disorders/suicidality	• Child Behavior Checklist • Children's Depression Index • Columbia Suicide Screen • K-SADS-PL • Revised Children's Anxiety and Depression Scale • Suicidal Ideation Questionnaire
Other anxiety disorders	• Child Behavior Checklist • K-SADS-PL • Multidimensional Anxiety Scale for Children • Revised Children's Anxiety and Depression Scale • Screen for Child Anxiety Related Disorders (SCARED)
Sleep disorders	• Children's Sleep Habits Questionnaire1

Finkelhor, Ormrod, & Turner, 2007). Other studies describe the potentiating effects of co-occurring symptoms. Runyon and colleagues (2002), for example, found that abused children with PTSD and major depressive disorder reported more intrusive PTSD symptoms than did children with PTSD alone. Although the wide range of symptoms displayed in children and adolescents can make diagnosis more difficult, accurate diagnosis of PTSD remains essential. Table 17.1 contains guidelines for assessing disorders that may be comorbid with PTSD.

DEVELOPMENTAL CONSIDERATIONS

There are several developmental factors to consider before assessing for PTSD in children and adolescents: The first, of course, is current age and developmental stage/ age at which the event(s) occurred; the second is the type, severity, and duration of the traumatic event(s); and the third is the context in which the trauma occurred, with particular attention on the child's immediate family and home environment. Other critical factors to be considered are parental support and level of parental distress because research suggests that these contribute significantly to either reduction or the development and maintenance of reactions and symptoms in children (Scheeringa & Zeanah, 2001; Williamson et al., 2017). This may be particularly true for very young children who are dependent on caregivers for safety, guidance, love, and support. Equally important is to consider the cultural perceptions, norms, and mores that may affect the response of the child and family. Other considerations include legal and other systemic involvement, such as child welfare or law enforcement, and the uncertainty and change that may accompany their interventions (e.g., removal from the home, incarceration of the perpetrator, and other secondary adversities). Finally, researchers and practitioners

must also consider whether the child has been exposed to previous traumatic events or secondary adversities (e.g., parental unemployment, poverty), and what strengths and protective factors he or she might have used to cope effectively. Taken together, these factors can be used to guide selection of the type of assessment tool(s) that will be most appropriate for assessing and evaluating symptoms in children and adolescents; to identify potential respondents and domains to be assessed; and to provide relevant information to augment coping, reduce distress, and foster resilience and recovery.

DIAGNOSTIC AND ASSESSMENT CHALLENGES

Much of the extant literature on PTSD focuses on children and adolescents who were exposed to an acute event or single incident of trauma (e.g., a school shooting, a natural disaster). This approach, however, fails to capture the more common "day-to-day" or chronic traumatic exposures (e.g., maltreatment, community violence) that tend to occur among children and adolescents presenting with symptoms of PTSD (Carrion, Weems, Ray, & Reiss, 2002; Danzi & La Greca, 2016; Scheeringa et al., 2012). The burgeoning research on chronic exposure to trauma has begun to delineate symptoms of PTSD, as well as a pattern of potential impairments across multiple domains (i.e., cognitive, physiological, social, emotional, and behavioral), which in turn have deleterious implications for a child's further growth and development (Anda et al., 2006; Anderson, 2005; Briere et al., 2001; Carroll et al., 2013; Chen, Turiano, Mroczek, & Miller, 2016; Cloitre et al., 2009; Danese & Mcewen, 2012; Felitti et al., 1998; Ford et al., 2009; Holmes, Stokes, & Gathright, 2014; Keeshin, & Campbell, 2011; McCormack & Thomson, 2017; Nader, 2004).

Efforts to effectively capture symptoms of PTSD in children and adolescents are ongoing. This has been the case for prior versions of the DSM; notably, many of the refinements and modifications of PTSD diagnostic criteria in DSM-IV-TR (APA, 2000) were an attempt to compensate for the differences in symptom presentation in children and adolescents given that the criteria were originally field-tested, developed, and based largely on the clinical presentations of adults. This is especially problematic in terms of accurately assessing symptoms and manifestations of PTSD in children. For example, reexperiencing symptoms (i.e., intrusive memories, flashbacks, trauma-specific nightmares), as noted in DSM-IV-TR, may be manifested in children as behavioral reenactment/repetitive play with trauma-related themes or as more generalized nightmares (e.g., dreams about monsters, dangerous or frightening situations) rather than trauma-specific content. The three symptom clusters (i.e., reexperiencing, avoidance/numbing, and hyperarousal) and related notes and comments in DSM-IV-TR, however, may have failed to capture the full array of symptoms that occur among children exposed to traumatic events (Carrion et al., 2002; Levendosky et al., 2002; Nader, 2011).

Some of the revisions in DSM-5 were intended to lead to significant advances in the field because it divides the diagnostic criteria for children by age and also acknowledges the broader impact on child and adolescent functioning. Moreover, DSM-5 has specific designations for the developmental presentations of PTSD for children age 6 and younger. This important modification of the previous edition can enhance practitioners' ability to capture the full array of symptoms that occur in young children exposed to traumatic events that was often not captured in the "adult version" of the diagnostic criteria (Carrion et al., 2002; Danzi & La Greca, 2016; Levendosky et al., 2002; Scheeringa et al., 2012). For example, it is common for children to behave more

aggressively following trauma. For young children, this may be expressed as an extreme temper tantrum. When aggression in children is not captured as part of a PTSD diagnosis; it is quite common for it to be omitted, misattributed, or disregarded (Nader, 2011).

However, the DSM-5 criteria for children meant that some of the assessment tools used to diagnose PTSD in children in general, and in young children in particular, needed to be amended by including the adult modifications that also apply to the diagnostic criteria for school-age children and adolescents (e.g., inclusion of negative cognitions in addition to hypervigilance), as well as the specific criteria for children age 6 and younger (Danzi & La Greca, 2016; see Friedman et al., Chapter 2, this volume, on DSM-5 criteria). Further complicating the assessment process, these differences in symptom presentation vary by developmental epoch of the child and are particularly pronounced among young children, who have limited verbal capacities. These developmental factors in turn have considerable implications for accurate assessment and for selection of appropriate treatment. In addition to complexities associated with DSM-5 in assessing childhood PTSD, many of the aforementioned factors related to the specific type, severity, timing, and duration of traumatic events that are most commonly experienced by children may contribute to variation in PTSD symptoms and behaviors (Allwood, Bell-Dolan, & Husain, 2002; Hyland et al., 2017).

ASSESSMENT OF PTSD IN CHILDREN

Any clinician working with children knows that they are difficult to assess because, on the one hand, they may still be acquiring cognitive, expressive language, and other developmental skills that may result in limited capacity to relate symptoms and experiences; on the other hand, they are developing rapidly, and both their perceptions and the type of situations they experience are continually changing. The developing complexities associated with assessing psychopathology in general are especially true for PTSD. Children may lack the language to describe internal states, certain events, or experiences (e.g., feelings of shame associated with rape and other forms of sexual abuse), and their perception of and reaction to traumatic events may be drastically different from that of adults (e.g., increased oppositional behavior is commonly seen in children following sexual abuse). In addition, children's reaction to and perception of traumatic events can change drastically as they develop and attain more complex and accurate language and knowledge relative to past traumatic events, which makes substantially delayed and varied reactions to trauma common in children. For example, it is common for children who were sexually abused early in childhood to first develop PTSD in early adolescence, when language and knowledge related to sexual behavior mature (Wondie, Zemene, Reschke, & Schröder, 2012). This is similarly true for neglect, which is often overlooked but substantially related to PTSD and attendant disability (Collin-Vézina, Coleman, Milne, Sell, & Daigneault, 2011).

Further complicating assessment, a child who is evaluated following trauma may not meet criteria for PTSD, but when assessed later in development may meet PTSD criteria for that same event because timing of the exposure and acquisition of new developmental skills can confer both new meaning and risks for the development of symptoms. Furthermore, the types of trauma associated with the disorder often make caregiver report, typically a hallmark of childhood assessment, less reliable in the case of PTSD due to the "behind closed doors" nature of a good deal of childhood trauma, particularly child abuse and neglect. Moreover, this is often complicated by the fact

that some parents are themselves the perpetrators, a fact that increases the likelihood that parents will either minimize or inaccurately report PTSD symptomatology based on their level of support, distress, and/or their ability to accurately identify children's internal affective states (Collin-Vézina et al., 2011).

Despite the many challenges of assessing PTSD in children and adolescents, it is clear that some of the many youth exposed to myriad traumatic events will have severe and debilitating reactions secondary to traumatic exposure that also require treatment. Thus, practitioners and clinicians need to be able to recognize PTSD reactions in youth, understand their unique developmental and cultural considerations, and offer an array of empirically supported treatments that foster recovery and promote resilience.

Central to expeditiously and effectively making these challenging clinical determinations are targeted assessments for the types of trauma and subsequent PTSD symptoms with which children typically present. Our goal for the remainder of this chapter is to cull extant measures of PTSD in childhood by providing a review of evidence-based instruments developed and validated for assessing PTSD in children and adolescents. In keeping with the structure put forth by the U.S. Department of Veterans Affairs National Center for PTSD, three categories of assessments are presented: clinical interviews, youth self-report, and caregiver report. For each of these childhood PTSD assessment instruments, the age group, number of items, time for administration, inclusion of multiple traumas, and relationship to DSM-5 criteria are summarized in Table 17.2. The focus is on measures that are specifically intended to assess childhood PTSD and do not include general psychological assessments that include PTSD as part of a broad symptom-based or DSM-based assessment (e.g., Child Behavior Checklist, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Trauma Symptom Checklist for Children). To illustrate the effective application of these assessments in evidence-based research, we have also included in Table 17.2 examples of peer-reviewed studies that have employed these measures as well as relevant information on psychometric properties (reliability and validity metrics). The field of child PTSD research is continually growing and rapidly evolving, particularly as we await additional information on the impact of DSM-5 and its recommended changes in assessment and diagnosis of PTSD; consequently, this list is not exhaustive.

Clinical Interviews

Clinician-Administered PTSD Scale for Children and Adolescents–5

The Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA; Nader et al., 1996, 2004) is a clinician-administered interview that has been updated to assess DSM-5 PTSD symptoms (CAPS-CA-5; Pynoos et. al., 2015) in children and adolescents (age 7 and above). Unlike the previous version, the CAPS-CA-5 requires the identification of a single index trauma to serve as the basis of symptom inquiry. The CAPS-CA-5 yields information on the impact of symptoms on functioning, overall PTSD severity, and specifics for the PTSD dissociative subtypes. See Table 17.2 for additional details about its fairly robust psychometrics properties.

UCLA PTSD Reaction Index

The University of California Los Angeles PTSD Reaction Index (UCLA-RI) for DSM-IV (Pynoos, Rodriguez, Steinberg, Stuber, & Frederick, 1998) has been updated for DSM-5

TABLE 17.2. Trauma and PTSD Measures for Children and Adolescents for DSM-5

Measures	Target age group (yr)	No. of items	Time to administer (min)	Allows multiple traumas?	Reliability (Cronbach's alpha[a])	Validity (*r*)	Example studies
Clinical interviews							
Clinician-Administered PTSD Scale for Children and Adolescents (CAPS-CA-5)	7–18	30	30–45	No	0.52–0.82	0.27–0.47	Diehle et al. (2013); Kletter et al. (2009); Pynoos et. al., 2015; Rosner et al. (2012); Weems et al. (2003)
UCLA PTSD Reaction Index for DSM-5	7–12 child, 13+ adolescent	48	15–20	Yes	0.69–0.95	0.51–0.55	Cross et al. (2018); Elbert et al. (2009); Ellis et al. (2006, 2013); Harder et al. (2012); Hodgdon et al. (2019); Kaplow et al. (2020); Loeb et al. (2011); Milne & Collin-Vézina (2015); Sachser et al. (2017); Stimmel, Cruise, Ford, & Weiss (2014); Wamser-Nanney (2016); Wolmer et al. (2011); Wu et al. (2008)
Youth self-report							
Child PTSD Symptom Scale (CPSS)	8–18	26	10–15	Yes	0.51–0.93	0.82–0.93	Foa et al. (2018); Havens et al. (2012); Kassam-Adams et al. (2016); Kataoka et al. (2009); Nixon et al. (2013)
Structured Trauma-Related Experiences and Symptoms Screener (STRESS)	7–18	55	15–20	Yes	0.73–0.92	0.66–0.77	Grasso et al. (2015) Wevodau (2016)
Caregiver report							
Young Child PTSD Checklist (YCPC)	1–6	42	15–20	Yes	0.39–0.74 (kappa)	.90	Scheeringa (2010, 2014); Scheering & Haslett (2010)

[a]Unless otherwise noted.

(see Elhai et al., 2013; Kaplow et al., 2020; Steinberg et al., 2013). This semistructured interview has multiple components that screen and assess (e.g., Trauma History Profile) for multiple types of trauma and loss, as well as for DSM-5 PTSD symptoms and severity. There is a child version for youth ages 7–12 years, and an adolescent version for youth ages 13 and older is also available; there is also a parent-report version of the measure. Recently, a caregiver version has been developed to assess DSM-5 PTSD symptoms in children 6 and under. This instrument is intended to serve as a tool in research and/or clinical settings. The UCLA PTSD-RI is one of the most widely used tools, and these additional versions bode well for ongoing clinical utility.

Youth Self-Report

Child PTSD Symptom Scale for DSM-5

The Child PTSD Symptom Scale (CPSS; Foa, Johnson, Feeny, & Treadwell, 2001) has been revised for DSM-5 (CPSS-5; Foa, Asnaani, Zang, Capaldi, & Yeh, 2018; Nixon et al., 2013). Two versions of the CPSS-5 are available. The self-report or CPSS-5-SR includes 20 items that map onto DSM-5 diagnostic criteria and that are assessed over the past month. The PTSD items are rated on a five-point scale of frequency and severity from 0 (not at all) to 4 (six or more times a week/severe). A cutoff score of 31 can be used for identifying a probable PTSD diagnosis in children and adolescents. The CPSS-5-SR also includes seven items that assess functioning rated as yes/no. The semistructured interview version or CPSS-5-I includes 27 items that assess DSM-5 diagnostic criteria and symptom severity over the past month (Foa, Asnaani, Zang, Capaldi, & Yeh, 2019). Growing evidence suggests that the CPSS-5-SR and the CPSS-5-I (*www.episcenter.psu.edu/sites/default/files/CPSS-V%20Scoring%20%26%20Psychometrics.pdf*) have strong psychometric properties. Paired with the low cost, this tool has considerable utility for children 8–18.

Structured Trauma-Related Experiences and Symptoms Screener

The Structured Trauma-Related Experiences and Symptoms Screener (STRESS; Grasso, Felton, & Reid-Quiñones, 2015) is a self-report measure that can be used with children and adolescents ages 7–18 to assess exposure to 25 adverse childhood experiences and potentially traumatic events. The STRESS also assesses symptoms of PTSD using the DSM-5 revised criteria, including impairment in functioning and dissociative subtypes. Beyond self-report, other versions of the STRESS are available. The STRESS can be administered as an interview or by an interactive computer program that reads the questions aloud, automatically scores the results, and provides feedback. Preliminary evidence highlights the robust psychometric properties of the STRESS. Although a relatively new tool, the ease of administration and scoring as well as the free cost for use and the nominal cost for computer scoring has helped foster widespread dissemination, particularly among community-based providers.

Caregiver Report

Young Child PTSD Checklist

The Young Child PTSD Checklist (YCPC; Scheeringa, 2010, 2014) is a developmentally sensitive measure designed to be administered to caregivers to screen young children (1–6 years) for symptoms of traumatic stress. The YCPC was updated to reflect the

changes in DSM-5. The first 13 items assess exposure to a range of traumatic events, items 14–36 assess PTSD symptoms, and items 37–42 assess functional impairments. A probable diagnosis of PTSD can be gleaned from scores above the cutoff of 26 or more on the PTSD items. Additionally, scores for functional impairment can also be calculated. The robust psychometric properties and the unique focus on very young children have made this measure a staple among those instruments serving young children.

FUTURE DIRECTIONS

Although there are many reliable, empirically based tools for assessing PTSD in childhood, the DSM-5 has contributed to revision of some assessment instruments, especially for children 6 years old and younger, but not others. This was a useful opportunity to ensure that these measures not only meet DSM-5 criteria for PTSD but also reflect our knowledge of the diverse experiences and reactions of children. These changes notwithstanding, a number of tools that were previously developed have demonstrated clinical utility that warrant further research to examine other developmental, cultural, and contextual considerations in the expression of PTSD among children and adolescents.

A central direction in DSM-5 is the first inclusion of a preschool-specific subtype for PTSD, intended for children under age 6. As is widely known, particularly related to child maltreatment, infants and preschool children are especially vulnerable to trauma and its sequelae due to their nascent and malleable development (Bogat, Levendosky, & Martinez-Torteya, 2013; Levendosky et al., 2002; Milot, Éthier, St-Laurent, & Provost, 2010). Trauma symptoms can manifest differently in young children due to the types of trauma they tend to experience (e.g., being neglected, witnessing domestic violence) and their developmentally specific responses to trauma. As such, future work is needed not only to evaluate current assessments geared toward young children but also to develop new measures. This will be especially challenging for preschool children, given that some parents may be both a central source of childhood trauma and a primary reporter of traumatic events and reactions in young children. Given the vital need to develop treatments that target the preschool-specific PTSD subtype, future work will need to target assessments to meet the diverse cultural and socioeconomic needs of young children presenting with PTSD in light of the often limited resources of those whose task is to assess young children at risk.

Furthermore, emerging research is demonstrating that neuroimaging shows promise for differentiating PTSD in youth (e.g., Carrion, Wong, & Kletter, 2013; McLaughlin, Sheridan, & Lambert, 2014). Research with school-age children has revealed structural and functional brain changes associated with diagnosis from structured clinical interviews for PTSD (De Bellis, Hooper, Woolley, & Shenk, 2010; Richert, Carrion, Karchemskiy, & Reiss, 2006). Although this research is still in the preliminary stages, there is mounting evidence that neuroimaging may become a worthwhile assessment tool for clinicians, with the power to reveal biomarkers underlying PTSD symptoms, as well as critical responses to treatment.

WEB RESOURCES

The following websites (current at the time of this writing) can connect the reader to three valuable resources:

The first is the link to the Measures Review site of the National Child Traumatic Stress Network (NCTSN) (*www.nctsn.org/resources/online-research/measures-review; www.nctsn.org/treatments-and-practices/screening-and-assessments/measure-reviews*). Many of the measures mentioned in this chapter, as well as others, can be found here, with a full description of psychometric properties, citations, reading level, and so forth.

The second link is to the Assessment Tools website for the California Evidence-Based Clearinghouse for Child Welfare (*www.cebc4cw.org/assessment-tools*). It shares many of the characteristics of the NCTSN website.

Finally, the reader is encouraged to explore the Internet for many emerging core competency documents, standards, and guidelines developed by several professional organizations (e.g., Council on Social Work Education, American Psychological Association, Academy on Violence and Abuse) to ensure that clinicians working in the field of traumatic stress possess trauma-informed assessment and treatment skills (e.g., *www.cswe.org/File.aspx?id=63842*; *www.avahealth.org; www.cswe.org/Education-Resources.aspx?searchtext=&searchmode=exactphrase&smartsearchfilter1=&smartsearchfilter_er1=2%3b&smartsearchfilter_er2=7%3b&smartsearchfilter=trauma*).

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CHAPTER 18

Early Intervention Following Trauma

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Exposure to a traumatic event, the most essential criterion for development of acute stress disorder (ASD) or posttraumatic stress disorder (PTSD), is a common experience. In the United States, the most recent data suggest that 68.6% of the U.S. population has had at least one such lifetime exposure (Goldstein et al., 2016). Exposure to more than one trauma is common among those who reported any such exposure. International surveys report exposure rates ranging from 28% in Switzerland to 73.8% in South Africa (Atwoli et al., 2013). Despite the high rates of traumatic exposure, relatively few people develop PTSD as defined by meeting DSM or International Classification of Diseases (ICD) criteria. In the United States, a recent epidemiological survey demonstrated past-year and lifetime prevalence of 4.7% and 6.1%, respectively, with higher rates for female, White, Native American, younger, and previously married respondents, those with high school education and lower incomes, and rural residents (Goldstein et al., 2016). Lifetime prevalence in international studies ranges from 1.3% in Japan to 8.8% in Northern Ireland (Atwoli, Stein, Koenen, & McLaughlin, 2015).

Thus, despite significant worldwide exposure to natural or human-made disaster, war, or terrorism, resilience—rather than PTSD—remains the expected response to traumatic experience. While distress reactions in the aftermath of combat have been described since the earliest writings about war, the expectation of recovery from combat formed the basis for far-forward management strategies for combat operational stress reactions—first called "shellshock," then "battle fatigue," and most recently "combat/operational stress reactions"—which utilized the PIES principles of proximity (management near the battlefront), immediacy (as soon as practical), simplicity (rest and respite), and expectancy (i.e., of recovery and return to duty). In the civilian sector many, if not most, persons exposed to trauma will develop transient symptoms of distress. In fact, after trauma exposure, an altered sense of safety, increased fear and arousal, concern for the future, and sleep difficulties may impact not only those who will go on to develop PTSD, but also resilient individuals who continue to work and care for their families and loved ones (Ursano, Fullerton, Weisaeth, & Raphael, 2007).

In public health emergencies such as disasters or mass violence, interventions for victims require rapid, effective, and sustained mobilization of resources (Ursano & Friedman, 2006; Ursano, Fullerton, Weiseth, & Rafael, 2017). Interventions must address individual care needs while sustaining the social fabric of the community (Ursano & Blumenfield, 2008). Psychiatric illness, distress responses, and health risk behaviors must all be addressed (Ursano et al., 2017). But those interventions designed to be rapidly deployed by first responders, community leaders, and laypersons to minimize distress across the community may not be sufficient either to identify those at risk for the development of PTSD or to successfully prevent its occurrence. For example, psychological first aid (PFA), for which there are now several models and multiple types of in-person and online training, has been defined by the World Health Organization (WHO) as "a humane, supportive response to a fellow human being who is suffering and who may need support" (Tol et al., 2011). It includes interventions such as listening, comforting, helping people to connect with others, and providing information and practical support to address basic needs. These interventions are consistent with the guidelines of Hobfoll and colleagues (2007) and center around five key principles: safety, connectedness, self and collective efficacy, calmness, and hope. While there is considerable evidence that these are key elements in reducing distress and improving mental health outcomes generally after exposure to mass violence (Hobfoll et al., 2007), there is no clear evidence to support PFA as an intervention to prevent PTSD (Dieltjens, Moonens, van Praet, De Buck, & Vandekerckhove, 2014).

The Inter-Agency Standing Committee (IASC), established in 1992 by the United Nations General Assembly to coordinate response to emergencies, has developed a helpful framework called the intervention pyramid for mental health and psychosocial support in emergencies (Figure 18.1). This framework identifies levels of intervention after mass trauma based on level of need. The framework recognizes that after such events, all persons exposed to trauma need to feel protected, so population-level interventions include establishing a sense of security and governance that addresses basic needs. At this level, the mental health response would include advocating for basic services and documenting any effects on mental health and psychosocial well-being.

FIGURE 18.1. Intervention pyramid for mental health and psychosocial support in emergencies.

The second tier represents the emergency response for a smaller number of people who would be expected to maintain their mental health and psychosocial well-being if they receive help in accessing community and family supports. Useful mental health responses in this tier include services such as family reunification, assisted mourning, mass communication on constructive coping methods, educational activities, and reactivation of social networks. The third tier represents the supports necessary for the still smaller number of people who additionally require more focused interventions by trained health care workers (who may not have formal training in mental health). PFA and basic mental health care are provided at this stage. Finally, the top tier of the pyramid represents the additional support required for the small percentage of the population who, despite the aforementioned support and services, have significant difficulties in basic daily functioning and show signs of emerging or worsening mental illness. Interventions at this level include specialized psychological or psychiatric care (IASC, 2008). While the pyramid provides a conceptual framework for the development of allocation of resources in the aftermath of mass trauma, it does little to address the question of how best to identify the subpopulations—let alone individuals—who will benefit from each tier of intervention.

Identifying individuals who are most at risk, as early as possible, is key to preventing symptom development. Investigators have identified a number of predictors of PTSD, including demographic factors, type-severity of traumatic events, gender and age, cumulative previous traumatic exposure, prior mental disorders, acute emotional and biological responses, and proximal social factors occurring in the days and weeks after traumatic event exposure (DiGangi et al., 2013; Sayed, Iacovielle, & Charney, 2015; Tolin & Foa, 2006).

While the previous literature offered no guidelines on how to combine these predictors into a PTSD algorithm, a 2014 exploratory study (Kessler, Rose, et al., 2014) examined retrospective reports from the WHO World Mental Health Surveys of 47,466 traumatic event exposures. With this information, existing machine learning methods were used to develop a preliminary model that predicted PTSD. Although this study demonstrated the ability to create a risk algorithm for PTSD, such efforts could be aimed at better identification of individuals in the immediate aftermath of a traumatic event (e.g., in an emergency room setting) who are likely to develop prolonged symptoms of PTSD. Such work would require further understanding in a number of areas to include more granular knowledge about risk factors associated with longer term development of PTSD.

Another strategy for understanding viable alternatives in the early detection, and possibly the prevention of PTSD, is understanding the biological state of individuals shortly after trauma exposure. Research on identifying suitable biomarkers for predicting PTSD symptoms has been underway for the past 10 years. In several studies, elevated heart rate (HR) 1 week posttrauma has predicted increased PTSD symptoms 4 months (Shalev et al., 1998), 6 months (Bryant, Harvey, Guthrie, & Moulds, 2000), and 2 years later (Bryant & Harvey, 2002). Similarly, posttrauma cortisol has been negatively related to increased PTSD symptoms (for a review, see DiGangi et al., 2013). Although such biological alterations have been examined in conjunction with PTSD, no current biological variable has surpassed the threshold to be considered a reliable PTSD biomarker (Lehrner & Yehuda, 2014). Nevertheless, the identification of biomarker panels associated with PTSD holds promise for directing future interventions. Once identified, biomarkers might help identify subpopulations likely to benefit from a specific treatment or to monitor for early evidence of biological response. Biomarkers

might also be useful for identifying individual candidates for preventive strategies. Ideally, if a relatively noninvasive procedure like a cheek swab was predictive, it could result in a recommendation, for example, that a trauma-exposed person participate in a specific short-term treatment to decrease their chance of developing PTSD given their recent exposure.

The Advancing Understanding of RecOvery afteR traumA (AURORA) study is a large-scale emergency department (ED)-based study that used adaptive sampling methods to collect a combination of genomic, neuroimaging, psychophysical, physiological, neurocognitive, digital phenotyping, and self-report data from trauma survivors, beginning in the early aftermath of trauma and continuing through treatment. The overarching goal of the AURORA study is to provide a well-powered, many-layered, publicly available dataset capable of helping to address the above barriers and advancing discovery. The AURORA study has the potential to markedly increase the success of precision medicine effort (McLean et al., 2020). However, these efforts remain years away and will require significantly more research, but recent results would suggest such a future is possible.

Despite advances in our understanding of the traumatic stress response and the ubiquity of traumatic experience over the past 30 years, there has not been a consistent or methodological approach to prevention research in PTSD. With the exception of brief cognitive-behavioral therapy (CBT) in persons with ASD, we lack evidence-based psychotherapeutic interventions to prevent the onset of PTSD in the general population of persons exposed to trauma. This lack of progress is due, at least in part, to the complexity and difficulty of studying early interventions after trauma. Prevention studies often require very large groups of individuals, ideally with similar attributes (e.g., similar trauma exposures, demographics, and past psychiatric histories), who must be assessed and provided with study intervention within a very short period of time after—or in anticipation of—the traumatic experience. Convenience populations such as those seen in an emergency room setting may not permit sufficient power once the sample is adjusted for covariates, including those noted above. Recruitment of individuals in the immediate aftermath of a traumatic experience, or recruitment of large numbers of subjects after a large-scale disaster may also be challenging. Complicating the evaluation of intervention efficacy, research must explore the best time (before anticipated exposure? immediately after exposure? at the emergence of symptoms?), place (home? work? clinic?), and means (face-to-face? telephone? Internet?) for deploying any study intervention. It is not surprising that our understanding remains limited. In addition, there is the challenge of rapid Institutional Review Board approval in the immediate aftermath of disaster; the need to address ethical questions surrounding randomization (i.e., to wait list or placebo) in populations where some level of care is needed; and the limitations of naturalistic, post hoc analysis comparing communities that received varying interventions.

Accurately identifying and targeting high-risk individuals for the prevention of both ASD and PTSD for prevention studies might help overcome the sample-size challenges noted above. An example would be active military exposed to combat, a group known to be more likely diagnosed with PTSD (Kessler, Heeringa, et al., 2014). Even higher risk populations might be studied if inclusion criteria were restricted, for example, to active military members exposed to more than 10 episodes of direct combat during a deployment and/or those who experienced a substantial physical injury during a combat exposure. Preidentification of service members with a history of known risk factors such as adverse childhood events might also allow for a more targeted study

population. Another consideration is the potential to readily identify prevention strategies for individuals who might already have ASD, but not necessarily PTSD. Although ASD has not reliably predicted PTSD, as initially hoped when the diagnosis was introduced in the DSM-IV, the presence of this time-limited diagnosis might serve as a signal for the appropriate timing of an intervention study.

The most recent Department of Veterans Affairs (VA) and Department of Defense (DoD) Clinical Practice Guideline (CPG; 2017) does not identify an evidence-based strategy for the prevention of PTSD in any population. The evidence is currently insufficient to recommend any existing particular psychotherapy, pharmacotherapy, or combination of therapies for prevention of PTSD. In light of these limitations, the following provides a review of treatments as early intervention strategies for the prevention of PTSD and other posttraumatic symptoms following trauma exposure.

PSYCHOSOCIAL INTERVENTIONS

Psychosocial interventions that have been considered for the prevention of PTSD include brief trauma-focused psychotherapy, debriefing interventions such as critical incident stress debriefing (CISD), derivatives such as Battlemind, and brief psychosocial interventions such as PFA. Regardless of their track record of efficacy in the treatment of chronic PTSD, these therapies have all been considered as candidates in preventing the onset of PTSD and development of trauma-related symptoms soon after exposure to a traumatic episode (Gartlehner et al., 2013).

Psychological Debriefing Interventions

Psychological debriefing (PD) is a brief crisis intervention usually administered shortly after experiencing a traumatic event (Raphael & Wilson, 2000). CISD, which falls under the PD umbrella, is a supportive, crisis-focused discussion of a traumatic event (frequently referred to as a critical incident). A debriefing session, especially if done with a group of individuals, can last 3–4 hours and may occur within 2–10 days following trauma. According to Mitchell (1983), by helping individuals who are exposed to trauma talk about feelings and reactions to the traumatic event, the facilitator aims to reduce the incidence, duration, severity, or impairment from traumatic stress. CISD is a psychoeducational process in which practical information is provided in order to normalize a group member's reaction to a critical incident and facilitate recovery (Mitchell, 2004).

Unfortunately, considerable research has demonstrated that not only is PD ineffective in preventing PTSD, but the intervention may increase the probability of being diagnosed with PTSD. As an example, a randomized controlled trial (RCT) by Bisson and colleagues (1997) assigned burn victims to either a debriefing session or an assessment-only condition. Burn victims in the treatment group received a single debriefing session that lasted 30–120 minutes, occurring 1 to 3 weeks after the traumatic event. The facilitator followed Mitchell's (1983) established protocol, and there were no significant differences between the groups at the initial assessment on questionnaire measures of mental health problems such as depression, anxiety, and posttraumatic stress. At the 90-day follow-up assessment, the rate of PTSD assessed by clinical structured interviews was similar in both the debriefed group (21%) and the control group (15%). However, at the 13-month assessment, the rate of PTSD was significantly higher in the debriefed

group (26%) than in the control group (9%). Furthermore, the debriefed group scored significantly higher on questionnaire measures of depression, anxiety, and PTSD relative to the control group. Based on this study, researchers concluded that debriefing should be discontinued as a method of preventing PTSD (Rose, Bisson, Churchill, & Wessely, 2002). Emmerik, Kamphuis, Hulsbosch, and Emmelkamp (2002) synthesized the evidence regarding the ineffectiveness of psychological debriefing, in their meta-analyses single-session PD after psychological trauma. Their findings suggested that CISD failed to improve or prevent PTSD symptoms but also appeared to inhibit natural recovery from other trauma-related disorders. In sum, existing evidence suggests that CISD is not a viable approach to prevention of PTSD.

Other Brief Psychosocial Interventions

From the disappointing results of CISD research, it might be reasonable to argue that administering any variation of PD, following a traumatic event is not warranted. However, a different perspective is that early intervention might be beneficial for at-risk populations and could possibly fulfill a range of diverse needs for individuals, rather than simply meeting the clinical goal of preventing PTSD. As an example, a modified version of debriefing, labeled Battlemind debriefing that was specifically designed for military personnel returning from deployment to a war zone, led to a range of better outcomes for soldiers who had high levels of combat exposure, but no differences for those with moderate and low levels of exposure (Adler, Bliese, McGurk, Hoge, & Castro, 2009). It is important to note that Battlemind differs from CISD in that it focuses not on recounting the traumatic event, but on positive changes resulting from a combat deployment. This positive focus in turn is thought to reinforce adaptive cognitions and behaviors. Preliminary data from Adler and colleagues' (2009) research suggested that when compared to soldiers who participated in stress education groups, only Battlemind training participants with high combat exposure reported fewer posttraumatic stress symptoms and lower levels of stigma. Additionally, participants, regardless of the level of combat exposure, reported fewer depression symptoms (as measured by the Patient Health Questionnaire (PHQ)–Depression score) and less sleep disturbance. Although this initial study of Battlemind debriefing produced mostly promising results, other studies suggest it does not contribute specifically to the reduction of PTSD symptoms. For example, Mulligan and colleagues (2012) evaluated the effectiveness of Battlemind debriefing in comparison to standard postdeployment briefs among a group of U.K. Armed Forces personnel. The results suggested that although Battlemind had a modest impact on the reporting of binge drinking, it did not reduce levels of PTSD symptoms.

Still other psychosocial interventions have been developed with the hope of preventing PTSD or reducing posttraumatic stress symptoms. For example, PFA is classified as an "evidence-informed" modular intervention to assist individuals in the immediate aftermath of trauma exposure. PFA was developed through a collaborative effort of the National Center for PTSD and the National Child Traumatic Stress Network. The goal of PFA is to reduce the initial distress caused by traumatic experiences by fostering short- and long-term adaptive functioning and coping. With PFA, interventions to foster calmness, social connectedness, and self and community efficacy are based on the notion that the majority of survivors of large-scale trauma will *not* eventually develop mental health problems, but most will experience a dynamic range of early and distressing reactions to the traumatic event. Subsequently, some of these reactions could very

well interfere with adaptive coping, which may influence the development of PTSD or other mental disorders, including depression or anxiety.

While PFA was initially developed for a civilian population, it appears to be beneficial in a military context as well. For example, the Israeli Defense Force (IDF) has developed a version of PFA called *Magen,* which translates to "shield." Like conventional PFA, Magen is designed to empower soldiers to identify and assist stressors in fellow soldiers following trauma while remaining on the battlefield. According to the IDF Medical Corps, the Magen Program helped more than 80% of combat-exposed individuals successfully return to fulfilling their respective duties during Operation Protective Edge (Ahronheim, 2017). However, the extent to which this population met or did not meet criteria for ASD or PTSD after (or even before) the intervention is not clear. While there is no clinical evidence at the time of this writing that definitively validates the efficacy of the Magen Program, such brief psychosocial interventions could play a pivotal role in developing effective interventions for the prevention of PTSD.

Cognitive-Behavioral Interventions

In general, CBT is best described as a collection of therapeutic approaches based on a common-core theoretical concept that emotional and behavioral symptoms are caused by thoughts, beliefs, and cognitions rather than external events (Field, Beeson, & Jones, 2015). It is important to note that various types of trauma-focused CBTs are based on different theoretical considerations that translate into different therapeutic approaches, but all still fall within the same core philosophy (see Bryant, Chapter 6, and Galovski et al., Chapter 19, this volume).

Shalev and colleagues (2012) found that full-length trauma-focused CBT was effective in some subpopulations but *not* for all who received the intervention. Their study compared early and delayed exposure-based, cognitive, and pharmacological interventions for preventing PTSD. On average, the treatment began 30 days posttrauma using full-length protocols (so in some, but not all, participants, PTSD may have already developed when the intervention was initiated). The results suggested that PTSD outcomes did not differ between trauma-focused cognitive therapy and PE groups at the 5- and 9-month follow-up, and at the 3-year mark, there remained no separation between the intervention and nonintervention groups (Shalev et al., 2016). This study did suggest, however, that cognitive therapy accelerated the recovery of individuals belonging to the slow-remitting group (the progressive decrease in PTSD symptoms over time), but it did not have any effect on the rapid-remitting or nonremitting groups (Galatzer-Levy et al., 2013).

While a recent meta-analysis of all types of multisession psychological interventions for the prevention of PTSD and treatment of ASD produced generally disappointing results (Roberts et al., 2019), some studies of CBT and Brief CBT have demonstrated efficacy in targeted populations. Foa, Zoellner, and Feeny (2006) applied one of three interventions to female assault survivors: brief CBT, repeated assessment of symptoms only, or supportive counseling. At study endpoint, all groups were similar. However, those receiving brief-CBT evidenced lower general anxiety at 3-month follow-up, and a trend toward lower self-reported PTSD severity, suggesting that this intervention might accelerate treatment response. Rothbaum and colleagues (2012) conducted a study using modified PE in patients 12 hours after trauma exposure. The intervention consisted of modified PE, including imaginal exposure to the trauma memory,

processing of traumatic material, and *in vivo* and imaginal exposure homework (Rothbaum et al., 2012). When compared to the assessment-only control group, intervention patients reported significantly lower PTSD symptoms at 4 and 12 weeks postinjury. Sijbrandij and colleagues (2007) compared brief in-session exposure CBT to a wait-list control protocol in participants who had acute PTSD (within 3 months of a traumatic event). The CBT group displayed significantly fewer symptoms of PTSD than the control group after 1 week, and the difference was no longer significant 4 months postintervention. Similarly, Bisson, Shepherd, Joy, Probert, and Newcombe (2004) examined the efficacy of a four-session Brief CBT 1 to 3 weeks following physical injury. Although the clinician-administered PTSD Diagnostic Scale scores were lower among the intervention group at 3- and 13-week follow-up, the differences were not significant.

Several studies have examined brief cognitive-behavioral therapies for trauma survivors who have ASD. Bryant, Harvey, Dang, Sackville, and Basten (1998) found five sessions of exposure-based CBT to be effective in reducing PTSD in participants with ASD. In another study, Bryant, Sackville, Dang, Moulds, and Guthrie (1999) evaluated 45 civilian trauma survivors with ASD who were treated with either exposure or supportive counseling within 2 weeks of trauma. At the 6-month follow-up, there were fewer cases of PTSD among patients receiving CBT, and at the 4-year follow-up of patients who completed this study, those who received CBT reported less intense symptoms of PTSD (Bryant, Moulds, & Nixon, 2003). In contrast, a small study conducted by Freyth and colleagues (2010) in ASD patients found no significant symptom improvement among a PE intervention group in comparison to a supportive counseling group.

Studies of modified CBT utilizing variations of electronic information and telecommunications technologies to make treatment more accessible have also produced mixed results. In an early intervention study, Irvine and colleagues (2011) administered telephone-based CBT to implantable cardioverter defibrillator patients within 2 months of the trauma. A significant improvement in PTSD symptoms at the 6- and 12-month follow-up for both men and women was observed. However, when Mouthaan and colleagues (2013) administered a self-guided Internet-based CBT intervention to prevent PTSD within 1 week of the trauma, both intervention and control group showed a significant decrease of PTSD symptoms, but no significant differences in trend between the two groups was observed over time.

In sum, the studies of CBT point to some evidence of preventive efficacy in targeted populations (e.g., persons with ASD). They also suggest, however, that CBT might not be appropriate for a large population of trauma survivors who do not demonstrate significant symptoms preintervention and that multiple-session interventions could have actually had adverse effects for some patients (Roberts et al., 2019).

PHARMACOLOGICAL INTERVENTIONS

Although RCTs have established a modest evidence basis for pharmacological treatment of PTSD, there is insufficient evidence to support the use of pharmacotherapy for the treatment of ASD or prevention of PTSD. Only two medications are FDA approved for the treatment of PTSD—sertraline and paroxetine—while none are approved for prevention. No pharmacotherapy is approved for the treatment of ASD. Furthermore, none of the current published practice guidelines recommend medication for the prevention of PTSD or treatment of ASD.

Over the past 25 years, several pharmacotherapies have been studied as possible PTSD preventatives or treatments for ASD. Initial research focused on the use of adrenergic blockers and benzodiazepines. Adrenergic blockers were investigated based on their demonstrated capacity to inhibit fear conditioning (Cahill, Prins, Weber, & McGaugh, 1994), while benzodiazepines were studied, at least in part, because of the effect on memory and the anxious component of many cases of PTSD. Benzodiazepines not only proved to be without benefit, but studies showed higher rates of PTSD (Gelpin, Bonne, Peri, Brandes, & Shalev, 1996) or impaired recovery during treatment (Price, Kearns, Houry, & Rothbaum, 2014), resulting in practice guidelines recommending against their use. While initial efforts with benzodiazepines were negative, more recent studies of early intervention in PTSD have similarly pursued investigations of drugs that interfere with traumatic memory formation or retrieval. These drugs, including antiepileptic drugs, glucocorticoids, and opioid receptor agonists (Amos, Stein, & Ipser, 2014; Qi et al., 2016), are reviewed below. Beyond these drugs there are a number of candidates in the early stages of investigation. One notable candidate is ketamine, which has recently gained traction as an intervention for refractory depression and has been identified as a potential candidate for treatment of PTSD, though to date there is no evidence of efficacy in the treatment or prevention of the psychiatric sequelae of trauma.

Results from more recent studies have suggested that hydrocortisone may be a viable means of preventing PTSD in acutely injured trauma patients, specifically those with no history of major psychopathology. One study of 64 trauma-injured patients randomized to receive 10 days of either hydrocortisone or placebo immediately after trauma exposure showed that those receiving hydrocortisone had fewer PTSD and depressive symptoms at 3-month follow-up. Notably those who had no prior history of mental health treatment had the lowest PTSD scores (Delahanty et al., 2013). In a randomized, placebo-controlled, double-blind study of high-dose hydrocortisone administered within 6 hours of a traumatic event to patients with acute stress symptoms, hydrocortisone treatment was associated with reduced symptoms of ASD and PTSD (Zohar et al., 2011). Patients who received the high dose of hydrocortisone displayed significant changes in the trajectory of exposure to trauma, with a reduced risk of developing PTSD symptoms posttrauma (Zohar et al., 2011). Similarly, Schelling and colleagues (2006) measured the effects of hydrocortisone in preventing PTSD symptoms among patients assigned to intensive care units (ICUs). Hydrocortisone administration during ICU stay resulted in a significant decline of PTSD symptoms for long-term survivors. Finally, a double-blind placebo-controlled study focusing on a veteran population with combat-related PTSD found that patients showed improvement in symptoms 1 week after hydrocortisone administration posttraumatic exposure in one symptom cluster (avoidance) but not in other symptom clusters. This initial improvement in avoidance symptoms disappeared by 1 month after hydrocortisone administration (Suris, North, Adinoff, Powell, & Greene, 2010). Given these findings, one might expect broader recommendations for the use of hydrocortisone among trauma-exposed individuals, but given the frequency of traumatic experiences (i.e., often requiring ICU stays) and the loss of benefit at 1 month in the 2010 study, it appears that further research is needed before the evidence would justify such a wide-ranging recommendation.

Propranolol is a beta-adrenergic antagonist that crosses the blood–brain barrier and is therefore capable of reducing the central nervous system adrenergic drive associated with defensive threat responses (Qi, Gevonden, & Shalev, 2016). It was previously

hypothesized that beta-adrenergic antagonists might reduce PTSD symptoms if immediately administered following a traumatic event. Nevertheless, a small pilot study (N = 31) suggested that, while propranolol was effective in the reduction of physiological responses to mental imagery of traumatic experiences 3 months after the traumatic event, there was no significant reduction in PTSD symptoms (Pitman et al., 2002). Subsequently, two additional controlled studies failed to show a preventive effect of propranolol (Hoge et al., 2012; Stein, Kerridge, Dimsdale, & Hoyt, 2007).

McNally and Westbrook suggested that the opioid receptor agonist, morphine, may produce retrograde amnesia for contextual-conditioned fear by decreasing cyclic adenosine monophosphate or activating receptors in the hippocampus region of the rat brain (McNally & Westbrook, 2003). Retrospective observational studies in humans have since assessed the effect of opiate analgesics administered within 48 hours post-traumatic exposure. Mouthaan and colleagues (2015) found that patients who received morphine were less likely than those who received beta-adrenergic blockers, corticosteroids, or benzodiazepines to meet PTSD diagnostic criteria 6 weeks later. The use of morphine has also been assessed in a military combat population. Among the 696 patients who were identified from the Navy-Marine Corps Combat Trauma Registry Expeditionary Medical Encounter Database, 243 military personnel received a diagnosis of PTSD. Among service members who were not diagnosed with PTSD, 76% received morphine. The results suggested that the use of morphine during early resuscitation and trauma care was significantly associated with a lower risk of PTSD after injury (Holbrook, Galarneau, Dye, Quinn, & Dougherty, 2010). Investigations such as a large-scale RCT of opiate administration in emergent trauma would be required before any assertion could be made about the utility of opiates in preventing PTSD.

COMPLEMENTARY AND INTEGRATIVE HEALTH APPROACHES

Complementary and integrative health (CIH) is most easily conceptualized as interventions outside the mainstream of current Western medical practice. CIH approaches as an early intervention following traumatic exposure has, to date, even less evidence than psychotherapy or pharmacotherapy. The most notable research efforts involving CIH after a traumatic event have been with yoga (Telles, Naveen, & Dash, 2007; Telles, Singh, Joshi, & Balkrishna, 2010; Thordardottir, Gudmundsdottir, Zoega, Valdismarsdottir, & Gudmundsdottir, 2014) and meditation (Catani et al., 2009; Iwakuma, Oshita, Yamamoto, & Urushibara-Myachi, 2017; Waelde et al., 2008; Yoshimura et al., 2015) shortly after a natural disaster. Overall, studies of these interventions have not yielded significant results, although some studies have shown modest promise. Furthermore, the studies of CIH as an early intervention following trauma have substantial limitations that would impede consideration for broader adoption or implementation. These studies include RCTs, case series, case reports, and pilot studies, all with a variety of notable limitations including small sample sizes, short follow-up windows, or suboptimal outcome measures. Despite the limited evidence regarding the efficacy of CIH treatments early after trauma, such practices are likely to be offered given the ease of dissemination, limited need for equipment or health care system inputs, and the relative low risk. Further research should be pursued regarding the utility of CIH as an early intervention after trauma, particularly given the lack of knowledge and the current use despite the lack of scientific evidence.

PREDICTIVE MODELS FOR TARGETING EARLY INTERVENTION

Since PTSD was first described in the DSM in the 1980s, researchers have identified numerous biopsychosocial correlates of PTSD and, as a result, potential treatment targets involving etiological mechanisms. Yet, these findings have had minimal effect on clinical interventions for PTSD prevention due in part to methodological limitations that impede the development and refinement of predictive algorithms, cost, time, or field utility limitations and ultimately because correlation does not equate to causation. More recently, efforts have focused on identifying predictors of PTSD, so as to better target immediate intervention in persons most at risk after mass exposure. For example, eye gaze avoidance of fearful stimuli has been found to successfully predict PTSD (Beevers, Lee, Wells, Ellis, & Telch, 2011). However, such procedures may be too invasive and time consuming to justify development and implementation as standardized measurements useful for predicting PTSD in real-time disasters.

Semistructured interviews such as the PTSD Symptom Scale Interview (PSS-I) have been used to measure symptoms of PTSD (Foa, Riggs, Dancu, & Rothbaum, 1993). When the PSS-I was used in combination with other measures obtained in the emergency room (i.e., heart rate, cortisol level, and assessment of dissociation at the time of the trauma), in an attempt to identify predictors for response to early intervention, only dissociation predicted response to early intervention and future development of PTSD symptoms in those who did not receive the early intervention (Price et al., 2014). Moreover, the PSSI must be administered by a trained clinician, making it difficult to scale after a large event. A possible method of overcoming this limitation is to develop machine learning models. Machine learning might succeed where previous efforts have failed because it relies on the collective strength of existing simple models built from individually weak predictors (Papini et al., 2018). In a recent study, machine learning yielded fair results in its ability to predict PTSD among ER patients based on area under the receiver operator characteristic curve (AUC = 0.78, 95% confidence interval; Galatzer-Levy, Karstoft, Statnikov, & Shalev, 2014). As noted previously, a combination of genomic, neuroimaging, psychophysical, physiological, neurocognitive, digital phenotyping, and self-report data from trauma survivors may ultimately help identify those at greatest risk for PTSD or other trauma-related psychopathology to target prevention strategies in those at highest risk (McLean et al., 2020). Unfortunately, the ability to rapidly and cost-effectively determine those persons most likely to develop disabling illness prior to traumatic exposure is not yet available.

CONCLUSION

The wide-ranging and common occurrence of trauma exposure and subsequent development of posttraumatic symptoms and PTSD highlight the need for intervention strategies designed to address a variety of transient symptoms, (and not merely prevent or mitigate PTSD) across various populations in the immediate and near-term aftermath of trauma exposure. The IASC framework provides a solid foundation for public health intervention. PFA, while lacking definitive evidence for prevention of PTSD, is likely to help many who are experiencing distress. For those who are at high risk for developing ASD, CBT has the strongest evidence. Despite several decades of research, evidence remains limited regarding best practices for preventive interventions in the acute aftermath of trauma. Frameworks and guidelines have been established for stratifying levels

of care across populations exposed to mass violence based on the observation that, for the majority of the population, the expected outcome is one of resilience and recovery. However, significant challenges remain with regard to identifying the subpopulations at greatest risk for developing PTSD and therefore at greatest need for IASC "fourth-" tier preventive interventions. While several studies suggest that some interventions may reduce the severity of PTSD symptoms in people experiencing posttraumatic symptoms or ASD in the acute aftermath of trauma, a substantial additional amount of research is needed, particularly in regard to identifying the persons at highest risk for the most debilitating illness, who may receive most benefit from interventions that are often costly and labor intensive. Other critical areas for future research include the optimal timing of interventions (immediate versus delayed), the duration of follow-up or preventive treatment, the relative utility of structured interviews versus self-report measures, and biomarkers to identify persons at highest risk. Future studies must also attempt to focus on subgroups categorized by demographic variables (e.g., educational level, race, gender), the nature of the trauma along with the severity, and the severity of baseline distress or pre-exposure illness. Studies in which outcomes may be adjusted for these factors may clarify the best "all-hazards" approach to prevention of PTSD for diverse populations. Ongoing studies of machine learning and biomarkers may help identify subpopulations for which unique prevention approaches may prove most beneficial, even as new pharmacologic or psychotherapeutic agents are identified. For now, the task of coordinating multileveled prevention efforts without the benefit of a robust scientific basis for sorting needs remains a daunting task for both public health officials and clinicians alike.

DISCLAIMER

All opinions, interpretations, conclusions, and recommendations contained herein are those of the authors and should not be construed as representing the positions or policies of an author's institution, including, but not limited to, the Uniformed Services University of the Health Sciences, the United States Department of Veterans Affairs, and the United States Department of Defense.

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CHAPTER 19

Psychosocial Treatments for Adults with PTSD

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Research on psychosocial treatments for posttraumatic stress disorder (PTSD) has proliferated in recent years. Once considered a chronic disorder, now a number of evidence-based psychotherapy (EBP) options are available with demonstrated success in improving recovery rates. This chapter first provides a brief overview of methodological considerations that are central to evaluating evidence for PTSD treatments. To guide our review, we summarize the major PTSD Clinical Practice Guidelines (CPGs) and comment on the generalizability of findings and challenges for future studies.

The CPGs are based on a systematic review of the available evidence for each empirically supported treatment of PTSD. Considering the type of comparison conditions used in randomized controlled trials (RCTs) when weighing empirical support for an intervention is important (Schnurr, 2007). For example, a *wait-list* comparison group (typically used in initial treatment studies) may be appropriate to control for the passage of time but cannot distinguish between beneficial and nonessential aspects of the active treatment. Comparison to *treatment as usual* (TAU) tests the benefit of the active condition over and above treatment that patients would usually receive. The use of a *nonspecific therapy* as a treatment comparison condition (e.g., supportive counseling) that does not contain the essential, active components of the experimental treatment allows the investigator to attribute differential treatment gains to the theorized active components of the intervention. As treatments for PTSD accumulate empirical support, *comparative treatment effectiveness* designs comparing two effective treatments in a head-to-head trial test which treatment is the most effective. *Predictor studies* may examine two active comparators to understand which patients may benefit from which treatment. *Augmentation studies* test a hypothesized enhancement or combination of individually effective treatments compared to the standard treatment to determine the degree of added benefit. In contrast, *dismantling studies* isolate essential elements of a treatment to test which aspects of the therapy are most effective.

Schnurr (2007) highlighted statistical considerations that are important to evaluating treatment trial outcomes. Effect sizes indicate the strength of treatment response. For wait-list-controlled studies, a large effect size would be expected. Medium effects might be expected for studies using a nonspecific treatment or TAU control, while the expected effect size of studies comparing two active treatments would be small. Studies need to have enough statistical power to detect the expected effect size. A small sample is generally sufficient to detect a large effect size in a wait-list-controlled study, while studies comparing two active treatments require more participants in order to detect a small effect.

Meta-analyses and systematic reviews summarize the efficacy of existing interventions across multiple studies. Watts and colleagues (2013) reviewed 112 RCTs of PTSD treatments for adults published between 1980 and 2012. They found larger effects for psychotherapy than for pharmacotherapy, with cognitive therapy, exposure therapy, and eye movement desensitization and reprocessing (EMDR) having the largest effects. In a Cochrane review of over 70 psychotherapy studies, Bisson, Roberts, Andrew, Cooper, and Lewis (2013) distinguised between trauma-focused therapies (those that directly target the trauma memory and related thoughts and feelings) and non-trauma-focused treatments (those that do not directly target trauma-related content). Bisson and colleagues concluded that trauma-focused cognitive-behavioral therapy (TF-CBT), EMDR, and non-TF-CBT were more effective than other treatments, and there was some evidence that TF-CBT and EMDR were more effective than non-TF-CBT at follow-up. However, the authors noted that the quality of evidence was low, limited by low sample sizes and high risk of bias. A more recent meta-analysis (Cusack et al., 2016) included 64 trials of psychological treatments for adults with PTSD and graded the strength of the evidence (SOE). Their findings supported the efficacy of exposure therapy, including prolonged exposure (PE; high SOE); cognitive therapy (CT), cognitive processing therapy (CPT), cognitive-behavioral therapy (CBT; moderate SOE), EMDR, and narrative exposure therapy (NET; low–moderate SOE).

CPGs integrate findings from multiple meta-analytic studies to provide recommendations for best practices in treating specific conditions. Five recent CPGs for PTSD developed by different workgroups (see Hamblen et al., 2019, for a summary) include the American Psychological Association (2017), International Society for Traumatic Stress Studies (ISTSS; 2018), National Institute for Health and Care Excellence (NICE, 2018), Phoenix Australia Centre for Posttraumatic Mental Health (2013), and the Department of Veterans Affairs and Department of Defense (VA/DoD, 2017). Compared to previous guidelines, which often made decisions based on consensus expert opinions, the current CPGs were based on empirical evidence (Hamblen et al., 2019). Quality of the evidence was rated as high, moderate, low, or very low and was considered alongside other relevant factors (e.g., risk of harm, generalizability of the treatment) to determine the final recommendation.

We relied on CPGs to construct our review of psychosocial treatments for PTSD. Despite some variation across recommendations, all five CPGs gave the strongest recommendations to trauma-focused treatments, although several non-trauma-focused treatments are also suggested. We focus on therapies with the most empirical support (e.g., we do not review studies with only a single published RCT to date), methodologically rigorous studies (i.e., RCT design and participants diagnosed with PTSD; outcomes include interviewer-assessed PTSD), and first-line treatments in the majority of CPGs.

TRAUMA-FOCUSED THERAPIES

In accordance with Bisson and colleagues' (2013) Cochrane review and the distinction between trauma-focused and non-trauma-focused therapies, we begin our review with trauma-focused therapies, starting with those informed by cognitive-behavioral theory.

Cognitive-Behavioral Trauma-Focused Therapies

In Chapter 6 (this volume), Richard Bryant provides an excellent overview of the major psychological models of the development, maintenance, and treatment of PTSD. Cognitive-behavioral theory, as it pertains to PTSD, finds its roots in learning and conditioning models that informed early behavioral theory. Including both classical and operant conditioning models of fear acquisition and maintenance, Mowrer's (1960) two-factor theory (see Bryant, Chapter 6, this volume) postulates that anticipatory fear is acquired through a two-step process in which classical conditioning explains an association between avoidance of the trauma memory (or trauma reminders) and relief. This relief reinforces avoidance as a response to fear, as explained by principles of operant conditioning.

Mowrer's two-factor theory adequately explained the avoidance and hyperarousal symptoms observed in PTSD, but it did not address the cognitive symptoms. Cognitive theory (including the early influence of Beck, Emery, & Greenberger, 1985; Foa, Steketee, & Rothbaum, 1989; Lang, 1977) posits that overly active danger schemas influence the onset and maintenance of PTSD, stresses the importance of the meaning of the trauma, and considers the role of memory function and information processing. The way in which people interpret the traumatic event and, subsequently, appraise the world, self, and others contributes to posttrauma adjustment. More recently, Ehlers and Clark's (2000) cognitive model postulated that persistent PTSD occurs because individuals perceive the threat and danger associated with the trauma as currently active due to negative appraisals of the trauma (inaccurate negative beliefs about why it occurred) and its sequelae (continuing impact of the trauma on current worldviews). Key characteristics of the memory disruption in PTSD include strong associative memory (paired associations between stimuli are particularly strong among details included in memories of traumatic events) and perceptual priming (details that were temporally associated with the trauma remain salient triggers for posttraumatic distress).

Our review of the PTSD treatment literature begins with two therapies informed by cognitive-behavioral theory and with the most accumulated empirical support to date, PE and CPT.

Prolonged Exposure Therapy

Theoretical Model. PE (Foa, Hembree, & Rothbaum, 2007) is based on emotional processing theory (Foa & Cahill, 2001; Foa & Kozak, 1985, 1986), which was influenced by early learning theories (e.g., Mowerer, 1960) and the bioinformational theory of fear (Lang, 1977, 1979). Emotional processing theory proposed that trauma-related emotions are represented in memory as cognitive structures that include information about stimuli, responses, and their meaning—which are interrelated such that inputs matching any part of the structure activate the entire structure. Normal emotional structures are only activated in threatening situations. Pathological emotional structures

are characterized by overgeneralization and excessive responding to safe stimuli. Emotional processing theory proposes that two conditions must be met for recovery: (1) activation of the emotional structure and (2) presence of new information that is incompatible with the pathological emotional structure.

The application of emotional processing theory to PTSD (Foa & Cahill, 2001) explains natural recovery, the development and maintenance of PTSD, and successful treatment. Natural recovery occurs when the emotional structure is repeatedly activated in the absence of feared consequences. In contrast, avoiding trauma-related content may increase PTSD risk by preventing corrective learning. In PE, repeated exposure to the trauma memory and trauma-related stimuli achieves several goals: (1) correcting exaggerated estimates of harm, (2) organizing the narrative and strengthening the distinction between remembering and experiencing trauma, and (3) reevaluating negative trauma-related cognitions about themselves and the world that are central to the emotional structure in PTSD (Foa & Rothbaum, 1998).

Therapy Description. PE consists of several components: psychoeducation, repeated, *in vivo* exposure, imaginal exposure, and processing of trauma information. Patients confront trauma cues during and between sessions to promote learning that trauma reminders are safe and that distress associated with trauma cues is tolerable. Breathing retraining is also part of the therapy. PE typically involves 8–15 individual 90-minute sessions delivered once or twice weekly.

Early Exposure Therapy Trials. Early studies of exposure therapy for PTSD focused on imaginal exposure. The first two trials demonstrated the efficacy of "implosive" (flooding) therapy compared to wait list (Cooper & Clum, 1989; Keane, Fairbank, Caddell, & Zimering, 1989). Flooding involved guiding the patient through graduated imaginal exposure to trauma-related scenes. A similar protocol was also found to be superior to counseling on self-reported PTSD (Boudewyns & Hyer, 1990). Boudewyns and Hyer's (1990) work informed the development of PE; this specific exposure therapy has now accumulated significant evidence. Although there have been many subsequent trials of exposure therapy for PTSD that are not PE (e.g., Başoğlu, Şalcioğlu, & Livanou, 2007; Bryant, Moulds, Guthrie, Dang, & Nixon, 2003; Tarrier et al., 1999; Vaughan et al., 1994), this chapter focuses on PE specifically. However, a few relevant studies that have tested treatments similiar to PE (i.e., including both *in vivo* and imaginal exposure) are included and described as such.

The initial trials of PE were RCTs with civilian women that compared PE with stress inoculation training (SIT) and cognitive restructuring (CR), either alone or in combination. The first study (Foa, Rothbaum, Riggs, & Murdock, 1991) found that SIT was superior to supportive counseling (SC) and wait list, but not PE, in reducing PTSD severity. The next study (Foa et al., 1999) tested the hypothesis that combining PE with SIT would yield more benefit than either treatment alone. The results showed that PE, SIT, and PE+SIT were all superior to wait list but did not differ from each other on reduction in PTSD severity, although the effect size for PE was largest (Foa et al., 1999). In the third and largest study, Foa and colleagues (2005) found that, contrary to hypothesis, adding CR to PE did not improve PTSD outcomes relative to PE alone, but that both PE and PE+CR were superior to wait list. These trials established PE as an efficacious treatment for PTSD in women with sexual assault-related PTSD and indicated that combining multiple efficacious treatment approaches may not yield additional benefit.

Efficacy of PE in Civilians. In general, PE has been found to be superior to wait-list controls in civilian studies (e.g., Resick, Nishith, Weaver, Astin, & Feuer, 2002; Rothbaum, Astin, & Marsteller, 2005) and TAU (Asukai, Saito, Tsuruta, Kishimoto, & Nishikawa, 2010). PE was not superior to supportive counseling in Foa and colleagues' (1991) study, but this trial was small (N = 10–14 per condition), which likely limited the power to detect treatment effects. Significant differences are rarely found when comparing PE to other active treatments among civilians. However, using an exposure therapy similar to PE in which imaginal and *in vivo* exposures were implemented sequentially, Taylor and colleagues (2003) found that exposure was superior to relaxation and EMDR. Most studies find that PE is efficacious but not superior to other active PTSD treatments, including SIT (Foa et al., 1991, 1999), CPT (Resick et al., 2002), and EMDR (Rothbaum et al., 2005). Similarly, neither PE plus cognitive restructuring nor PE plus SIT was superior to PCT (McDonagh et al., 2005) or EMDR (Lee, Gavriel, Drummond, Richards, & Greenwald, 2002), respectively. Studies comparing PE with other variants of CBT that include exposure also fail to demonstrate superiority (e.g., Langkaas et al., 2017). Consistent with this pattern but using a different design, Markowitz and colleagues (2015) found that interpersonal therapy was not inferior to PE, demonstrating that non-trauma-focused treatment for PTSD can also be effective. In an important demonstration of the efficacy of PE in patients with complex comorbidity, a trial in the Netherlands demonstrated that both PE and EMDR, without modification or preparatory treatment, were safe and effective in treating PTSD among those with comorbid psychosis (van den Berg et al., 2015). Finally, in the only RCT comparing PE with pharmacotherapy to date, Zoellner, Roy-Byrne, Mavissakalian, and Feeny (2018) found that both PE and sertraline significantly reduced PTSD severity, although PE was superior on several secondary metrics. More research comparing PE with evidence-based pharmacotherapies is needed.

The PE manual has been translated into seven languages, and the efficacy of PE has been demonstrated by several research groups outside of the United States. The overall pattern is summarized by a meta-analysis showing that PE is associated with large effect sizes compared to wait-list conditions, medium effects compared to non-specific active controls (e.g., relaxation, supportive counseling), and small or no differences when compared with active treatments such as CPT and EMDR (Powers, Halpern, Ferenschak, Gillihan, & Foa, 2010).

Efficacy of PE in Military Samples. Once established in civilian samples, researchers sought to determine whether the efficacy of PE extended to military populations. The first RCT of PE in a military sample found that PE was superior to PCT in reducing PTSD severity among women veterans and active-duty military personnel (Schnurr, Friedman, et al., 2007). Several smaller RCTs also demonstrated the efficacy of PE in veterans, both in the United States and internationally (e.g., Nacasch et al., 2011). Consistent with the civilian literature, PE has not always been found superior to non-trauma-focused interventions. In small trials that likely had limited power, PE was not superior to PCT (Rauch et al., 2015), or minimal attention (Yehuda et al., 2014). PE was found to be noninferior to transcendental meditation (Nidich et al., 2018), with a smaller effect size for PE than those seen in civilian studies. PE was recently tested in active-duty service members in a trial showing that 10 daily sessions of PE were superior to minimal attention and noninferior to 10 weekly PE session, but that weekly PE was not superior to its comparator, weekly PCT (Foa et al., 2018). The effect sizes for PE in this trial were smaller than those observed in civilian trials. Thus, while PE

is efficacious with veterans and active duty, the degree of improvement appears modest relative to civilians, a pattern that has been oberserved for other trauma-focused psychotherapies as well. A recent review of EBP trials with military samples highlights the idea that there is room for improvement in PTSD outcomes (Steenkamp, Litz, & Marmar, 2020).

Modifications to PE. Once PE was well established, a logical next step was to test modifications of PE to meet the needs of new populations or settings. Comorbid substance use disorders, traditionally treated separately from PTSD, have been targeted in concurrent and integrated treatment programs that include PE. In civilians with comorbid smoking dependence, PE plus varenicline was superior to varenicline alone in reducing PTSD, but there were no group differences in smoking cessation (Foa et al., 2017). In civilians with comorbid alcohol dependence, naltrexone and medication counseling with and without PE were equally effective in reducing PTSD (Foa et al., 2013). Alcohol consumption declined in all groups, but PE showed superior maintenance 6 months after treatment ended (Foa et al., 2013). In contrast, most trials of combined or integrated treatments for PTSD and substance use have found that PE is associated with improvements in PTSD but not substance use. For example, an integrated treatment called concurrent treatment of PTSD and substance use disorders using PE has been found superior to comparison conditions in reducing PTSD and similarly efficacious in reducing substance use in civilians and veterans (e.g., Back et al., 2019; Norman et al., 2019). PE has also been integrated with dialectical behavior therapy (DBT) for individuals with PTSD and comorbid borderline personality disorder. A pilot RCT found that those who received DBT+PE, wherein participants began PE combined with DBT after meeting borderline personality disorder-related stability criteria, yielded significantly greater improvements in PTSD severity and self-injurious behavior than DBT alone (Harned, Korsland, & Linehan, 2014).

Researchers have also sought to determine whether PE is efficacious when delivered in condensed formats that are better suited to certain settings. For example, PE for primary care, which involves four 30-minute sessions of PE delivered by behavioral health consultants in integrated primary care settings, was superior to minimal control in reducing PTSD in veterans (Cigrang et al., 2017). Other work aims to determine whether 60-min PE sessions are non-inferior to the standard 90-minute sessions. This is currently being tested in a large trial (Foa, Zandberg, et al., 2019), but preliminary studies suggest that sessions can be shortened without negatively impacting outcomes (Nacasch et al., 2015). This could make it much easier to implement PE, given the ubiquity of the 60-minute session framework. Together, these findings have the potential to make PE more accessible to PTSD patients across settings.

PE Augmentation. Several studies have explored whether PE can be augmented by incorporating additional therapeutic approaches. As noted above, neither SIT nor CR augments PE, althought Bryant and colleagues (2008) found that adding CR to an exposure protocol that included *in vivo* and imaginal exposure did yield superior outcomes. However, this study did not use PE; post-imaginal exposure processing was omitted. Because processing likely overlaps with CR in terms of therapeutic mechanisms, the results of Bryant and colleagues do not suggest that CR enhances PE.

Studies of cognitive enhancers hypothesized to enhance extinction learning have not yet demonstrated a clear beneficial effect. Despite showing initial promise, d-cycloserine, a partial *N*-methyl-D-aspartate (NMDA) receptor agonist, has generally

not been found to augment PE (e.g., de Klein, Hendriks, Kusters, Broekman, & van Minnen, 2012). Meta-analyses across anxiety-related disorders indicate a small augmentation effect (Mataix-Cols et al., 2017) that is impacted by dosing and dose timing (Rosenfield et al., 2019). Some alternate cognitive enhancers have shown promise as PE augmentation strategies in pilot work (e.g., oxytocin: Flanagan, Sippel, Wahlquist, Maria, & Back, 2017; yohimbine: Tuerk et al., 2018), but replication with larger samples is needed.

Findings from trials combining PE with pharmacological treatments do not provide strong evidence for their combination, with one exception: PE + paroxetine was more efficacious than PE + placebo in reducing PTSD severity (Schneier et al., 2012). In contrast, Popiel, Zawadzki, Pragłowska, & Teichman (2015) found no evidence for additing paroxetine to PE. Similarly, a large trial by Rauch and colleagues (2019) found that PE + sertraline, PE + placebo, and sertraline + enhanced medication management were all efficacious in reducing PTSD, with no significant differences across groups.

The efficacy ceiling for PE is high, and overall, PE augmentation studies have not identified strategies to improve outomes, with the possible exception of certain cognitive enhancers that show promise in preliminary work. Research that focuses on minimizing dropout or selective augmentation that targets patients identifed early on as probable nonresponders may prove more promising than approaches that aim to boost overall efficacy.

The Integration of Technology into PE. Virtual reality (VR) technology has been used to facilitate imaginal exposure using head-mounted computer simulations of sights, sounds, vibrations, and smells related to the individual's trauma. VR-facilitated PE has not been found superior to standard PE (Reger et al., 2016). Although a purported advantage of VR is helping patients who struggle to engage with the trauma memory with sufficient detail and affective magnitude (Beidel et al., 2014), Reger and colleagues (2019) found no evidence that VR exposure therapy increased emotional activation over standard PE.

PE delivered via home-based telehealth has been found to significantly reduce PTSD severity (Yuen et al., 2015) and was noninferior to in-person PE delivery (Acierno et al., 2017). A self-guided web version of PE with asynchronous therapist support was recently shown to significantly reduce PTSD severity in veterans and active-duty military personnel (McLean et al., 2020). Both telehealth and web treatment are promising strategies to overcome some of the barriers to in-person treatment, including lack of available services, distance from clinics, difficulty scheduling during work hours, and stigma associated with mental health problems (Morland et al., 2017).

Cognitive Processing Therapy

Theoretical Model. CPT (Resick, Monson, & Chard, 2017) is predominantly informed by Beckian cognitive theory (Beck, Rush, Shaw, & Emery, 1979), based on the premise that people organize incoming information into schemas (belief systems). Schemas help people make sense of the world and inform choices that enable them to navigate their environment. Traumatic events can disrupt schemas and drastically alter the way people view the world, themselves, and others. Prior research (Janoff-Bulman, 1985; McCann, Sakheim, & Abrahamson, 1988) demonstrated that beliefs about safety, trust, power and control, esteem, and intimacy are particularly susceptible to disruptions after a trauma. Because disruptions in beliefs can keep trauma survivors "stuck"

in distress, CPT seeks to identify "stuck points" (or inaccurate thoughts) and challenge them through Socratic questioning, with the goal of arriving at more accurate and balanced conclusions. Targeting stuck points also dissipates lingering manufactured emotions like shame and guilt (as opposed to natural emotions, which, like fear and sadness, will run their course). As patients approach the trauma memory, allow natural emotions to run their course, process the trauma memory and information, and come to more accurate and balanced conclusions, patients' distress decreases and PTSD resolves.

Therapy Description. CPT was developed as a 12-session therapy delivered in groups or individually in weekly or twice-weekly sessions. CPT content is delivered across three phases. Phase 1 consists of psychoeducation, information gathering, and identification of stuck points. During Phase 2, patients learn to challenge these inaccurate beliefs, and in Phase 3, those trauma-related stuck points begin to resolve. Throughout therapy, the patient is given many real-world practice opportunities, with the help of worksheets. The patient may also choose to write a detailed narrative about the event.

Early CPT Trials. CPT was first developed and tested in a group format in civilian women with PTSD secondary to rape. The first RCT compared CPT to PE and to a minimal-attention wait-list control (Resick et al., 2002) in a sample of female survivors of sexual trauma. Both CPT and PE were successful in reducing PTSD and depression, with gains maintained 3 and 9 months posttreatment. Both active treatments were more effective than wait list. A long-term follow-up study conducted 5–10 years after completion of treatment showed excellent maintenance of gains in both CPT and PE (Resick, Williams, Suvak, Monson, & Gradus, 2012), suggesting that if PTSD is successfully treated by one of these two therapies, it is unlikely that symptoms will recur.

Efficacy of CPT in Civilians. Fairly early in the development of CPT, Resick and colleagues (2008) conducted a dismantling study to test the relative efficacy of the theorized active elements of CPT. The full CPT protocol (which originally included written exposure) was compared to a written exposure only condition and to a cognitive therapy only condition (CPT-C). All three treatments demonstrated efficacy; however, participants in CPT-C showed more improvement than those in written exposure. CPT-C led to faster improvements in PTSD, with fewer dropouts than either of the other conditions. The results of this trial informed the evolution of the CPT protocol to include the written account of the trauma as optional versus standard. Sloan, Marx, Lee, and Resick (2018) later compared CPT (including written trauma narratives) to written exposure therapy (WET) conducted in five sessions and found largely equivalent outcomes, with the exception of baseline to posttreatment effects favoring CPT and lower dropout favoring the shorter treatment (WET).

Subsequent RCTs in civilian samples continued to establish the efficacy of CPT, replicating results in other areas of the world. To date, CPT has been translated into eleven languages, and RCTs have been conducted worldwide. For example, Nixon (2012) tested the efficacy of CPT compared to symptom-monitoring delayed treatment in the immediate aftermath of trauma exposure among Australian civilian assault survivors diagnosed with acute stress disorder (ASD). Large effects favoring CPT were observed. Comparing CPT to individual supportive counseling, Bass and colleagues (2013) randomized women sexual assault survivors in the Democratic Republic of Congo by village. Results favored CPT over supportive therapy in reducing PTSD, depression, and

improving functioning—all with large effects. This trial demonstrated that PTSD treatment can be successful even when treatment occurs in the context of ongoing danger and violence. Weiss and colleagues (2015) compared CPT to a wait-list control in civilian survivors of systematic violence in southern Iraq and found that CPT was superior to wait list. Finally, Butollo, Karl, König, and Rosner (2016) conducted a a comparison trial in Germany with civilians who had experienced different types of trauma and found that CPT and an integrative gestalt-derived intervention called dialogical exposure therapy were both successful in their ability to reduce symptoms of PTSD.

Maxwell and colleagues (2016) compared CPT to memory specificity training in an effort to understand the role of memory reconsolidation in trauma recovery. CPT was superior to the comparison condition in reducing PTSD, and the two interventions fared equally well in increasing the ability to retrieve memories. Pearson, Smartlowit-Briggs, Belcourt, Bedard-Gilligan, and Kaysen (2019) compared culturally adapted CPT to a wait-list condition among Native American and Alaskan Native women with PTSD, substance use disorders (SUDs), and high-risk sexual behaviors. Large effects favoring CPT were found for PTSD and reductions in high-risk sexual behaviors, with moderate to large effects favoring CPT on alcohol use. Taken together, this research demonstrates a large and growing evidence base for CPT both in the United States and globally.

Efficacy of CPT in Military Samples. As studies in CPT proliferated in the civilian population over the last two decades, researchers also began to test the efficacy of the therapy in the military samples. Monson and colleagues (2006) first tested CPT in a veteran sample and found the therapy to be significantly more effective than wait list in treating PTSD and depression. A second study with Australian veterans compared CPT to TAU and also showed significantly greater effects favoring CPT (Forbes et al., 2012). In a study comparing CPT to present-centered therapy (PCT) in a veteran sample with PTSD secondary to military sexual trauma, PTSD and depression improved significantly in both treatments, but with no differential improvement in the clinician-administered primary PTSD outcome (Suris, Link-Malcolm, Chard, Ahn, & North, 2013).

Resick and colleagues (2015) first tested CPT in a U.S. active-duty sample, with PTSD secondary to combat-related trauma. Group CPT was compared to group PCT, with both conditions showing large effects in reducing PTSD and depressive symptoms. Participants in the CPT condition reported greater decreases in PTSD on self-report measures, but not on clinician-rated outcomes. In a second study with active-duty service members, Resick and colleagues (2017) compared group versus individual CPT. Interestingly, those participants who received individual CPT fared almost twice as well as those who received group CPT.

Modifications to CPT. The first modification extended the length of CPT for survivors of childhood sexual assault (CPT-SA), adding five sessions designed to address topics thought to be specific to traumatic events in childhood. Conducted in combined group and individual format, CPT-SA was found superior to minimal attention control (Chard, 2005). Galovski, Blain, Mott, Elwood, and Houle (2012) next sought to flexibly apply CPT by using participants' progress in therapy (good end-state functioning and loss of PTSD diagnosis) to determine treatment length. This study allowed for emergency sessions as needed, included survivors of childhood sexual assault, and was the first CPT civilian trial to include male participants. The allowance of emergency sessions did not disrupt recovery from PTSD and the flexible length of therapy resulted in

better outcomes for more participants. This study also demonstrated similar outcomes for men and women (Galovski, Blain, Chappuis, & Fletcher, 2013), as well as similar lengths of therapy and outcomes for individuals with and without comorbid Axis II disorders and with extensive trauma histories, including childhood trauma (Galovski, Harik, Blain, Farmer, Turner, & Houle, 2016).

CPT Augmentation. Throughout the course of this line of research, a number of RCTs have sought to augment CPT to enhance outcomes beyond PTSD and depression. Augmenting protocols that are designed to treat single disorders with interventions that may target commonly occurring clinical correlates and comorbid disorders can move the needle further toward more holistic recovery. The first such augmentation trial of CPT was conducted with female civilians with PTSD secondary to interpersonal assault. This trial added a sleep-directed hypnosis intervention to CPT designed to improve sleep prior to CPT. Results showed that hypnosis was effective in improving sleep compared to a control condition, but the improved sleep only augmented recovery from depression, not PTSD (Galovski, Harik, Blain, Elwood, Gloth, & Fletcher, 2016). In a study of post-9/11 veterans, Jak and colleagues (2019) tested the added benefit of a SMART (Symptom Management and Rehabilitation Therapy) intervention (a compensatory cognitive training program) designed to target cognitive symptoms of traumatic brain injury. The results showed that CPT and SMART CPT improved PTSD and depression, and that SMART CPT participants experienced improvements in neurobehavioral symptoms. Finally, Kozel and colleagues (2018) hypothesized that the addition of transcranial magnetic stimulation (rTMS; an intervention with empirical support in the treatment of depression and, to a lesser extent, PTSD) to CPT would result in improved clinical outcomes compared to CPT with sham rTMS. The results indicated that the addition of rTMS improved outcomes with medium effect.

The Integration of Technology into CPT. A number of studies with veterans have tested the relative efficacy of delivering CPT via telemental health. Both methods of service delivery have been found to be equally beneficial for male Vietnam-era veterans (Morland et al., 2014), female veterans, reservists, National Guard, and civilians (Morland et al., 2015), and post-9/11 veterans (Maieritsch et al., 2016). These studies provide evidence that therapists can successfully administer CPT virtually, thus increasing access to care for those who cannot travel to treatment facilities.

Other Trauma-Focused Cognitive-Behavioral Therapies

Therapy Description. TF-CBT focuses on changing patterns of thoughts, behaviors, and feelings with a variety of techniques, including psychoeducation, stress management, cognitive restructuring, acquisition of adaptive coping strategies, and exposure. TF-CBTs have been administered and tested in individual and group formats. We include Ehlers and Clark's cognitive therapy (CT) and other versions of cognitive therapy here, given their alignment with the cognitive theoretical underpinnings of the larger CBT framework. CT is typically administered across 12–16 weekly sessions over a 3-month period and focuses on (1) elaborating the trauma memory and integrating it into the context of the patient's life narrative, (2) identifying and modifying unhelpful appraisals of the trauma that maintain the overestimations of threat, and (3) preventing dysfunctional behavior and cognitive strategies that prevent memory elaboration or reassessment of problematic appraisals.

Efficacy of TF-CBT in Civilian Samples. A number of studies designed to test the efficacy of CBT in treating PTSD compared the active CBT condition to a wait-list control condition in trauma survivors with PTSD secondary to several different types of traumatic events. Considered together, clinical trials testing CBT for PTSD showed that battered women (Kubany, Hill, & Owens, 2003; Kubany et al., 2004), Cambodian refugees with treatment-resistant PTSD and comorbid panic attacks (Hinton, 2005). and motor vehicle accident survivors treated individually (Maercker, Zollner, Menning, Rabe, & Karl, 2006) and in group format (Beck, Coffey, Foy, Keane, & Blanchard, 2009) evidenced significantly greater reductions in PTSD than those randomized to the wait-list condition (or minimal contact therapy; Beck et al., 2009) with large effects. When compared to participants in the active treatment conditions such as supportive psychotherapy, participants in the CBT treatment condition typically show significantly greater effects across trauma populations, with some exceptions. For example, in an early RCT comparing CBT to a relaxation training treatment condition in a sample of sexual assault survivors, Echeburua, De Corral, Zubizarreta, and Sarasua (1997) found that CBT was superior to the control condition. Blanchard and colleagues (2003) conducted an RCT with motor vehicle accident survivors with PTSD, comparing CBT to a supportive psychotherapy condition and a wait-list control. CBT participants improved significantly more on primary outcomes such as PTSD, with the gains well maintained at a 3-month follow-up assessment.

The range of therapeutic strategies and techniques informed by cognitive-behavioral theory contributes to an inherent flexibility in modifying CBT protocols to adapt to different cultures and sociopolitical situations. Bryant and colleagues (2011) tested exposure therapy and cognitive restructuring, modified to incorporate Thai meditation and modifying cognitive restructuring to evaluate actual danger and intervene accordingly. Among terrorist attack survivors in southern Thailand under continued threat of violence, CBT participants reported greater reductions in PTSD, depression, and complicated grief than TAU participants. Of note, therapists in this trial were psychiatric nurses with minimal training and no ongoing expert supervision. Results support the efficacy of CBT in non-Western settings by nonspecialist providers.

A series of studies testing CT demonstrates its efficacy in treating PTSD. An early trial of a CT protocol based on Beck, Emery, and Greenberg (1985) and Resick and Schnicke (1993) found no differences in symptom reduction when comparing CT with imaginal exposure (Tarrier et al., 1999). Ehlers and colleagues (2003) compared CT to a self-help booklet condition and a repeated assessment control condition among survivors of recent motor vehicle accidents. The results were encouraging, with CT participants improving significantly more than those in the comparison conditions on symptoms of PTSD, depression, and anxiety. A small, follow-up RCT comparing CT to wait list showed similar results; CT participants improved more on PTSD and depression with large effects (Ehlers, Clark, Hackmann, McManus, & Fennell, 2005). More recently, in an elegant four-arm trial, Ehlers and colleagues (2014) compared CT delivered over 7 days (intensive CT) to standard CT (weekly sessions), weekly emotion-focused supportive therapy, and a wait-list control. Both CT conditions were superior to supportive therapy and a wait list, with moderate to large effects on primary outcomes. Notably, 73% of participants in the intensive arm achieved the same rates of recovery in 1 week as compared to recovery over a standard 3-month weekly CT (77% recovered). Forty-three percent of participants in the supportive condition also recovered from PTSD; ;this condition was superior to a wait list on primary outcomes but not quality of life. This important study demonstrated the safety and feasibility of intensive PTSD

treatment. Finally, in a large RCT comparing a cognitive restructuring (CR) therapy to cognitive-behavioral stress management among refugees with chronic and complex negative mental health outcomes including PTSD, Carlsson, Sonne, Vindbjerg, and Mortensen (2018) found very little improvement on a number of outcomes, including PTSD symptoms measured by self-report in either condition and no differences between treatment condition on PTSD symptoms. The authors attributed the lack of change to the chronic and substantial psychopathology in this patient population.

Efficacy of TF-CBT in Military Samples. A large RCT ($N = 360$) by Schnurr and colleagues (2003) compared the effects of trauma-focused group therapy (comprising psychoeducation, coping skills training, exposure, cognitive restructuring, and relapse prevention) to present-centered group therapy among Vietnam veterans with PTSD. The results showed no significant differences between groups, though dropout was higher from the trauma-focused treatment. A study evaluating trauma management therapy (TMT), described as exposure therapy plus group treatment to address broader areas of functioning and other outcomes such as anger, depression, and social support, as compared to exposure therapy in Vietnam veterans, found no evidence of superiority for either treatment (Beidel, Frueh, Uhde, Wong, & Mentrikoski, 2011).

Narrative Exposure Therapy. Designed for implementation by nonmental health professionals in low-resource countries, narrative exposure therapy (NET; Schauer, Schauer, Neuner, & Elbert, 2005, 2011) is a brief treatment developed for individuals who have experienced multiple traumas over an extended period. NET draws from emotional processing and cognitive theories, suggesting that distortion of autobiographic memory of traumatic events leads to a fragmented narrative of the memories, which maintains PTSD symptoms (Ehlers & Clark, 2000). The focus of NET is twofold: (1) the habituation of emotional responding to trauma reminders through exposure and (2) the construction of a detailed narrative of the event and its consequences. NET aims to connect "hot" memories (memories containing sensory information, cognitive and emotional perceptions, and physiological responses) with "cold" memories (declarative episodic memories, including contextualized information about one's life) to facilitate engagement with the emotion of the memory while integrating contextual information. This is accomplished by constructing an autobiographical representation of traumatic events within the individual's life narrative.

A number of trials show NET to be effective in reducing symptoms of PTSD (see Robjant & Fazel, 2010, and McPherson, 2012, for reviews). Most studies were conducted in developing countries among refugees (e.g., Ertl, Pfeiffer, Schauer, Elbert, & Neuner, 2011; Neuner et al., 2008) or migrated refugees and asylum seekers in Western countries (e.g., Hensel-Dittman et al., 2011; Hijazi et al., 2014; Stenmark, Catani, Neuner, Elbert, & Holen, 2013). Results of these studies found significant reductions in PTSD severity at posttreatment and follow-up, with low dropout rates. Most studies compared NET to wait list or TAU; no studies have compared NET to EBPs for PTSD, and most studies are limited by small sample sizes (i.e., less than 20 per group). A recent meta-analysis of 16 RCTs using NET (Lely, Smid, Jongedijk, Knipscheer, & Kleber, 2019) found high external validity and methodological quality equivalent to other CPG-supported trauma-focused interventions. These findings suggest that NET is effective for reducing PTSD in diverse international samples with multiple traumas, although larger studies comparing NET to other EBPs for PTSD in different PTSD samples are needed.

Written Exposure Therapy. Written exposure therapy (WET; Sloan & Marx, 2019) is a brief exposure therapy derived from Pennebaker and Beall's (1986) written disclosure procedure in which individuals write repeatedly about a traumatic experience. Through written exposure, individuals experience an increase in negative affect, which is reduced across sessions as the conditioned fear response to the trauma memory is extinguished (Sloan & Marx, 2004). WET consists of five sessions with 25 minutes of therapist contact in Session 1 and 10 minutes or less in the remaining four sessions, making WET easily administered.

The first WET RCT found that WET was superior to wait list in reducing PTSD symptoms among motor vehicle accident survivors, with large between-group effect sizes and only 9% dropout among WET participants (Sloan, Marx, Bovin, Feinstein, & Gallagher, 2012). A larger RCT compared WET to CPT in veteran and nonveteran adults (Sloan et al., 2018). WET was not inferior to CPT in reducing PTSD symptoms over 24 weeks, with a lower dropout rate, suggesting that WET may be a promising treatment for PTSD.

The Integration of Technology into TF-CBT. Within the past decade, interest in telehealth and eHealth delivery of CBT for PTSD has grown. Internet-delivered CBT (i-CBT) was effective in reducing PTSD compared to wait list (Kuester, Niemeyer, & Knaevelsrud, 2016; Lewis, Roberts, Simon, Bethell, & Bisson, 2019; Spence et al., 2011, 2014). However, one study found no advantage compared to Internet-based non-CBT treatment (Lewis et al., 2019), and another study found that i-CBT was less effective than active control conditions (i.e., writing interventions or psychoeducation; Kuester et al., 2016). In contrast, i-CBT was more efficacious than an online supportive counseling control group (Litz, Engle, Bryant, & Papa, 2007).

Limited studies support the efficacy of CBTs delivered by telehealth among veterans and active-duty service members. An early study of telehealth CBT found it to be inferior to in-person CBT among veterans with combat-related PTSD at posttreatment but not significantly different at the 3-month follow-up (Frueh et al., 2007). A small study ($N = 18$) of Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) veterans found that telehealth CBT was not significantly different than in-person CBT, but that participants reported greater satistfaction with the telehealth condition (Ziemba et al., 2014). A more recent study of TMT, which included virtual reality exposure therapy (VRET) plus group treatment for anger, depression, and isolation, found the treatment to be similarly efficacious to VRET with a psychoeducation control condition in reducing PTSD symptoms among OIF/OEF veterans (Beidel et al., 2019).

Other Trauma-Focused Therapies

Eye Movement Desensitization and Reprocessing

Theoretical Model. EMDR is based on Shapiro's adaptive information-processing (AIP) model (Shapiro, 2001). According to AIP theory, trauma memories are stored in a raw, unprocessed, maladaptive form when usual processing is disrupted. When trauma memories are stored in this raw form, the brain is unable to connect those memories to other memory networks that would aid processing with adaptive information. Because they are unprocessed, these dysfunctionally stored memories can be activated by internal or external stimuli, leading to maladaptive responses and the symptoms

that comprise PTSD. Because symptoms are thought to arise from impairments in processing, EMDR aims to reactivate information processing to allow for reprocessing the traumatic memories by linking maladaptive memories with adaptive information contained in other memory networks. Bilateral stimulation (e.g., eye movements guided by the therapist's moving hand) is thought to facilitate reprocessing by improving access to maladaptive memories and inducing an altered mental state similar to REM sleep to allow for easier processing. Reprocessing the dysfunctionally stored memories helps the patient to integrate the trauma memories into a cohesive memory network and resolution of PTSD symptoms.

The necessity of the bilateral stimulation component of EMDR is controversial (Jeffries & Davis, 2013). Several meta-analyses and reviews of EMDR found no significant added benefit to eye movements (Cahill, Carrigan, & Freuh,1999; Davidson & Parker, 2001), though Lee and Cuijpers (2013) reported that effect sizes were larger when eye movements were used. More recently, Sack and colleagues (2016) found that visual attention on the therapist may produce superior treatment outcomes than no instruction on attentional focus, and the induction of eye movements by following the therapist's moving hand did not offer an advantage compared to visually fixating on a nonmoving hand.

Therapy Description. EMDR consists of eight phases distributed across 6–12 sessions of 60–90 minutes each. The first phase focuses on assessing identifying trauma memories to be targeted during therapy. In Phase 2, the therapist teaches stress reduction techniques, and Phase 3 includes the identification of all components of the target trauma memories, including associated physical sensations. The next four phases consist of treating the unprocessed memories with imaginal exposure and bilateral stimulation, with the goal of facilitating reprocessing. In the final phase, the patient and the therapist review progress.

Efficacy of EMDR in Civilian Samples. The first published study of EMDR (Shapiro, 1989) tested a single session of EMDR in a small sample of civilians with diverse trauma experiences. EMDR was superior to a modified flooding control condition in reducing symptoms, and gains were maintained at 1- and 3-months posttreatment. Rothbaum (1997) found that EMDR was more effective in reducing PTSD compared to wait list among women sexual assault victims. In a similar sample, Rothbaum and colleagues (2005) compared EMDR, PE, and wait-list control and found significant symptom improvements in both EMDR and PE compared to wait list with no differences between active conditions. EMDR was also found to be effective in reducing work-related PTSD symptoms for Swedish public transportation workers compared to wait list (Högberg et al., 2007). Although many EMDR RCTs are limited by small sample sizes, a larger study of men and women with mixed-trauma-related PTSD showed that EMDR was more efficacious than treatment as usual, which included non-trauma-focused psychotherapy, medication, and/or group therapy (Marcus, Marquis, & Sakai, 1997).

Several studies have been conducted using EMDR in refugee populations with mixed results. Among Syrian refugees with PTSD, EMDR was superior to wait list delivered individually (Acarturk et al., 2016) and in a modified group format (Yurtsever et al., 2018). These trials suggest that EMDR is effective with patients experiencing ongoing threat of violence. However, among asylum seekers and refugees in the Netherlands, EMDR was not more efficacious than a stabilization procedure with a focus on safety,

stress management, and cognitive restructuring (ter Heide, Mooren, van de Schoot, de Jongh, & Kleber, 2016). This finding suggests that EMDR may be an effective treatment for refugees but should not be considered a singular treatment in this population.

EMDR has been found to be similarly efficacious to PE alone (Laugharne et al., 2016) and PE plus SIT (Lee et al., 2002; Rothbaum et al., 2005; van den Berg et al., 2015). An exception is the Taylor and colleagues study showing that EMDR was significantly less efficacious than PE and was comparable to relaxation training (Taylor et al., 2003).

Efficacy of EMDR in Military Samples. Albright and Thyer (2010) conducted a meta-analysis including six RCTs that examined the effects of EMDR on PTSD among military combat veterans. Findings across studies were equivocal, with some studies demonstrating the efficacy of EMDR and others failing to find significant differences between EMDR and the comparison conditions. Furthermore, the studies included in the analysis had significant methodological limitations, including very small sample sizes, unclear treatment fidelity, and unblinded assessors. Another meta-analysis of therapies for veterans with PTSD (Haagen, Smid, Knipscheer, & Kleber, 2015) included four studies of EMDR and found that EMDR was less effective than exposure therapy and CPT. The authors noted that the inferiority of EMDR may be due to study design characteristics, suggesting that head-to-head trials comparing EMDR and other treatments are needed. A more recent meta-analysis by Kitchiner, Lewis, Roberts, and Bisson (2019) of RCTs with military samples included the same four studies examining EMDR and found that EMDR was not effective, when compared to wait list/usual care, at reducing PTSD symptoms. Consistent with these findings, the NICE guidelines recommend EMDR only for PTSD due to noncombat-related trauma.

Brief Eclectic Psychotherapy

Brief eclectic psychotherapy (BEP; Gersons, Meewisse, & Nijdam, 2015) is a 16-session treatment that combines elements from psychodynamic, cognitive-behavioral, and directive psychotherapy. Sessions include psychoeducation, imaginal exposure, use of mementos, and writing assignments. Patients focus on meaning-making and integration of the trauma experience and then engage in a farewell ritual to leave the traumatic event behind (Gersons & Schnyder, 2013).

The first RCT to evaluate BEP in a small sample of police officers with PTSD found BEP superior to wait list in reducing PTSD (Gersons, Carlier, Lamberts, & van der Kolk, 2000). Two other small RCTs found BEP superior to wait list among community samples (Lindauer et al., 2005; Schnyder, Muller, Maercker, & Whittmann, 2011). The only large RCT used an active control and compared BEP to EMDR in civilian trauma survivors (Nijdam, Gersons, Reitsma, Jongh, & Olff, 2012). Results showed that both treatments reduced PTSD symptoms, but reductions were faster for EMDR. Based on these studies, the VA/DoD guidelines recommend BEP, and the American Psychological Association guidelines list BEP with a moderate recommendation.

NON-TRAUMA-FOCUSED THERAPIES

Although trauma-focused therapies have the highest recommendations in all CPGs, in cases where there is no access to these treatments or patients are not interested in

receiving these therapies, CPGs suggest the use of several non-trauma-focused interventions over no treatment. Treatment effects for these therapies are not as large as those seen in trauma-focused treatments, and the level of recommendation is varied across treatment guidelines (Hamblen et al., 2019). We highlight the non-trauma-focused treatments with the strongest evidence base below.

Present-Centered Therapy

Present-centered therapy (PCT) was originally developed as an active comparison for the nonspecific benefits of psychotherapy in clinical trials (Schnurr, 2003). Key elements of the present-centered approach include psychoeducation about PTSD, identifying daily stressors and difficulties, and addressing current symptoms. Components of PCT include the establishment of positive interpersonal connections, normalization of symptoms and validation of experiences, provision of emotional support, and increasing sense of mastery in managing current problems (Schnurr, Friedman, et al., 2007). PCT can be implemented in group or individual formats, generally in 60- to 90-minute sessions over 10–30 weeks. Although originally designed as a control, studies have shown PCT to be an effective treatment for PTSD. As noted previously, a number of trials examining the efficacy of trauma-focused treatments did not find trauma-focused treatment to be superior to PCT. In one study, Schnurr and colleagues (2003) failed to find a difference between group PCT and group trauma-focused therapy among Vietnam veterans, a finding that was replicated among female survivors of childhood sexual abuse (Classen et al., 2011). A small trial comparing individual PCT to CBT involving imaginal and *in vivo* exposure and cognitive restructuring and to wait list found no significant differences between active treatments (McDonagh et al., 2005). Recent large RCTs with active-duty military found no differences in PTSD outcomes between PE and PCT (Foa et al., 2018) and group CPT and PCT (Resick et al., 2015). A study of veterans who experienced military sexual trauma also found no differences in clinician-rated PTSD symptom change between PCT and CPT, although CPT resulted in greater reduction of self-reported PTSD symptoms (Suris et al., 2013).

Taken together, the recent Cochrane review of 12 studies that included PCT (Belsher et al., 2019) found PCT to be more effective than control conditions and failed to find that PCT was not inferior to trauma-focused CBT. Trauma-focused CBT resulted in stronger effects than PCT, although these differences decreased over time. PCT had approximately 14% lower treatment dropout rates compared to TF-CBT, suggesting that the treatment may be more tolerable. PCT is currently recommended in several CPGs.

Stress Inoculation Training

Stress inoculation training (SIT; Meichenbaum, 1985) is based on cognitive-emotional theories and involves the acquisition of coping skills for the management of anxiety symptoms (Meichenbaum, 1988). Structured exposure to a stressor is intended to build tolerance and a sense of mastery over anxiety in order to protect against future significant stressors. SIT can be implemented in group or individual formats and has been included as a comparator for other active treatments in several trials (Foa et al., 1991, 1999; Lee et al., 2002). A recent systematic review of PTSD treatments for adults determined that there is insufficient evidence to determine the efficacy of SIT (Cusack et al., 2016), and only the VA/DoD guideline includes SIT as a suggested treatment.

Interpersonal Psychotherapy

Interpersonal psychotherapy (IPT; Weissman, Markowitz, & Klerman, 2000, 2017) is a time-limited therapy initially developed to treat major depression and then adapted to address other psychiatric diagnoses, including PTSD. The theoretical framework of IPT posits that symptoms are a result of four interpersonal problem areas: grief, interpersonal role disputes, role transitions, or interpersonal deficits (Weissman et al., 2000). IPT for PTSD aims to increase social skills, reduce feelings of helplessness and demoralization, increase agency, facilitate corrective emotional experiences, and assist in generating adaptive coping strategies (Markowitz et al., 2009). IPT may be delivered in a group or individual format over the course of 8–16 sessions each lasting 1–2 hours. Several pilot studies and open trials of IPT for PTSD have been conducted (see Markowitz, Lipsitz, & Milrod, 2014, for a review), along with three RCTs. In a small sample of low-income women with multiple traumas, IPT showed greater reductions in PTSD and improvements in interpersonal functioning than wait list (Krupnick et al., 2008). Another small RCT found that IPT was superior to TAU in a sample of Sichuan earthquake survivors, with large effect sizes (Jiang et al., 2014). The only RCT to date comparing IPT to an active treatment compared IPT, PE, and relaxation in a community sample (Markowitz et al., 2015). IPT was noninferior to PE in reduction of PTSD symptoms, although improvements in IPT were not significantly different than relaxation, and remission rates were similar across groups. The VA/DoD CPG suggest the use of IPT, while ISTSS has determined that there is insufficient evidence for a recommendation at this time.

Skills Training in Affective and Interpersonal Regulation

Skills training in affective and interpersonal regulation (STAIR) is a cognitive-behavioral treatment developed to treat survivors of childhood abuse (Cloitre, Koenen, Cohen, & Han, 2002) in order to address affect dysregulation and interpersonal difficulties. STAIR is an eight-session skills training intervention adapted from dialectical behavior therapy (Linehan, 1993). The first four sessions focus on developing emotional regulation skills; the final four sessions concern addressing interpersonal problems. STAIR was developed with the idea that enhancing emotion regulation and building interpersonal effectiveness will increase readiness for, and success with, exposure therapy.

There are two published RCTs of STAIR as a preparatory treatment for exposure. The first study tested a phase-based treatment of STAIR followed by imaginal exposure and found that among women with childhood abuse-related PTSD, those in the active treatment condition showed significant improvements in affect regulation, interpersonal skills, and PTSD symptoms compared to wait list, with further symptom improvements at 9-month follow-up (Cloitre et al., 2002). The second RCT compared STAIR + exposure to two control conditions: supportive counseling + exposure and STAIR + supportive counseling (Cloitre et al., 2010). Posttreatment PTSD diagnostic status did not differ between treatment groups, but those receiving STAIR + exposure had lower rates of dropout and were more likely to achieve sustained PTSD remission at 3- and 6-month follow-up than those in support + exposure. Support for STAIR is inconsistent across CPGs. ISTSS issued a standard recommendation for cognitive-behavioral therapies without a trauma focus, such as STAIR. The American Psychological Association guidelines did not evaluate STAIR, while the VA/DoD CPG determined that there is

insufficient evidence to recommend STAIR as there are no published RCTs of STAIR as a stand-alone treatment for PTSD at this time.

CHALLENGES FOR THE FUTURE

The breadth and strength of evidence supporting a psychotherapy should be paramount in informing clinical decision making. However, it is worth remembering that the absence of evidence is not the same as evidence against a treatment and that newer treatments may prove to be as effective as established treatments as more evidence accumulates. Moreover, although most patients receiving first-line psychotherapy complete treatment and experience significant and lasting symptom reduction, there is considerable room for improvement. Dropout is a significant concern, not only in therapies designed to treat PTSD, but also in cognitive-behavioral therapy more broadly. In a meta-analysis examining the magnitude, timing, and moderators of dropout from CBTs, Fernandez, Salem, Swift, and Ramtahal (2015) found that approximately 16% of patients drop out of therapy prior to treatment and another 26% drop out after they've started. Estimates from meta-analytic PTSD studies suggest that approximately one out of five participants drop out of treatment prematurely (Imel, Laska, Jakupcak, & Simpson, 2013). In routine clinical care settings, dropout rates appear to be even higher, ranging from 38 to 68% (e.g., Garcia, Kelley, Rentz, & Lee, 2011; Kehle-Forbes, Meis, Spoont, & Polusny, 2016). One study found that many patients who terminate CPT early have experienced benefit (Szafranski, Smith, Gros, & Resick, 2017), but other evidence suggests that dropout is associated with treatment failure (Berke et al., 2019).

Optimizing Outcomes

Treatment optimization will require a better understanding of the underlying processes and mechanisms responsible for treatment change. Translational research and increased collaboration between basic and applied clinical research has potential to yield important insights that could inform treatment modifications and optimize outcomes. For example, there is accumulating evidence that PTSD treatment response is associated with changes in glucocorticoids and neurosteroids (e.g., Rauch et al., 2015), although how these factors relate to treatment change remains unclear. Integrated treatment outcome and biomarker studies (e.g., McLean et al., 2018) are well positioned to address this gap. Linking treatment response with biomarkers can allow mechanism-informed selection of critical treatment components. As unessential treatment components are identified and removed, treatments become more efficient, which could minimize dropout and hasten recovery. Increased efficiency of treatment improves acceptability for patients and clinicians, and can also increase access, by treating and terminating with patients more quickly.

Idiographic approaches to identifying patient demographic and clinical characteristics (e.g., gender, ethnic/racial groups, war era, trauma type, comorbidities) that predict treatment outcomes are also needed. Most RCTs are not powered for subgroup analyses that could determine which treatment works best for whom, so there is little evidence to guide clinicians on treatment selection. Studies that identify patient characteristics, ideally those that are easily measured pretreatment, could be leveraged to make clinically useful predictions about which treatment a given patient is most likely to complete and benefit from (Imel et al., 2013). Early work in this area has identified

univariate (Markowitz et al., 2015) and multivariate models (Keefe et al., 2018) of patient factors that predict differential risk of dropout in EBPs for PTSD. Further research on moderators of PTSD treatment is needed in order to develop treatment selection models that can increase the clinical impact of EBPs by matching them with patients who are most likely to benefit.

Engaging patients in treatment selection is another strategy to improve outcomes (Watts et al., 2015; Zoellner et al., 2018). Although RCTs assume clinical equipoise, most psychotherapies are likely sensitive to patient preference. A better understanding of how to incorporate patient preference in trials and leverage this effect in routine clinical care is needed.

Addressing Comorbidities

PTSD is a treatable disorder, even when comorbid with other disorders, clinical complexities, and extensive trauma histories and in novel clinical settings (see Norman et al., Chapter 24, this volume). Patients with comorbid disorders may prefer integrated treatments addressing multiple problems rather than treatment focused on single disorders (Schiøtz, Høst, & Frølich, 2016). Integrated therapies for PTSD and commonly co-occurring disorders (e.g., COPE; Back et al., 2019) provide an efficient model for addressing interrelated problems. Research is needed regarding how to best address many commonly comorbid disorders (e.g., sleep disorders, severe mental illness, substance use), including whether and how treatments should be combined, sequenced, or integrated to maximize outcomes.

Impairments in functioning represent important outcomes that are often overlooked or considered secondary in clinical trials, even though criterion G of PTSD stipulates that significant impairment in functioning is a requirement for the diagnosis of PTSD. The relative lack of attention to impairments in functioning is discrepant with patients' reports of the meaningfulness of these impairments in their lives. Future research should consider flexible applications or modifications of EBPs that are designed to specifically target functional impairment. Intentionally and thoughtfully building on the success of the skills acquired in EBPs and expanding those skills to specifically target functional outcomes warrant further exploration.

Increasing Reach

Despite publication of CPGs and provider training initiatives, estimates of EBPs' reach across mental health systems are low (Borah, Holder, Chen, & Gray, 2017; Rosen et al., 2017). The causes of major gaps in EBP implementation are beginning to be identified, but scalable solutions are urgently needed. Among all patients with PTSD, only some receive mental health treatment; fewer receive an EBP, an adequate dose, or significant benefit. The public health impact of EBPs for PTSD is a function of their efficacy and reach; future work must endeavor to make improvements on both fronts. This includes identifying strategies to minimize barriers for clinicians to learn and implement EBPs as well as strategies to increase the availability of EBPs to patients with PTSD. The emergence of telehealth, web programs, and mobile apps may serve to increase awareness and access to EBPs for PTSD (see Ruzek, Chapter 28, and Morland et al., Chapter 29, this volume). Studies comparing the effectiveness and relative merits of different dissemination and implementation models are needed. Models that go beyond training to address organizational factors such as policies and incentives, as well as leadership,

resources, and support that may facilitate or impede EBP use, are particularly needed to increase the likelihood of sustained adoption of best practices.

In sum, trauma-focused therapies, particularly PE, CPT, and EMDR, have to date shown the most evidence supporting their use in the treatment of PTSD. Numerous emerging, trauma-focused psychotherapies also show substantial promise and provide additional excellent treatment options. Non-trauma-focused therapies (e.g. SIT, PCT, and IPT) are effective alternatives when patients have no access to, or are reluctant to engage in, trauma-focused options. Treatments with more accumulated empirical support give us more confidence in their efficacy and effectiveness. However, patient attrition, failure to respond, and increasing reach and access are issues the field must continue to address.

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CHAPTER 20

Psychosocial Treatments for Children and Adolescents with PTSD

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METHODOLOGICAL CONSIDERATIONS

This chapter reviews the current status of evidence-based psychosocial treatments developed and tested for children and adolescents with posttraumatic stress disorder (PTSD; hereafter referred to as "children with PTSD"). Adult PTSD psychosocial treatments (e.g., prolonged exposure and cognitive processing therapy; see Galovski et al., Chapter 19, this volume) may be effective for some adolescents with PTSD, as discussed below, but developmental considerations unique to children with PTSD (e.g., the benefits of including parents or caregivers in treatment; the necessity of interfacing with multiple youth-serving systems during treatment) should be considered carefully when selecting an optimal treatment. *Evidence-based treatments* are defined here as those that have been tested through standard scientific methodology and found to effectively reduce children's PTSD diagnosis/symptoms. Treatment guidelines suggest that the strongest level of evidence for treatment efficacy derives from randomized controlled treatment trials, which, among other characteristics, include (1) clearly defined target symptoms, (2) reliable and valid measures, (3) unbiased assignment to two or more alternative treatment conditions, (4) equipoise among treatment conditions, (5) appropriate measures for ensuring treatment adherence, and (6) proper data-analytic procedure ensuring that all randomized and treated subjects are included and reported in data analyses (APA Working Group on Journal Article Reporting Standards, 2008; Schulz, Altman, Moher, & the CONSORT Group, 2010). Unique methodological challenges may occur when attempting to ensure that each of these conditions is met in child trauma treatment studies, as addressed below.

Recruitment Issues

Any treatment study's value depends on its ability to recruit and retain participants who are representative of other children with PTSD, therefore making the results more

generally applicable. In contrast to interventions for adults, children with PTSD themselves rarely seek treatment but instead are usually brought to treatment by parents or other caretaking adults (hereafter referred to as "parents"), and the decision to continue in treatment and/or to participate in research requires ongoing parental agreement/consent. In some situations (e.g., after a child discloses sexual abuse and receives an evaluation at a Child Advocacy Center), parents may specifically seek trauma-focused treatment. However, most parents of children with PTSD do not recognize or seek mental health treatment for their children's PTSD symptoms. Typically, these parents seek mental health intervention for their children's concerning behavioral or emotional problems (e.g., irritability, anger, noncompliance, sadness, anxiety) because these are the symptoms that parents or other adults can most easily observe. In some cases, parents may be aware that their children experienced past trauma, but in other cases, they have no knowledge of the extent or impact of their children's traumatic experiences. In either situation, parents are often surprised to receive referrals for trauma-focused treatment.

Having parents with personal trauma histories and PTSD symptoms is common among children with PTSD; therefore, addressing the parent's personal trauma cognitions and how they influence their support of the child is a core component of many child trauma interventions, as described below. However, for many parents, addressing past trauma experiences is too painful. Trauma avoidance is a core PTSD issue and may impact the parent's and/or child's willingness to agree to trauma treatment and/or research participation. Parents may refuse research participation due to their desire to protect the child and/or personally avoid addressing traumatic material. Avoidance may also lead the child and/or the parent to underreport the frequency or severity of trauma symptoms during the initial assessment. Assessors must be trained to account for this during assessment procedures.

CLEARLY DEFINING TARGET SYMPTOMS; SELECTING APPROPRIATE ASSESSMENT INSTRUMENTS

Methodological issues regarding the definition of child PTSD and assessment are beyond the scope of this chapter and are described in more detail elsewhere (Kisiel, Conradi, Fehrenback, Togersen, & Briggs, 2014; see Briggs et al., Chapter 17, this volume). Despite the reality that many children experience multiple traumatic events and often cannot connect some PTSD symptoms to specific event(s), DSM criteria require that this be done. This is adequate for studies evaluating the impact of treatment on a specified trauma type, but it is less appropriate for treatments that address multiple or chronic PTSD traumatic experiences. Appropriate assessment strategies and definitions of target symptoms must be developed for children with multiple/chronic traumatic experiences, who appear to comprise the majority of treatment-seeking children with PTSD.

PTSD symptoms in young children are manifested differently than the way they are in older children and adults. As noted elsewhere (see Friedman et al., Chapter 2, this volume), developmentally sensitive PTSD diagnostic criteria have been established in DSM-5 (American Psychiatric Association, 2013) for children 6 and under, including a reduction in the number of symptoms needed to meet diagnostic thresholds. Researchers must use age-appropriate criteria and developmentally adapted assessment instruments to assess PTSD symptoms in these children.

Traumatic experiences impact children in multiple domains other than PTSD. For this reason, researchers should consider assessing other outcomes, in addition to PTSD, such as externalizing, internalizing, and/or sexualized behavior problems, attachment difficulties, or other outcomes of interest. Assessors must be carefully trained to achieve reliability standards using these alternative algorithms before starting the study.

Unbiased Assignment to Alternative Treatments

A critical issue is selecting appropriate comparison treatment conditions that are (1) theoretically sound and effective for traumatized children; (2) acceptable to families; (3) of duration and intensity equivalent to that of the index treatment; and (4) well defined, in that they have a treatment manual, structured training, and fidelity monitoring. In most *clinical* settings, a wait-list control condition would not meet these requirements. In nonclinical settings, such as schools or refugee camps, wait-list control conditions are often acceptable, since usual care in these settings typically does not include the provision of mental health treatment. However, a wait-list control condition is more likely to produce significant differences from the treatment being studied than selecting an alternative active treatment; as we discuss later, researchers should be aware that this will limit the generalizability of findings. Once treatment conditions are selected, the comparison condition must receive an equivalent amount and quality of training, supervision, and attention to fidelity to that of the index treatment throughout the course of the study.

Treatment Adherence

Child trauma treatment frequently requires the therapist to manage children's behavioral crises ("crises of the week"), placement disruption, and other significant life issues that may impinge on the therapist's ability to follow a strict treatment protocol. Allowing some flexibility and time for case management within defined limits of treatment fidelity is necessary in order to provide effective treatment that can be generalized to the broader population of children with PTSD. For example, if the child discloses abuse perpetrated by the parent participating in treatment or his or her current partner, this scenario creates both treatment and research challenges that study personnel must be trained to manage sensitively. When crises arise, the therapist must balance the demands of the treatment protocol to maintain fidelity with the need to manage the crisis.

CURRENT STATE OF THE ART

In the past 25 years, the number of evidence-based treatments for child PTSD has grown from none to more than 20. These include psychodynamic/attachment-based treatments (Lieberman, Ippen, & Marans, 2009), individual child–parent cognitive-behavioral treatments (Cohen, Mannarino, Deblinger, & Berliner, 2009; Ruf et al., 2010; Smith et al., 2007), and group-based treatments provided in schools and other settings (Jaycox, Stein, & Amaya-Jackson, 2009; Jensen, Cohen, Jaycox, & Rosner, 2020).

Before we describe specific models, it is important to recognize that most effective treatments for child PTSD share several common core concepts and components (National Child Traumatic Stress Network [NCTSN] Core Concepts and Curriculum Workgroup, 2013). These evidence-based treatments:

1. Include parents or other important caregivers in recognition of both the disruption that trauma often causes in central attachment relationships and the vital role that parents have in correcting this.
2. Provide phase-based treatment that typically includes (a) initial stabilization skills, (b) trauma narration and cognitive processing, and (c) treatment consolidation/closure.
3. Address complex domains impacted by childhood trauma exposure.

Including Parents in Evidence-Based Treatments

Most children live in the context of families. Secure attachments with protective and loving parents form the basis for positive emotional, physical, and social child development. It is a sad reality that some children with the most severe PTSD have experienced early, multiple interpersonal traumas such as child maltreatment and domestic and/or community violence. These intentional acts perpetrated by members of the family or extended community from whom the child expects protection often lead to loss of safety, attachment disruption, and a sense of betrayal. Most evidence-based trauma treatments for children include parents or other caregivers, such as direct care staff in residential treatment facilities, as a critical way to reverse these negative impacts (i.e., to build safety and trust, and to heal disruptions in primary attachment relationships). Addressing and correcting attachment disruptions caused by early interpersonal trauma (and, by extension, including a parent or caregiver in the treatment process) is a core feature of psychodynamic attachment treatments such as child–parent psychotherapy (CPP); and is one of several central components for individual child and parent cognitive-behavioral therapies (CBTs), such as trauma-focused cognitive-behavioral therapy (TF-CBT). In contrast, this is a peripheral or optional component for group models that often do not include parents, such as cognitive-behavioral interventions for trauma in schools (CBITS). As noted earlier, in some cases, the parents themselves have significant trauma experiences and PTSD (or other mental health) symptoms. Addressing these symptoms and helping the parent provide more effective, supportive parenting is often one of the most significant impacts (as well as one of the largest challenges) of providing trauma-focused child psychotherapy.

Phase-Based Treatment

As described in earlier chapters in this volume, PTSD impacts children across many functional domains, resulting in dysregulation of affect, behavior, biological functioning (e.g., sleep–wake cycles, eating, pain management, and immunological status), interpersonal relationships, and cognitions (see Copeland & McGinnis, Chapter 5, this volume). Phase-based treatment provides the opportunity for children to gain self-regulation skills in these important areas and helps parents enhance their understanding and support of their children with regard to trauma impact. This important work occurs before children embark on the difficult work of describing and processing their personal trauma experiences. Providing an initial skills-building (stabilization) phase is particularly critical for children who have experienced chronic, interpersonal ("complex") traumatic events. These youths often are the most dysregulated and may require more stabilization before moving on to trauma narration and processing. After these phases have been completed, a final consolidation phase encourages the child and parents to integrate and apply what they each have learned during previous phases, and to work together to move toward treatment closure.

Addressing Complex Trauma Outcomes

In addition to PTSD, most of the evidence-based treatments described here address multiple other outcomes, including disruptions in trust, attachments, and relationships with others; affective regulation problems such as depression, anxiety, anger, or severe affective dysregulation; behavioral regulation problems such as problem sexual behaviors or externalizing behavior problems, substance abuse, or self-injury; cognitive and perceptive problems such as dissociation; changes in biological functioning; and problems with school and learning, and/or problems with adaptive functioning. This array of problems is sometimes referred to as "complex PTSD" or "complex trauma," and although not included in DSM-5, the proposed ICD-11 diagnostic criteria include both PTSD and complex PTSD. Children with these complicated outcomes present diagnostic challenges, as trauma exposure also significantly increases the risk for youth to subsequently develop a variety of psychiatric disorders other than PTSD (e.g., McLaughlin et al., 2012). Regardless of diagnosis, helping children to gain affective, behavioral, and cognitive regulation and to improve the quality of their relationships with others is critical in ensuring positive, long-term outcomes.

The following sections describe three prototypical treatment models for child PTSD with the strongest current evidence bases: a dyadic psychodynamic/attachment model (CPP); a parallel child and parent CBT model (TF-CBT) that can be provided individually or in groups; and a school-based group treatment model (CBITS). For each model we describe theoretical underpinnings, target symptoms and problems the model addresses; age, trauma types, or settings; treatment components or principles; and treatment–outcome data. For more comprehensive information about other evidence-based and promising treatments for childhood PTSD, readers may refer to the California Clearinghouse for Evidence-Based Practices for Child Welfare (*www.cebc4cw.org*) for scientific ratings of efficacy; or the NCTSN's treatment intervention pages for descriptive information about a variety of effective and promising practices (*www.nctsn.org/treatments-and-practices/trauma-treatments/interventions*).

Psychodynamic/Attachment-Based Treatment: CPP

Psychodynamic trauma-focused, evidence-based treatments focus on promoting growth and healthy development, as well as symptom resolution. For children with PTSD, the therapist accomplishes this by making meaning of the child's traumatic experiences. The therapist follows the free play of younger children and the spontaneous expressions of older children to promote coherence and cognitive mastery of overwhelming emotional responses to traumatic experiences, as well as to correct misperceptions and promote reality testing. For younger children, parents are included as allies during the treatment and participate either during the child's session or in their own individual conjoint sessions (Lieberman et al., 2009).

CPP (Lieberman & van Horn, 2008), a dyadic model based on psychodynamic attachment principles, views the child–parent relationship as the best change agent for addressing young children's traumatic attachment disruption and related trauma impacts. Target symptoms and problems of CPP include child PTSD and externalizing behavior problems, as well as problems in the child–parent attachment relationship for children ages 0–7 years and their primary caregiver. Types of traumatic experiences include domestic violence, traumatic death, and other types of interpersonal violence. CPP is typically provided in home or clinic settings, in English or Spanish, and lasts for

40–50 treatment sessions. All CPP treatment sessions include the child–parent dyad, with some additional sessions provided for the parent alone, if indicated.

CPP focuses on decreasing maladaptive behaviors, supporting developmentally appropriate interactions, and assisting the child and parent in developing a joint trauma narrative. The CPP therapist sees the child and parent together in all CPP treatment sessions. The child–parent interactions guide the course of the CPP. The CPP therapist observes and actively interprets these interactions. Goals include directing the dyadic interactions in more positive and adaptive ways; helping the child and parent to better understand each other and develop a more positive relationship; improving regulation of behavior and affect; and adjusting unhelpful interactions, behaviors, and beliefs. CPP addresses disruptions of the child's biological rhythms (e.g., sleep, eating), dangerous and aggressive behaviors, as well as punitive and critical parenting and the relationship with the perpetrator of the violence and/or absent parent.

One randomized controlled trial of CPP examined PTSD outcomes. Lieberman, van Horn, and Ippen (2005) randomized 75 children ages 3–5 years who had witnessed their mothers' domestic violence, and their mothers who were the direct victims of the victimization, to CPP or to case management plus referral to individual treatment as usual in the community. Families were from diverse ethnic backgrounds, and most had experienced other traumas. At posttreatment, children receiving CPP showed significantly greater reductions in total behavior problems and PTSD symptoms; mothers also showed significant improvement in PTSD avoidant symptoms. At 6-month follow-up, child behavior problems and maternal symptoms continued to differ significantly between the two groups (Lieberman, Ippen, & van Horn, 2006).

Several related models fall under the CPP "umbrella," including infant–parent psychotherapy, toddler–parent psychotherapy, and preschooler–parent psychotherapy. These models have examined many constructs relevant to child maltreatment (e.g., young children's mental representations of self and parent; secure attachment), but none has specifically evaluated PTSD outcomes in children.

Parallel Child and Parent CBT: TF-CBT

Similar to psychodynamic treatments, evidence-based cognitive-behavioral treatment for traumatized children and their parents focuses on both improving children's symptomatic functioning and promoting long-term healthy relationships, growth, and development. Like psychodynamic therapy, CBT includes parents in treatment; the degree to which this is true varies according to the model, with some models, such as TF-CBT (Cohen, Mannarino, & Deblinger, 2017; *www.tfcbt2.musc.edu*), providing as much treatment time for parents as for children. However, in contrast to CPP, in which all sessions include the child and parent interacting together, in TF-CBT, the parent and child are seen in individual or group, parallel sessions, with some conjoint child–parent sessions included toward the end of treatment. As the name suggests, TF-CBT focuses both on overcoming traumatic avoidance through graduated exposure to trauma reminders and memories and on exploring the meaning (cognitions) that children and parents form related to traumatic experiences and reevaluating maladaptive understandings about these experiences and their connections with negative affective states and behaviors. TF-CBT is relatively structured and time limited, with specifically designated treatment components that have a well-defined order and time frame in which the components are to be provided.

TF-CBT is a CBT approach that also incorporates attachment, family, developmental, neurobiological, and empowerment principles. TF-CBT is appropriate for children who have experienced any type of traumatic experience, including complex/multiple traumas, and for their nonoffending parents or primary caregivers. TF-CBT was developed to address the multiple impacts of trauma, including PTSD, affective, biological, behavioral, cognitive, dissociation, and relationship problems, as well as adaptive functioning. TF-CBT is appropriate for children ages 3–18 years. It is typically provided over the course of 12–20 sessions in outpatient clinic settings, but it is also provided in home, school, refugee camp, residential treatment, inpatient and juvenile justice settings. The TF-CBT treatment components, summarized by the acronym PRACTICE, include Psychoeducation; parenting skills; Relaxation skills; Affect modulation skills; Cognitive processing skills; Trauma narration and processing; *In vivo* mastery of trauma reminders; Conjoint child–parent sessions; and Enhancing safety and future developmental trajectory.

Like CPP, TF-CBT includes parents as critical change agents during treatment, in recognition of the central role of attachment in developing and healing trauma-related problems. During most TF-CBT sessions, parents and children are seen in parallel individual or group sessions to enable them to openly communicate their most difficult trauma-related feelings and thoughts to the therapist. After processing these feelings and thoughts during separate sessions, the child and parents come together for several conjoint dyadic sessions. TF-CBT includes gradual exposure throughout each component to address children's learned and generalized trauma avoidance.

TF-CBT is a phase-based treatment. The first phase includes several coping skills to help children reregulate affective, behavioral, biological, and cognitive trauma impacts. The second phase includes trauma narration, in which children develop a detailed narrative about their trauma experiences and process trauma-related cognitions. Children with complex PTSD develop a narrative around a trauma theme that unifies specific traumatic experiences and episodes that are included and processed within the narrative. The final phase helps the children and parents to integrate the earlier components and move toward treatment closure. When TF-CBT is provided in group format, therapists meet individually with each child during individual breakout sessions to develop and process the child's individual trauma narrative, and in child–parent dyads so that the child only shares the narrative with their own parent (Deblinger, Pollio, & Dorsey, 2015). TF-CBT also has specific components to address traumatic grief (Cohen et al., 2017) and traumatic separation (Cohen & Mannarino, 2019).

TF-CBT is the most tested child trauma treatment, with 11 completed individual randomized controlled trials (Cohen, Deblinger, Mannarino, & Steer, 2004; Cohen & Mannarino, 1996; Cohen, Mannarino, & Iyengar, 2011; Cohen, Mannarino, & Knudsen, 2005; Deblinger, Lippman, & Steer, 1998; Deblinger, Mannarino, Cohen, Runyon, & Steer, 2011; Diehle, Opmeer, Boer, Mannarino, & Lindauer, 2015; Dorsey et al., 2019; Goldbeck, Muche, Sachser, Tutus, & Rosner, 2016, Jensen et al., 2013; King et al., 2000; Murray et al., 2015), and four completed group randomized controlled trials (Deblinger, Stauffer, & Steer, 2001; McMullen, O'Callaghan, Shannon, Black, & Eaken, 2013; O'Callaghan, McMullen, Shannon, Rafferty & Black, 2013) summarized in Table 20.1. Results indicate that TF-CBT consistently is superior to active comparison conditions for reducing PTSD diagnosis and symptoms in children, as well as affective problems (depression, anxiety, and fear), behavior problems (internalized, externalized, total behavior, and problem sexual behaviors), cognitive problems, dissociation, and relationship and adaptive functioning.

TABLE 20.1. Summary of TF-CBT Randomized Controlled Trials

Sample (reference)	Ages (yr)	N^a	Index treatment; comparison[b]	Major findings
Individual studies				
Sexually abused children (Deblinger, Lippman, & Steer, 1998)	8–14	100	22 community TAU 22 TF-CBT, parent 24 TF-CBT, child 22 TF-CBT, parent + child	TF-CBT to child significantly more effective than TAU for PTSD; TF-CBT to parent significantly more effective than TAU for child depression, behavior problems, and parenting skills.
Sexually abused preschoolers (Cohen & Mannarino, 1996)	3–6	86	28 NST 39 TF-CBT	TF-CBT significantly more effective than NST for PTSD, internalizing and sexualized behavior problems, and parental emotional distress and support of child, which mediated child improvement.
Sexually abused children with multiple trauma (Cohen, Deblinger, Mannarino, & Steer, 2004)	8–14	203	91 CCT 89 TF-CBT	TF-CBT significantly more effective than CCT for PTSD, depression, behavior problems, and shame; and for parenting skills, parental support of child, parental depression, and parental distress related to child's abuse.
Australian sexually abused children (King et al., 2000)	5–17	36	12 TF-CBT, child 12 TF-CBT, family 12 WL	TF-CBT significantly more effective than WL for PTSD; family TF-CBT significantly more effective than child TF-CBT for fear.
Sexually abused children (Cohen, Mannarino, & Knudsen, 2005)	8–14	82	41 TF-CBT 41 NST	TF-CBT significantly more effective than NST for social competence and depression posttreatment; PTSD and dissociation at 12 months.
Sexually abused children (Deblinger et al., 2011) Dismantling study with or without TF-CBT TN component and treatment length	4–11	210	TF-CBT with 44 8-week no TN 43 8-week yes TN 44 16-week no TN 48 16-week yes TN	All effective at improving PTSD; 8-week, yet TN most effective and efficient for improving high fear, anxiety, and parental distress; 16-week no TN more effective for improving high behavior problems and parenting skills.
DV with multiple traumas, conducted in community DV center (Cohen, Mannarino, & Iyengar, 2011)	7–14	124	60 CCT, 8 sessions 64 TF-CBT, 8 sessions both provided in community DV center	TF-CBT significantly more effective than CCT for PTSD and anxiety.
Norwegian children with multiple traumas, conducted in community mental health clinics (Jensen et al., 2013)	10–18	156	79 TF-CBT 77 TAU	TF-CBT significantly more effective than TAU for PTSD, depression, general mental health, and adaptive functioning.

(continued)

TABLE 20.1. *(continued)*

Sample (reference)	Ages (yr)	N^a	Index treatment; comparison[b]	Major findings
Traumatized Dutch children (Diehle, Opmeer, Boer, Mannarino, & Lindauer, 2015)	8–18	48	24 TF-CBT 24 EMDR, 8 sessions, 1 hour	TF-CBT and EMDR equally effective and efficient in improving PTSD symptoms; TF-CBT significantly superior for improving children's depressive and ADHD symptoms
Multiply traumatized, HIV-affected Zambian children, conducted at community sites, provided by trained lay counselors (Murray et al, 2015)	5–18	257	131 TF-CBT 126 UCC, 10–16 sessions, length of sessions flexible to accommodate cultural needs of setting	TF-CBT significantly superior to UCC for improving PTSD and adaptive impairment
Traumatized German children in community clinics (Goldbeck, Muche, Sachser, Titus, & Rosner, 2016; Sachser, Keller, & Goldbeck, 2016)	7–17	159	76 TF-CBT, 12 sessions; 83 WL	TF-CBT significantly superior to WL for improving PTSD symptoms, maladaptive cognitions, adaptive functioning, depressive, anxiety and behavioral symptoms but not quality of life. Using proposed ICD-11 complex PTSD diagnostic criteria, improvement in PTSD symptoms was comparable for youth with standard PTSD vs. youth with complex PTSD who received TF-CBT.
Group studies				
Sexually abused preschoolers (Deblinger, Stauffer, & Steer, 2001)	2–8	44	21 TF-CBT group 22 supportive group	TF-CBT group significantly more effective than supportive group for children's safety knowledge and parental PTSD symptoms
Sexually exploited, war-exposed Congolese girls (O'Callahan et al., 2013)	12–17	52	24 TF-CBT group 28 WL	TF-CBT significantly superior to WL for improving PTSD, anxiety, depression, conduct symptoms, and prosocial behavior
War-exposed Congolese boys (McMullen et al., 2013)	13–17	50	25 TF-CBT group 25 WL	TF-CBT significantly superior to WL for improving PTSD, depression, anxiety, conduct symptoms, and prosocial behaviors
Traumatized orphans in rural and urban Tanzania and Kenya (Dorsey et al., 2020)	5–17	640	320 TF-CBT group 320 UC	TF-CBT significantly superior to UC for improving PTSD and maladaptive grief in urban and rural Kenya and urban Tanzania, but not rural Tanzania

Note. ADHD, attention-deficit/hyperactivity disorder; CCT, child-centered therapy; EMDR, eye movement desensitization and reprocessing; HIV, human immunodeficiency virus; ICD-11, *International Classification of Diseases,* 11th edition; NST, nondirective supportive therapy; TAU, treatment as usual; TF-CBT, trauma-focused cognitive-behavioral therapy; TN, trauma narration and processing component; UC, usual care; UCC, usual community care; WL, waitlist.

Notable among these investigations was a recent large study in Africa, which documented that TF-CBT provided by trained lay counselors was superior to usual care for HIV-affected youth in improving PTSD and adaptive functioning (Murray et al., 2015); and two randomized controlled treatment studies that provided evidence for the effectiveness of group TF-CBT provided by trained lay counselors in the Democratic Republic of Congo. The first study documented that, compared to a wait list, TF-CBT led to significantly greater improvement in PTSD, depression, and externalizing behavior problems for former male soldiers (McMullen et al, 2013). The second study documented similar superior outcomes for sex-trafficked girls in the Democratic Republic of Congo who received group TF-CBT compared to a wait-list control group (O'Callaghan et al., 2013). Another study found that group TF-CBT provided by lay counselors was superior to usual care for improving PTSD and prolonged grief symptoms in three of the four sites where it was evaluated in Africa (Dorsey et al., 2020).

Group School-Based Therapy: CBITS

Most children attend school. Offering treatment in the school setting overcomes access issues for many parents or other caregivers who would not take their children to treatment in a clinic setting due to stigma, insurance or transportation issues, or other barriers. Providing treatment in groups may also help children to feel less isolated and stigmatized about having experienced trauma or trauma symptoms. Limitations of school-based treatment include the fact that schools usually do not approve of therapists addressing intrafamilial traumas, such as child abuse or domestic violence, and parents often do not participate in school-based treatments. School-based group treatment models therefore typically focus on community violence, accidents, disasters, or traumatic grief (although once children are participating in group treatment, they may spontaneously address other types of traumas as well) and make parental participation optional.

CBITS (Jaycox, 2004) is the most widely used school-based intervention for child PTSD. It was initially designed to address the impact of PTSD and secondarily, depression, on middle school children following community violence. However, early during its implementation, it became clear that participating children had experienced multiple other types of traumas (e.g., family violence, traumatic loss). CBITS includes the PRACTICE components described earlier. The skills components are provided in approximately five or six group sessions. Each child in the group then receives two individual "breakout" sessions with the group therapist, during which he or she develops a brief individual trauma narrative. The group then reconvenes to complete the final treatment components. Optional parent and teacher sessions are also provided during which parents and teachers learn about trauma impact and help children use the skills they are learning in the group. CBITS has been tested in one randomized controlled trial that documented its superiority to a wait-list control group for improving PTSD and depression (Stein et al., 2003). A modified version for primary school-age children, Bounce Back, has been tested in a randomized controlled trial with children in grades K–5 experiencing significant improvement in child- and parent-reported PTSD as well as depressive and anxiety symptoms (Langley, Gonzalez, Sugar, Solis, & Jaycox, 2015). CBITS has been successfully implemented in schools after community disasters (e.g., Hurricane Katrina; Jaycox et al., 2010). A pilot study suggests that CBITS also can be successfully implemented by trained, non-mental-health educational professionals (e.g.,

school counselors, teachers) working with children who have less severe PTSD symptoms (Jaycox et al., 2009).

Schools may be particularly critical for delivering trauma-focused treatments after community disasters that often not only severely impact children but also may lead to serious morbidity or death of parents, thus limiting typical access to outpatient mental health treatment. Others in the community besides parents may be injured, killed, or develop severe PTSD or other mental health symptoms, and community infrastructure may be damaged or destroyed (e.g., after Hurricane Katrina), making it more difficult to access services (including mental health services) in usual locations. Schools are often among the first facilities to reopen after these incidents, providing children with a needed sense of safety, continuity, and community, and they often provide a setting in which children may access needed services that they otherwise might not receive. For example, following Hurricane Katrina, a study that offered children CBITS in schools or TF-CBT in clinics found that although both groups experienced significant improvements in PTSD and depressive outcomes, school treatment was far more accessible (Jaycox et al., 2010).

DO CURRENT FINDINGS APPLY MORE GENERALLY?

The generalizability of a treatment model increases as the model has been tested with populations that are most representative and in settings where these individuals most often are served. There is substantial evidence that current findings apply more generally. For example, CPP was tested among ethnically diverse children whose mothers had experienced multiple trauma exposures; treatment was provided at a community hospital known for serving populations with high levels of trauma exposure and PTSD severity. All of these factors contributed to high generalizability of CPP findings. Since the children in CBITS school studies were identified through universal schoolwide screening for trauma exposure and symptoms rather than among those seeking treatment, they were highly representative of the child trauma population. TF-CBT has outperformed other treatments in usual settings (e.g., community domestic violence setting; foster care; community clinics). This treatment has also included diverse settings, developmental levels, cultures, trauma types, and format (e.g., individually or in groups) and been delivered by lay counselors, thus providing direct evidence of general applicability. Although not yet supported by empirical evidence, it is likely that the same generalizability will hold true for other evidence-based child trauma treatments and that these treatments also will be effective for diverse populations of children and adolescents with PTSD. However, evidence-based child trauma treatments need to be further tested and refined for use in at least two important populations.

One question related to generalizability is the degree to which PTSD treatments originally designed for adults might be effective for children and/or adolescents. Three adult models have been examined in this regard. A pilot study compared an adult trauma-focused evidence-based treatment, eye movement desensitization and reprocessing (EMDR), to TF-CBT for 48 Dutch children ages 8–18 years, hypothesizing that EMDR would be superior in terms of efficiency but equivalent in terms of efficacy in improving PTSD symptoms for youth. Secondary hypotheses explored relative efficacy for other outcomes (symptoms of depression and attention-deficit/hyperactivity disorder [ADHD]). This study failed to find significant differences between EMDR and

TF-CBT efficiency or efficacy for children or teens but documented that TF-CBT was superior for improving co-occurring depressive and ADHD symptoms (Diehle et al., 2015). Two adult treatments have been examined with adolescent populations. Prolonged exposure therapy adapted for adolescents (PE-A) was found to be superior to supportive therapy in one randomized controlled trial for improving PTSD among adolescents (ages12–18 years) who were victims of rape (Foa, McLean, Capaldi, & Rosenfield, 2013). Developmentally adapted cognitive processing therapy for adolescents (D-CPT) was evaluated for young people (ages 14–21 years, mean age 18.1 years) and found to be superior to wait list with treatment advice (WL/TA) for improving PTSD and other symptoms (Rosner et al., 2019). The older age of youth in the latter study raises questions about the applicability to adolescent populations.

Scant empirical information is available to guide the treatment of children who have PTSD with comorbid conditions. Given the high risk of children developing other mental health disorders after trauma exposure, conducting scientific studies about how best to time the delivery of trauma-focused with other evidence-based treatments for children who have PTSD with other comorbid disorder(s); and/or how to tailor current evidence-based trauma treatments to address comorbidities, is a pressingly urgent priority. As we have noted in our review, several studies have documented that evidence-based treatments for PTSD also effectively decrease other mental health symptoms (e.g., depression: Cohen et al., 2004, 2005; Deblinger et al., 1998; Jaycox et al., 2010; Jensen et al., 2020; Stein et al., 2003; anxiety: Cohen et al., 2011; Deblinger et al., 2011; King et al., 2000; behavior problems: Cohen & Mannarino, 1996; Cohen et al., 2004; Deblinger et al., 1998, 2011; Lieberman & van Horn, 2008), but it is important to note that none of these studies required children to meet diagnostic criteria for any comorbid disorders nor reported on how many met diagnostic criteria for disorders other than PTSD. In a TF-CBT dismantling study, it was found that young children who initially presented with high externalizing behavioral symptoms experienced significantly greater improvement in these symptoms if they received TF-CBT *without* the trauma narrative component (i.e., more focus on behavioral stabilization and parenting skills), whereas children who initially presented with higher anxiety or fear experienced significantly greater improvement in these symptoms if they received TF-CBT *with* the trauma narrative (i.e., focus on desensitization to trauma-specific fears; Deblinger et al., 2011). However, children in this study were not required to have comorbid diagnoses. Studies are needed to address optimal treatment strategies for the many children who have PTSD co-occurring with other mental health disorders, particularly depression, substance abuse, and/or externalizing behavior disorders.

Despite the fact that many traumatized children currently receive pharmacological treatment combined with psychosocial treatment, very little is known about the effectiveness of such combined treatment. One pilot study examined the impact of TF-CBT + sertraline versus TF-CBT + placebo (Cohen, Mannarino, Perel, & Staron, 2007). Although adding sertraline to TF-CBT did not result in significant benefit (children in both conditions experienced significant and comparable improvement with regard to PTSD diagnosis and symptoms), the study was underpowered to detect significant differences between the two conditions. Another RCT evaluated the relative benefits of adding the partial NDMA agonist D-cycloserine versus placebo to CBT but failed to find significant differences for improving pediatric PTSD (Scheeringa & Weems, 2014). No other studies have evaluated the impact of either combined psychosocial and pharmacological treatment or the sequential impact of pharmacological and psychosocial

treatments (e.g., pharmacological treatment for psychosocial nonresponders or vice versa). Given the high rate of psychotropic prescribing for traumatized children (e.g., children in foster care; U.S. General Accountability Office, 2011) and the lack of efficacy of psychotropic medication for improving childhood PTSD, these are also critical issues to address.

Community clinicians often express concern about whether evidence-based treatments are effective for children who have experienced multiple, chronic traumas that began in early childhood. (These children may or may not meet current DSM criteria for PTSD, depending on who does the assessment and how strongly the assessor weighs the child's trauma history as an etiological factor relative to other factors.) All of the treatments we describe have been used for youth with complex trauma exposure and have shown positive outcomes in terms of both PTSD and other complex trauma outcomes; TF-CBT was documented to be effective for improving outcomes in youth who met the proposed ICD-11 complex PTSD criteria (Sachser, Keller, & Goldbeck, 2016). As we describe next, challenges remain with regard to helping therapists understand how to apply these models to the children they see in usual community practice and how to engage families in trauma-focused treatment.

CHALLENGES FOR THE FUTURE

Challenges remain in providing effective psychosocial treatment to children with PTSD. These therapies include dissemination and implementation, prevention, and neurobiological impact of psychosocial treatments.

One of the most important challenges is learning how to best disseminate and implement existing evidence-based treatments to community therapists who are most likely to encounter children with PTSD in usual care settings. No matter how effective current treatments are, or how well they apply to children with PTSD in general, they will not be helpful if therapists do not use them in clinical practice. Evidence suggests that dissemination is a slow process: The time from initial publication of a randomized trial to community adoption of the treatment is 17 years (Berwick, 2003). Successful initiatives are currently evaluating a variety of dissemination and implementation models, including the Institute for Healthcare Improvement (*www.ihi.org*) learning collaborative method, most notably implemented through the Substance Abuse and Mental Health Administration-funded NCTSN; distance learning methods; and training and consultation programs funded by a variety of states and public and private organizations. A number of these evidence-based treatment programs have instituted Train the Trainer and Train the Supervisor programs in order to enhance long-term sustainability at organizational, local, and/or state levels. Some data suggest that these strategies have been effective in widely disseminating evidence-based treatments for children with PTSD. As one example, the Medical University of South Carolina offered a free TF-CBT distance learning course, TF-CBTWeb, for 12 years, during which it attracted an increasing number of users each month, with more than 350,000 users from 150 countries when the course transitioned to its second version in 2018.

Yet it is not enough for many mental health professionals to learn about evidence-based treatments for children with PTSD; we must also ensure that they implement and sustain the practice with adequate fidelity (see Stirman, Chapter 32, this volume). Developing the methodology to support effective implementation is still in its early

stage, but it appears that one-time training is less effective than providing ongoing support to help therapists learn how to implement evidence-based models for their own clients. A randomized clinical trial of TF-CBT dissemination/implementation for adjudicated youth in residential treatment facilities documented that providing both web-based and live training with ongoing expert consultation calls was significantly more effective than web-based training and consultation alone in facilitating therapists' ability to conduct trauma screening, to use TF-CBT with fidelity, and to complete TF-CBT treatment in these settings (Cohen et al., 2016).

Another challenge is learning whether PTSD can be prevented soon after exposure to trauma or even earlier (e.g., through resiliency skills training), developing and testing such interventions, and identifying optimal candidates to receive it. More research is needed with regard to early identification and prevention of children at risk and development of true preventive psychosocial interventions for children at risk of developing PTSD. A new study is implementing an algorithm to identify children at greatest risk for developing subsequent PTSD at the time of initial trauma exposure (e.g., in pediatric emergency departments), in order to provide early preventive interventions before these youth develop acute PTSD (Schreiber, 2018).

Finally, as we have described, although the psychological manifestations of PTSD improve with psychosocial treatments, it is also critical to document whether the neurobiological changes associated with PTSD revert to normal with effective psychosocial treatments. Studies are starting to demonstrate these changes when children receive evidence-based trauma-focused treatment (e.g., pre- to post-TF-CBT treatment improvement in PTSD symptoms was correlated with pre-to posttreatment activation in posterior cingulate, midcingulate, and hippocampus areas; Garrett et al., 2019). Identifying biomarkers for child PTSD may emerge from such research and allow for identification and early preventive intervention for children at risk.

In summary, in 25 years, the child trauma field has made enormous progress. In this period, researchers have increased the number of evidence-based treatments for child PTSD from zero to more than 20. At the time of this writing, the treatments with the strongest evidence from among psychodynamic/attachment, child and parent cognitive-behavioral, and group school-based treatments are, respectively, CPP, TF-CBT, and CBITS. Distance learning is making great strides in disseminating these treatments, so that they are more accessible to the thousands of children who are impacted by trauma each year. More research is critical to improve treatment for children with PTSD and coexisting psychiatric conditions, to clarify the place of psychotropic medications in the treatment of children with PTSD, and to improve implementation science. The best is yet to come for transforming the lives of children with PTSD through improved, effective psychosocial treatments.

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CHAPTER 21

Empirically Supported Couple and Family Therapies for PTSD

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The association between posttraumatic stress disorder (PTSD) symptoms and myriad couple and family problems is well established (for meta-analyses, see Birkley, Eckhardt, & Dyskstra, 2016; Taft, Watkins, Stafford, Street, & Monson, 2011). In addition, PTSD symptoms are associated with individual mental health problems in spouses and children (for meta-analyses, see Lambert, Engh, Hasbun, & Holzer, 2012; Lambert, Holzer, & Hasbun, 2014). Accumulating data indicate that couple and family functioning are associated with PTSD treatment seeking, delivery, and outcomes. Individuals with PTSD who have healthier intimate and familial relationships are more likely to seek individual treatment for PTSD (Meis, Barry, Kehle, Erbes, & Polusny, 2010) and to profit from existing individual evidence-based treatments when they receive them (Evans, Cowlishaw, Forbes, Parslow, & Lewis, 2010; Meis et al., 2019; Monson, Rodriguez, & Warner, 2005; Price, Gros, Strachan, Ruggiero, & Acierno, 2011; Tarrier, Sommerfield, & Pilgrim, 1999). Meanwhile, there is minimal evidence that individual PTSD treatments improve couple and family functioning, and even some evidence of worsening in these relationships at posttreatment (Glynn et al., 1999; Lunney & Schnurr, 2007; Monson, Fredman, et al., 2012).

Consequently, efforts have been made to innovate and test couple and family interventions for PTSD that facilitate treatment engagement, improve individual PTSD symptoms, enhance couple and family functioning, and enhance the mental health and well-being of family members. This chapter outlines a heuristic for clinicians and researchers to consider when including couple/family interventions in the treatment of PTSD; organizes the interventions that have been empirically tested to date according to this framework; and offers challenges and suggestions for future research.

A HEURISTIC FOR CONCEPTUALIZING THE INCLUSION OF FAMILY MEMBERS IN PTSD INTERVENTIONS

Research on couple/family interventions for PTSD has lagged behind research on individual interventions. A variety of factors have likely contributed to this lag, including some traumatized individuals who do not have intimate partners/family members to participate in therapy (or are reluctant to include them in treatment) and belong to health care systems and benefit plans that do not include couple and family therapy as part of their care. There is also more complexity in conducting couple and family treatment trials (i.e., scheduling sessions with more people, collecting outcome data from multiple participants, and analyzing nested data). In addition, there is a smaller pool of researchers with interest and expertise in couple/family intervention trials. Yet, the past 15 years have seen substantial advances in the development and testing of these interventions. These advances have brought greater clarity to understanding how partners and family members can be incorporated to improve PTSD treatment delivery and therapeutic outcomes.

When discussing couple/family interventions for any mental health condition, including PTSD, it is important to consider the target of the intervention. Are the target improvements in family functioning, PTSD symptoms, or both? Or is there another target, such as utilizing the family member to engage the individual in treatment? In this chapter, we describe a heuristic that we have previously introduced (Monson, Macdonald, & Brown-Bowers, 2012) to help researchers and clinicians consider how to include family members in interventions for PTSD (see Figure 21.1). Interventions are organized based on an interaction of their focus of improving relational functioning and/or PTSD. The specific objectives and desired outcomes of these interventions differ based on the manner in which family members are included in the interventions. All of the interventions discussed here fall into the broader category of couple/family therapy in that they address the close relational system in which the individual with PTSD exists. Our heuristic expands on Baucom, Shoham, Mueser, Daiuto, and Stickle's (1998) prior conceptualization of empirically supported couple and family therapies for adult mental health problems by considering the range of concerned loved ones such as parents, siblings, close friends, and extended family that the patient with PTSD might consider "family." Some interventions reviewed below specifically target the couple relationship within the family, whereas others include other types of family members. When reviewing these therapies, we describe the therapy format (e.g., couple or family) according to the authors' description. An additional extension of this framework is that we take into account interventions that are not designed to explicitly improve PTSD or another mental health condition or relationship problem but may be used to enhance treatment delivery by increasing family knowledge or support in the provision of other treatments. As noted in the lower right-hand quadrant of Figure 21.1, family members may be used to engage loved ones in assessment and treatment or to educate them about PTSD and the rationale for evidence-based treatments. Improvements in PTSD symptoms or relationship functioning are not the targets of the intervention; rather, *engagement* and/or *education* are the goals. This is important in the case of PTSD because many people do not access PTSD treatment in the first place, drop out of treatment prematurely, or only partially respond to our existing treatments.

Family members may be involved in what we term generic or general couple or family therapy with the PTSD patient. This approach has the single goal of improving relationship functioning and is generally how clinicians have conceptualized the

TARGET: ENHANCE RELATIONSHIP	TARGET: IMPROVE PTSD: Yes	TARGET: IMPROVE PTSD: No
Yes	**Disorder-Specific Couple/Family Therapy** Cognitive-behavioral conjoint therapy for PTSD (Monson & Fredman, 2012) Couple treatment for addiction and PTSD (Schumm et al., 2015) Strategic approach therapy (Sautter et al., 2009) Emotionally focused couple therapy (Johnson, 2002)	**Generic Couple/Family Therapy** Behavioral couple therapy (Jacobson & Margolin, 1979) Behavioral family therapy (Mueser & Glynn, 1995) K'oach program (Rabin & Nardi, 1991) REACH program (Sherman et al., 2009)
No	**Partner-Assisted Therapy** Lifestyle Management Course (Devilly, 2002)	**Family Education and Facilitated Engagement** Support and Family Education Program (Sherman, 2003)

FIGURE 21.1. Empirically supported couple/family interventions for PTSD according to treatment target.

inclusion of couple/family therapy for adults with mental health problems. Improvements in relationship functioning may, in fact, improve a patient's PTSD symptoms and the health and well-being of family members by decreasing the ambient stress in their interpersonal environment. However, the objective of including the family members is to improve the relational milieu in which the patient and their family exist and does not specifically target the mechanisms thought to maintain the individual disorder. In this way, couple/family therapy is adjunctive to other interventions designed to address PTSD symptoms.

Family members may also be involved in partner-assisted interventions in which the family member serves as a surrogate coach or therapist for the patient. These interventions aim to facilitate the patient's treatment by educating family members about the rationale for therapy so that they can actively support the patient in treatment or enhance therapies typically delivered in an individual format. Relational issues are not the focus of these interventions; supported delivery of the individual intervention(s) is the goal.

Finally, family members may participate in disorder-specific family therapies, that is, therapies that have been specifically developed with the simultaneous goals of improving relationship functioning as well as PTSD. To be maximally efficient in the therapy, the interventions are generally developed to target mechanisms known to contribute to the development and maintenance of PTSD *and* relational distress. The relationship is the patient, and the ways in which the family members are interacting are conceptualized to contribute to the maintenance of PTSD symptoms and relationship distress.

Although the mental health and well-being of loved ones are not specific outcomes of the interventions, some of these interventions have, in fact, yielded improvements in family members' health and well-being and are reported where available. Given the

state of research on couple/family therapy for PTSD, we used the following specific inclusion criteria when reviewing studies for this chapter: (1) objective outcome data were analyzed at the group level, (2) results were published (including as theses or dissertations), and (3) the interventions tested included the patient with PTSD and at least one other adult family member for at least one session of treatment, except for the treatment engagement/education cell. Because of this cell's focus on engaging the patient with PTSD into treatment, inclusion for this cell only required published, group-level data analysis. Theoretical writings, individual case studies, and presentations were not included in this review.

EFFICACY OF INTERVENTIONS BY TYPE OF INVOLVEMENT STRATEGY

Table 21.1 includes a summary of evidence regarding outcomes related to the stated intervention target (i.e., individual PTSD outcome and/or relationship adjustment outcome). Consistent with the description above, we begin with those interventions designed to improve treatment engagement in assessment and treatment of PTSD or knowledge about PTSD.

Education and Engagement

Support and Family Education Program

The Support and Family Education (SAFE) program is a multisession educational program for families of veterans in the United States VA system grappling with a wide range of mental illnesses (e.g., PTSD, major depression, bipolar disorder, schizophrenia; Sherman, 2003). The intervention involves various family members (e.g., spouse, parent, siblings) in 14 sessions of educational material covering a range of topics for loved ones of a person with a mental illness, and 4 sessions of skills training in problem solving and minimizing stress. Because this is an educational program, the material is provided in once-monthly, 90-minute workshops, and attendance is based on family member interest.

In a 5-year program evaluation, Sherman (2006) reported on 127 family members who participated in at least one workshop (average 6.5 sessions); 53% of those who attended more than one session had a loved one with PTSD. Participant satisfaction was high (18.2 out of a possible high score of 20), and there was a positive correlation between the number of sessions attended and understanding of mental illness, awareness of U.S. VA resources, and ability to engage in self-care activities. Caregiver distress was negatively correlated with the number of sessions attended. No data regarding patient PTSD or other mental health outcomes for the family members or veterans, or rates of veteran engagement in treatment were reported.

PTSD Family Education

Sautter, Glynn, Cretu, Senturk, and Vaught (2015) created PTSD Family Education (PFE) as a control condition in their randomized controlled trial (RCT) of structured approach therapy (SAT; Sautter, Glynn, Thompson, Franklin, & Han 2009). PFE tested in this trial consisted of 12 60-minute conjoint sessions adapted from SAFE and the family education sections of behavioral family therapy (BFT; Mueser & Glynn, 1999;

described below). The protocol required clinicians to avoid skills training and other therapeutic interventions. PFE resulted in significant improvements in clinician-assessed and veteran-reported PTSD symptoms, but 93% of veterans still met diagnostic criteria for PTSD at the end of follow-up (compared with 52% in SAT). PFE did not result in improvements in veterans' or partners' reported anxiety, depression, relationship adjustment, or intimate relationship attachment problems.

Generic Couple/Family Therapy

Behavioral Couple/Family Therapy

We use the abbreviation BCT (behavioral couple therapy) when referring to studies involving couples only and BFT (behavioral family therapy) in those studies involving a range of family members. Whether applied to couples or families more broadly, BCT/BFT generally involves behavioral exercises to increase positive, reinforcing exchanges in couples and families, as well as communication skills training (i.e., sharing thoughts and feelings, problem solving; Jacobson & Margolin, 1979). BCT has been identified as an empirically supported practice for general couple distress according to treatment guidelines (e.g., Sexton et al., 2011).

Two completed RCTs have tested variants of generic BCT/BFT with PTSD patients. Both of these studies were conducted with samples of male combat veterans and their family members. In a dissertation study, Sweany (1987) compared generic group BCT with a wait list control. Compared with those on the wait list, veterans and their female partners receiving BCT experienced significant self-reported improvements in relationship satisfaction and significant partner-reported improvements in veterans' PTSD symptoms. In a larger controlled trial, Glynn and colleagues (1999) tested the incremental utility of sequentially adding BFT focused on improving communication and problem-solving skills (Mueser & Glynn, 1999) to directed therapeutic exposure (DTE; Carroll & Foy, 1992). Thus, veterans and one of their family members (89% conjugal partners) were randomized to DTE alone, DTE→BFT, or a wait list. Participants in the active treatment conditions improved more than those on the wait list in regard to what the authors refer to as "positive" PTSD symptoms (i.e., reexperiencing, hyperarousal) but not the "negative" symptoms of PTSD (i.e., avoidance, numbing) or social adjustment. Participants who completed DTE → BFT also showed statistically significant improvements in interpersonal problem solving compared with DTE only.

There has been one uncontrolled study of group BCT with veterans. Cahoon (1984) reported the results of a 7-week group BCT focused on communication and problem-solving training for combat veterans and their female partners. Group leaders reported statistically significant improvements in veterans' PTSD symptoms and coping abilities, and female partners reported significant improvements in relationship satisfaction and problem-solving communication skills. The veterans did not report improvements in relationship functioning.

K'oach Program

The Israeli K'oach program is an intensive treatment program for combat veterans with PTSD in which wives are included at several points during the program (Rabin & Nardi, 1991; Solomon, Bleich, Shoham, Nardi, & Kotler, 1992). The program includes psychoeducation about PTSD, plus communication and problem-solving skills training

TABLE 21.1. Couple/Family Interventions for PTSD

Citation	Conditions tested	Study characteristics	Key findings
Family-facilitated engagement and education for PTSD			
Support and Family Education (SAFE) program			
Sherman (2003, 2006)	SAFE	• Sample: 115 family members of U.S. veterans with mental health disorders, including PTSD (n = 39) • Family: spouse, parent, siblings • Single condition, no randomization • Assessment pretreatment and posttreatment (varied depending on how many sessions family member attended), 5-year follow-up	• At posttreatment, family members reported high satisfaction with the program, and program attendance was positively associated with improvements in family members' self-care • In a 5-year follow-up, program attendance was positively associated with understanding of mental illness, awareness of VA resources, and engagement in self-care activities and negatively associated with caregiver distress
PTSD Family Education (PFE)			
Sautter, Glynn, Cretu, Senturk, & Vaught (2015)	SAT (reviewed below) versus PFE	• Sample: 57 Operation Iraqi Freedom (OIF) and Enduring Freedom (OEF) male U.S. veterans • Family: 57 female spouses/partners • Random assignment • Assessments at pretreatment, posttreatment and 3-month follow-up	• PFE resulted in significant improvements in clinician-assessed and veteran-reported PTSD symptoms, but 93% of veterans diagnosed with PTSD at follow-up • PFE did not improve veterans' or partners' reported anxiety or depression • PFE did not improve veterans' or partners' relationship adjustment or intimate relationship attachment problems
Generic family interventions for PTSD			
Behavioral couple/family therapy (BC/FT)			
Sweany (1987)	Group BCT versus wait list	• Sample: 14 male U.S. veterans with PTSD • Family: 14 female spouses/partners • Random assignment • Assessments at pretreatment and posttreatment	• Veterans and partners receiving BCT experienced significant improvements in relationship satisfaction compared with wait list • Significant partner-reported improvements in PTSD symptoms for BCT compared with wait list
Cahoon (1984)	Group BCT	• Sample: 60 male U.S. veterans with PTSD • Family: 60 female spouses/partners • Single condition, no randomization • Assessments pretreatment and posttreatment	• Decreases in group-leader assessed PTSD symptoms • Partners reported significant improvements in relationship satisfaction and problem-solving communication skills

Glynn et al. (1999)	Individual directed therapeutic exposure (DTE) versus DTE followed by BFT versus wait list	• Sample: 42 male U.S. veterans with PTSD • Family: 42 spouses/partners, siblings, or parents • Random assignment to condition • Assessments at pretreatment, posttreatment, and 6 months posttreatment	• Significant improvements in PTSD reexperiencing and hyperarousal symptoms for DTE and DTE→BFT compared with wait list • DTE→BFT had significantly improved interpersonal problem solving compared with DTE and wait list
Rabin & Nardi (1991); Solomon, Bleich, Shoham, Nardi, & Kotler (1992)	K'oach	• Sample: 40 male Israeli veterans with PTSD • Family: 26 female spouses • Single condition, no randomization (follow-up analyses compared Ko'ach group with control condition of veterans with PTSD) • Assessments at pretreatment, posttreatment, and 9 months posttreatment	• 68% of the veterans and their wives reported relationship improvements • No significant decreases in veterans' PTSD symptoms from pre- to posttreatment • At 9-month follow-up comparison, K'oach participants had more severe PTSD symptoms compared with quasi-control group
Sherman, Fischer, Sorocco, & McFarlane (2009); Fischer, Sherman, Owen, & Han (2013)	REACH	• Sample: 100 mostly male U.S. veterans with PTSD • Family: 96 family members (mostly women: 96%; mostly intimate partners: 91%) • Single condition, no randomization • Assessments at pretreatment and at the end of each treatment phase	• Significant improvements in veteran-reported levels of knowledge of PTSD, coping with PTSD, levels of empowerment, social support, depression, and quality of life from pre- to posttreatment (no significant changes in family problem solving and communication or intimate relationship satisfaction) • Significant improvements in all of the above outcomes for family members from pre- to posttreatment
Family-assisted interventions for PTSD			
Lifestyle Management Course (LMC)			
Devilly (2002)	LMC	• Sample: 111 male Australian veterans with PTSD • Family: 98 female partners • Single condition, no randomization • Assessments at pretreatment, 3 months posttreatment, and 6 months posttreatment	• Reduced PTSD symptoms in veterans • Reduced anxiety, depression, and stress in both veterans and partners • No significant improvements in relationship satisfaction

(continued)

TABLE 21.1. *(continued)*

Citation	Conditions tested	Study characteristics	Key findings
Disorder-specific interventions for PTSD			
Cognitive-behavioral conjoint therapy for PTSD (CBCT for PTSD)			
Monson, Schnurr, Stevens, & Guthrie (2004); Monson, Stevens, & Schnurr (2005)	CBCT for PTSD	• Sample: 7 male veterans diagnosed with combat-related PTSD and their female partners • Family: Spouses/partners • Single condition, no randomization • Assessments at pre- and posttreatment	• Significant improvements in PTSD • No significant improvements in Veterans' relationship satisfaction • Significant improvements in partners' relationship satisfaction, general anxiety, and social functioning
Monson et al. (2011)	CBCT for PTSD	• Sample: 6 male and female community members with PTSD and their partners • Family: Spouses/partners • Single condition, no randomization • Assessments at pre- and posttreatment	• Significant improvements in PTSD • Significant improvements in partners' relationship satisfaction
Monson et al. (2012); Fredman et al. (2016); Landy, Pukay-Martin, Vorstenbosch, Torbit, & Monson (2015); Macdonald, Pukay-Martin, Wagner, Fredman, & Monson (2016); Shnaider, Pukay-Matin, Fredman, Macdonaled, & Monson (2014); Shnaider et al. (2015); Shnaider, Sijercic, Wanklyn, Suvak, & Monson (2017); Wagner et al. (2016)	CBCT for PTSD vs. wait list	• Sample: 40 male and female community members with PTSD • Family: 40 male and female spouses/partners • Random assignment to CBCT for PTSD or wait list • Assessments at pretreatment, posttreatment, and 3 months posttreatment	• Significant improvements in PTSD for CBCT for PTSD compared with wait list • Significant improvements in PTSD symptom clusters and maladaptive cognitions for CBCT for PTSD compared with wait list • Significant improvements in posttraumatic growth for CBCT for PTSD compared with wait list • Significant improvements in PTSD patients' relationship satisfaction for CBCT for PTSD compared with wait list • Treatment gains in the CBCT for PTSD condition maintained at 3-month follow-up • At higher levels of baseline partner accommodation, greater improvements in patients' PTSD, depression, and relationship satisfaction in CBCT for PTSD compared with wait list • Higher perceived partner social support associated with larger decreases in PTSD severity for those in CBCT for PTSD condition but not those in the wait-list condition • Significant improvements in partners' mental health among those experiencing clinical levels of psychological distress at baseline

			• Gains in PTSD symptoms not predicted by pretreatment patient or partner relationship satisfaction • Participants who were in the relationally dissatisfied range prior to treatment experienced greater gains in relationship satisfaction relative to those who were not relationally distressed at baseline • Significant improvements in parenting competence among participants who were parents
Schumm, Fredman, Monson, & Chard (2013	CBCT for PTSD	• Sample: 6 male Iraq or Afghanistan U.S. veterans with PTSD • Family: 6 female spouses/partners • Single condition, no randomization • Assessments at pretreatment and posttreatment	• Significant improvements in PTSD symptoms
Pukay-Martin et al. (2015)	Present-centered CBCT for PTSD	• Sample: 7 male and female community members with PTSD • Family: Spouses/partners • Single condition, no randomization • Assessments at pretreatment and posttreatment	• Significant improvements in patients' PTSD symptoms • Significant improvement in partners' relationship satisfaction
Fredman et al. (in press)	Abbreviated, intensive, multicouple group CBCT for PTSD	• Sample: 24 mostly male (96%) U.S. post-9/11 active-duty service members and veterans with PTSD • Family: Spouses/partners • Single condition, no randomization • Assessments at pretreatment, 2-week postretreat, 1-month postretreat, and 3-months postretreat	• Significant improvements in patients' PTSD symptoms at each assessment point, with gains increasing over the follow-up period • Significant improvements in partners' depressive symptoms, anxiety, and relationship satisfaction by 3-months post-retreat
Couple treatment for addiction and PTSD (CTAP)			
Schumm, Monson, O'Farrell, Gustin, & Chard (2015)	CTAP	• Sample: 9 male U.S. veterans with PTSD • Family: 9 female spouses/partners • Single condition, no randomization • Assessment at pretreatment and posttreatment	• Significant improvements in veterans' PTSD severity • Significant improvements in veterans' days of heavy drinking • Significant improvements in veterans' and partners' depression • No significant improvements in veterans' or partners' relationship adjustment

(continued)

TABLE 21.1. *(continued)*

Citation	Conditions tested	Study characteristics	Key findings
Disorder-specific interventions for PTSD *(continued)*			
Strategic approach therapy (SAT)			
Sautter, Glynn, Thompson, Franklin, & Han (2009)	SAT	• Sample: 6 male U.S. Vietnam veterans with PTSD • Family: 6 female spouses • Single condition, no randomization • Assessments at pretreatment and posttreatment	• Significant improvements in total PTSD, avoidance, and numbing symptoms pre- to posttreatment • Relationship functioning not reported
Sautter, Glynn, Arseneau, &Yufik (2014)	SAT	• Sample: 7 male Iraq/Afghanistan U.S. veterans with PTSD • Family: 7 female spouses • Single condition, no randomization • Assessments at pretreatment and posttreatment	• Significant improvements in total PTSD symptoms • No significant improvements in veterans' or spouses' relationship adjustment • Decreases in spouses' anxiety
Sautter, Glynn, Cretu, Senturk, & Vaught (2015); Sautter et al. (2016)	SAT vs. PFE	• Sample: 57 (all male but 1 female) Iraq/Afghanistan U.S. veterans with PTSD • Family: 57 (all female but 1 male) spouses/partners • Random assignment to SAT or PFE • Assessments at pretreatment, posttreatment, and 12-week follow-up	• Significant improvements in veterans' PTSD symptoms for SAT compared with PFE • Significant improvements in veterans' relationship adjustment, attachment avoidance, and state anxiety for SAT compared with PFE • Significant improvement in partners' attachment anxiety, but not relationship adjustment, state anxiety or depression, for SAT compared with PFE, • Superiority of SAT relative to PFE attributable to improvements in emotion regulation and fear of emotions among patients in SAT condition

Emotionally focused couple therapy for trauma (EFCT)			
Macintosh & Johnson (2008)	EFCT	• Sample: 10 females with childhood sexual abuse history • Family: 10 male spouses/partners • Single condition, no randomization • Assessments at pretreatment and posttreatment	• All patients evidenced clinician-rated improvements in PTSD; 50% self-reported improvements in PTSD • 50% of participants reported improvements in relationship satisfaction; three couples reported decreased satisfaction and increased emotional abuse
Weissman et al. (2018)	EFCT	• Sample: 15 male U.S. veterans with PTSD • Family: 15 female partners • Single condition, no randomization • Assessment at pretreatment and posttreatment	• 53% of couples did not complete treatment • Among completers, veterans' self-reported PTSD symptoms improved, but no significant improvements in clinician-rated PTSD, relationship satisfaction, depression, general life satisfaction, or global distress • Among completers, partners' relationship satisfaction, general life satisfaction, and depression improved
Dalton, Greenman, Classen, & Johnson (2013)	EFCT vs. wait list	• Sample: 24 females with childhood abuse history • Family: 24 male spouses/partners • Random assignment to EFCT vs. wait list • Assessments at pretreatment and posttreatment	• Couples recruited were all relationally distressed • Significant improvements in overall relationship adjustment (and females' relationship adjustment) compared with wait list • No significant improvements in trauma-related symptoms compared with wait list

for the couples. Some outcome data have been reported on the program. In one study, 68% of the male veterans and their wives reported relationship improvements but there were no decreases in veterans' PTSD symptoms (Solomon et al., 1992).

Reaching Out to Educate and Assist Caring, Healthy Families Program

The Reaching out to Educate and Assist Caring, Healthy Families (REACH) program is based on a multifamily group model adapted for U.S. veterans living with PTSD and mood disorders (Sherman, Fischer, Sorocco, & McFarlane, 2009). REACH has three phases. Phase I consists of four single-family sessions focused on rapport building and goal setting. Phase II consists of six weekly 90-minute sessions for cohorts of four to six veterans and their families. These sessions include a focus on problem-solving skills, psychoeducation about symptom management, communication skills training, depression and stress management, and anger/conflict resolution. In Phase III, veterans and their families attend six monthly multifamily groups to support maintenance of gains.

Program evaluation of REACH found high levels of attendance, retention, and participant satisfaction (Sherman et al., 2009). Research with 100 (99% male) U.S. veterans with PTSD and their family members showed significant improvements on veteran-reported knowledge of PTSD, coping with PTSD, levels of empowerment, social support, depression, anxiety, and quality of life from pre- to posttreatment (no significant changes in family problem solving and communication or intimate relationship satisfaction). Family members reported improvements in all of the outcomes noted above from pre- to posttreatment (Fischer, Sherman, Owen, & Han, 2013).

Partner-Assisted Intervention

Lifestyle Management Course

Devilly (2002) described the results of an uncontrolled study of Australian combat veterans and their partners who participated in an intensive week-long residential group intervention that included psychoeducation about PTSD and PTSD symptom management techniques. At follow-up, both veterans and their partners reported significant, but small, reductions in anxiety, depression, and stress; Veterans reported a significant reduction in PTSD symptoms. Small improvements were also observed for anger and quality of life but not for relationship satisfaction.

Disorder-Specific Interventions

Cognitive-Behavioral Conjoint Therapy for PTSD

Cognitive-behavioral conjoint therapy (CBCT) for PTSD is a 15-session, manualized therapy developed by Monson and Fredman (2012) that is designed to simultaneously improve PTSD symptoms and enhance relationship functioning. It is composed of three phases: (1) psychoeducation about PTSD and its impact on relationships and increasing safety, (2) communication-skills training and dyad-oriented approach exercises to overcome behavioral and experiential avoidance, and (3) cognitive interventions aimed at changing problematic trauma appraisals and beliefs most relevant to the maintenance of PTSD and relationship problems (e.g., acceptance, blame, intimacy).

Three uncontrolled studies with Vietnam veterans (Monson, Schnurr, Stevens, & Guthrie, 2004), Iraq and Afghanistan War veterans (Schumm, Fredman, Monson, &

Chard, 2013), and community members (Monson et al., 2011) and their intimate partners indicate improvements in PTSD symptoms and relationship functioning in couples who may or may not be clinically distressed at the outset of therapy. Improvements in partners' mental health symptoms have also been found (Monson, Stevens, & Shnurr, 2005).

An RCT of CBCT for PTSD was completed with a sample of individuals with a range of traumatic events and different types of intimate couples (i.e., married, cohabitating, noncohabitating, same sex; Monson, Fredman, et al., 2012). This trial found significant improvements in PTSD and comorbid symptoms for CBCT for PTSD compared with the wait list, with treatment effects similar to those found in individual evidence-based treatment for PTSD. There was also a significant improvement in patient reports of relationship satisfaction, though not partner reports of relationship satisfaction, which were maintained at 3-month follow-up. Improvements have also been observed for PTSD symptom clusters and maladaptive trauma-related cognitions (Macdonald, Pukay-Martin, Wagner, Fredman, & Monson, 2016), partners' mental health (Shnaider, Pukay-Martin, Fredman, Macdonald, & Monson, 2014), patients' posttraumatic growth (Wagner et al., 2016), and parenting competence (Landy, Pukay-Martin, Vorstenbosch, Torbit, & Monson, 2015).

Examination of potential treatment moderators of CBCT has provided knowledge about which patients may be especially likely to profit from the treatment. For example, Fredman and colleagues (2016) found that partners' baseline accommodation of patients' PTSD symptoms (i.e., the extent to which partners report altering their own behaviors to reduce patient distress and/or PTSD-related relationship conflict; Fredman, Vorstenbosch, Macdonald, Wagner, & Monson, 2014) moderates treatment outcomes for patients undergoing CBCT for PTSD. Specifically, the beneficial effects of CBCT for PTSD relative to wait list with respect to patients' PTSD symptoms, depression, and relationship satisfaction were more pronounced among patients whose partners engaged in higher levels of accommodation compared with those who engaged in lower levels. Relatedly, Shnaider, Sijercic, Wanklyn, Suvak, and Monson (2017) demonstrated that patients with higher levels of perceived social support from their partners at baseline were especially likely to benefit from CBCT for PTSD. Finally, Shnaider and colleagues (2015) found that neither patient nor partner pretreatment relationship satisfaction predicted PTSD outcomes but that participants who were relationally distressed prior to treatment experienced larger improvements in relationship satisfaction by the end of treatment relative to those who were relationally satisfied at baseline.

Pukay-Martin and colleagues (2015) investigated a present-centered version of CBCT for PTSD in a sample of seven community couples. This version of CBCT for PTSD includes psychoeducation and safety building, behavioral strategies to enhance relationship satisfaction and improve communication, and cognitive interventions to address here-and-now maladaptive thoughts but no direct historical reappraisals of the trauma itself. There were significant and medium-to-large decreases in patients' PTSD symptoms, along with significant and medium effect size improvements in partners' relationship satisfaction and accommodation of patients' PTSD symptoms. Findings suggest that this version of CBCT for PTSD may be a viable alternative for patients (or couples) who are not willing to engage in a trauma-focused treatment.

In an effort to increase treatment efficiency and scalability, Fredman and colleagues (2020) tested an abbreviated, intensive, multicouple group version of CBCT for PTSD (AIM-CBCT for PTSD) in a sample of 24 couples that included an active-duty service member or veteran who had served in the post-9/11 conflict and was diagnosed

with PTSD. Treatment consisted of the first seven sessions of CBCT for PTSD delivered over a single weekend to groups consisting of two to six couples at a time. All 24 couples completed treatment. By the 3-month follow-up assessment, there were significant and large reductions in patients' PTSD and significant and moderate or moderate-to-large reductions in comorbid symptoms. There were also significant improvements in partners' depressive and anxiety symptoms and relationship satisfaction.

Couple Treatment for Addiction and PTSD

Couple treatment for addiction and PTSD (CTAP) is a 15-session protocol that integrates CBCT for PTSD (Monson & Fredman, 2012) with behavioral couples therapy for substance use disorders (O'Farrell & Fals-Stewart, 2006). In an uncontrolled study, eight of nine U.S. veterans with PTSD showed clinically significant improvements in their PTSD severity (Schumm et al., 2015). Significant reductions in clinician-rated, veteran-rated, and partner-rated PTSD severity were found. There were also significant improvements in veterans' days of heavy drinking; six veterans had clinically reliable reductions in this outcome. Veterans and partners had significant improvements in depression. Findings were mixed with respect to relationship outcomes, with a similar proportion showing improvements versus deterioration, and the group-level findings were nonsignificant.

Structured Approach Therapy

In the prior edition of this chapter, we categorized structured approach therapy (SAT) as a partner-assisted intervention. Based on emerging evidence of its efficacy in improving relationship satisfaction, we recategorized SAT as a disorder-specific intervention. SAT is a 10- to 12-session manualized BCT originally developed by Sautter and colleagues (2009) to target the avoidance/numbing symptoms of PTSD. The intervention consists of psychoeducation about PTSD and strategies for enhancing motivation for treatment, behavior exchange to reinforce the expression of behaviors associated with positive emotions and intimacy, and partner assistance in approaching and tolerating feared stimuli.

Findings from six male U.S. Vietnam-era combat veterans and their female partners who completed a 10-session version of the intervention include significant improvements in total PTSD symptoms according to patient, partner, and clinician ratings. However, when clinician-assessed symptom clusters were examined, there were only changes in emotional numbing and avoidance symptoms, but not reexperiencing or hyperarousal symptoms (Sautter et al., 2009). A subsequent study of seven male U.S. Iraq/Afghanistan War veterans and their wives also found significant reductions in both self- and clinician-related PTSD symptoms (Sautter, Glynn, Arseneau, Cretu & Yufik, 2014). There were also significant decreases in spousal anxiety. Although there were no overall significant improvements in relationship adjustment in either partner, seven of nine participants who were relationally distressed at pretreatment evidenced clinically significant improvements in relationship adjustment.

An RCT compared SAT to PFE described above for U.S. Iraq/Afghanistan veterans with PTSD and their intimate partners (Sautter, Glynn, Cretu, Senturk, & Vaught, 2015). In the sample of 57 couples, SAT was statistically superior to PFE in reducing veterans' clinician-rated and self-reported PTSD symptoms at posttreatment and 3-month follow-up. SAT was also superior to PFE in improving veterans' general anxiety and

depression. With regard to relationship outcomes, veterans receiving SAT reported significant improvements in their relationship adjustment and attachment avoidance compared with PFE. Only partners' relationship anxiety, but not relationship adjustment, improved in SAT compared with PFE. Follow-up analyses indicated that the superiority of SAT versus PFE in PTSD symptoms was attributable to greater improvements in emotion dysregulation and fear of emotions among patients in the SAT group relative to those receiving PFE (Sautter et al., 2016).

Emotionally Focused Couple Therapy

Emotionally focused couple therapy (EFCT) is a short-term (12 to 20 sessions), experiential intervention with a focus on understanding and processing emotions that are connected to the traumatic experience and the broader attachment behaviors and styles that affect relational processes and communication (Johnson, 2002). EFCT is divided into three main stages that focus on (1) stabilizing the couple through the assessment, identification, and sharing of negative interaction patterns, (2) building relational skills in the couple through acceptance and communication, and (3) integrating therapeutic gains by developing coping strategies and better interaction patterns.

A study of 10 heterosexual couples, including an adult woman who had experienced childhood sexual abuse, provided initial support for the efficacy of EFCT (Macintosh & Johnson, 2008). In that study, the couples completed between 11 and 26 sessions of therapy and completed assessments at pre- and posttreatment. All participants experienced at least one standard deviation worth of improvements on clinician-assessed PTSD symptoms and that half of the participants self-reported clinically significant improvements in PTSD symptoms. Also, half of the participants self-reported clinically significant improvements in relationship satisfaction. Three couples who reported decreased satisfaction and increased emotional abuse terminated their relationships during the course of therapy. The authors suggested that EFCT for trauma may not be appropriate for couples in which there is emotional abuse.

Weissman and colleagues (2018) conducted an uncontrolled trial investigating EFCT with 15 U.S. veterans diagnosed with PTSD and their intimate partners. Only seven of the couples completed treatment (26 to 36 weekly sessions). For those veterans and their partners who completed treatment, there were no significant improvements in veterans' clinician-rated PTSD symptoms, relationship satisfaction, depression, general life satisfaction or global psychological distress at posttreatment (though some were approaching significance). There were significant improvements in the veterans' self-reported PTSD symptoms. Partners reported significant improvements in their relationship satisfaction, general life satisfaction, and depression at posttreatment. The authors noted that the substantial dropout in this study is of concern and that five of the eight couples who were excluded were required to withdraw due to alcohol/drug abuse (exclusion criteria for this study).

An RCT with 24 couples was conducted to more rigorously examine the efficacy of EFCT for improving relationship satisfaction in heterosexual couples, including women with childhood physical or sexual abuse (Dalton, Greenman, Classen, & Johnson, 2013). Couples were randomized to 24 sessions of EFCT or a delayed treatment wait list. This study's inclusion criteria differed from most in this review because couples were recruited on the basis of experiencing clinically significant relationship distress and a female partner who had suffered childhood abuse but may or may not have been diagnosed with PTSD (PTSD diagnosis was not established or used as inclusion

criterion). There was no dropout in the group receiving EFCT immediately. There were significant improvements in relationship adjustment for the male and female partners combined at posttreatment compared with wait list (only female partners' relationship adjustment was subsequently tested separately and found to be significantly improved). However, no significant improvements in the EFCT group compared with wait list in trauma-related symptoms, as measured with the Trauma Symptom Inventory (Briere, 1995) and Dissociative Experiences Scale (Bernstein & Putnam, 1986).

CONCLUSIONS AND FUTURE DIRECTIONS

There is growing recognition of the larger interpersonal context in which PTSD exists, as well as a desire to build and test interventions that include family members from that larger interpersonal network to improve PTSD, relationship functioning, and/or the health and well-being of those affected by PTSD. In this chapter, we reviewed a heuristic for conceptualizing how family members might be incorporated in PTSD interventions. The available data suggest that psychoeducational programs specific to PTSD do not necessarily improve PTSD or relational functioning but do increase significant others' knowledge about mental health, awareness of resources, and perhaps their own self-care. Future research might determine if these programs facilitate the delivery of PTSD treatments (e.g., decrease dropout, increase treatment engagement) or perhaps yield other symptom or functional outcomes.

Given the number and specific types of barriers that exist for patients with PTSD to present for assessment and treatment (for a review, see Kantor, Knefel, & Lueger-Schuster, 2017) and the number of family members who want to help but are unsure how to approach their loved one, and/or may "help" in inadvertently detrimental ways (e.g., accommodating or co-dependent behaviors that reinforce PTSD-related avoidance), methods to engage those with PTSD are still needed. "Coaching into Care" is a telephone-based support service designed to help family members of U.S. veterans to encourage veterans with mental health issues to access their health care benefits. The intervention is designed to provide support to family members and to help the family member plan and implement an informed, noncoercive approach when talking with a troubled veteran about seeking or resuming VA mental health care. Program evaluation indicates that Coaching into Care may have moderate success in getting veterans to engage in mental health care (Picanso et al., 2017).

There are not yet much data to support partner-assisted methods in PTSD treatment, although more recently efforts have been made to incorporate significant others into evidence-based treatments for PTSD (Meis et al., 2013). We look forward to seeing if these efforts prove fruitful in improving the tolerance, engagement, and outcomes for existing individual evidence-based therapies for PTSD. As expected, given the target of the intervention, studies of generic BCT or BFT with patients and their families have generally yielded improved relationship functioning but provide minimal evidence regarding significant improvements in PTSD symptoms. Regarding disorder-specific interventions for PTSD, there are accumulating data to support the efficacy of CBCT and SAT in simultaneously improving PTSD and relationship adjustment. Initial research on CBCT for PTSD also shows that this intervention improves PTSD regardless of pretreatment levels of relationship satisfaction and improves partners' individual mental health and well-being. In addition, there may be moderators in the effectiveness of CBCT for PTSD (e.g., highly accommodating partners, more perceived social

support from partners). The efficacy of EFCT for improving PTSD and/or relationship adjustment is mixed and may be due to methodological considerations (e.g., high dropout in one study with U.S. veterans, recruitment based on relationship distress, or trauma history versus PTSD diagnosis).

As noted in this review, the "family" portion of the "couple/family" label has been relatively neglected in research on PTSD interventions. More research is needed on interventions that apply to broader family functioning and the effects of parental mental health problems on children to better intervene at the family level. Gilman, Chard, and Monson (2019) have developed and tested a version of CBCT for PTSD that includes elements of parent management training (CBCT-PMT). Initial results of a recently completed RCT of 34 male U.S. Afghanistan/Iraq veterans and their female partners reveal an advantage of CBCT+PMT over CBCT alone in parent–child relationship and child behavioral outcomes at 3-month follow-up (Gilman et al., 2019). In addition, although a significant proportion of clients are married and have children, there is still a sizable minority who are not in committed intimate relationships, and some clients are in committed same-sex relationships. We need to consider inclusion of a broader range of clients' close others when striving to enhance engagement, assessment, and treatment of PTSD.

Most of the research to date on couple/family therapies for PTSD has investigated male veterans with PTSD (many of them from the United States) and their female partners. This is in spite of epidemiological research indicating that women are about twice as likely to have PTSD (Goldstein et al., 2016) and that women with PTSD may be especially at risk for relationship problems and divorce (e.g., Creech et al., 2019; Gold et al., 2007). Nonetheless, administrative data from U.S. VA medical records indicate that when family members are incorporated into veterans' mental health care, women's PTSD symptoms appear to be particularly improved (Laws, Glynn, McCutcheon, Schmitz, & Hoff, 2018). With an aging population and data indicating that the developmental transition of retirement is linked with relationship distress, as well as the appearance of PTSD symptoms (Schnurr, Lunney, Sengupta, & Spiro, 2005), it will be crucial to consider how these interventions might be applied or adapted for this segment of the population. Age-related physical conditions and their treatment may also increase relationship distress or exacerbate PTSD symptoms (e.g., cardiovascular incidents; cognitive changes).

Many questions remain regarding the most efficacious elements of the interventions reviewed. As the field identifies efficacious treatments, future dismantling studies may provide evidence about the essential components of these interventions. In addition, more research is needed on the most optimal mode of delivery (e.g., conjoint therapy delivered to individual dyads, in a group of dyads, via telehealth methodologies, paired with individual therapy). Morland and colleagues (2019) are currently conducting an RCT of an abbreviated version of CBCT for PTSD delivered in office or by video into U.S. veterans' homes compared with in-office PFE. Monson and colleagues (2020) have also completed an uncontrolled trial of CBCT for PTSD facilitated by 3,4-methylenedioxymethamphetamine (i.e., MDMA) in a sample of six community couples in which a partner was diagnosed with treatment-resistant PTSD. In this trial, which included MDMA dosing of both partners and compressed delivery of CBCT, there were significant improvements in PTSD and common comorbid conditions, relationship satisfaction in both partners, and partner psychological outcomes.

Another important evolution in the PTSD treatment outcome field more generally is the notion of treatment matching based on patient characteristics and preferences.

There may be clients who prefer couple/family therapy over individual therapy for PTSD, or vice versa. Results from a head-to-head trial of CBCT for PTSD versus prolonged exposure (PE; Foa, Hembree, & Rothbaum, 2007) in U.S. active-duty service members and their intimate partners illustrate this issue (Monson et al., 2017). In this study, dropout from PE was 66%, and dropout from CBCT for PTSD was 27%. The authors noted that these two treatments may not have been equally desired in this sample in which service members with PTSD had an intimate partner willing and able to participate in treatment, resulting in significantly more dropout from the individual treatment.

Although there are currently no algorithms or empirically derived decision trees for treatment selection, we have previously offered some suggestions based on our own thinking and clinical experiences (Monson, Macdonald, & Brown-Bowers, 2012). Education/engagement is likely most appropriate when clients with PTSD have been unwilling to engage in treatment in order to support family members and increase the likelihood of treatment engagement. If a client with PTSD is engaged in individual evidence-based treatment for PTSD, does not wish for a family member to be integrated into that treatment, and the family member is experiencing relationship distress, adjunctive generic couple/family therapy may be the treatment of choice. Generic couple/family therapy may also be pursued if the client is unwilling or not yet ready to engage in trauma-focused psychotherapy for PTSD and is experiencing relationship distress.

Partner-assisted interventions might be selected when the client is receiving individual evidence-based treatment and the therapist wishes to include a supportive family member to maximize treatment delivery (e.g., facilitating *in vivo* exposures). One cautionary note about this method of including family members comes from agoraphobia treatment research (Barlow, Mavissakalian, & Hay, 1981). If there is distress in the relationship, we do not advise using partner-assisted interventions because of the potential for increased conflict associated with a family member acting as surrogate therapist or coach. Given the accumulating evidence for the efficacy of some of the PTSD-specific couple/family interventions to achieve multiple treatment outcomes in an efficient manner, we recommend these treatments as a stand-alone option whenever there is a client with PTSD and a partner willing to engage in them. Some clinicians may be inclined to consider these interventions only when there is relationship distress. It is important to note that the existing disorder-specific conjoint interventions for PTSD have been tested in a range of satisfied couples (i.e., relationship distress has not been an inclusion criterion). Data show that the extent to which patients' experience improvements in PTSD symptoms does not depend on pretreatment levels of relationship satisfaction (Shnaider et al., 2015).

A final challenge that we anticipate for the future relates to dissemination of empirically supported couple/family therapies for PTSD. Many mental health providers are not trained, or may not perceive themselves to be adequately trained, in couple/family interventions. Training programs in empirically supported couple/family therapy interventions are emerging to help fill this gap. For example, the U.S. VA is systematically disseminating CBCT for PTSD among its couple/family therapy training offerings (Sayers, Glynn, & McCutcheon, 2014). Future studies on the dissemination and implementation of these therapies are sorely needed to determine the individual clinician training elements that need to be provided in order for clinicians to deliver these treatments with fidelity and ultimately efficacy. Organizational facilitators for, and barriers to, the delivery of couple/family therapies for patients with PTSD will

also need to be evaluated and addressed for successful implementation of this class of therapies.

Given the robust association between intimate relationship maladjustment and PTSD (e.g., Birkley et al., 2016; Taft et al., 2011) as well as the associations between partner mental health difficulties and PTSD (e.g., Lambert et al., 2012), additional research is clearly needed to develop and test couple- and family-based interventions for those with PTSD. The recent innovations in couple- and family-based PTSD treatments are encouraging with respect to improving patient outcomes and relationship functioning. Additional research is needed on ways to improve partner well-being as well. We are hopeful that future research will reveal the most effective approaches to involving family members and improving the relationships between individuals with PTSD and their loved ones.

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CHAPTER 22

Group Treatments for PTSD

J. Gayle Beck and Denise M. Sloan

The use of group treatment for posttraumatic stress disorder (PTSD; Foy et al., 2000; Horowitz & Solomon, 1975) originated at about the same time as the formal diagnostic criteria for the disorder were introduced in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association [APA], 1980). Originally, group treatment was designed to offset social isolation in veterans with PTSD; groups often were led by fellow veterans and were sometimes called "rap groups." Since this era, group treatment has evolved considerably, with numerous variations described in the literature. However, research on group therapy for PTSD has been slow to develop, owing to methodological challenges (e.g., Sloan, Bovin, & Schnurr, 2012). In this chapter, we provide an update on the empirical literature on group treatments for PTSD anchored on our previous chapter (Beck & Sloan, 2014). It is important to note that treatments conducted in a group format for PTSD have been shown to be less effective than the same treatments conducted in an individual format, a finding supported by meta-analyses (e.g., Ehring et al., 2014; Taylor, & Harvey, 2010) as well as one individual study (Resick et al., 2017). As such, the literature on group treatments for PTSD has been focused on its relative efficacy, with increasing emphasis on the use of these interventions in environments that have limited resources. Beginning with a brief overview about group treatments, the current chapter will summarize the available evidence on a variety of group treatments, discuss methodological considerations within this literature, highlight limits to generalization, and discuss future directions.

DESCRIPTION OF GROUP TREATMENTS FOR PTSD

Available group treatments vary along many dimensions, including theoretical orientation, size of membership, number and training of therapists, open versus closed format, duration of the group, and emphasis on skill building versus group process. A

common denominator across these variations is the presence of a supportive group environment, where trauma survivors can develop trust in other members, provide understanding to one another for common posttrauma issues, and obtain feedback about their perceptions, beliefs, and behaviors. When these are the primary goals of the group, treatment is conceptualized as a support group. Support groups usually are open to new members at any time, do not have a structured agenda, and rarely emphasize attendance. As discussed by Sloan and colleagues (2012), support groups can be led by a trained therapist or by a peer.

Cognitive-behavioral therapy (CBT) in a group format has gained in popularity, particularly in environments with a shortage of available trained mental health professionals to provide individual treatment. CBT groups are structured and focus on developing adaptive coping skills. Group CBT can have many different foci when used to treat patients with PTSD. Some CBT approaches focus expressly on exposure-based interventions in the treatment of PTSD, to emphasize extinction of trauma-related fear responses (e.g., Castillo et al., 2016; Ready et al., 2008). Other group CBT approaches emphasize cognitive interventions (e.g., Resick & Schnicke, 1992); still other approaches represent package treatments, with interventions designed to address extinction, dysfunctional cognitions, anger, social isolation, and other facets of PTSD (e.g., Beck, Coffey, Foy, Keane, & Blanchard, 2009). Group CBT tends to be time-limited, require a closed format, and be led by at least one clinician. Attendance is tracked, given the emphasis on skill development. In group CBT, clinicians announce the ground rules for absences in the first group session because a member who misses too many sessions can impede the overall progress of the group.

In addition to support groups and group CBT, psychodynamic and/or interpersonal group therapy has been used to treat PTSD. Group psychodynamic treatment intends to foster insight among members with respect to how the trauma affects their sense of self, emotional experiences, and internal conflicts (e.g., Sharpe, Selley, Low, & Hall, 2001). The pace of group psychodynamic therapy is set by group members; therapy does not follow a manual or treatment guidelines and typically lasts longer than group CBT. Interpersonal group therapy developed from the work of Harry Stack Sullivan (1953), a psychoanalyst who emphasized interpersonal functioning. Group interpersonal therapy focuses on developing awareness of patterns of relationship difficulties following trauma exposure, with an emphasis on changing relational patterns through interaction with fellow group members (e.g., Roth, Dye, & Lebowitz, 1988). Both psychodynamic and interpersonal group therapies usually involve a closed-group format and are led by at least one trained therapist.

In addition to these three types of group PTSD treatments, a number of other group approaches have been developed, including mind–body skills groups (e.g., Gordon, Staples, Blyta, & Bytyqi, 2004), feminist-oriented forms of group therapy (e.g., Westbury & Tutty, 1999), group interventions designed to address dyadic and family functioning for patients with PTSD (e.g., Sherman, Fischer, Sorocco, & McFarlane, 2011), and various CBT approaches that are intended for patients with comorbid PTSD and a second mental health condition, such as a serious mental illness (e.g., Mueser et al., 2007) and substance use disorder (Hien et al., 2009). As well, investigators have developed treatment approaches that combine individual and group therapy (e.g., Beidel, Frueh, Uhde, Wong, & Mentrikoski, 2011; Chard, 2005).

As we note in this brief description, group interventions are viewed as a useful approach to reach an increasing number of patients with PTSD. This is particularly

important in environments where mental health professionals are absent or in short supply. Group treatment also may be more cost-effective for the treatment of PTSD, although a specific cost analysis has not been conducted on this topic. Many group interventions have been reported descriptively in the literature or examined using an uncontrolled case study approach. These types of publications are important and yet leave key questions unanswered concerning the effectiveness of specific group treatment approaches. In the next section, we examine treatments that are supported by randomized controlled trials (RCTs).

RCTs: CURRENT STATE OF THE LITERATURE

RCTs provide the strongest evidence of efficacy and effectiveness of any form of intervention, relative to other research designs. In this section, the review of group RCTs for PTSD is limited to studies that examined a group treatment for either PTSD or trauma survivors, samples that included participants who were at least 18 years old, measures that included a PTSD symptom outcome assessment, designs that involved a between-condition randomized comparison group, investigations that involved group treatment only, and reports that were written in English. The majority of these studies have included a wait-list comparison condition, which only provides information on whether the treatment under examination is better than no treatment. This type of RCT is more likely to result in a large between-group effect (e.g., Schnurr, 2007). Not surprisingly, a meta-analysis by Sloan and colleagues (2013) found that type of comparison condition served as a moderator of the overall between-group effect, with studies that used a wait-list comparison condition having a significantly larger effect ($d = 0.56$) relative to studies that included a treatment comparison condition ($d = 0.09$).

Within the collection of RCTs on group therapies, CBT has received the most attention. Cognitive and exposure-based interventions predominate in this category, which is understandable given efficacy data for PTSD treatment trials using an individual format (for reviews, see Department of Veterans Affairs & Department of Defense [DoD/VA], 2017; Institute of Medicine, 2008). Some recent studies have examined group cognitive processing therapy (GCPT). For example, Resick and colleagues (2015) compared GCPT with group present-centered therapy (GPCT), a non-trauma-focused intervention that helps patients improve their problem-solving based on peer support (Schnurr, Friedman, Lavori, & Hsieh, 2001). GPCT has been shown to produce small changes in veterans diagnosed with PTSD (e.g., Sloan, Unger, Lee, & Beck, 2018). In the Resick and colleagues (2015) study, both group treatments produced large reductions in PTSD symptoms in a sample of active-duty U.S. Army soldiers.

A collection of other studies has considered group CBT packages (e.g., Beck et al., 2009; Bradley & Follingstad, 2003; Castillo et al., 2016; Classen et al., 2011; Hinton, Hofmann, Rivera, Otto, & Pollack, 2011; Hollifield, Sinclair-Lian, Warner, & Hammerschlag, 2007; Schnurr et al., 2003; Sloan et al., 2018). Typically, these group approaches integrate exposure, cognitive restructuring, assertion training, behavioral activation, relapse prevention, and other CBT interventions. The design of these GCBT packages ranged from 14 to 30 weeks; group sizes varied between 3 and 10 members, depending on the protocol. Target samples have included veterans, women who experienced childhood sexual abuse, incarcerated prisoners who had experienced childhood abuse, motor vehicle accident survivors, and mixed trauma samples. Although significant reductions in PTSD symptom severity are commonly observed in these studies,

treatment outcome in group CBT outperforms when the comparison condition is wait list but not when the comparison condition is an active group treatment.

In addition to CBT, two recent RCTs have examined mindfulness-based stress reduction and meditation approaches to PTSD in veteran samples (Lang et al., 2019; Polusny et al., 2015). These authors suggest that alternative treatment approaches to PTSD may be more tolerable for patients, relative to trauma-focused treatments. Lang and colleagues (2019) compared a compassion meditation protocol to a mind–body intervention that focuses on relaxation. Polusny and colleagues (2015) compared mindfulness-based stress reduction with GPCT. These recent trials support patient credibility and satisfaction with these interventions, as well as initial support for their efficacy. This is an area of growing interest within the group treatment literature, particularly with increased recognition that interventions that are trauma-focused may not be a good match for some patients (Imel, Laska, Jakupcak, & Simpson, 2013).

Recognizing that PTSD is closely associated with poor emotion regulation, particularly for individuals with a history of interpersonal trauma (e.g., Herbert, Rose, Rosengard, Clarke, & Stein, 2007), several RCTs have focused on interventions designed to teach affect regulation skills. Ford, Chang, Levine, and Zhang (2013) examined the efficacy of a 12-week group intervention focusing on a sequential set of skills for affect regulation in a sample of incarcerated women with victimization-related PTSD symptoms. The comparison condition was supportive group therapy. Both group treatments were associated with a significant reduction in PTSD symptoms, with no between-group differences at posttreatment; the affect regulation intervention showed significant improvements in increasing a sense of forgiveness toward others who have caused harm, relative to supportive group therapy. An earlier trial focusing on affect management used a somewhat different intervention; Zlotnick and colleagues (1997) examined a group intervention that targeted sleep problems, flashbacks, emotion identification, anger management, distress tolerance, and relaxation. Relative to a wait-list control condition, individuals who completed the affect-management treatment group reported significantly fewer posttreatment symptoms of PTSD and less dissociation relative to those in the wait-list condition. Importantly in this study, all patients continued to receive individual psychotherapy and medication throughout the trial, a feature that complicates interpretation. With increased attention to interventions that target underlying psychological processes (rather than specific symptoms), we anticipate increased study of group interventions to address emotion dysregulation.

A small collection of other group interventions also has been examined in RCTs, including imagery rescripting for trauma-related nightmares (Cook et al., 2010; Krakow et al., 2000), spiritually integrated therapy (Harris et al., 2011), interpersonal therapy (Krupnick et al., 2008), and eye movement desensitization and reprocessing (Rogers et al., 1999). As has been noted in other components of the current chapter, significant differences between the group intervention and the control condition have typically been noted in these studies when a wait-list control condition was used. If an active control condition was employed instead, between-group differences were not observed (Cook et al., 2010; Rogers et al., 1999). Although this handful of other interventions are promising, research on these group treatments has not progressed.

Several investigators have also explored the efficacy of combining group and individual sessions (e.g., Beidel et al., 2011; Chard, 2005). Another set of interventions have addressed psychiatric comorbidity, which is very common among patients with PTSD (e.g., Smith, Goldstein, & Grant, 2016). How best to treat comorbidity has been a topic of considerable discussion, with some arguing that comorbid conditions can be successfully

treated within the context of PTSD interventions (Henslee & Coffey, 2010; van Minnen, Zoellner, Harned, & Mills, 2015), whereas others suggest that the presence of comorbid conditions requires specific treatment approaches (e.g., Najavits et al, 2009). A number of investigators have examined the efficacy of treatments designed to treat a variety of comorbid conditions such as depressive disorder, panic, HIV/AIDS, and problem drinking/substance use disorder (e.g., Dunn et al., 2007; Falsetti, Resnick, & Davis, 2008; Hien et al., 2009; Sikkema et al., 2007, Valenstein-Mah et al., 2019; Zlotnick, Johnson, & Najavits, 2009). The between-group effect for PTSD outcome for these RCTs is small, ranging from 0.01 to 0.31. Only one of these studies obtained a significant between-group effect for PTSD outcome, and this study used a wait-list comparison condition (Falsetti, Resnick, & Davis, 2008); the other four studies included a psychoeducation comparison condition and did not find a significant between-condition effect.

Since publication of our chapter in the previous edition of this handbook, a small but growing literature has emerged, focused on the use of group treatments for PTSD and related symptoms in environments that traditionally have few or no mental health providers. Professionals are beginning to address mental health needs among refugees, asylum seekers, and survivors of systemic regional violence. Ongoing stressors in these populations (e.g., limited legal rights, housing instability, economic insecurity, gender-based violence, and limited access to health care; Smith, 2012) may amplify mental health symptoms that originated from trauma exposure in the person's country of origin (e.g., Afifi, Afifi, Merrill, & Nimah, 2016). Group interventions have been viewed as a cost-effective method for addressing emotional distress and reducing PTSD symptoms in these populations; in some of these studies, groups were led by paraprofessionals or local health workers using a strategy called "task shifting" (Kazdin, 2018). Task shifting is a strategy used to expand the mental health workforce via training laypersons to administer psychological treatments. Different types of group interventions have been examined to date, including treatments focused on increasing emotion regulation and decreasing somatic focus (Shaw, Ward, Pillai, & Hinton, 2018), and transdiagnostic approaches emphasizing cognitive, emotional, and behavioral interventions (e.g., Bonilla-Escobar et al., 2018; Khan et al., 2017). These two types of intervention have shown promise. Greater methodological rigor is needed in this literature, recognizing the difficulty of conducting an RCT in a low-resource environment where care needs are paramount. An example of a methodologically strong study in this domain was published by Bass and colleagues (2013); this study used GCPT, focused on women survivors of sexual assault in the Democratic Republic of Congo, and utilized paraprofessionals (psychological assistants) as therapists. Results indicated that GCPT was markedly more effective in reducing PTSD symptoms, compared with individual support services (d = 1.4 at posttreatment). At present, there are few group RCTs in this growing literature, although given the increases in research attention, we anticipate that more controlled trials of group interventions in low-resource settings will be conducted.

METHODOLOGICAL CONSIDERATIONS

Presently, the field has clear standards about what type of empirical evidence is needed to determine whether a specific therapy works. RCTs are widely regarded as the "gold standard" for determining a treatment's effectiveness. Typically, the first step in examining the efficacy of a treatment involves comparison of the treatment to a no-treatment or wait-list condition. This type of control condition addresses threats to internal validity

(Kazdin, 2017). Subsequent steps include comparing the treatment with another active treatment, often a treatment that controls for "nonspecific" or common therapeutic processes. This type of control condition addresses threats to construct validity and aids in interpreting the specific impact of the target treatment (Kazdin, 2017).

When this approach to experimental design is applied to the study of a group treatment, several additional issues surface. First, unlike an RCT conducted on an individual-format therapy, it is necessary to collect a relatively large cohort of patients. Once recruited, individuals within a cohort are then randomized to conditions, resulting in treatment groups of six to eight patients. Some investigators have conducted high-intensity recruitment drives in order to minimize the amount of time that individuals must wait for a cohort to form (e.g., Schnurr et al., 2001; Sloan et al., 2018). Additionally, provision of clinical management and crisis services is necessary for RCTs of group treatment, given the typical wait time between entering a study (e.g., completing the baseline assessment) and when randomization occurs.

A second issue pertains to the optimal size of each group. Ultimately, the size of a group should be determined by the particulars of the treatment involved. However, the methodological approach needs to account for attrition. As summarized by Imel and colleagues (2013), the average attrition rate is 18% for PTSD psychotherapy trials, with considerable variation across studies. Of particular relevance to this chapter, an average dropout rate of 36% was reported for trauma-specific treatments, whereas PCT averaged a 22% dropout rate. Group treatments in general had higher rates of dropout relative to individual treatments. To accommodate treatment dropout, investigators need to begin a given group with a sufficient number of individuals, so that a reasonable-size group remains should several patients leave treatment. Given higher rates of dropout and greater difficulty in accommodating individual patients' last-minute schedule problems, investigators may wish to quantify treatment completion based on receipt of an adequate dose of the intervention, rather than the specific number of sessions that a patient attends.

Third, determination of the sample size for an RCT involving one or more group treatments contains an additional, statistical consideration. Because group treatment naturally is conducted in a small group, individuals are clustered within their unique treatment environment. Irrespective of the statistical approach that is selected, data analysis from a group treatment trial must account for this clustering effect. As discussed by Baldwin, Murray, and Shadish (2005), many RCTs on group treatments that have failed to account for the clustering of patients within groups result in findings that suggest the difference between the treatment and comparison groups is statistically significant, when, in fact, it may not be (a Type I error). Inclusion of clustering in the analytic plan for an RCT involving group treatment typically increases the necessary sample size to a significant degree, often requiring more than one data collection site (Sloan et al., 2012). As such, the design of an RCT on group treatment requires consideration of specific design features that outpace those typically noted in trials on individual treatment.

In addition to design elements, well-conducted treatment studies often utilize a treatment manual, wherein specifics of the intervention are described, along with the desired pacing across sessions. Some approaches to group PTSD treatment do not conceptually embrace the use of manuals, which makes standardization of treatment difficult to ensure. In this instance, some type of guidelines for therapists would be optimal in order to provide direction on essential elements of this intervention (e.g., Waltz, Addis, Koerner, & Jacobson, 1993). For example, within the context of an RCT

on group psychoanalytic treatment, both a list of interventions characteristic of and unique to this form of treatment and a list of conceptually prohibited interventions could facilitate implementation. It is ideal to have some independent verification that treatment was administered in a valid and competent fashion (treatment adherence and competency), irrespective of the presence or absence of treatment manuals.

Another methodological issue that surfaces in this literature is the targeted sample. In the literature on group treatment of PTSD, some authors have elected to include mixed-trauma samples (e.g., Zlotnick et al., 2009), whereas others have chosen to focus on one specific form of trauma survivors (e.g., Sloan, Unger, & Beck, 2016). Although each of these choices offers unique strengths, this decision impacts the extent to which we can generalize the results of a RCT to a specific care environment. Related to this issue, some studies naturally select single-sex samples (e.g., treatment of incarcerated women with PTSD stemming from interpersonal victimization; Ford et al., 2013), whereas others deliberately strive for inclusion of both genders.

Assessment of targeted treatment outcomes is a salient methodological concern for RCTs on group treatment. When assessing PTSD, clinician-administered interviews have become the method of choice (Bovin & Weathers, 2012), although this approach is resource-intensive. Given the larger sample size that is required for most RCTs on group treatment, investigators need to be judicious in their use of time-intensive, costly measures. A number of self-report instruments are available for assessment of PTSD but may be subject to response biases (see Bovin & Weathers, 2012, for more detailed discussion). Because most RCTs include follow-up assessments after treatment completion, a careful mixture of clinician-administered and self-report measures can strike a balance among these concerns. Additionally, there is clear consensus that PTSD treatment studies benefit from inclusion of assessment measures targeting comorbid conditions, including depression, anxiety, and substance misuse, particularly in studies that focus on patients with chronic PTSD (e.g., DoD/VA, 2017). Inclusion of measures of functional impairment and quality of life also is important when examining broadband outcomes of group treatments for PTSD (e.g., Holowka & Marx, 2012).

The type of comparison condition is another important methodological design feature, as the comparison condition affects interpretation of treatment outcome findings. Although many group treatment studies include a wait-list comparison condition, several studies included both a wait-list comparison condition and a treatment–comparison condition (Classen et al., 2011; Hollifield et al., 2007; Sikkema et al., 2007). This approach can be particularly informative as a wait-list condition permits determination of whether reductions observed in PTSD symptoms for both treatment approaches are the result of the group treatment or of some other factor (e.g., regression to the mean, natural recovery). One RCT used a noninferiority design to examine anger management group treatment delivered via videoconferencing to anger management group treatment delivered in person (Morland et al., 2010). The noninferiority design is helpful in determining whether one type of group intervention is comparable to another type of group intervention.

LIMITS TO GENERALIZATION OF THE AVAILABLE DATA

Despite the gradual growth of the literature on group treatments for PTSD, several key limitations exist at present. These include reliance on focal patient samples,

underemphasis on examination of some forms of group treatments, and the relatively low number of RCTs generally that examine group therapy for PTSD.

First, the majority of studies have focused on women (e.g., Castillo et al., 2016; Ford et al., 2013). One reason for this focus is the choice to address a specific trauma sample (e.g., interpersonal violence). A similar issue has emerged with studies targeting veteran samples, wherein most studies only include men (e.g., Beidel et al., 2011; Dunn et al., 2007; Rogers et al., 1999; Schnurr et al., 2003; Sloan et al., 2018). The focus on specific trauma samples can be informative for specific treatment environments, such as rape crisis centers. However, findings from these studies have limited generalizability and may be particularly restricted when applications to different care environments are considered. Although one can argue that trauma- and gender-specific interventions can be powerful, it is imperative for the field to examine interventions that can be adapted for use with survivors of many different types of trauma, branching across gender, ethnic, racial, economic, and educational categories. Because of the promise of group treatments for PTSD, generalization of findings is an important consideration when critiquing this literature.

Second, the majority of RCTs on group treatments have focused on some form of CBT. Although several forms of CBT are effective in the treatment of PTSD (e.g., American Psychological Association, 2017; DoD/VA, 2017), it is important to recognize that we need as broad an array of interventions as possible so that we can account for individuals who are not responsive to particular treatments, as well as patient preference. The near-exclusive focus on CBT therefore represents a limit to the generalizability of this literature. Third, preliminary data suggest that group treatments may not be the preferred mode of mental health services, at least for U.S. veterans from post-9/11 combat deployments. Kracen, Mastnak, Loaiza, and Matthieu (2013) reported the results of an anonymous survey of 110 recent veterans, examining perceptions of group therapy; results revealed concerns about being labeled or stigmatized for taking part in a treatment group, discomfort expressing feelings in a group context, and apprehension about being misunderstood. We need larger studies on veteran preferences for group therapy, particularly given current practices within the VA health care system. Kracen and colleagues' data stand in contrast to referral patterns for post-9/11 combat veterans presenting for services within the Department of Veteran Affairs; Mott, Barrera, Hernandez, Graham, and Teng (2014) note that approximately 24% of referrals during a 4-year interval were for group therapy. Greater attention to developing group treatments for PTSD among veterans that include elements to address concerns about being stigmatized, uncomfortable, and misunderstood would be helpful. Conceivably, these interventions may also be welcomed by other care environments that currently incorporate group treatments as a way to maximize their limited number of mental health professionals.

Last, it is important to note that the study of group treatment has lagged greatly behind the study of individual treatments for PTSD. As we discussed, methodological considerations present challenges and increase resources required to conduct an RCT on a group therapy, including the number of trained assessors and the required large sample size. Usually, a RCT examining the efficacy of a group treatment will require muiltiple study sites in order to meet the required large sample size; such a trial feature increases the complexity and expense of the trial. Most trials in this area have relied on a wait-list comparison condition, which is more likely to result in a large between-group effect (e.g., Schnurr, 2007) and require a smaller sample size, owing to greater statistical

power. Continued work in this domain will need to extend the choice of comparison conditions and, by definition, become more methodologically complex.

CHALLENGES FOR THE FUTURE

As our field in general grapples with the increasing challenges of mental health delivery (e.g., Kazdin, 2018), discussions of group-based treatments are evolving. Although the number of controlled trials of group treatments for PTSD is limited, the literature on group treatments in general is fairly large (e.g., Jensen et al., 2012; Rainey, Readdick, & Thyer, 2012; Yalom, 1995). Embedded within this general literature are a number of interesting ideas and concepts that could enrich the literature on group treatment of PTSD. For example, many clinical opinions have been offered concerning the impact of specific patient characteristics in a group treatment environment (e.g., Herman & Schatzow, 1984; Yalom, 1995). The PTSD treatment literature could profit from greater research examining patient characteristics, including demographic features and personality because these variables influence both the process and the outcome of group therapy. As an example, Cloitre and Koenen (2001) examined the impact of borderline personality disorder (BPD) on the outcome of interpersonal process group therapy for women with PTSD related to childhood abuse. These authors note that treatment groups without individuals with BPD showed larger treatment gains relative to groups that contained members with BPD. Additionally, individuals who were treated within groups that had a member with BPD reported higher levels of anger at posttreatment, leading the authors to hypothesize an "anger contagion" effect within these treatment groups. These findings underscore the impact that group members have on each other. Studies such as this one could help to advance our empirically grounded understanding of salient variables that impact the delivery and outcome of group therapy for PTSD.

A related challenge for the future is the development and testing of group treatments outside of the usual Western culture. As an example, Hinton and colleagues (2011) developed and tested a culturally adapted CBT for Hispanic women with treatment-resistant PTSD; this treatment was delivered in Spanish and empirically tested within the context of an urban outpatient clinic serving Caribbean Latino patients. Bass and colleagues (2013) also demonstrated that CPT can be culturally adapted for use with women who experienced sexual violence in the Democratic Republic of Congo. Importantly, CPT was delivered by paraprofessionals in this study, suggesting that laypersons can be taught to use this cognitively oriented form of CBT. As the trauma field becomes increasingly focused on disseminating effective services for trauma survivors worldwide, the ability to adapt available treatments to become culturally suitable is salient.

Thinking ahead, it also would be prudent to begin to examine more deeply the impact of patient preferences as these intersect with group-format treatments. Patient preferences is an understudied component of evidence-based practice, which creates a knowledge gap that leaves the field operating in a vacuum. Importantly, research on patient preference can occur within naturalistic care environments, as exemplified by Ryan, Nitsun, Gilbert, and Mason (2005). These authors collected data within the National Health Services in the United Kingdom, examining the efficacy of (patient-selected) individual or group integrative psychotherapy among women who had experienced childhood sexual abuse. At this junction, we have a limited understanding of the role of patient preferences in treatment outcome, particularly the way preferences intersect with the format of treatment (e.g., individual, group, Internet, telehealth). As

the field moves closer to reliance on evidence-based care, research on patient preferences will become increasingly important in developing treatment options for trauma survivors.

Throughout this chapter, we have discussed methodological challenges that are intrinsic to the study of group treatment for PTSD. In considering research on group therapy, we have emphasized the resource-heavy nature of this work, owing in large part to the increased sample sizes that are needed. In many respects, experimental research on group therapy could be augmented by greater emphasis on quasi-experimental designs and the integration of data collection within clinical care environments. We have noted several exemplars of this kind of research in this chapter, providing examples of ways in which useful data can be collected outside the confines of an RCT. It is our hope that this type of work can enhance our understanding of group treatment for PTSD, alongside RCTs, because group treatment holds considerable potential as an approach for reducing PTSD-related suffering and impairment.

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CHAPTER 23

Pharmacotherapy for PTSD

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Therapeutic goals for the management of posttraumatic stress disorder (PTSD) most commonly include reduction in nightmares, intrusive thoughts, hyperarousal, irritability, insomnia, and phobic avoidance, as well as concurrent depression and anxiety, so that the patient can ultimately achieve more stable relationships, meaningful employment, and optimal quality of life. Individual differences in symptom presentation and response to treatment are wide ranging. Many of these PTSD symptoms are difficult to treat, particularly sleep disturbances, reexperiencing of symptoms, behavioral avoidance, and emotional numbing, which commonly lead the prescriber to switch or combine medications. Clinical practice guidelines by the American Psychological Association (2017), Department of Veterans Affairs and Department of Defense (VA/DoD, 2017), International Society for Traumatic Stress Studies (ISTSS, 2019), National Institute for Health and Care Excellence (2018), and Phoenix Australia Centre for Posttraumatic Mental Health (2013) provide guidance as to first-step monotherapy pharmacologic treatment, but give little direction for next-step approaches for treatment-resistant PTSD (Hamblen et al., 2019). Recent systematic reviews and meta-analyses provide a comprehensive review of the randomized controlled trials (RCTs) and synthesis of the magnitude of effectiveness for each drug tested (Hoskins et al., 2015; Jonas et al., 2013; Lee et al., 2016). Only two medications are approved by the U.S. Food and Drug Administration (FDA) for the treatment of PTSD, sertraline and paroxetine, which is a strikingly low number compared to the number of drugs approved for other common mental disorders. All other medications reviewed in this chapter are considered off-label use in the treatment of PTSD.

Clinicians commonly prescribe psychotropic medications for the treatment of PTSD. According to studies examining archival electronic medical and pharmacy records, 50–86% of patients with a recent diagnosis of PTSD are prescribed a psychotropic medication, including an antidepressant (69–84%), antipsychotic (15–56%), mood stabilizer (19–57%), and/or hypnotic/benzodiazepine (23–51%), with the highest rates of prescriptions for Medicaid recipients compared to privately insured or

veterans enrolled in Veterans Health Administration (VHA) services (Ivanova et al., 2011; Spoont, Murdoch, Hodges, & Nugent, 2010; Vojvoda, Stefanovics, & Rosenheck 2017). A recent archival record review for a 1-year period from October 2011 to September 2012 (Vojvoda et al., 2017) found that 83% of the Iraq/Afghanistan and 86% of Vietnam War veterans enrolled in VHA were prescribed a psychotropic medication (most commonly an antidepressant) and 17% and 20%, respectively, were prescribed three or more psychotropics. Because of the high comorbidity of major depressive, panic, anxiety, and psychotic disorders, treatment for the patient with PTSD may include a medication that is off-label for PTSD but otherwise FDA-approved treatment for the comorbid disorder. Considerations for selecting the most appropriate medication in the treatment of PTSD include its evidence of efficacy, side effect profile, and potential for drug–drug interactions. These considerations are discussed in this chapter for each class of psychotropic drug, and overall treatment recommendations are summarized in Table 23.1.

ANTIDEPRESSANTS

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are a cornerstone of treatment for PTSD due to their relative proven effectiveness, safety, tolerability, and low cost. SSRIs increase serotonin in the brain through reuptake inhibition at the presynaptic serotonin transporter pump, albeit with different affinity and selectivity for each SSRI (Mandrioli, Mercolini, Saracino, & Raggi, 2012). Like all antidepressants, SSRIs go beyond that of increasing the level of the synaptic concentrations of monoamines, that is, serotonin, noradrenaline, and dopamine. Antidepressants also desensitize presynaptic autoreceptors responsible for governing the release of the monoamine, alter the number and/or sensitivity of postsynaptic receptors, increase brain-derived neurotropic factor, and increase neuronal plasticity (Abdallah, Southwick, & Krystal, 2017). These actions take time, which explains the 2-week delayed onset of antidepressant efficacy and need for 2 or more months of treatment to achieve maximum benefits. Drug–drug interactions are based on the degree of cytochrome P (CYP)-450 liver enzyme inhibition, which varies considerably between the SSRIs. Therefore, SSRIs must be used with caution in patients who are also taking warfarin, thiazide diuretics, beta blockers, and codeine, especially in the elderly because elimination of these drugs may be affected by age. This broad group of medications includes sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, and escitalopram. All clinical practice guidelines recommend sertraline, paroxetine and fluoxetine as pharmacotherapy for PTSD, with a confidence level that ranges from strong (VA/DoD, 2017) to low (ISTSS, 2019), depending on how the evidence was weighted. Presently, only sertraline and paroxetine are approved by the FDA for the treatment of PTSD, but others have been studied to some extent, especially fluoxetine.

Evidence for sertraline's efficacy includes two large RCTs in adults with PTSD resulting from mostly civilian trauma (Brady et al., 2000; Davidson, Rothbaum, van der Kolk, Sikes, & Farfel, 2001). Extending sertraline for an additional 24 weeks converts some initial nonresponders to responders and increases remission rates from 30 to 55% (Davidson et al., 2001; Londborg et al., 2001; Rapaport, Endicott, & Clary, 2002). In contrast, a large RCT of sertraline in U.S. military veterans with predominantly Vietnam combat-related PTSD did not replicate the results seen in predominantly civilian

TABLE 23.1. Pharmacotherapy for Treatment of PTSD

Drug class	Drug name	Advantages	Caution	Side effects
Recommended by all PTSD clinical practice guidelines				
SSRI antidepressants	Sertraline[a]; paroxetine[a]; fluoxetine[a]	Effective, tolerable, low cost, once-a-day dosing, and treats comorbid panic, depression, phobia	Drug–drug interaction via CYP-450 liver enzymes; FDA warning of suicidal tendencies	Insomnia, headache, restlessness, nausea, anxiety, sexual dysfunction
SNRI antidepressants	Venlafaxine[a]	Same as above, plus pain relief	May elevate blood pressure and pulse at higher dose	Same as above
Suggested by VA-DoD (2017), but no other PTSD clinical practice guidelines				
Tricyclic antidepressants	Imipramine[a]	Same as above, plus pain relief, sedative properties, lab for therapeutic range	QT prolongation; lethal in overdose; orthostatic hypotension increases risk of falls	Sedation, dry mouth, constipation, orthostatic hypotension
MAOI antidepressants	Phenelzine[a]	Low cost, broad spectrum of CNS activity, treats depression	Strict diet low in tyramine; do not use with stimulants, antidepressants	Elevated blood pressure, risk of hypertensive crisis
Other antidepressants	Nefazodone[a]	Low cost, treats depression, sedative	Hepatotoxicity (FDA warning)	Sedation, dry mouth, weight gain, dizziness, constipation
More evidence is needed to recommend for or against treatment				
Antidepressants	Eszopiclone, escitalopram, bupropion[c], desipramine[c], doxepin, duloxetine, desvenlafaxine, fluvoxamine, levomilnacipran, mirtazapine, nortriptyline, trazodone, vilazodone[c], vortioxetine			
Noradrenergic	Terazosin, doxazosin, clonidine, propranolol			
Antipsychotics	Aripiprazole, asenapine, olanzapine[a,c], quetiapine[a], ziprasidone[c]			
Other	Buspirone, cyproheptadine, D-serine, hydroxyzine, methylphenidate, propranolol, zaleplon, and zolpidem			
Recommended against by VA-DoD (2017) clinical practice guidelines				
Antidepressants	Amitriptyline, citalopram			
Noradrenergic	Prazosin[a,b,c], guanfacine[c]			
Antipsychotics	Risperidone[c], quetiapine[a,c]			
Anticonvulsants	Divalproex[c], tiagabine[c], lamotrigine, topiramate, pregabalin			
Benzodiazepines	Alprazolam[c], clonazepam, lorazepam, diazepam			
Other	Baclofen, hydrocortisone, d-cycloserine, ketamine, cannabis and derivatives			

[a]Randomized controlled trials have been conducted and have shown positive findings.
[b]Recent meta-analyses raise questions about this determination.

groups (Friedman, Marmar, Baker, Sikes, & Farfel, 2007). However, a small RCT in Israeli military veterans with less chronic PTSD found a significantly positive signal for sertraline compared to placebo (Zohar et al., 2002). It is possible that Vietnam veterans receiving treatment for PTSD in VHA settings may represent a more chronic, severely impaired, and treatment-refractory cohort than civilian or more recently discharged military service members. In all studies, sertraline was found to be well tolerated.

Paroxetine is a potent SSRI that has additional inhibitory actions at the norepinephrine reuptake site. As shown in two large, multisite RCTs in adults with PTSD, paroxetine is efficacious and well tolerated (Marshall, Beebe, Oldham, & Zaninelli, 2001; Tucker et al., 2001). Although these studies found no added benefit of the higher 40 mg/day dose compared to the 20 mg/day dose of paroxetine, it is common practice to increase the dose to up to 60 mg/d if minimal or no clinical response is seen after several weeks.

Some, but not all, pilot RCTs supported the effectiveness of fluoxetine in the treatment of PTSD (Connor, Sutherland, Tupler, Malik, & Davidson, 1999; Davidson, Roth, & Newman, 1991; Hertzberg, Feldman, Beckham, Kudler, & Davidson, 2000; McDougle, Southwick, Charney, & St. James, 1991; Meltzer-Brody, Connor, Churchill, & Davidson, 2000; Nagy, Morgan, Southwick, & Charney, 1993; van der Kolk et al., 1994, 2007). These studies justified conducting a larger RCT, which confirmed the efficacy of fluoxetine in significantly reducing PTSD symptoms over 12 weeks and decreasing rates of relapse at 24 weeks compared to placebo (Martenyi, Brown, Zhang, Koke, & Prakash, 2002; Martenyi, Brown, Zhang, Prakash, & Koke, 2002). A subanalysis revealed that fluoxetine significantly improved PTSD symptoms and reduced the risk of relapse in the participants with combat-related PTSD (Martenyi & Soldatenkova, 2006). However, an RCT in a large sample of mostly women ($N = 411$; 72% women) did not support the original finding of fluoxetine's superiority over placebo (Martenyi, Brown, & Caldwell, 2007), possibly due to differences in dosing strategy, higher dropout rate due to adverse events, and higher placebo response.

Fluvoxamine, citalopram, and escitalopram have demonstrated positive improvements in PTSD symptoms in small open-label studies (De Boer et al., 1992; Escalona, Canive, Calais, & Davidson, 2002; Marmar et al., 1996; Neylan et al., 2001; Qi, Gevonden, & Shalev, 2017; Robert, Hamner, Ulmer, Lorberbaum, & Durkalski, 2006; Seedat, Stein, & Emsley, 2000; Tucker et al., 2000). However, placebo-controlled studies are needed to substantiate these findings. Vilazodone is an SSRI and partial agonist of serotonin$_{1A}$ receptors that has the effect of reducing rapid-eye-movement (REM) sleep, which may be beneficial in addressing insomnia associated with PTSD (Murck, Frieboes, Antonijevic, & Steiger, 2001). However, in a small 12-week RCT in mostly male military veterans, vilazodone was not significantly better than placebo on measures of PTSD, sleep, or depression (Ramaswamy et al., 2017).

An SSRI can be safely combined with trauma-focused psychotherapy and is very often an effective approach, but RCTs do not definitively support combination over medication alone. Early trials combining prolonged exposure (PE) therapy with an SSRI have mixed results, with one study showing more positive outcomes with PE combined with paroxetine in adult survivors of the 2001 World Trade Center attack compared to PE plus placebo (Schneier et al., 2012) and two studies finding no clear benefit of combination treatment after failing initial treatment with PE (Simon et al., 2008) or an SSRI (Rothbaum et al., 2006). In a larger clinical trial in 228 adults diagnosed with PTSD following a motor vehicle accident, the combination of PE and paroxetine did not differentiate from either monotherapy group in terms of self-rated PTSD symptom

reduction, rates of remission, or early dropout, whereas, PE led to significantly higher PTSD remission rates (65%) compared to paroxetine (43%) based on a clinician assessment, but not based on PTSD self-rated measure (Popiel, Zawadzki, Pragłowska, & Teichman, 2015). The combination of PE and paroxetine resulted in a remission rate of 51%, which was not significantly different from either PE or paroxetine monotherapy. A recent multisite RCT in 223 predominantly male U.S. service members or veterans of the Iraq or Afghanistan wars found no difference in clinician-rated or self-rated PTSD severity, response, or remission at 24 weeks between PE plus sertraline, PE plus placebo, and sertraline plus 30 minutes of medication management (Rauch et al., 2019). However, the combination group had a greater number of early responders (19%) compared to PE plus placebo (9%) and sertraline (6%) groups. The rate of early dropout from treatment was significantly higher for the groups assigned to PE plus placebo (48%) and PE combined with sertraline (41%) compared to sertraline plus enhanced medication management (27%). This suggests that adherence to treatment is much better with sertraline plus enhanced medication management compared to combination treatment or PE plus placebo.

Patient choice is an important factor in terms of promoting adherence and improved outcomes, as some patients may prefer psychotherapy options and others may not have the time, interest, or resources to attend psychotherapy sessions. In a doubly randomized preference trial of PE versus sertraline, patients who received their preferred treatment (PE or sertraline) were more likely to lose their diagnosis of PTSD, achieve responder status, adhere to treatment, and show an overall improvement in self-reported PTSD, depression, and anxiety symptoms (Zoellner, Roy-Byrne, Mavissakalian, & Feeny, 2019). Although there was no differential effect observed on interviewer-rated PTSD severity between groups, PE was better than sertraline on interviewer-rated loss of PTSD diagnosis, responder status, and self-reported PTSD symptoms. Of note, more study participants expressed a preference for PE over sertraline at baseline, which may have contributed to some of the PE advantages.

Serotonin–Norepinephrine Reuptake Inhibitors

Venlafaxine, desvenlafaxine, and duloxetine exert their effects by blocking the presynaptic reuptake of both serotonin and norepinephrine (SNRI). Unlike SSRIs, most SNRIs have an ascending rather than a flat dose–response curve due to their capacity to bind predominantly at the serotonin transporter at low doses and achieve more binding of the norepinephrine transport as the dose increases (see Shelton, 2019, for review). Venlafaxine and its metabolite desvenlafaxine do not inhibit CYP enzymes, so these medications are a good option if drug–drug interaction is a concern. However, venlafaxine may interact with CYP-2D6 inhibitors, and desvenlafaxine is subject to CYP-3A4 metabolism, which makes it vulnerable to enzyme inhibition or induction. At low doses, SNRIs can cause nausea, diarrhea, fatigue, and erectile dysfunction due to their prevailing serotonergic effects, and at higher doses where norepinephrine is enhanced, they can cause mild increases in blood pressure (dose dependent), tachycardia, diaphoresis, tremor, and anxiety. Desvenalfaxine is an active metabolite of venlafaxine and is FDA-approved for the treatment of major depressive disorder. It has higher affinity for serotonin receptors compared to norepinephrine and negligible affinity for dopamine and other receptors, leading to a relatively benign side effect profile (Faquih, Memon, Hafeez, Zeshan, & Naveed, 2019). Duloxetine is a moderate inhibitor of CYP-2D6 and

should be monitored closely and used at lower doses when used in combination with other CYP-2D6 metabolized drugs.

As far as efficacy goes, venlafaxine is very effective for the treatment of PTSD, as demonstrated in two multicenter RCTs that showed its superiority over placebo at 12 weeks in reducing PTSD symptoms (Davidson, Rothbaum, et al., 2006) and enhancing rates of remission at 6 months (Davidson, Baldwin, et al., 2006), confirming that many patients benefit from a longer treatment duration. All clinical practice guidelines recommend venlafaxine in the treatment of PTSD, ranging from strong (VA/DoD, 2017) or moderate (American Psychological Association, 2017; National Institute for Health and Care Excellence, 2018) to low (Bisson et al., 2020; ISTSS, 2018) level of confidence that is comparable to the SSRIs fluoxetine, paroxetine, and sertraline.

As far as other SNRIs are concerned, desvenlafaxine, levomilnaciptran, and milnacipram have not been tested in the treatment of PTSD, and duloxetine has received very limited pilot testing. A 12-week open label in military veterans with PTSD found that duloxetine was effective in about half the participants and possessed good tolerability (Villarreal, Cañive, Calais, Toney, & Smith, 2010). A naturalistic study of 21 treatment refractory male combat veterans also supported the use of duloxetine in this complex population (Walderhaug et al., 2010). Given the prevalence of pain conditions in patients with PTSD, duloxetine may offer dual benefit to a subset of PTSD patients. Placebo-controlled trials are needed to confirm these initial findings.

Tricyclic Antidepressants

As a group, the tricyclic antidepressants (TCAs) encompass a wide range of drugs that exert their primary action by blocking the presynaptic reuptake of serotonin and/or norepinephrine (i.e., imipramine, nortriptyline), with the notable exceptions of clomipramine, which is strongly serotonergic and has the least noradrenergic activity, and desipramine, which is highly specific for noradrenergic reuptake inhibition. Many tricyclic agents also affect nontarget receptors (i.e., cholinergic, histaminic), which can generate unintended side effects such as constipation, dry mouth, sedation, and urinary retention (Wang et al., 2018). In addition, TCAs have the dose-dependent potential to prolong the QTc interval, resulting in fatal cardiac toxicity in overdose. With the emergence of better tolerated SSRI and SNRI antidepressants, TCAs are rarely used as a primary treatment for psychiatric disorders, although they continue to be prescribed at low doses for headache prophylaxis, neuropathic pain, and insomnia.

The VA/DoD clinical practice guideline (2017) lists imipramine as a suggested treatment for PTSD based on small positive RCT (Kosten, Frank, Dan, McDougle, & Giller, 1991). No other clinical practice guideline has included a TCA as a recommended treatment. Amitriptyline has also demonstrated effective PTSD symptom reduction (Davidson et al., 1990), but it is listed as "moderate recommendation against" or "insufficent evidence" in several clinical practice guidelines.

Enthusiasm for desipramine as a treatment for PTSD was dampened by a negative RCT that was limited in size (N = 18) and duration (4-week crossover; Reist et al., 1989). However, in a study comparing paroxetine and desipramine with concurrent naltrexone versus placebo, Petrakis and colleagues (2012) found that both antidepressants were associated with significant reductions in PTSD symptom severity in a small sample (N = 88) of veterans diagnosed with comorbid PTSD and alcohol use disorder.

In this study, concurrent naltrexone treatment did not improve results with either antidepressant and desipramine was superior to paroxetine in terms of study retention and alcohol use outcomes. More investigation of desipramine is warranted.

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) act by inhibiting the enzyme responsible for intraneuronal breakdown of key monoamine neurotransmitters: dopamine, norepinephrine, and serotonin. MAOIs are efficacious in the treatment of major depression, and there is some evidence that supports their use in the treatment of social anxiety disorder. However, clinicians avoid prescribing MAOIs out of concern for problematic and serious side effects (i.e., serotonin syndrome and hypertensive crisis) that can occur as a result of drug–drug and dietary interactions. For this reason, clinical use and further research on MAOIs in PTSD has been limited. Open-label studies and one crossover study in the treatment of PTSD have generated mixed results.

The MAOI phenelzine showed a significant reduction in PTSD-related reexperiencing and arousal symptoms in an RCT in Vietnam combat veterans (Kosten et al., 1991), elevating it to a suggested treatment in the VA/DoD clinical practice guideline. Other clinical practice guidelines still regard MOAIs as having insufficient evidence to make a recommentation for or against treatment. Despite a positive European RCT (Katz et al., 1995), brofaromine, a rapidly reversible and selective MAO type A inhibitor, failed to show a significant difference compared to placebo in a diverse group of 146 adults with PTSD in the United States (Baker et al., 1995). Another highly selective reversible inhibitor of MAO type A is moclobemide, a drug that is not currently marketed in the United States but is available in more than 50 countries worldwide (Chen & Ruch, 1993). Unlike earlier MAOIs in which clinical use is limited by dietary restriction, side effects, and drug interactions, moclobemide has a favorable side effect profile with no dietary restrictions, minimal weight gain, and few sexual side effects (Bonnet, 2003). Additionally, it has been used safely in combination with other antidepressants. Two open-label studies of moclobemide suggest its potential to reduce symptoms of PTSD (Neal, Shapland, & Fox, 1997; Onder, Tural, & Aker, 2006). A placebo-controlled trial with moclobemide in the treatment of PTSD would be of interest.

Other Classes of Antidepressants

Trazodone and nefazodone are antidepressants that enhance serotoninergic activity by combining the reuptake inhibition of an SSRI with postsynaptic blockade of serotonin$_2$ receptor. Introduced in 1981, trazodone remains widely used in the treatment of sleep disturbances in patients with PTSD due to its pronounced sedative effects, relative safety, low cost, and nonaddictive property (Brownlow, Harb, & Ross 2015; Warner, Dorn, & Peabody, 2001). Trazodone is prescribed to approximately one-third of veterans treated for PTSD in VHA (Krystal et al., 2017). Trazodone is most often added to SSRI or SNRI therapy as an adjunctive sleep medicine. Although it is generally well tolerated, trazodone has the potential for residual daytime sedation at higher doses and is associated with the development of priapism (Mann & George, 2017). Despite its very wide use, trazodone's effectiveness for insomnia or other PTSD-related symptoms has not been tested in a randomized controlled trial. However, the VHA is embarking on a multisite adaptive-designed study to compare the effects of trazodone against

eszopiclone, gabapentin, and placebo in the treatment of sleep-related disturbances associated with PTSD (*ClinicalTrials.gov* Identifier: NCT03668041).

First marketed in 1994 for the treatment of major depression and after numerous open-label studies (see Hidalgo et al., 1999), nefazodone was shown to be more effective than placebo in a veteran sample in one study (Davis et al., 2004) and was no different than sertraline in two RCTs (McRae et al., 2004; Saygin, Sungur, Sabol, & Çetinkaya, 2002), leading to its recommendation as a suggested treatment for PTSD in VA/DoD clinical practice guidelines (2017). Although still available in the United States, nefazodone was withdrawn from the marketplace in several countries outside the United States due to rare but serious liver toxicity occurring in approximately 1 in every 250,000 patient years. Although not yet tested in clinical trials, vortioxetine is a multimodal antidepressant that combines modulation of multiple serotonin receptors and inhibition of the serotonin transporter. Preclinical animal studies have shown that its administration immediately after trauma exposure might reduce anxiety and cognitive/neuronal impairment (Brivio, Corsini, Riva, & Calabrese, 2019, Ozbeyli et al., 2019).

Bupropion selectively blocks the presynaptic reuptake of norepinephrine and dopamine. While it was initially available as an immediate release form, it is now available in sustained release once daily tablets. Small studies have failed to show that bupropion is helpful in the treatment of core symptoms of PTSD (Becker et al., 2007; Hertzberg, Moore, Feldman, & Beckham, 2001). Specifically, an 8-week RCT of bupropion versus placebo in addition to their usual pharmacological care showed no significant difference between the treatment groups in reduction of PTSD (Becker et al., 2007). However, bupropion has shown some evidence that it may be effective in reducing symptoms of depression (Canive, Clark, Calais, Qualls, & Tuason, 1998) and in facilitating smoking cessation in patients with PTSD (Hertzberg et al., 2001).

Mirtazapine is a novel antidepressant that works as an antagonist of the adrenergic $alpha_2$ autoreceptor and $alpha_2$ heteroreceptor and blocks $serotonin_2$ and $serotonin_3$ receptors, resulting in a net increase in noradrenergic and serotonergic neurotransmission (Anttila & Leinonen, 2001). Mirtazapine is often used as an adjunctive treatment for insomnia and nightmares because of its relatively benign side effect profile when compared to benzodiazepines and antipsychotics (Detweiler et al., 2016). Early pilot studies showed success in the treatment of PTSD (Alderman, Condon, & Gilbert, 2009; Bahk et al., 2002; Connor, Davidson, Weisler, & Ahearn, 1999; Kim, Pae, Chae, Jun, & Bahk, 2005) prompting further trials, including a small RCT that showed a significantly better response rate for mirtazapine (65%) compared to placebo (22%) and the advantage of mirtazapine in some, but not all, PTSD outcomes (Davidson et al., 2003). An open-randomization study comparing mirtazapine to sertraline showed nondifferential improvement in PTSD, except that mirtazapine led to a significantly greater number of responders (88%) compared to the sertraline group (69%) at week 6 (Chung et al., 2004). A 24-week RCT found that mirtazapine plus SSRI showed significantly greater improvement in depression and the PTSD remission rate (39%) than SSRI plus placebo (11%). However, no significant group differences in PTSD symptom reduction or improvement in sleep were found (Schneier et al., 2015). Davis and colleagues (2020) did not find a significant difference between mirtazapine and placebo as monotherapy for the treatment of PTSD in U.S. military veterans. Overall, mirtazapine as monotherapy or in combination with sertraline has shown insufficient efficacy in the treatment PTSD, and its potential for weight gain and daytime sedation limit its use (Cipriani et al., 2018).

NORADRENERGIC AGENTS

Alpha$_1$ Antagonists

The premise of an alpha$_1$ receptor antagonist is that it blocks the effects of norepinephrine at the postsynaptic alpha$_1$ receptor and dampens the central nervous system noradrenergic activity that contributes to PTSD hyperarousal symptoms and nightmares. Prazosin is an antihypertensive agent with a benign side effect profile that has been the most widely studied alpha$_1$ antagonist in the treatment of PTSD. Initially, it was recognized as the agent of choice to target traumatic nightmares, especially in combat veterans and active-duty soldiers. Prazosin is well tolerated and can be used as monotherapy or safely as an adjunct to SSRI or SNRI treatment. A 2016 meta-analysis of six controlled trials found a significant correlation between the use of prazosin and improvement in overall PTSD symptoms, traumatic nightmares, and sleep time (Khachatryan, Groll, Booij, Sepehry, & Schutz, 2016). While earlier RCTs observed that prazosin significantly reduced nightmare severity, increased total sleep time, and improved overall PTSD (Germain et al., 2012, Raskind et al., 2003, 2007, 2013; Taylor et al., 2008), a recent large VHA multisite RCT failed to replicate this benefit compared to placebo (Raskind et al., 2018). It should be noted that the VHA trial had a large placebo effect, which may have been attributable, in part, to the lower severity of illness and more concurrent psychotherapy and psychopharmacologic treatments in participants at baseline compared to earlier studies.

Based on the negative results of the VHA study by Raskind and colleagues (2018), the VA/DoD clinical practice guideline recommends against the use of prazosin for the treatment of PTSD. However, many investigators assert that the findings of this VHA study do not entirely negate the positive outcomes seen in earlier trials. Two systematic reviews and meta-analyses that included the VHA study have since been conducted. Both meta-analyses determined that prazosin is effective for the treatment of nightmares, and one confirmed its therapeutic effects for PTSD. Specifically, the pooled effect estimates from six RCTs including 429 patients showed that prazosin has a statistically significant benefit on overall PTSD symptoms and sleep disturbances, including nightmares and sleep quality (Reist et al., 2020). A meta-analysis of eight RTCs, including 575 patients, reported similar findings (Zhang et al., 2020). The Zhang and colleagues (2020) meta-analysis included the two RCTs in people with concurrent PTSD and alcohol use disorder (Petrakis et al., 2016; Simpson et al., 2015), whereas Reist and colleagues (2020) confined their meta-analysis to RCTs in PTSD samples. These findings suggest that prazosin has moderate benefit, and additional studies in broader populations are needed before definitive treatment recommendations can be made. Identifying a PTSD phenotype that would be responsive to α_1-adrenoreceptor antagonists might also contribute to the design of future RCTs. For example, Raskind and colleagues (2016) showed that relatively high pretreatment blood pressure significantly predicted greater therapeutic response to prazosin in active-duty combat soldiers with PTSD. In addition, polysomnographic characterization of physiological concomitants of nightmares and/or clinical indicators of increased autonomic arousal, such as nocturnal sweating, would potentially help identify the PTSD phenotype responsive to prazosin.

Terazosin and doxazosin are other alpha$_1$ antagonists that may benefit PTSD and PTSD-related nightmares, as reported in case reports/series (Calegaro, Mosele, Duarte, da Silva, & Trindade, 2019; Nirmalani-Gandhy, Sanchez, & Catalano, 2015; Salviati et al., 2013; Sethi & Vasudeva, 2012), a retrospective chart review (Detweiler et al., 2016;

Roepke et al., 2017), a small open-label study (Richards et al., 2018), and a small crossover study (Rodgman et al., 2016). An RCT has not been conducted with the alpha$_1$ antagonists terazosin or doxazosin. However, an RCT of doxazosin for the treatment of co-occurring PTSD and alcohol use disorder in military veterans is currently underway (Back et al., 2018).

Alpha$_2$ Agonists

Alpha$_2$-adrenergic agonists have been investigated as a potential treatment for PTSD due to their ability to reduce presynaptic norepinephrine release. To date, clonidine has only retrospective chart reviews (Detweiler et al., 2016; Wendell & Maxwell, 2015) and one open-label study using clonidine in combination with imipramine (Kinzie & Leung, 1989), suggesting that it may improve PTSD symptoms and PTSD-related nightmares. Guanfacine was tested in two RCTs in veterans with PTSD, and these studies failed to show a significant difference between drug and placebo in reduction of PTSD (Davis et al., 2008; Neylan et al., 2006), despite previous positive case reports (Horrigan, 1996; Horrigan & Barnhill, 1996) and an open-label study (Connor, Grasso, Slivinsky, Pearson, & Banga, 2013). Current guidelines do not recommend the use of clonidine or guanfacine for management of PTSD or PTSD-related nightmares. Larger trials are needed to determine the role, if any, of alpha$_2$ agonists in the management of PTSD.

Beta Antagonists

Beta antagonists, commonly known as beta blockers, particularly those with lipophilic qualities that cross the blood–brain barrier, have the theoretical potential to prevent or reduce PTSD symptoms by blocking memory enhancement caused by emotional arousal and by dampening norepinephrine release during stress. Though several lipophilic beta blockers exist, propranolol has been the most frequently investigated agent of interest. Studies have focused on propranolol as an intervention to (1) treat PTSD symptoms, (2) deter the onset of PTSD immediately after a traumatic event, and (3) decrease physiological response to memory reactivation.

Little research has been conducted on the use of propranolol as a primary treatment for PTSD. A small prospective off-on-off designed study found a significant decrease in PTSD symptoms while on propranolol compared to placebo in 11 children with physical or sexual abuse-related chronic PTSD (Famularo, Kinscherff, & Fenton, 1988). A systematic review and meta-analysis both concluded that propranolol was no better than placebo in improving PTSD symptoms (Steenen et al., 2016).

Treatment with the beta blocker propranolol before or immediately posttrauma is theoretically effective at decreasing physiological reactivity in trauma survivors and secondarily preventing PTSD, although studies have shown mixed results. Pitman and colleagues (2002) studied the effect of posttrauma administration of propranolol to prevent the development of PTSD in emergency department patients using physiological reactivity as a proxy measure. At the 3-month follow-up, none of the propranolol group versus 43% of the placebo group exhibited physiological reactivity during subsequent script-driven traumatic imagery. Although not statistically significance, 10% of propranolol recipients as compared to 30% of placebo recipients met PTSD criteria a month following the traumatic event. Subsequently, Vaiva and colleagues (2003) observed a significant reduction in PTSD symptoms in adults who were given propranolol for 2 weeks immediately after a traumatic event compared to those who

received placebo. Conversely, a retrospective chart review of burned soldiers who received propranolol compared to matched controls did not see a difference in the postburn prevalence of PTSD (McGhee et al., 2009). Furthermore, two small RCTs of a short trial of propranolol started within 12 hours after a traumatic injury found no overall group differences in the prevention of PTSD (Hoge et al., 2012; Nugent et al., 2010). Another lipophilic beta blocker, metoprolol, started immediately after cardiac surgery led to a significant reduction in the number of standardized traumatic memories and PTSD symptoms in female patients, but not male patients, indicating there may be a gender relationship to the effects of beta blocker therapy (Krauseneck et al., 2010). A meta-analysis concluded that, compared to placebo, early posttrauma treatment with propranolol was no different than placebo in preventing the development of PTSD, although there was a nonsignificant trend toward decreasing the physiological response to emotional reminders of the traumatic event (Argolo, Cavalcanti-Ribeiro, Netto, & Quarantini, 2015).

In an open-label study, propranolol administered at weekly intervals to PTSD patients while actively recalling their traumatic experiences led to reductions in PTSD symptom severity, presumably due to disruption of reconsolidation of traumatic memories (Poundja, Sanche, Tremblay, & Brunet, 2012). A more recent study found that compared to placebo, propranolol given 90 minutes before a weekly trauma-focused therapy devoted to reactivation of the trauma memories led to significant improvement in PTSD symptoms in chronic PTSD patients (Brunet et al., 2018). These studies suggest that there is potential for propranolol to disrupt the reconsolidation of traumatic memories during exposure-type therapeutic exercises, but larger controlled trials are needed to confirm these initial findings.

ANTIPSYCHOTICS

Atypical antipsychotics have been studied as a potential psychopharmacological treatment option for the management of PTSD for over two decades. Atypical antipsychotics, also called second-generation neuroleptics, have varying degrees of the serotonin to dopamine receptor affinity ratio as well as varying affinities for $alpha_1$- and $alpha_2$-adrenergic receptors, all of which are implicated in the symptomatology of PTSD (Kelmendi et al., 2016). Targeted approaches that have been investigated include treatment as augmentation to antidepressants for treatment-refractory patients, as monotherapy treatment, and for concurrent psychotic features. Based on the current evidence, antipsychotics are not recommended for the treatment of PTSD by current clinical practice guidelines (American Psychological Association, 2017; ISTSS, 2018). The VA/DoD guideline went so far as to recommend against the use of atypical antipsychotics (VA/DoD, 2017). These recommendations are based on limited benefit shown in previous studies, including the negative VHA multisite study of risperidone, as well as the known risks of atypical antipsychotics such as metabolic complications, cardiovascular events, involuntary movement disorders, and extrapyramidal symptoms (Blanchet, 2003; De Hert et al., 2012). However, the use of antipsychotics for the treatment of concurrent psychotic symptoms may be justifiable, but the evidence is insufficient to make definitive recommendations.

Despite some literature supporting the use of antidepressants as a relatively effective treatment for PTSD, treatment failure or a partial response is often the result. Because atypical antipsychotics have been successfully used adjunctively for treatment-resistant

major depression (Mohamed et al., 2017), these medications have been tested as adjunctive agents (with antidepressants) in refractory PTSD patients. Retrospective and open-label studies have shown significant improvement when the atypical antipsychotics were added to current psychotropic treatment in PTSD patients who had not responded fully to initial therapy. However, these results have not been entirely confirmed in RCTs (Pilkinton et al., 2016; Richardson, Fikretoglu, Liu, & McIntosh, 2011; Robert, Hamner, Durkalski, Brown, & Ulmer, 2009; Robert et al., 2005; Sokolski, Denson, Lee, & Reist, 2003). Although two small randomized placebo-controlled trials found benefit with risperidone ($N = 65$; Bartzokis, Lu, Turner, Mintz, & Saunders, 2005) or olanzapine ($N = 21$; Stein, Kline, & Matloff, 2002) as adjunct therapy in combat veterans with treatment-resistant PTSD, the largest multisite RCT to date ($N = 247$), concluded that risperidone was no better than placebo over 6 months when added to current SSRI treatment (Krystal et al., 2011). This finding confirmed a separate smaller RCT in which risperidone was no better than placebo when added to sertraline in partial responders (Rothbaum et al., 2008). Neither aripiprazole (Naylor et al., 2015) nor ziprasidone (Hamner et al., 2019) differentiated from placebo in small RTCs in participants with PTSD who were refractory to prospective trial of an SSRI. In summary, a meta-analysis of the RCTs including risperidone, olanzapine, and aripiprazole concluded that, in comparison to placebo, adjunctive antipsychotics fail to significantly improve the core PTSD symptoms in patients who have previously failed antidepressant monotherapy (Lee et al., 2016).

Regarding monotherapy, open-label studies of atypical antipsychotics, including risperidone, quetiapine, olanzapine, and aripiprazole, showed significant improvement in PTSD symptoms (Mello, Costa, Schoedl, & Fiks, 2008; Petty et al., 2001; Villarreal et al., 2007; Youssef et al., 2012). However, subsequent randomized clinical trials have had mixed results. Small RCTs show an effect compared to placebo for risperidone (Reich, Winternitz, Hennen, Watts, & Stanculescu, 2004), olanzapine (Carey, Suliman, Ganesan, Seedat, & Stein, 2012), and quetiapine (Villarreal et al., 2016) monotherapy, while others did not differentiate risperidone (Padala et al., 2006), olanzapine (Butterfield et al., 2001), or ziprasidone (Ramaswamy, Driscoll, Smith, Bhatia, & Petty, 2016) from placebo.

Perhaps the most obvious potential for atypical antipsychotics is in the management of PTSD with secondary psychotic features. Indeed, open-label studies of risperidone (Kozaric-Kovacic, Pivac, Muck-Seler, & Rothbaum, 2005) or quetiapine (Kozaric-Kovacic & Pivac, 2007) observed a significant improvement in both overall PTSD symptoms and psychotic symptoms in this population. Only one study compared an atypical antipsychotic to placebo; it found that risperidone improved psychotic symptoms but not overall PTSD symptoms in combat veterans (Hamner et al., 2003). A trial comparing olanzapine to the typical antipsychotic fluphenazine in patients with PTSD and psychotic features found that olanzapine significantly improved overall PTSD and psychotic symptoms in combat veterans with PTSD compared to fluphenazine (Pivac, Kozaric-Kovacic, & Muck-Seler, 2004), but this study lacked a placebo control. It may be reasonable to use antipsychotics in PTSD patients who present with psychotic features, although the evidence is limited. It is imperative to distinguish PTSD dissociative symptoms from a primary psychotic disorder through a comprehensive assessment of behaviors and symptoms to optimize the potential benefit of PTSD treatment and minimize the risk associated with antipsychotic use. Furthermore, when antipsychotics are prescribed, follow-up and reassessment are essential to monitor the metabolic side effects and avoid extended use in patients who receive no benefit.

ANTICONVULSANTS

Anticonvulsant medications were originally suggested as potential treatments for PTSD due to similarities in proposed mechanisms of hypersensitivity in seizure disorder and rekindling of recurrent memories and flashbacks in PTSD (Post, Weiss, Li, Leverich, & Pert, 1999). Anticonvulsants, including topiramate, lamotrigine, divalproex, tiagabine, and pregabalin, have been tested mostly as monotherapy in the treatment of PTSD. Topiramate was suggested to be efficacious in the treatment of PTSD, particularly in regard to hyperarousal symptoms (Batki et al., 2014; Varma, Moore, Miller, & Himelhoch, 2018); however, results of studies and meta-analyses are conflicting. According to a systemic review by Lee and colleagues (Lee et al., 2016), topiramate did not show a significant difference from placebo. Additionally, although two previous meta-analyses concluded that topiramate yielded moderate-to-large effect sizes as monotherapy (Jonas et al., 2013; Watts et al., 2013), these meta-analyses were based on two small 12-week placebo-controlled studies, one of which only showed improvement in secondary PTSD outcomes (Tucker et al., 2007) and the other of which was not significantly different from placebo, except for the avoidance/numbing symptom cluster (Yeh et al., 2011). Furthermore, in the treatment of co-occurring alcohol use disorder and PTSD, topiramate failed to demonstrate efficacy in improving the primary symptoms of PTSD, despite showing effectiveness in reducing alcohol consumption, alcohol craving, and hyperarousal symptoms (Batki et al., 2014). This is of concern given the high comorbidity of PTSD and alcohol use disorder (up to 52%) among both civilian and military populations (Baker et al., 2009; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). There is only one small study to date indicating that lamotrigine improves PTSD symptoms (e.g., avoidance/numbing and reexperiencing symptoms), but due to its small sample size, the results could not be compared statistically (Hertzberg et al., 1999).

Two RCTs failed to show differences between divalproex and placebo in the treatment of PTSD in veterans with chronic PTSD (Davis et al., 2008; Hamner et al., 2009). Similarly, a trial in 232 adults with a diagnosis of PTSD concluded that tiagabine monotherapy was ineffective compared to placebo (Davidson, Brady, Mellman, Stein, & Pollack, 2007). In a 2016 meta-analysis, both divalproex and tiagabine failed to demonstrate effectiveness when compared to placebo, and divalproex was also ineffective when combined with an antidepressant (Lee et al., 2016). The VA/DoD clinical practice guideline (2017) strongly recommends against the use of divalproex and tiagabine in the treatment of PTSD.

Currently, the only published trials of pregabalin are small, single-site studies that are considered at high risk of bias and have therefore been excluded from several systemic reviews (Hoskins et al., 2015; Lee et al., 2016; Watts et al., 2013). An augmentation trial of pregabalin concluded that pregabalin was effective at reducing the severity of PTSD symptoms in 37 male patients with combat-related PTSD, all of whom were simultaneously receiving an SSRI (Baniasadi, Hosseini, Fayyazi Bordbar, Rezaei Ardani, & Mostafavi Toroghi, 2014). This study has methodological and bias concerns that bring into question the validity of its findings.

Anticonvulsants have several known adverse effects and associated risks, such as an increased risk of suicidal thoughts or behaviors. Topiramate can cause cognitive side effects such as transient impaired learning and memory, as well as paresthesia, kidney stones, and hyperammonemia. When dose titration recommendations are not carefully followed, lamotrigine can cause serious rash, especially when combined with valproate.

Divalproex carries a significant risk of polycystic ovarian syndrome, hirsutism, weight gain, and teratogenicity, and requires monitoring of liver enzymes and platelets. Pregabalin is associated with the increased risk for several adverse events, especially those affecting cognition and coordination (Zaccara, Gangemi, Perucca, & Specchio, 2011). Due to the lack of strong evidence for their efficacy and/or the known adverse effects and associated risks, anticonvulsants are not recommended for the treatment of PTSD in any of the clinical practice guidelines. Prescribing practices appear to be following this guideline, as shown in an analysis of electronic medical and pharmacy record. Although 25% of VHA patients with PTSD receive an anticonvulsant in their initial year of PTSD treatment, 95% had an indication unrelated to PTSD, such as pain and headache disorders (Shiner, Westgate, Bernardy, Schnurr, & Watts, 2017).

BENZODIAZEPINES AND NONBENZODIAZEPINE SEDATIVE–HYPNOTICS

Clinical practice guidelines unanimously recommend against the use of benzodiazepines for the primary treatment of PTSD because the risks far outweigh any potential benefit. A systematic review concluded that benzodiazepines are ineffective for PTSD and relatively contraindicated due to potentially overall worsened PTSD outcomes, exacerbated aggression and depression, risk of tolerance, dependence, and high abuse potential (Guina, Rossetter, DeRhodes, Nahhas, & Welton, 2015). Historically in clinical settings, benzodiazepines were frequently used "as needed" for the treatment of PTSD despite the lack of evidence of efficacy in clinical trials. Alprazolam (Braun, Greenberg, Dasberg, & Lerer, 1990) and clonazepam (Cates, Bishop, Davis, Lowe, & Woolley, 2004) failed to show significant differences in reduction of PTSD severity compared to placebo in very small prospectively randomized studies. Use of benzodiazepines in veterans diagnosed with PTSD was associated with a higher rate of VHA inpatient and emergency room visits, higher rates of suicidal thoughts and behaviors, and a nearly threefold increased risk of death due to suicide compared to those not prescribed a benzodiazepine (Deka et al., 2018). Risk of respiratory complications in people with chronic obstructive pulmonary disease and PTSD is a highlighted risk, and yet, approximately 25% of veterans with COPD and PTSD were prescribed a long-term benzodiazepine in VA medical centers between 2010 and 2012 (Donovan et al., 2019). However, benzodiazepine use has been decreasing overall in veterans with PTSD, especially in VA medical centers that have targeted educational academic detailing (Bounthavong et al., 2020).

A class of nonbenzodiazepine drugs, called "Z-drugs" (including zolpidem, zopiclone, eszopiclone, and zaleplon), emerged in the 1990s as a safer alternative to benzodiazepines for the intermittent treatment of insomnia. This class of medications modulates the benzodiazepine-specific subunit site as a specific agonist of the gamma-aminobutyric acid A receptor. Although purported to be safer, these drugs have serious risks, such as impaired driving causing motor vehicle accidents, falls leading to fracture, and respiratory disease exacerbation, especially when combined with opiates (Brandt & Leong, 2017). One randomized, double-blind, placebo-controlled crossover study evaluated the effects of eszopiclone and placebo in 24 patients with PTSD and insomnia who were receiving psychotherapy or antidepressants for more than one month and found that eszopiclone significantly improved PTSD symptoms and sleep latency; however, the total duration of sleep was not significantly different between groups (Pollack et al.,

2011). This evidence is considered insufficient in determining a recommendation for use of eszopiclone in the treatment of PTSD.

N-METHYL-D-ASPARTATE ANTAGONISTS

Recent FDA approval of intranasal esketamine, a rapid-acting antagonist of *N*-methyl-D-aspartate (NMDA) glutamatergic receptors, for treatment-resistant major depressive disorder (Daly et al., 2018) has accelerated interest in testing the efficacy of ketamine-type medications in PTSD. Ketamine and esketamine (the S enantiomer of ketamine) act to induce glutamate neurotransmission, which brings about a transient "surge" of glutamate neurotransmission in the prefrontal cortex, release of brain-derived neurotrophic factor, and a sustained increase in prefrontal cortex synaptic connectivity (Abdallah, Sanacora, Duman, & Krystal, 2018). A double-blind randomized crossover trial in 41 patients with PTSD showed significant and rapid improvement in PTSD and depressive symptoms after intravenous ketamine compared to the active control, midazolam, with longer periods of remission for those who received ketamine first (Feder et al., 2014). In addition to a number of case reports, an open-label study of repeated ketamine infusions (6 over 12 days) for the treatment of comorbid PTSD and treatment-resistant depression in veterans showed that this regimen induced a rapid and significant response in PTSD and depressive symptoms that was more durable than that reported for single-infusion studies (Abbott et al., 2018). Esketamine has not been tested in PTSD. Six or more clinical trials with ketamine are ongoing or were recently completed as of the writing of this chapter, either as stand-alone treatment or in combination with PE therapy. Ketamine and esketamine are controlled drugs with potential for abuse and misuse. Consistent with properties of an anesthetic, their side effects include transient sedation, lightheadedness, increased blood pressure, dissociative symptoms, confusion, and blurred vision. Thus, the patient is monitored for several hours after treatment is administered in a clinic setting. These medications are at the investigational stage for the treatment of PTSD, and the early results have not been included in meta-analysis or clinical practice guidelines.

Other NMDA receptor antagonists are also being explored in the treatment of PTSD. Memantine is an antagonist of NMDA receptors that may also have activity at serotonin, acetylcholine, and nicotinic receptors that led to improvement in cognitive functioning and reduced PTSD symptoms in two open-label pilot studies (Battista, Hierholzer, Khouzam, Barlow, & O'Toole, 2007; Ramaswamy, Madabushi, Hunziker, Bhatia, & Petty, 2015). Inhaled nitrous oxide (N_2O), or "laughing gas," is a weak, rapid-acting noncompetitive inhibitor of NMDA that has long been in use as a short-acting antiesthetic in dental practices, but only recently has it been explored for its use in treatment-resistant depression, which showed that N_2O led to a significant improvement in depression at 2 hours and 24 hours compared to placebo (Nagele et al., 2015). While formal studies in PTSD are lacking, an RCT of N_2O suggests that it may be useful in reducing intrusive memory recall in a time-dependent manner (Das et al., 2016). However, its use in participants with a high level of dissociative symptoms increased the frequency of intrusive recall. Additionally, chronic administration of N_2O has been associated with acute vitamin B_{12} deficiency and neurological sequelae (Garakani et al., 2016). Xenon is an inhaled gas that also functions as a noncompetitive antagonist of NMDA and can affect reconsolidation of fear memories in preclinical studies (Meloni, Gillis, Manoukian, & Kaufman, 2014). At this point, these agents are entirely

experimental and should not be tried in a clinical setting until efficacy and safety signals can be confirmed.

MEDICATION-ASSISTED PSYCHOTHERAPY

NMDA glutamatergic receptors are found in the central nervous system where they affect brain plasticity, learning, and memory (Folch et al., 2018). As such, theories of assisting new learning during cognitive-behavioral therapy or PE therapy with medications from this class have become popular (Michael et al., 2019). Several agents that act to enhance cognition and support fear extinction are under study, including D-cycloserine, cortisol, yohimbine, methylene blue, and oxytocin. All studies to date suffer from small sample sizes and limited control groups, resulting in substantial risk of bias.

Preclinical and clinical evidence suggests that D-cycloserine, an NMDA receptor agonist, could improve fear extinction, facilitate extinction learning, and reduce fear reinstatement (Davis, Ressler, Rothbaum, & Richardson, 2006) and that benzodiazepines may interfere with the extinction of fear conditioning and/or potentiate the acquisition of fear responses and worsen recovery from trauma (Hebert, Potegal, Moore, Evenson, & Meyerhoff, 1996; Matar, Zohar, Kaplan, & Cohen, 2009). This finding has been translated in the clinical research setting in a placebo-controlled augmentation of PE therapy, with either D-cycloserine or alprazolam given 30 minutes prior to virtual reality exposure sessions in combat veterans with PTSD (N = 156). Although no significant differences were found between the three groups in terms of PTSD outcomes, the alprazolam group had a significantly greater proportion of participants who continued to meet full PTSD criteria relative to the placebo group at 3-month follow-up, but these differences were not maintained at the 12-month follow-up (Rothbaum et al., 2014). In total, three of four placebo-controlled studies did not show a differential benefit of D-cycloserine administered prior to PE therapy sessions over a 6- to 12-week follow-up compared to placebo (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012; Difede et al., 2014; Litz et al., 2012; Rothbaum et al., 2014). Although cortisol is less often studied, one double-blind placebo-controlled trial (N = 24) revealed significant benefit for assisting PE therapy with a presession dose of cortisol compared to placebo (Yehuda et al., 2015). Although no difference between groups were seen in terms of PTSD or depressive symptom changes, yohimbine, an alpha$_2$-adrenergic receipt antagonist, resulted in a significantly stronger reduction of the trauma-cued heart-rate reactivity compared to placebo when paired with weekly exposure therapy. Small trials of pre-PE-session dosing with oxytocin, a nonaneuropeptide belonging to the rhodopsin type (Class 1) of the G-protein-coupled receptor superfamily (Flanagan, Sippel, Wahlquist, Moran-Santa Maria, & Back, 2018) and methylene blue, an inhibitor of nitric oxide synthase and guanylate cyclase, did not show any differences compared to placebo in assisting PE (Zoellner et al., 2017).

Several psychedelic drugs that have risk of misuse and abuse are being tested in the treatment of PTSD (see Nutt, 2019, for a historical review), including psilocybin and lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (MDMA). MDMA, a psychoactive compound that targets multiple domains, most predominantly serotonergic systems, is being explored as a treatment to facilitate psychotherapy (8-hour sessions) in the treatment of PTSD (Feduccia & Mithoefer, 2018). Five small trials have been conducted, and although each study was underpowered to unequivocally

demonstrate effectiveness, a recent meta-analysis indicated support for MDMA effects in decreasing PTSD symptoms and yielding a clinical response (Bahji, Forsyth, Groll, & Hawken, 2020). One of the studies included 26 military veterans with chronic PTSD who were randomized to one of three doses of MDMA-administered in two 8-hour sessions of psychotherapy about 1 month apart. At 1-month follow-up, 86% of the 75 mg group, and 58% of the 125 mg group no longer met criteria for PTSD, compared to 29% in the 30 mg active control (Feduccia et al., 2019). These MDMA-assisted psychotherapy studies all suffer from design flaws, including small sample size, quasi-randomization, lack of adequate control, and unmasking of treatment during sessions due to obvious psychomimetic drug effects. A Phase 3 study is now underway at 16 sites in the United States, Canada, and Israel.

OTHER PSYCHOTROPICS

Methylphenidate is a stimulant that augments cerebral dopaminergic and noradrenergic function and is typically used in the treatment of attention-deficit/hyperactivity disorder. In an RCT of methylphenidate compared to galantamine (a cholinesterase inhibitor) in adults with PTSD and/or history of mild traumatic brain injury, McAllister and colleagues (2016) found a clinically meaningful and statistically significant improvement compared to placebo for methylphenidate and measures of cognition, postconcussive symptoms, and PTSD, including all PTSD symptom clusters. The effect size for the PTSD outcome was very large (effect size = 1.88) over the 12-week follow-up period, and treatment was well tolerated. A larger trial is needed to confirm these promising results.

Buspirone is a partial serotonin$_{1A}$ agonist that is used as an adjunctive agent in the treatment of depression and anxiety disorders. Buspirone has a benign side effect profile and lacks addiction potential. Small open-label trials and case reports in PTSD treatment showed some benefit as monotherapy (Duffy & Malloy, 1994; Wells et al., 1991) and as a potentiator of antidepressant treatment (Hamner, Ulmer, & Horne, 1997).

Cyproheptadine is an antihistamine that possesses antagonist effects on the serotonin$_{2A–C}$ receptors. Its sedating antihistaminic properties and serotonergic activity prompted initial interest in the treatment of PTSD-related sleep issues; however, an open-label study of cyproheptadine in 16 patients with PTSD did not show any consistent benefit, and the drug was poorly tolerated by study subjects (Clark et al., 1999). Case reports suggest that it may be useful for the reduction of nightmares in some individuals with PTSD (Gupta et al., 1998; Rijnders, Laman, & van Diujn, 2000); it has been recommended as an alternative for PTSD-associated nightmares by the American Academy of Sleep Medicine (Morgenthaler et al., 2018). However, Jacobs-Rebhun and colleagues (2000) found that the cyproheptadine treatment group had nonsignificant worsening of nightmares compared to placebo.

N-Acetylsysteine (NAC) is familiar to many clinicians as a treatment for acetaminophen overdose, but there is increasing interest in it due to its antioxidant potential as a precursor to glutathione and its modulating activity at glutamatergic, dopaminergic and neurotropic sites. An RCT of NAC plus cognitive-behavioral therapy for substance use disorder in veterans with concurrent PTSD showed significant improvements in PTSD symptoms, depression, and cravings compared to placebo (Back et al., 2016). Larger studies are needed to replicate these initial findings.

POLYPHARMACY

Polypharmacy in the treatment of PTSD is common due to the difficulty in achieving remission with monotherapy. From 1996 to 2006, trends for the percentage of visits with a psychiatrist in which any psychotropic medication was prescribed significantly increased from 73 to 86% for one medication, 43 to 60% for two or more medications, and 17 to 33% of those visits in which three or more psychotropic medications were prescribed by office-based physicians (Mojtabai & Olfson, 2010). This increase was particularly noted for the antidepressant and antipsychotic medication combination for any disorder and for an antidepressant plus sedative-hypnotic combination for an anxiety disorder, a category that included PTSD—that is, before 2013, when DSM-5 placed PTSD in a different diagnostic category (Mojtabai & Olfson, 2010). The average number of medications increased by 40% for psychiatric disorders across the board. In U.S. Iraq/Afghanistan War veterans, the use of five or more central nervous system (CNS)–acting medications was seen in 8.4% of a total VHA cohort in 2011 and was most strongly associated with a diagnosis of PTSD, depression, and traumatic brain injury (Collett et al., 2016). Polypharmacy was independently associated with a significantly increased number of drug/alcohol overdoses and suicide-related behaviors (Collett et al., 2016). In addition, polypharmacy puts the patient at risk of drug–drug interactions and side effects. Thus, a prescriber should always consider the risks of polypharmacy with an intentional goal of discontinuing ineffective medications prior to adding new medications.

After decades of data collection on the demographic and phenotypic aspects of trauma and PTSD, researchers are looking toward epigenetic studies to advance diagnosis and precision treatment. While no single gene has been implicated in the development of PTSD, a number of candidate genes have been identified that appear to modulate this risk (Blacker, Frye, Morava, Kozicz, & Veldic, 2019; see Bustamante et al., Chapter 11, this volume). A potential epigenetic marker in peripheral blood, NR3C1, which encodes the glucocorticoid receptor, was examined in an RCT of GSK561679, a corticotropin-releasing factor 1 receptor antagonist (Pape et al., 2018). Although GSK561679 was not found to be superior to placebo in the overall study population, further analysis found that the women with high-baseline NR3C1 methylation and child abuse experienced the greatest change in PTSD symptoms after receiving the study drug. Future research on epigenetic markers may help lead to more precision in treatment and reduce unnecessary polypharmacy.

CONCLUSION

The greatest evidence combined with the fewest risks in the management of PTSD appears to be the SSRI and SNRI antidepressants as first-step pharmacotherapy. Other antidepressants, such as nefazodone, imipramine, and phenelzine, have shown some evidence of effect, but due to their unsatisfactory side effect profile, they must be used with caution. The use of prazosin is still being debated, but given its benign side effect, it is still commonly used in the treatment of PTSD. Due to a high risk of aversive side effects and/or negative studies, benzodiazepines, antipsychotics, and anticonvulsants are not recommended for the treatment of PTSD. Additional research is needed on the effects of newer generations of atypical neuroleptics. Other psychotropics tested in PTSD groups have shown insufficient evidence to support a recommendation for

or against treatment. Research is still very active in trying to understand the place for controlled medications, such as stimulants and NMDA antagonists, in the treatment of PTSD. Suggestions for future research include the pursuit of identifying phenotypes and genetic polymorphisms to guide precision medicine, studies on next-step switch or combination treatments, and translational research that brings novel drugs into the clinical trial forum.

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CHAPTER 24

Treating PTSD When Common Comorbid Disorders Are Present

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Understanding how to treat posttraumatic stress disorder (PTSD) when a comorbid condition is present is crucial, as most individuals with PTSD have additional mental health diagnoses (Goldstein et al., 2016). The presence of comorbidities often raises questions regarding whether clients may be too complicated or fragile to handle evidence-based treatment for PTSD in which trauma processing is required (Cook et al., 2013), such as prolonged exposure (PE; Foa, Hembree, & Rothbaum, 2007) or cognitive processing therapy (CPT; Resick, Monson, & Chard, 2017). Another common question is whether PTSD and comorbid conditions should be treated concurrently or sequentially. In this chapter, we review research evidence and recommendations from clinical practice guidelines regarding how to treat PTSD when comorbidities are present. We also discuss potential complications that may accompany comorbidities.

SUBSTANCE USE DISORDERS

The National Epidemiologic Survey on Alcohol and Related Conditions–III (NESARC-III), which surveyed U.S. adults, found that PTSD was significantly associated with substance use disorders (SUDs) even after adjusting for sociodemographic and diagnostic covariates (odds ratio [OR] = 1.3–1.5; Goldstein et al., 2016). Comorbid PTSD-SUD is associated with a more severe clinical profile than either disorder alone, including more physical health diagnoses, psychiatric comorbidities, suicidality, inpatient hospitalizations (Bowe & Rosenheck, 2015; Norman, Haller, Hamblen, Southwick, & Pietrzak, 2018), and a range of psychosocial and functional impairments, such as unemployment and social support problems (Drapkin et al., 2011).

According to the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013), SUDs result from

the problematic use of substances. SUD symptoms fall within four categories: impaired control, social impairment, risky use, and pharmacological criteria. To meet criteria for SUDs, individuals must experience at least 2 out of 11 possible symptoms within a 12-month period.

Treatment of PTSD-SUD

According to the most recent Department of Veterans Affairs and Department of Defense clinical practice guideline for SUDs (VA/DoD, 2015), a variety of evidence-based pharmacological and psychosocial interventions exist for treating SUDs. For instance, for alcohol use disorder (AUD), evidence exists for several pharmacotherapy options, including acamprosate, disulfiram, naltrexone, and topiramate. Recommended psychosocial interventions include cognitive-behavioral approaches and motivational enhancement therapy.

When SUD occurs alongside PTSD, the VA/DoD (2017) clinical practice guideline for PTSD recommends treating both disorders with evidence-based treatments, such as PE and CPT for PTSD. This stands in contrast to common clinician beliefs that individuals with comorbid PTSD-SUD should receive SUD treatment and achieve abstinence prior to engaging in trauma-focused treatment. This sequential model assumes the *Pandora's Box hypothesis*—that active substance use interferes in the ability to process trauma and that trauma-focused treatment may exacerbate SUD symptoms or lead to relapse (Souza & Spates, 2008).

There has been growing recognition that PTSD-SUD should be treated in a concurrent or integrated fashion in part due to evidence that PTSD improvement is more likely to be associated with future SUD improvement (Hien et al., 2010; Kaczkurkin, Asnaani, Alpert, & Foa, 2016) than the reverse (Hien et al., 2010). Integrated therapies for PTSD-SUD include both non-trauma-focused and trauma-focused approaches. Seeking Safety, a non-trauma-focused integrated intervention, has been extensively studied in both civilian and veteran samples (Lenz, Henesy, & Callender, 2016). Seeking Safety focuses on enhancing coping strategies to better manage PTSD and SUD symptoms, and includes up to 25 topics covering interpersonal, cognitive, behavioral, and case-management domains. A 2015 meta-analysis and subsequent studies show that Seeking Safety has no added value to SUD-only treatment since both reduce PTSD symptoms and SUD use comparably (Garland, Roberts-Lewis, Tronnier, Graves, & Kelley, 2016; Roberts, Roberts, Jones, & Bisson, 2015; Schäfer et al., 2019).

In contrast, integrated trauma-focused treatments, such as PE integrated with SUD treatment, have resulted in better PTSD outcomes and sometimes SUD outcomes than SUD-only treatments (Roberts et al., 2015). As a result, the VA/DoD (2017) clinical practice guideline for PTSD recommends trauma-focused treatments together with evidence-based SUD treatment as a first-line approach for individuals with PTSD-SUD. One of the most well-studied integrated exposure-based treatments for PTSD-SUD is concurrent treatment of PTSD and SUDs using PE (COPE; Back et al., 2015), which integrates PE with relapse prevention skills for substance use. COPE results in better PTSD outcomes relative to SUD interventions and coping skills therapies for PTSD-SUD across diverse adult samples (Mills et al., 2012; Norman et al., 2019; Ruglass et al., 2017). COPE generally results in similar SUD decreases when compared to SUD treatment or coping skills therapies (Back et al., 2019; Mills et al., 2012; Norman et al., 2019).

The literature on pharmacological treatments for PTSD-SUD is limited. In a recent review of pharmacological treatments for PTSD and AUD, Petrakis and Simpson (2017) outlined findings of pharmacological interventions targeting PTSD (e.g., sertraline), AUD (e.g., naltrexone), or both disorders (e.g., prazosin), in PTSD-AUD samples. Overall findings were mixed, with weak evidence in support of naltrexone to target AUD symptoms and some evidence in support of sertraline to treat PTSD. Similarly, inconclusive findings emerged with regard to medications aiming to target both disorders, such as prazosin. Importantly, the literature suggests that medications designed to target either PTSD or AUD symptoms are safe to prescribe to individuals presenting with both disorders. Nevertheless, there is clearly a need to continue to investigate additional pharmacological treatments, such as topiramate, which has demonstrated promise in treating both PTSD and AUD symptoms.

Future Directions

Future research is needed to examine the efficacy of additional evidence-based PTSD treatment modalities such as CPT and written exposure therapy (WET; Sloan & Marx, 2019), and pharmacological agents, such as topiramate, which have the potential to target both disorders. Most research has been with AUD or mixed substances. Thus, more information is needed about treating PTSD with other specific SUDs such as opioids or methamphetamines. Furthermore, there is limited research on the effect of treatment setting or session spacing on PTSD-SUD therapies. For instance, providing PTSD treatment within residential SUD settings in a massed format is promising (Norman et al., 2016) but has not yet been evaluated in a randomized controlled trial (RCT). While it is presumed that integrated treatment is better than sequential, only one RCT thus far has directly compared the two models (Kehle-Forbes et al., 2019). Integrated and sequential treatment did not have significantly different outcomes, but dropout was comparably high across both conditions.

MAJOR DEPRESSIVE DISORDER AND ANXIETY DISORDERS

Major depressive disorder (MDD) is the most common co-occurring psychiatric disorder with PTSD. A systematic review that included 57 studies showed that 52% of individuals with current PTSD also had co-occurring MDD (Rytwinski, Scur, Feeny, & Youngstrom, 2013). The study found that individuals with PTSD who were in the military or had interpersonal traumas had higher rates of MDD than civilians or those who experienced natural disasters. In another study with a representative U.S. sample (Goldstein et al., 2016), the presence of PTSD was strongly associated with MDD (OR = 1.6) and anxiety disorders (OR = 2.8).

The co-occurrence of PTSD with MDD is associated with higher subjective distress and impairment than PTSD without MDD (Ikin, Creamer, Sim, & McKenzie, 2010; Momartin, Silove, Manicavasagar, & Steel, 2004; Nixon, Nishith, & Resick, 2004; Post, Zoellner, Youngstrom, & Feeny, 2011). Individuals with both disorders utilize more mental and physical health care (Boscarino, Adams, & Figley, 2005; Chan, Cheadle, Reiber, Unutzer, & Chaney, 2009; Stapleton, Asmundson, Woods, Taylor, & Stein, 2006) and have greater distress and functional impairment than individuals with PTSD or MDD only (Shah, Shah, & Links, 2012).

Treatment of PTSD-MDD

According to VA/DoD clinical practice guidelines for MDD (VA/DoD Management of Major Depressive Disorder Work Group, 2016b), front-line treatments for MDD include cognitive-behavioral therapy (CBT), behavior therapy/behavioral activation, acceptance and commitment therapy (ACT), and mindfulness-based cognitive therapy (MBCT). Evidence-based pharmacotherapy for MDD includes selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion. The guideline does not give a higher recommendation to either psychotherapy or pharmacotherapy.

Many studies have shown that MDD symptoms improve through PTSD treatment and that PTSD can still be effectively treated with evidence-based PTSD treatment when MDD is present. A recent review of PTSD treatments conducted for the Agency for Research Healthcare and Quality (AHRQ; Forman-Hoffman et al., 2018) found that the strength of the evidence for reducing depression was high for CBT-exposure (these treatments include PE, virtual reality exposure, and WET) and CBT-mixed (these included CBTs with other components such as stress management, relaxation training or mindfulness training) PTSD treatments. The review found moderate strength of evidence for reducing depression using other trauma-focused therapies that included CPT, cognitive therapy, and eye movement desensitization and reprocessing therapy (EMDR). In regard to medications for PTSD, the AHRQ report found moderate strength of evidence for reducing depression symptoms using paroxetine and venlafaxine. There was low strength of evidence or no difference from control conditions for sertraline and fluoxetine.

Another meta-analysis that examined depression symptoms in psychotherapy and medication RCTs for PTSD also found that PTSD treatment was generally effective in decreasing depression symptoms (Ronconi, Shiner, & Watts, 2015), with paroxetine, CPT, and PE showing the highest effect sizes. The review also found a strong correlation between the effect size for depression outcomes and the effect size for PTSD outcomes, indicating that a treatment's efficacy for PTSD was similar to its efficacy for depressive symptoms and that PTSD treatment was effective when MDD comorbidity is present. The VA/DoD (2017) clinical practice guideline for PTSD states that co-occurring MDD often shows reduction in intensity when PTSD is treated. However, if PTSD treatment does not resolve depression symptoms, additional MDD treatment may be warranted.

Treatment of PTSD-Anxiety

Less is known about treating PTSD when anxiety disorders are present. A systematic review of whether PTSD treatment also treated panic disorder found that only 5% of included PTSD treatment RCTs ($N = 3$) reported rates of comorbid panic disorder more than once during the study (Teng et al., 2013). Of the three studies that did, 56% of people who had panic disorder at the start of treatment no longer met criteria after receiving PTSD treatment. PTSD treatment outcomes when panic disorder was present were not reported. Another study examined sertraline versus placebo to treat PTSD (Brady & Clary, 2003). Among 395 participants, 17.7% had a comorbid anxiety disorder (panic, social anxiety, generalized anxiety, or obsessive–compulsive disorder, which was then an anxiety disorder). PTSD symptoms improved significantly in those treated with sertraline compared to placebo regardless of whether they had an anxiety disorder. The small body of literature on treating PTSD with anxiety disorders is consistent with

recommendations to treat PTSD with evidence-based approaches when comorbidities are present.

Future Directions

More research is needed on which clients with PTSD-MDD are likely to respond to PTSD treatment and who may need additional treatment. Integrating CBT for MDD into PTSD treatment by more explicitly targeting cognitions associated with depression (e.g., "I am a failure") along with cognitions associated with PTSD (e.g., "The world is dangerous") could be investigated as a method for further improving outcomes. Comparatively little is known about the prevalence and presentation of PTSD when anxiety disorders are present. Research is needed to understand how best to treat comorbid PTSD and anxiety disorders. This research should look at both specific anxiety disorders (e.g., panic, social anxiety, generalized anxiety) and transdiagnostically across anxiety disorders.

TRAUMATIC BRAIN INJURY

Mild traumatic brain injury (mTBI), or a concussion, is defined as an injury to the head from an external force resulting in loss of consciousness (LOC) for 30 minutes or less and/or alteration of consciousness or posttraumatic amnesia lasting no longer than 24 hours, and no findings on structural neuroimaging (VA/DoD, 2016a). Recovery from mTBI is typically a complete resolution of TBI-related sequelae and return to baseline functioning within 3 months (e.g., Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Karr, Areshenkoff, & Garcia-Barrera, 2014). However, a minority of individuals with a history of mTBI report cognitive, somatic, and psychiatric complaints a year or more after the injury (Belanger, Kretzmer, Vanderploeg, & French, 2010; MacDonald et al., 2015). Postconcussive symptoms (PCS) are nonspecific and overlap with psychiatric symptoms (e.g., irritability, anxiety/depression, slowed thinking). Thus, it is not surprising that mental health plays a significant role in the etiology of persistent PCS (Belanger et al., 2010).

TBI can occur in the context of traumatic events such as military combat, motor vehicle accidents, and assault (Carlson et al., 2011). Sustaining a TBI increases the risk for developing PTSD (Greer et al., 2020; Loignon, Ouellet, & Belleville, 2020), with evidence from a recent meta-analysis indicating that this risk is greater in military samples relative to civilians (Loignon et al., 2020). For example, among Iraq and Afghanistan War veterans, one review found that approximately 33–39% of those with a history of TBI had probable PTSD (Carlson et al., 2011), and another review found notably higher prevalence (63–77%) among those utilizing VA care (Greer et al., 2020). The majority of research examining comorbid PTSD and TBI has focused on mild TBI (mTBI) since the majority of TBIs experienced (approximately 80%) are mild in severity (Defense and Veterans Brain Injury Center, 2018; Dewan et al., 2018).

Treatment of PTSD-TBI

Some clinicians treating veterans with PTSD and a history of TBI have expressed concern that symptoms attributed to TBI will negatively impact PTSD treatment or that TBI should be the focus of treatment instead (Cook, Dinnen, Simiola, Thompson, &

Schnurr, 2014; Sayer et al., 2009). However, cognitive symptoms may be misattributed to TBI when they are better explained by PTSD or other common co-occurring mental health disorders (Vasterling, Jacob, & Rasmusson, 2018). In fact, the VA/DoD (2016a) clinical practice guideline for mTBI recommends that individuals with a history of mTBI with symptoms attributed to mTBI be assessed and treated for comorbid psychiatric disorders. This aligns with the VA/DoD (2017) clinical practice guideline for PTSD's recommendation that individuals with comorbid conditions receive evidence-based treatments for PTSD (e.g., PE, CPT).

Consistent with clinical practice guidelines, the literature thus far indicates that trauma-focused treatment is beneficial for individuals with a history of PTSD and mTBI (Chard, Schumm, McIlvain, Bailey, & Parkinson, 2011; Sripada et al., 2013; Walter, Dickstein, Barnes, & Chard, 2014; Wolf et al., 2015). Results have shown no differences in response to PE or CPT when comparing those with and without a history of TBI (Ragsdale & Voss Horrell, 2016; Sripada et al., 2013), and the reduction in PTSD and depression symptoms observed in those with a history of TBI is comparable to the treatment response documented in other PTSD treatment studies (Walter et al., 2014; Wolf et al., 2015). In addition, TBI characteristics (e.g., presence of LOC, time since injury) do not appear to negatively influence CPT and PE outcomes (Crawford et al., 2017; Crocker et al., 2019). Similar outcomes in other types of PTSD treatment, including present-centered therapy (PCT), have also been observed in those with and without a history of TBI (Bomyea et al., 2017). However, it is important to note that the research published thus far regarding PTSD psychotherapy outcomes for those with a history of TBI have been retrospective studies using clinical data/medical records and secondary analyses of clinical trials focused on veterans and service members (Ackland et al., 2019).

In addition to decreasing PTSD symptoms, PTSD psychotherapy also decreases nonspecific PCS (Jak et al., 2019; Walter et al., 2012; Wolf et al., 2018; Wolf, Strom, Kehle, & Eftekhari, 2012). In fact, CBT appears to be five to six times more effective in reducing chronic PCS than cognitive rehabilitation approaches (Vanderploeg, Belanger, Curtiss, Bowles, & Cooper, 2019). However, cognitive rehabilitation has been shown to be effective specifically in improving cognitive difficulties in those with TBI history (Twamley et al., 2015). In order to optimize treatment, SMART-CPT, which combines CPT with cognitive symptom management and rehabilitation therapy (CogSMART; Jak et al., 2019), was developed to integrate cognitive rehabilitation strategies, rehabilitation therapy and psychoeducation about TBI into CPT. SMART-CPT also includes modifications to CPT to simplify worksheets, utilize concrete language, and include written summaries and reviews. SMART-CPT demonstrated similar reductions in PTSD and PCS to standard CPT in veterans with mild to moderate TBI (Jak et al., 2019) and led to greater improvement in cognitive functioning in attention, verbal learning and memory, and problem solving relative to CPT (Jak et al., 2019). Thus, integrated approaches may be beneficial for optimizing outcomes across domains in individuals with PTSD-TBI.

Only two RCTs have examined the effectiveness of medications in individuals with comorbid PTSD and a history of TBI (Ackland et al., 2019; Mikolić, Polinder, Retel Helmrich, Haagsma, & Cnossen, 2019). While several studies have evaluated hyperbaric oxygen therapy (HBOT) for TBI and have included participants with PTSD (e.g., Weaver et al., 2018), conclusions regarding the efficacy of HBOT for PTSD cannot be drawn from these studies. Studies of individuals who have PTSD with and without TBI are needed for this. Thus, with a lack of empirical evidence, current recommendations

generally remain in line with guidelines for pharmacological treatment of PTSD alone (VA/DoD, 2017). The consensus is to pay attention to possible side effects that may exacerbate TBI-associated problems and to start medications in low doses and titrate slowly (Vasterling et al., 2018).

Future Directions

More information about TBI prevalence in nonveteran PTSD is needed to understand the scope of the comorbidity and associated problems. To better understand the role of TBI in PTSD treatment outcomes, it would be helpful for PTSD treatment RCTs to include assessment of TBI using standardized measures, at least in populations in which PTSD was prevalent. Future studies should explore whether findings to date, which have been primarily with veterans of recent conflicts with mTBI, are applicable across TBI severities, trauma types (e.g., motor vehicle accidents, physical assaults), and various populations, particularly civilians. Research is also needed on outcomes such as quality of life, functioning, and suicidality.

INSOMNIA

Insomnia is defined as dissatisfaction with sleep quantity or quality, associated with difficulty falling or staying asleep, and associated impaired functioning (APA, 2013). Although sleep disturbances are symptoms of PTSD (e.g., trouble falling or staying asleep), insomnia disorder may be best considered a co-occurring and independent disorder (Colvonen et al., 2018; Spoormaker & Montgomery, 2008). First, insomnia may precede traumatic events and predict the development of PTSD (Babson & Feldner, 2010; Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2010; Gehrman et al., 2013; Germain, Buysse, & Nofzinger, 2008). Second, trouble sleeping may initially occur in the context of PTSD, but it can become an independent disorder when behavioral and cognitive responses to acute insomnia lead to perpetuating factors (e.g., napping, sleeping pills) and conditioned arousal (Perlis, Giles, Mendelson, Bootzin, & Wyatt, 1997).

PTSD and insomnia often co-occur. In one older study using a representative U.S. sample, 35% of individuals with PTSD also had insomnia (Ohayon & Shapiro, 2000). Furthermore, insomnia is correlated with severity of PTSD, major depression, impaired daytime functioning (Nadorff, Nazem, & Fiske, 2011), negative long-term health consequences (Baran, Pace-Schott, Ericson, & Spencer, 2012), and suicide risk (Nadorff et al., 2011).

Treatment of PTSD-Insomnia

Untreated sleep problems including insomnia may interfere with change in PTSD symptoms over the course of PTSD treatment. In a study of individuals who received cognitive therapy for PTSD, poorer self-reported sleep with greater depression symptoms was associated with worse PTSD treatment outcomes (Lommen et al., 2016). However, another study found that while poorer self-reported sleep quality was related to more severe PTSD symptoms at baseline, baseline sleep quality was not associated with reduced effectiveness of PE treatment or slope of PTSD symptom changes (Sexton et al., 2017). In general, PTSD sleep symptoms tend to show small improvements over the course of PTSD treatment but often remain clinically significant posttreatment

(Colvonen et al., 2018), including following CPT and PE (Gutner, Casement, Gilbert, & Resick, 2013; Schnurr & Lunney, 2019).

CBT for insomnia (CBT-I) is considered the first-line treatment for insomnia by the American College of Physicians (Qaseem, Kansagara, Forciea, Cooke, & Denberg, 2016) and the VA/DoD (2019) clinical practice guideline for insomnia disorder and obstructive sleep apnea. Additionally, the VA/DoD clinical practice guideline for the management of chronic insomnia disorder and obstructive sleep apnea recommends CBT-I over pharmacotherapy and when comorbid psychiatric disorders, including PTSD, are present. This guideline also suggests the use of brief behavioral therapy for insomnia. Only short-term pharmacotherapy is recommended, specifically low-dose doxepin or nonbenzodiazepine receptor agonists, including zolpidem, zaleplon, eszopiclone, and zaleplon (i.e., Z-drugs). The insomnia guideline advises against use of the antipsychotic drugs trazadone and benzodiazepines.

CBT-I is recommended for comorbid PTSD/insomnia in the VA/DoD PTSD (2017) and insomnia (2019) treatment guidelines. A recent meta-analysis showed large effect sizes for CBT-I in reducing insomnia symptoms when PTSD is present (Wu, Appleman, Salazar, & Ong, 2015). Two other meta-analyses showed medium effect sizes for CBT-I in reducing PTSD symptoms (Ho, Chan, & Tang, 2016; Talbot et al., 2014).

Although CBT-I is recommended for PTSD/insomnia, optimal sequencing with PTSD treatment is unclear. There is ongoing work to examine whether treating insomnia prior to PTSD has benefits to sleep, PTSD, and quality of life (Colvonen, Drummond, Angkaw, & Norman, 2019). Other nonpharmacological treatments that have been studied for the treatment of PTSD-insomnia include imagery rehearsal therapy (IRT) and exposure, relaxation, and rescripting therapy (ERRT), which involve rescripting selected nightmares during the day (Rybarczyk et al., 2005). While IRT and ERRT may improve subjective sleep quality and reduce nightmares in PTSD individuals, there is no evidence that they decrease insomnia symptoms (Hansen, Höfling, Kröner-Borowik, Stangier, & Steil, 2013). Thus, these are not recommended as front-line treatments for insomnia or PTSD/insomnia.

Long-term pharmacotherapy is not recommended for treating insomnia in PTSD or otherwise (VA/DoD, 2019). There is a strong recommendation against the use of benzodiazepines for PTSD or insomnia due to myriad negative side effects (VA/DoD, 2019). Z-drugs carry fewer risks but need further evaluation, with long-term follow-ups on tolerance and withdrawal effects in PTSD/insomnia. There are mixed reviews of prazosin, with evidence that it increases sleep quality and may decrease nighttime arousals (Khachatryan, Groll, Booij, Sepehry, & Schütz, 2016). A recent multicenter study of prazosin in veterans with PTSD found no effects on sleep or any other PTSD symptom cluster (Raskind et al., 2018). Trazodone (Mendelson, 2005), antihistamines (Sateia, Buysse, Krystal, Neubauer, & Heald, 2017), and antipsychotics (Krystal et al., 2016) are often given to help promote sleep in individuals with PTSD, but evidence that they are effective is lacking, and each presents with moderate side effects. Thus, they are not recommended for the treatment of insomnia or PTSD (VA/DoD, 2017, 2019).

Future Directions

Whether insomnia interferes with PTSD treatment is still unclear; thus, more research is needed to understand optimal sequencing of CBT-I and PTSD treatment. Theoretically, addressing sleep problems first or concurrently with PTSD treatment may increase fear learning/recall, decrease emotional reactivity, increase emotional coping

and emotional processing, and increase cognitive abilities/concentration necessary for successful trauma-focused therapy (Colvonen, Straus, Acheson, & Gehrman, 2019). Another approach is to treat PTSD first and treat insomnia after if symptoms remain. While PTSD treatments are effective for PTSD symptom reduction, insomnia often seems to require direct intervention. Increasing focus on screening and treating both insomnia and PTSD are important for optimizing treatment outcomes.

CHRONIC PAIN

The World Health Organization (2019) defines chronic pain as pain that recurs for more than 3 months. Chronic primary pain refers to chronic pain resulting in significant emotional distress or functional impairment that cannot be explained by another chronic pain diagnosis (e.g., fibromyalgia; Treede et al., 2015).

Chronic pain frequently co-occurs with PTSD and may have a common (i.e., from the same traumatic event) or distinct etiology. In a nationally representative sample of U.S. adults, among those with past-year PTSD, 31.6% had a musculoskeletal chronic pain condition, 25.3% had a chronic nerve pain condition, and 12.8% had a chronic digestive pain condition (Bilevicius, Sommer, Asmundson, & El-Gabalawy, 2018). Individuals with comorbid PTSD and chronic pain may present with more severe psychiatric and functional impairments and have greater health care utilization than those with a single disorder (Outcalt et al., 2015; Outcalt, Yu, Hoen, Pennington, & Krebs, 2014).

Treatment of PTSD-Chronic Pain

There are several recommended psychotherapeutic and pharmacologic treatments for chronic pain. For example, the VA/DoD (2017) clinical practice guideline for chronic lower back pain recommends CBT and mindfulness-based stress reduction (Cherkin et al., 2016). Recommended pharmacological approaches include nonsteroidal anti-inflammatory drugs (NSAID) and duloxetine, an antidepressant.

Comorbid PTSD-chronic pain is associated with increased risk for opioid use disorder (OUD; Bilevicius et al., 2018) over either disorder alone. Among U.S. Iraq/Afghanistan War veterans receiving care for pain-related conditions, PTSD is associated with high-risk opioid use (e.g., more than one opioid prescription, highest quintile dosages, concurrent sedative–hypnotics, and early refills) and adverse events, including overdoses (Seal et al., 2012). Accordingly, other forms of treatment should be considered for chronic pain when PTSD is present. The VA/DoD (2017) clinical practice guideline for using opioid therapy to treat chronic pain recognizes PTSD as a risk factor for adverse opioid-related outcomes. If opioids are prescribed when PTSD or other risk factors are present, risk-mitigation strategies are recommended, including informed consent regarding risks and benefits, exploration of alternative therapies, random urine drug testing, assessment of suicide risk, use of prescription drug monitoring programs, providing education regarding overdose and naloxone rescue, and naloxone prescription (VA/DoD, 2017).

There have been few studies examining the impact of chronic pain on PTSD treatment outcomes. In a meta-analysis, Goldstein and colleagues (2019) found that RCTs of interventions for PTSD/chronic pain led to significant reductions of PTSD severity, but nonsignificant changes in pain severity and disability. Only 1 of the 10 included trials evaluated a trauma-focused treatment (specifically, trauma-focused CBT). In this study,

trauma-focused CBT led to significant reductions in PTSD severity and neck pain disability when compared to a wait-list control (Dunne, Kenardy, & Sterling, 2012). The VA/DoD (2017) clinical practice guideline for PTSD does not make recommendations about interventions for PTSD-chronic pain, due to lack of studies examining treating both concurrently.

Assessing problems associated with PTSD-chronic pain is critical. For example, SUD in addition to PTSD/chronic pain represents a unique risk factor for suicidality, and their co-occurrence may have an additive effect (Racine, 2018; Shorter, Hsieh, & Kosten, 2015). Therefore, it is important to assess SUD and suicide risk when treating PTSD/chronic pain.

Future Directions

There are very few studies of treating comorbid PTSD-chronic pain. Future RCTs should examine whether trauma-focused treatments reduce chronic pain and associated disability and whether augmenting trauma-focused treatments with evidence-based psychotherapies for chronic pain or pharmacotherapies has added value when treating both disorders.

IMPLICATIONS ACROSS COMORBIDITIES

In this chapter, we focused on some of the comorbidities that commonly co-occur with PTSD. Specifically, we discussed SUD, MDD, anxiety, TBI, insomnia, and chronic pain. Other common comorbidities were not discussed, but a smaller body of research suggests that trauma-focused treatments are also effective in the face of these. For example, in a review, van Minnen, Harned, Zoellner, and Mills (2012) concluded that PE was a promising treatment of PTSD when borderline personality disorder and psychotic disorders were present.

The high rates of comorbidity and associated impairment highlight the importance of assessing common comorbidities and associated problems (e.g., consequences of TBI, chronic pain) when treating PTSD. In addition to using well-validated measures for PTSD, clinicians should screen individuals for common comorbidities using validated instruments with follow-up diagnostic assessment if indicated. Baseline assessment allows clinicians to develop a treatment plan that comprehensively addresses the issues that may be contributing to a patient's distress and impairment. Assessment should continue on a regular basis (i.e., every session or two) through the end of PTSD treatment. Such measurement-based care allows clinicians and patients to assess if treatment is working, identify symptoms that may need more attention, and adjust the treatment plan if needed.

SUMMARY AND CONCLUSIONS

PTSD frequently co-occurs with a number of psychiatric and medical conditions. Indeed, comorbidities are the norm, and not the exception. PTSD with additional psychiatric comorbidities is often associated with greater clinical and functional impairments, including greater PTSD symptom severity and worse long-term health outcomes, than having a single disorder.

A substantial body of evidence supports the use of trauma-focused treatments for individuals presenting with a range of comorbidities and common associated problems, such as TBI consequences and chronic pain. Studies have generally found that trauma-focused treatments alleviate PTSD symptoms and do not exacerbate comorbid symptomatology. As a result, the VA/DoD (2017) clinical practice guideline for PTSD recommends trauma-focused treatments as a first-line approach for individuals presenting with PTSD and comorbidities, including the ones outlined in this chapter. Given the symptom interplay between PTSD and a number of comorbidities, withholding trauma-focused treatments from individuals with comorbidities may delay recovery from both disorders.

In order to continue to move the field forward and advance treatments for PTSD and associated comorbidities, it is critical to assess comorbidities in PTSD treatment trials, to study treatments that address PTSD and comorbidities, and to assess subsamples of participants with specific comorbidities using large datasets, ideally, that merge study-level or patient-level data across multiple studies. These approaches will allow for a more nuanced understanding of the most effective treatment of PTSD and comorbidities and the treatments that work best for whom.

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CHAPTER 25

Trauma Exposure, PTSD, and Physical Health

Paula P. Schnurr, Jennifer S. Wachen, Bonnie L. Green, and Stacey Kaltman

Exposure to a traumatic event can affect numerous domains of a person's functioning and well-being, including physical health (Koenen & Galea, 2015; Pacella, Hruska, & Delahanty, 2013; Ryder, Azcarate, & Cohen, 2018). This chapter updates a review by Schnurr, Wachen, Green, and Kaltman (2014) that was based on a model by Schnurr and Green (2004) to explain the association between trauma and physical health through psychological, biological, attentional, and behavioral mechanisms. Additional literature has emerged to provide stronger evidence of how trauma and posttraumatic stress disorder (PTSD) are related to poor health.

A MODEL OF HOW TRAUMATIC EXPOSURE AFFECTS PHYSICAL HEALTH

Consider a man who fractures his back in a motor vehicle accident or a woman who is infected with a sexually transmitted disease while being raped. It is plausible they might have health problems that require treatment and impair their quality of life. Yet most individuals are not seriously injured or exposed to disease during a traumatic event; for example, only 17% of a sample of over 2,700 soldiers who had experienced combat reported being injured (Hoge, Terhakopian, Castro, Messer, & Engel, 2007). Furthermore, the types of health problems typically reported by trauma survivors are not directly related to the types of events experienced. In the classic Adverse Childhood Experiences study, childhood trauma was associated with increased likelihood of adult cancer, ischemic heart disease, chronic lung problems, and other conditions that had no known or direct etiological bases in the childhood events (Felitti et al., 1998). How could traumatic exposure lead to such seemingly unrelated health problems?

Building on prior work (Friedman & Schnurr, 1995; Schnurr & Jankowski, 1999), Schnurr and Green (2004) proposed a model to explain how a traumatic event could affect physical health (Figure 25.1). The model is based on two key assumptions. The first is that following trauma exposure, distress—manifested either as PTSD or as other

serious psychological conditions—is necessary for adverse health outcomes to develop. Thus, the model applies broadly to all trauma survivors, even when an individual does not suffer direct physical consequences of exposure.

The second assumption is that the effects of PTSD and other posttraumatic distress reactions are mediated through interacting biological, psychological, attentional, and behavioral mechanisms. *Biological mechanisms* include alterations of the two primary systems of the stress response: the locus coeruleus/norepinephrine sympathetic system and hypothalamic–pituitary–adrenal systems. Friedman and McEwen (2004) summarized the literature on these systems, as well as other neurobiological changes associated with PTSD, and discussed the possible implications of the changes for physical health. *Psychological mechanisms* include depression, hostility, and poor coping, all of which have been linked to adverse health effects. For example, depression is associated with greater likelihood of cardiovascular disease and the mechanisms that could explain this association, including greater platelet activation, decreased heart rate variability, and greater likelihood of hypertension (Dhar & Barton, 2016). Regarding *attentional factors,* Pennebaker (2000) has suggested avoidance of thinking about a trauma and mislabeling of the autonomic and emotional consequences of such avoidance (in addition to actual biological changes and secondary gain), both of which are associated with poor health. *Behavioral mechanisms* associated with trauma and PTSD include substance use or abuse (smoking, abuse of alcohol, drugs, food), failure to engage in preventive strategies (exercise, diet, safe sex, regular health care), and failure to adhere to medical regimens (Taggart Wasson et al., 2018; van den Berk-Clark et al., 2018; Zen, Whooley, Zhao, & Cohen, 2012).

Allostatic load is defined as "the strain on the body produced by repeated up and downs of physiological response, as well as the elevated activity of physiological systems

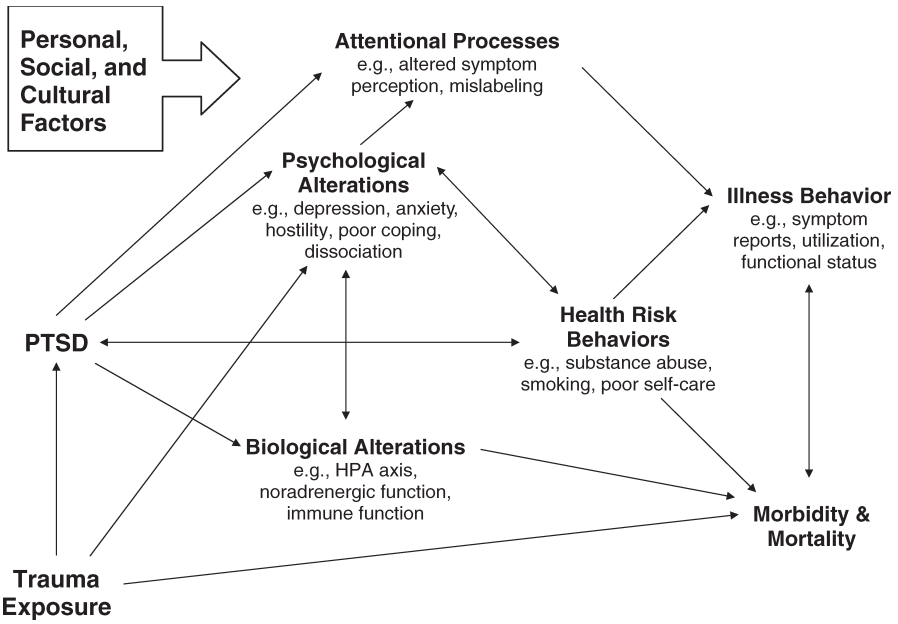

FIGURE 25.1. A model relating traumatic exposure and PTSD to physical health outcomes. From Schnurr and Green (2004, p. 248). In the public domain.

under challenge, and the changes in metabolism and wear and tear on a number of organs and tissues" (McEwen & Stellar, 1993, p. 2094). It has been proposed as a unifying mechanism to explain how the numerous and sometimes subtle neurobiological, psychological, and behavioral changes associated with PTSD might jointly affect health (Friedman & McEwen, 2004; Schnurr & Green, 2004; Schnurr & Jankowski, 1999). Because the construct emphasizes cumulative and interactive effects across multiple systems, it is useful for understanding how changes that are clinically insignificant by themselves could combine to produce disease. Schnurr and Jankowski (1999) gave the example of elevated levels of arousal and hyperreactivity in PTSD, which alone are unlikely to cause cardiovascular disease. However, in combination with behavioral risk factors such as substance abuse and smoking, allostatic load might sufficiently increase to cause disease (see Figure 25.2). Schnurr and Jankowski proposed that allostatic load might be greater in PTSD than in other disorders.

Psychiatric disorders such as depression and substance abuse, which have known effects on physical health, are frequently comorbid with PTSD (Goldstein et al., 2016). According to the model, PTSD is the key mechanism through which trauma leads to poor health, although other types of distress, particularly depression, may lead to poor health in the absence of PTSD. Furthermore, depression and other types of distress that are comorbid with PTSD may mediate the effects of PTSD. Yet PTSD appears to have a distinctive effect on health beyond that associated with these comorbid conditions. In the next section, we present evidence supporting these points, after we review evidence of how trauma and PTSD are associated with physical health. First, we consider methodological issues.

METHODOLOGICAL CONSIDERATIONS

Physical health comprises interacting components reflected in both objective and subjective domains that exist on a continuum of increasing complexity (Wilson & Cleary, 1995). Biological and physiological variables—the underlying changes that represent disease or alterations of the physical system—are the most basic level. Next are the

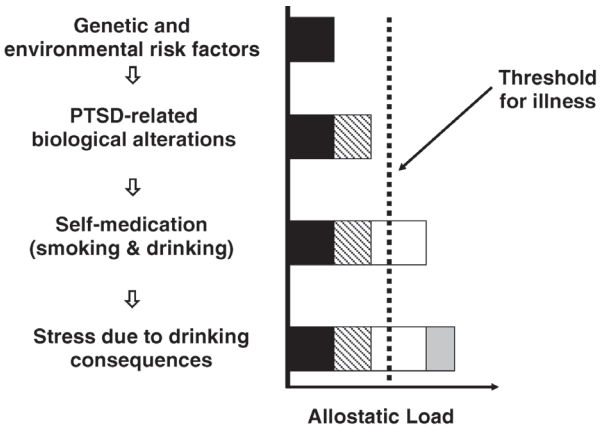

FIGURE 25.2. A hypothetical example of how biological and behavioral factors could combine to increase allostatic load in an individual with PTSD.

symptoms, the individual experiences, which are imperfectly correlated with biological and physiological variables such as lipid levels or blood pressure. Functional status is the next level, followed by health perceptions. Health-related quality of life is at the most complex level. Personal and environmental factors influence all levels of this continuum.

Measurement Issues

Given its multidimensional character, physical health is measured through self-reports, laboratory tests, physical exams, and archival records. A particular implication of Wilson and Cleary's (1995) model, or any model that includes both objective and subjective components, is that self-reports are valid indicators of health. Self-reports can be used to assess outcomes across almost the entire range of Wilson and Cleary's continuum, from the biological (e.g., "What is your weight?") through health-related quality of life. However, self-reports do not always agree with other sources of information. Studies that have compared self-reports with information in medical charts or databases typically find some lack of correspondence. A study by the National Center for Health Statistics found that self-reported medical conditions were both over- and underreported relative to information in medical charts, depending on the type of condition and whether an individual was receiving ongoing treatment for that condition (Edwards et al., 1994). Using archival data to verify self-reports may cause accurately reported information to appear inaccurate because archival sources may not be complete if individuals seek care from more than one source.

There is a history of controversy about the use of self-report methods for studying physical health because self-reports are affected by psychological and emotional factors, such as negative affectivity (Watson & Pennebaker, 1989). Symptom reports are most affected, although reports of health status and functional health are also affected (Schnurr & Jankowski, 1999). The concern that self-reports do not reflect physical status as much as emotional status does is only a problem if one assumes that health is strictly biological. Rather than dismiss self-reports as invalid, readers should view them as one of a range of perspectives that are necessary for thoroughly capturing the multidimensional complexity of physical health.

Design Issues

Because physical health is affected by many factors, it is important to identify the way these factors interact with trauma. For example, depression and substance abuse, which are associated with PTSD, have known adverse effects on physical health. Statistically controlling for the effects of these problems to eliminate potential "confounding" will reduce the observed effect of PTSD if the problems are actually mechanisms through which PTSD influences health. This control approach is appropriate only if the goal is to determine the unique effect of PTSD beyond that which is mediated by its consequences. The approach is inappropriate if one's goal is to determine the total effect of PTSD or to understand how PTSD affects health. In the former case, either simultaneous multiple regression analysis or analysis of covariance is an acceptable technique. In the latter, hierarchical regression, path analysis, or structural equation modeling should be used to test for mediation.

Although most trauma survivors are not injured or made ill as a direct consequence of their exposure (e.g., Hoge et al., 2007), some types of events, such as torture, accidents,

and physical assault, are likely to involve physical injury or illness. In such cases, designs and analytic strategies need to distinguish between health effects that directly result from trauma exposure per se and effects that result from mechanisms stemming from posttraumatic reactions. Also, Schnurr and Green (2004) noted that health is influenced by many factors in addition to trauma: personal characteristics, including genetics, social factors, and ethnic and cultural background (Wilson & Cleary, 1995). It may not always be feasible or necessary to isolate the effect of exposure and its consequences as distinct from these other factors, but it is important to ensure that such factors are adequately controlled if they provide an alternative explanation for a given finding.

CURRENT STATE OF THE ART

Many literature reviews summarize the evidence that indicates trauma exposure and PTSD are associated with poor health (Friedman & Schnurr, 1995; Green & Kimerling, 2004; Pacella et al., 2013; Ryder et al., 2018; Schnurr & Jankowski, 1999). Below we present selected studies as examples of more general findings or to emphasize key points.

Is Trauma Exposure Associated with Poor Health?

Exposure to a traumatic event is associated with self-reported (e.g., Kline et al., 2010; Paras et al., 2009; Scott et al., 2011) and objective (e.g., Crum-Cianflone et al., 2014; Hendrikson et al., 2013; Spitzer et al., 2011) indicators of poor health. Individuals who are exposed to trauma also use more medical services, in comparison with unexposed individuals. For example, Walker and colleagues (1999) found that female members of a health maintenance organization who had experienced childhood abuse or neglect had higher median annual health care costs than women who reported no childhood maltreatment.

Most investigations of the relationship between trauma exposure and mortality suggest that exposure is related to increased mortality. Studies of veterans have shown that the increase is primarily due to external causes such as accidents and suicide rather than disease (e.g., Catlin Boehmer, Flanders, McGeehin, Boyle, & Barrett, 2004). High war-zone exposure was associated with increased risk of all-cause, but not disease-specific, mortality in Vietnam veterans in the National Vietnam Veterans Longitudinal Study, even when PTSD was taken into account (Schlenger et al., 2015). Trauma exposure also is associated with mortality in nonveterans (e.g., Chen, Turiano, Mroczek, & Miller, 2016; Elliot, Turiano, Infurna, Lachman, & Chapman, 2018).

Is PTSD Associated with Poor Health?

As described in our model, a primary pathway from the experience of trauma exposure and adverse health outcomes is the reaction to the exposure, specifically PTSD. An increasing number of studies have employed longitudinal designs to study the incidence of self-reported disease onset among healthy individuals. For example, reports on participants in the Nurses Health Study found associations of PTSD with incidence of rheumatoid arthritis (Lee et al., 2016) and lupus (Roberts et al., 2017). A study of almost 45,000 service members from the Millennium Cohort revealed that baseline PTSD was associated with increased risk of self-reported diabetes at 3-year follow-up (Boyko et al., 2010).

PTSD also is associated with poor outcomes when physical health is measured by objective indicators. Longitudinal studies offer particularly compelling evidence. Some have focused broadly on multiple disorders. In one study, PTSD symptoms were associated with increased onset of physician-diagnosed arterial, musculoskeletal, gastrointestinal, and dermatological disorders in older male veterans, even when other factors predictive of health status (age, smoking, body mass index, and alcohol use) were statistically controlled (Schnurr, Spiro, & Paris, 2000). In another study, PTSD was associated with increased risk of developing physician-diagnosed vascular, dermatological, and musculoskeletal problems; survivors with PTSD were almost twice as likely to develop new vascular problems in the 2 years after initial PTSD assessment (Dirkzwager, van der Velden, Grievink, & Yzermans, 2007).

Other longitudinal studies have focused on specific types of disorders, such as autoimmune (O'Donovan et al., 2015; Song et al., 2018), gastrointestinal (Gradus et al., 2017), and cerebrovascular (Chen et al., 2015) disorders. Cardiovascular disorders have been a particular focus (e.g., Beristianos, Yaffe, Cohen, & Byers, 2016; Vaccarino et al., 2013). A meta-analysis found that PTSD was associated with a 55% greater risk of coronary heart disease, although the risk decreased to 27% after adjustment for depression (Edmondson, Kronish, Shaffer, Falzon, & Burg, 2013). Evidence on cancer is more limited, and a recent study found that PTSD was not associated with increased incidence of cancer in the Danish population (Gradus et al., 2015).

If PTSD is associated with poor health, then it makes sense that individuals with PTSD also would have greater health care utilization. PTSD is indeed associated with increased use of medical care services (e.g., Hoge et al., 2007; Schlenger et al., 2016; Walker et al., 2003). PTSD also is associated with increased medical care costs (Walker et al., 2003).

Most studies of mortality in individuals with PTSD have found that PTSD is associated with excess mortality, but almost all investigations have found that the excess mortality is primarily due to external causes or related to substance use. For example, a recent study found that veterans with PTSD had elevated all-cause mortality and mortality due to suicide, accidents, and viral hepatitis relative to the general population (Forehand et al., 2019). Another study of VA patients found that PTSD was associated with all-cause mortality only in unadjusted analyses that did not account for demographic, behavioral, and clinical factors (Chwastiak, Rosenheck, Desai, & Kasis, 2010). Similarly, a study of Australian Vietnam War veterans failed to find the effects of PTSD or other psychiatric diagnoses on mortality (O'Toole, Catts, Outram, Pierse, & Cockburn, 2010).

There is now solid empirical evidence of the link between PTSD and poor health. Studies have revealed that PTSD is associated with poorer self-reported outcomes, including overall health, somatic symptoms, number of chronic health conditions, and functional status (e.g., Hoge et al., 2007; Lee et al., 2016; Pacella et al., 2013; Roberts, 2017).

Does PTSD Mediate the Relationship between Trauma Exposure and Poor Health?

Evidence consistent with the hypothesis that PTSD mediates the relationship between trauma exposure and self-reported health has been observed in a diverse range of samples (e.g., Norman et al., 2006; Smith et al., 2011; Wachen et al., 2013). In an early study, a path analysis of data from over 900 older male veterans, 90% of the effect of combat

exposure on health was mediated through PTSD (Schnurr & Spiro, 1999). A prospective study of 2,301 Gulf War veterans found that combat exposure predicted health status in both men and women 18–24 months following return from the Gulf (Wagner, Wolfe, Rotnitsky, Proctor, & Erickson, 2000). The association was substantially reduced when PTSD was included in the regression model, which is consistent with the idea that PTSD is mediating the relationship. However, some studies have failed to find complete evidence of mediation (Norman et al., 2006; Schnurr et al., 2000).

Are the Effects of PTSD Distinct from the Effects of Other Mental Disorders?

Because PTSD is often comorbid with other disorders (Goldstein et al., 2016), an important question is whether PTSD has a specific impact beyond that caused by these disorders. Almost all studies that have examined the unique contribution of PTSD in explaining physical health problems by controlling for other mental disorders have found that PTSD has an independent effect. In particular, although depressive symptoms may mediate the effects of PTSD on physical health, PTSD has effects that are independent of depression (e.g., Edmondson et al., 2013; Gradus et al., 2017; Scherrer et al., 2019). Studies also have shown a specific impact of PTSD when controlling for additional mental health disorders (e.g., Beristianos et al., 2016; Gradus et al., 2017; O'Donovan et al., 2015; Song et al., 2018). However, some studies indicate that the effects of PTSD on mortality may not be independent of the effects of other psychiatric disorders (e.g., Abrams, Vaughan-Sarrazin, & Vander Weg, 2011; Kinder et al., 2008).

What Is the Evidence on Mediators of the Relationship between PTSD and Physical Health?

No single study has comprehensively examined all of the potential mediators of the effect of PTSD on health, and few studies have directly examined the meditational role of potential mechanisms through which PTSD could affect health. Instead, studies have documented the association between PTSD and factors that could affect health. Behavioral factors, such as smoking and substance abuse, and psychological factors, such as depression, are often considered to be confounds, but because they are associated with PTSD, they are mechanisms through which PTSD can adversely affect health (Schnurr & Green, 2004).

Some studies have failed to find that health risk behaviors such as smoking and substance abuse mediate the relationship between PTSD and poor health (e.g., Del Gazio, Elhai, & Weaver, 2011; Schnurr & Spiro, 1999), whereas others have found that these factors are partial mediators (e.g., Crawford, Drescher, & Rosen, 2009; Flood, McDevitt-Murphy, Weathers, Eakin, & Benson, 2009). Thus, poor health behaviors do not completely explain the relationship between PTSD and physical health. Researchers who have controlled for these factors still find that PTSD is related to poor health (e.g., Beristianos et al., 2016; Gradus et al., 2017; Lee et al., 2016; Roberts et al., 2017; Schnurr et al., 2000)—which suggests that other mediators are involved.

Depression is an important potential mediator because it has known associations with poor health (Dhar & Barton, 2016). Although the effects of PTSD are distinct from the effects of depression and other mental disorders (see the prior section), accounting for the effects of depression typically reduces the strength of associations between PTSD and health. For example, Scherrer and colleagues (2019) found that adjusting for

depression reduced the risk of cardiovascular disease from PTSD from a hazard ratio of 1.41 to 1.20. Depression fully mediated the relationship between PTSD and pain severity in another study (Poundja, Fikretoglu, & Brunet, 2006) and substantially mediated the relationship between PTSD and poor health behaviors (physical inactivity and medication nonadherence) in yet another (Zen et al., 2012).

There is increasing evidence on potential biological mediators. PTSD has been linked not only to individual risk factors but also to metabolic syndrome, which includes obesity, hyperlipidemia, hyperglycemia, and hypertension. A meta-analysis found that PTSD was associated with a relative risk of 1.82 for metabolic syndrome (Rosenbaum et al., 2015). A longitudinal study using cross-lagged panel analysis to test the direction of influence between PTSD and metabolic syndrome found results consistent with a causal role for PTSD. PTSD predicted increased metabolic syndrome severity, which did not predict increased PTSD (Wolf et al., 2016). Meta-analyses also suggest low-grade inflammation (Passos et al., 2015) and advanced cellular aging (Wolf et al., 2018) as other potential biological mediators. The association between PTSD and metabolic syndrome, which was first suggested by Friedman and McEwen (2004), is consistent with the idea that the adverse effects of PTSD on physical health are due to increased allostatic load. To our knowledge, no one has yet tested this hypothesis, but there is some evidence that allostatic load is elevated in PTSD (Glover, Stuber, & Poland, 2006; Thayer et al., 2016).

Scherrer and colleagues' (2019) study of PTSD and cardiovascular disorder illustrates the complexity of factors that need to be considered when testing mediation. PTSD was associated with a range of potential mediators beyond depression, including smoking, substance use, anxiety disorder, sleep disorder, obesity, diabetes, hypertension, and hyperlipidemia, all of which were associated with cardiovascular disorder. The effect of PTSD remained in analyses that adjusted for these factors separately and was reduced after adjustment for diabetes, obesity, hypertension, and hyperlipidemia. PTSD was no longer related to increased risk of cardiovascular disorder when smoking, substance use, sleep, anxiety, and depression were included simultaneously. This finding suggests full mediation, but multivariate regression is not optimal for testing mediation. Structural equation modeling would have allowed the investigators to statistically determine the direct versus indirect effects of PTSD thorough these potential mediators.

Does Treating PTSD Affect Physical Health?

It follows that if PTSD is a pathway through which individuals exposed to trauma develop physical health impairment, then treating PTSD should improve physical health outcomes. However, few studies have specifically examined physical health as an outcome of PTSD treatment. In one of the earliest studies to examine this topic, Malik and colleagues (1999) reported no effect of fluoxetine on physical functioning. Schnurr and colleagues (2007) failed to find an effect of prolonged exposure (PE) on physical functioning. In contrast, other studies have reported the benefits of cognitive-behavioral treatment on self-reported symptoms (Galovski, Monson, Bruce, & Resick, 2009; Rauch et al., 2009; Shipherd, Clum, Suvak, & Resick, 2014) and functioning (Beck, Coffey, Foy, Keane, & Blanchard, 2009; Dunne, Kenardy, & Sterling, 2012; Neuner et al., 2008; Sofko, Currier, & Drescher, 2016). Some studies have shown that amount of reduction in PTSD symptoms during treatment is related to amount of improvement in health and functioning (e.g., Shipherd et al., 2014; Sofko et al., 2016).

CHALLENGES FOR THE FUTURE

Schnurr and Green (2004) discussed practice and policy issues that arise from the evidence on the adverse physical health consequences of trauma and PTSD. Schnurr and colleagues (2014) summarized these issues and suggested an agenda for future research. Below we update where we are today and suggest directions for research to fill the gaps that still exist.

Practice

If trauma increases the likelihood of disease, attention should be paid to the physical health needs of trauma survivors in mental health settings. Attention also should be paid to the mental health needs of trauma survivors in medical settings, where trauma-related distress may go unrecognized (Cohen et al., 2010; Graves et al., 2011; Greene, Neria & Gross, 2016).

Mental Health Care Settings

Given the high levels of medical comorbidities associated with PTSD, mental health clinicians need to attend to the physical health problems of traumatized patients. Psychoeducation is critical. Helping individuals who have PTSD or other trauma-related disorders to understand the links between their distress and their physical health can facilitate management of both physical and mental health problems (Kilpatrick, Resnick, & Acierno, 1997).

Mental health clinicians also should attend to health risk behaviors by either identifying the behaviors and making a referral or addressing them directly in treatment. Integrated treatments targeting PTSD and health behaviors can be successful in treating both issues. For example, Foa and colleagues (2017) found that PE integrated with smoking cessation counseling and varenicline resulted in higher levels of smoking abstinence among patients with moderate or high levels of PTSD than varenicline plus smoking cessation counseling alone. An example of another integrated treatment, concurrent treatment of PTSD and substance use disorders using PE also has demonstrated efficacy in reducing both PTSD symptoms and substance use (e.g., Back et al., 2019; Mills et al., 2012; Norman et al., 2019).

Offering physical health care in a mental health clinic, when feasible, can be another useful strategy. Druss, Rohrbaugh, Levinson, and Rosenheck (2001) compared two models of primary care for patients with serious psychiatric disorders (including PTSD): care integrated in a mental health clinic versus usual care in a general medical clinic. The integrated care group had better medical outcomes, was more likely to receive preventive care, and produced higher satisfaction, without increased costs.

Medical Care Settings

Identifying individuals who have PTSD or other types of posttraumatic distress is the first step in treating trauma-related problems. Green and Kimerling (2004) noted that studies finding high rates of trauma in medical settings have tended to recommend universal screening procedures, even though screening may not be possible or desirable. The ideal screening procedure has optimal efficiency and adds minimal burden in terms of cost or other resource demands. A brief self-report screen collected as part

of a medical history is an easy way to obtain information about PTSD. Screening for a disorder like depression alone is inadequate unless cases are followed with a more thorough examination prior to the initiation of treatment because different treatments may be indicated for PTSD than for depression. Several good PTSD screens are available (Prins et al., 2016; Weathers et al., 2013).

Integrated care in which behavioral health is a routine part of medical care offers particular promise. There are multiple models of integrated care. Care management interventions, the mode with the most research evidence, are effective for depression (Archer et al., 2012). The evidence for PTSD is mixed, with some randomized controlled trials finding improved clinical and process outcomes (Engel et al., 2016; Fortney et al., 2015) and others finding no benefit over usual care (Meredith et al, 2016; Schnurr et al., 2012). Future research may focus on the impact of type of treatment received in care management. Toward this end, one implementation of a collaborative care model for low-income immigrants with a high level of trauma exposure required modifications to the treatment model to better address the specific needs of the patient population (Kaltman, Pauk, & Alter, 2011). Fortney and colleagues (2015) found that benefit was mediated by the receipt of cognitive processing therapy, an evidence-based psychotherapy for PTSD (see Cohen & Mannarino, Chapter 20, this volume). Research has also focused on developing effective primary care models of evidence-based psychotherapies for PTSD (Cigrang et al., 2017).

Primary care behavioral health (PCBH), another model of integrated care, focuses on meeting the mental health needs of the primary care clinic's patient population through services provided by a generalist mental health clinician and typically does not have a specific disease target (Reiter, Dobmeyer, & Hunter 2018). A meta-analysis of PCBH identified robust findings for process measures, including shorter wait times for treatment, higher likelihood of accessing care, and attending more visits (Possemato et al., 2018). There is also emerging evidence that participation in PCBH is associated with improved symptoms and functioning (Hunter et al, 2018; Possemato et al., 2018). However, research with more rigorous designs is needed.

Education for patients and providers is essential. Patients may need basic information about trauma and PTSD, and about how their symptoms may relate to their physical problems and self-care behaviors. This information can be delivered by a provider, other staff, written materials, and the Internet. Research suggests that patients are comfortable with primary care providers conducting screening for trauma and PTSD (Goldstein, Athale, Sciolla, & Catz, 2017), although many primary care providers report discomfort in discussing trauma and feel unprepared to do so (Green et al., 2011). The concept of "trauma-informed care," first used in substance abuse and child welfare treatment, is now being adopted in primary care settings (Machtinger et al., 2019). The idea is that medical providers can interact with patients in a way that is sensitive and does not retraumatize patients or increase their fear and anxiety. Green, Saunders, and colleagues (2015) and Greene and colleagues (2016) recently developed training for primary care providers that resulted in increased patient-centered behaviors, and increased patients' ratings of their providers' partnership behaviors.

Policy and Systems Issues

The relationship of traumatic exposure and PTSD with poor health has important implications for health policy. Trauma may be one of the root causes of serious public health concerns—both the behavioral risk factors that may lead to disease and the

diseases themselves. By increasing utilization, trauma and PTSD increase costs for individuals, health care systems, and society as a whole. We suggest that awareness of trauma exposure and its consequences be addressed in public health efforts targeting mental disorders and the prevention of exposure to accidents, violence, and other (possibly) avoidable events. Integration of care is a key issue that requires changes at the systems level; we mentioned multiple models of such integration earlier, along with reasons why integration may support better outcomes.

Research

Research is needed to help us understand and treat the physical health consequences of traumatic exposure. First are design issues. Research should be based on large, representative samples to enhance the generalizability of findings. Despite growth in studies from populations outside of North America (e.g., Chen et al., 2015; Gradus et al., 2017; Song et al., 2018), there is still a need for research in developing countries. This research should include measures of PTSD and other significant posttraumatic reactions, in addition to or even instead of measures of traumatic exposure. Measures of morbidity based on physical examinations or laboratory tests (and not just self-reports) are essential.

Next are content issues. We need to know which physical health problems are associated with PTSD. Although the range of behavioral and biological correlates of PTSD could affect multiple body systems, some problems may be more likely than others. By knowing the specific outcomes most strongly associated with PTSD, we could begin to examine the mechanisms through which PTSD leads to poor health, particularly the biological mechanisms. Studies of biological factors in PTSD should include measures of health status in order to permit tests of how these factors relate to health. Progress is being made. There is now more prospective evidence linking PTSD with physician-diagnosed disorder (e.g., Beristianos et al., 2016; Chen et al., 2015; Gradus et al., 2017) and with mechanisms that could explain how PTSD could lead to poor health, including metabolic syndrome (Rosenbaum et al., 2015), inflammation (Passos et al., 2015), and advanced cellular aging (Wolf et al., 2018). However, there has not been much research on the concept of allostatic load (Glover et al., 2006; Thayer et al., 2016).

We also have recommended that future research include measures of both PTSD and other types of distress in order to address questions about the unique effects of PTSD on physical health. One question that remains is the extent to which PTSD affects health, independent of disorders that are comorbid with PTSD. A related question is whether other trauma-related disorders affect physical health. Depression is a particularly important construct to consider given its comorbidity with PTSD (Goldstein et al., 2016) and diverse effects on physical health (Dhar & Barton, 2016).

There is a particular need to increase the study of whether treating PTSD and other outcomes in trauma survivors improves physical health. Studies with objective physical health indicators are especially needed, as are studies of PTSD treatment in patients with defined medical disorder. Another important question is whether interventions designed to improve physical health affect PTSD and other clinically significant distress reactions. Trauma survivors may need targeted health promotion interventions to address the ways their symptoms prevent them from engaging in positive health practices, and such interventions should be evaluated. Interventions that target providers and systems of care also need to be evaluated. The cost-effectiveness of clinical interventions should be evaluated as well.

CONCLUSIONS

The physical health consequences of traumatic exposure have important public health implications. Trauma may substantially contribute to many behaviors that are the target of current public health programs, such as smoking, exercise, and diet. Prevention is a key issue. Public health campaigns focused on high-risk behaviors that lead to accidents, disasters, child abuse, and sexual assault could help reduce the likelihood of traumatic exposure, but it is not likely that all trauma can be eliminated. Public health campaigns could also point out the trauma–high risk behavior link, so that it is better understood. That could help shape the nature of preventive messages that are used, with perhaps more empathy toward those who engage in these behaviors. Secondary prevention is also important because it may be possible to prevent the physical health consequences of traumatic exposure. These consequences occur primarily in individuals who develop trauma-related distress. Therefore, strategies that enhance the detection and treatment of PTSD could result in improved physical and mental health outcomes among individuals who have experienced a traumatic event.

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PART IV

EMERGING TERRITORY

CHAPTER 26

Culture, Trauma, and Traumatic Stress among Refugees, Asylum Seekers, and Postconflict Populations

Derrick Silove and Louis Klein

The number of persons worldwide exposed to traumatic events related to mass conflict, political persecution, and forced displacement has reached record levels in modern history. The level of conflict occurring at a global level has resulted in 1 in 100, or 70 million persons, being forcibly displaced within their own countries or across national borders (UN High Commissioner for Refugees [UNHCR], 2019). The types of traumatic events experienced by these populations, including combat, torture, and gender-based violence, are known to be particularly potent in generating mental disorders such as posttraumatic stress disorder (PTSD; Kessler et al., 2017; Koenen et al., 2017). Although diverse in backgrounds, populations exposed to mass conflict share common characteristics that define a field of research and clinical practice, here referred to as refugee, asylum, and postconflict (RAPC) mental health.

Modern forms of armed conflict occur primarily within and between countries with culturally diverse backgrounds that differ in key respects from those of technologically advanced societies of the West (hereafter referred to as Western countries). Culture therefore is a central focus of professionals working in the RAPC mental health field (Alarcón, 2009), whether in research, policy development, service design, or direct clinical interventions. Although diverse within themselves, the majority of contemporary conflict-affected countries share certain characteristics, including a tradition of collectivism—where the primary focus of members is on the integrity and well-being of the family and kinship group—to holistic concepts of health that blur the distinction between mental and physical symptoms, and the belief that supernatural or animistic factors are central to the causation of ill health (Choudhry, Mani, Ming, & Khan, 2016). Western principles of psychology are relatively new to these cultures, in particular, the assumption that traumatic events can generate psychiatric morbidity and disability (Alarcón, 2009).

At the same time, the world is undergoing unprecedented cultural change (Bhugra, 2014), a process that is being accelerated by a convergence of factors, including the mass movement of populations, the aggregation of groups from diverse cultures in large urban concentrations, and the ever wider reach of telecommunications and the social media. The consequence is an increasing movement toward conditions of cultural pluralism or "hybridization" in which there is an amalgamation of belief systems, languages, and practices derived from a range of traditions and customs (Kirmayer, 2006). The extent to which individuals adopt these hybrid cultures tends to differ across the generations; in general, older generation are more likely to strive to preserve traditional cultures, religious practices, and taboos (e.g., restrictions on selection of marriage partners and constraints on sexual behaviours), whereas younger generations are more open to embrace cultural change. The result is a tension that can generate intrafamilial and communitywide conflict. Understanding these complex shifts in cultural dynamics is vital to the work of professionals engaged in the RAPC mental health field.

In the present chapter, we draw on research undertaken over several decades in the RAPC mental health field by a team based at the School of Psychiatry, University of New South Wales, Australia. Although this is our primary source, we make selective reference to the wider literature to highlight issues of importance to practitioners working in research, program development, and clinical work relevant to the broader field of psychiatric traumatology. In so doing, we consider definitional issues relating to culture; the key historical influences that have shaped the modern RAPC mental health field; the evolution of theoretical models in the field; cross-cultural issues in diagnosis and classification of traumatic stress disorders; and key areas of progress and remaining challenges in the development of treatment approaches for refugees and related populations.

DEFINITIONS OF CULTURE

Although most people have an intuitive understanding of the term *culture,* a precise definition of the construct remains elusive (Fernando, 1988). In the restricted sense, culture refers to the shared beliefs and practices that distinguish one group of people from others, usually based on a common ethnobiological legacy, a history of geographical co-location and concentration, and other factors that create differences in identity between peoples, such as a shared set of mores, customs, and practices specific to each group. We apply the term *culture* in this stricter sense, while noting that in modern usage (particularly within pluralistic, cosmopolitan environments), the concept has been widened to denote groups who share a single characteristic or identity, for example, sexual orientation.

ESTABLISHMENT OF THE MODERN FIELD OF RAPC MENTAL HEALTH

Several factors converged in the 1970s to give impetus to the modern field of RAPC mental health. Psychiatrists and psychologists played a prominent role in the worldwide anti-torture campaign, culminating in the adoption of the Convention Against Torture in 1976 (UN General Assembly, 1984). Sensitization of professionals to the mental health needs of torture survivors—many of whom had sought asylum in Western countries—provided the momentum to establish the first specialized mental health

services for refugees in Europe, North America, and Australasia. The large influx into Western countries of refugees following the wars in Southeast Asia added momentum to the establishment of services for these populations (Ghosh, 2016).

Contemporaneous developments in the broader field of psychiatric traumatology—in particular, the adoption of an operationalized category of PTSD in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association [APA], 1980)—influenced the focus of research and clinical practice in the emerging RAPC field. In the early years, some leaders in the RAPC field resisted adoption of the PTSD diagnosis based on the argument that there was no equivalent notion in other cultures and its application tended to undermine traditional explanatory models of mental illness held by indigenous people exposed to mass conflict and torture (Silove, 1999). An additional concern was that applying Western diagnoses to persons exposed to gross human rights violations tended to "medicalize" normative psychosocial reactions and overshadow recognition of the need to overcome the political and social factors that were the source of the suffering experienced by refugees. In countries of resettlement, where refugees are a minority, assigning psychiatric diagnoses to this group could add to the risk of stigmatizing and marginalizing these persons (Silove, 1999).

Early theoretical models attempted to incorporate these concerns by emphasizing the need to embed clinical programs focusing on the treatment of traumatic stress disorders within a framework in which human rights, culture, and psychosocial needs were all afforded priority attention. The overall aim was to promote the adaptation and acculturation of refugees and their communities within the new host environment. Nevertheless, interdisciplinary tensions persisted in the RAPC field, particularly between advocates of trauma-focused clinical programs as opposed to broader psychosocial approaches. Gradually, a consensus was reached with the adoption of a multitiered conceptual system that acknowledged the diversity of the psychosocial and mental health needs of RAPC populations. This principle was reflected in widely adopted guidelines that continue to be applied in developing and implementing service models (Inter-Agency Standing Committee [IASC], 2007).

CONTEMPORARY ECOLOGICAL MODELS

Contemporary ecological models maintain a multisystem perspective in the RAPC field in which, at the most general level, the influence of global and geopolitical factors is recognized as being influential in determining the fate of refugees and the care and support they receive. At the intermediate level, international, regional, and national policies governing migration play a central role in determining key issues regarding the security and future of displaced populations. At the local level, the amount of social acceptance or hostility to newcomers determines the extent to which newcomers feel a sense of belonging and are able to forge a new identity. In that regard, provisions vary greatly across reception countries regarding the legal mechanisms applied in processing refugee applications and in the provisions governing the freedom or otherwise of displaced persons to live in and function in the new society. This includes their right to participate in employment and access services, factors that are known to influence traumatic stress and mental health outcomes. Within the community itself, cultural cohesion and the integrity of families can be instrumental in providing support for individuals recovering from traumatic stress reactions.

Although leading theoretical models overlap in acknowledging the influence of the multitiered system in determining social and mental health outcomes for refugees, they differ in the emphasis given to key elements. The conservation of resources (COR) model—a more general theory applied not just to refugees—highlights the role of loss and deprivation as being critical to the capacity of societies and individuals exposed to duress to regain their resilience and hence avert risk of mental disorder. Losses extend to both material and psychosocial resources (Hobfoll, 1989) and range from the capacity to meet basic needs, such as food, water, shelter, and health care, to psychosocial support and interpersonal networks through to the sense of belonging and identity. A related model (Miller & Rasmussen, 2010; 2017) gives particular emphasis to the role of daily stressors in determining the mental health and resilience of refugees. These models tend to prioritize the immediate environment over past experiences, for example, exposure to traumatic events. The implication is that restoration of resources and capacities should take precedence over a psychotherapeutic focus on events, such as exposure to traumatic experiences, in promoting the psychosocial well-being of refugees.

The adaptation and development after persecution and trauma (ADAPT) model attempts to integrate past, present, and future challenges in understanding the mental health and psychosocial needs of refugees (Silove, 2013; Silove, Ventevogel, & Rees, 2017). Refugees progress through an ever-changing sequence of challenging environments during the phases of mass conflict and persecution in the home country; upheaval and flight; the undertaking of hazardous journeys in search of safety and asylum; sequestration in places of temporary asylum, often in protracted settings of deprivation, uncertainty and threat; and for some, permanent resettlement. According to the ADAPT theory, humans attempt to integrate and make sense of these cumulative past and ongoing experiences in their effort to adapt to new challenges. The process involves a continuous feedback loop in which the intrapsychic world reflects and makes meaning of the ever-changing environment. Whether or not this process is successful determines the overall mental status and adaptation of the community.

The ADAPT model postulates that the refugee experience erodes five core psychosocial pillars, In stable societies, these pillars provide the foundations for social and psychological adaptation and mental health. The five systems are those that support safety and security; the integrity of interpersonal bonds and networks; access to justice; the capacity to preserve and develop roles and identities; and the freedom to make meaning of life by pursuing activities in the spiritual, religious, political, or social domains (Silove, 1999). All societies rely on the maintenance and integrity of these psychosocial pillars to foster and sustain the adaptation and mental health of citizens. Culture, in the form of traditions, mores and norms, shapes the way institutions are created to give expression to these psychosocial pillars; for example, how the individual relates to the family and kinship group differs across collectivist and individualistic societies; and practices in implementing justice vary across societies. Nevertheless, as a universal principle, mass violence and forced displacement erode these pillars across all displaced societies, thereby creating individual vulnerability to traumatic events and stressors. Early research provides support for this model by showing that the stressors associated with the erosion of the ADAPT pillars exerts multiple influences on pathways leading from traumatic events and postmigration stressors to PTSD symptoms (Tay et al., 2015a).

The ADAPT framework has been used as a guiding model in designing comprehensive refugee mental health programs among Iraqi refugees in Syria (Quosh, 2013).

More recently, it has been used to develop a specific psychological intervention for refugees in the form of integrative ADAPT therapy (IAT) as outlined later in this chapter (Tay et al., 2020).

EPIDEMIOLOGY

The renewed focus on refugee mental health initiated in the 1970s and 1980s led to an upsurge in epidemiological research among displaced populations worldwide. A review and meta-regression of accumulated data (Steel et al., 2009) provided the foundation for estimating the pooled prevalence of PTSD and depression in these populations. On average, 30% of refugees across studies experienced clinically significant symptoms of PTSD or depression, and comorbidity was common. Notably, among the more rigorous studies, prevalence rates were lower, ranging from 12 to 15% for PTSD (Steel et al., 2009). Even so, the rates for PTSD were many times higher than those observed in civilian populations not directly exposed to conflict. Torture was the most potent risk factor for PTSD, whereas depression tended to be associated with a wider range of traumatic events. A more recent review of studies to date found that, on average, 4% of persons from RAPC communities were assigned to a composite category of severe mental disorder (Charlson et al., 2019). This figure is consistent with research conducted in individual postconflict countries such as Timor-Leste (Silove et al., 2008).

Nevertheless, all reviews in the field have identified the high degree of heterogeneity in the prevalence rates of common mental disorders, including PTSD, observed across studies in the RAPC field. A common assumption is that transcultural error in diagnosis and assessment accounts substantially for this pattern of heterogeneity, an inference that casts doubt on the validity and hence value of conducting further research of this type in the field (van Ommeren, 2003). An alternative explanation, however, is that variation in prevalence rates is an indicator of the accuracy of studies in determining veridical differences in the histories of traumatic exposure and postconflict conditions in each community. We illustrate this point by making a comparison between epidemiological studies conducted among the Vietnamese and Cambodians.

Although differing in ethnic background, language, and culture, Vietnamese and Cambodian societies share some important characteristics, including a long history of colonization as well as exposure to prolonged periods of internal conflict. The conclusion of the Indo-Chinese wars in the mid- to late 1970s led to large outflows of refugees from both Vietnam and Cambodia, and many refugees were resettled in Western nations of North America, Europe, and Australasia (Ghosh, 2016). Scrutiny of the relatively large body of research undertaken among these groups reveals a consistent pattern in which Cambodians report higher rates of PTSD and other common mental disorders than the Vietnamese (noting that most studies are restricted to investigating one or other of these populations). For instance, a rigorously conducted epidemiological study among Cambodian refugees exposed to the Khmer Rouge regime in their home country and resettled for over 20 years in California found that more than half the sample met the criteria for PTSD and/or depression (Marshall et al., 2005). In contrast, a representative population study among Vietnamese resettled in Sydney, Australia, conducted during the same time period and using the same case-finding structured interview, found that only 1 in 12 respondents met the criteria for a common mental disorder (CMD), including PTSD and depression, a rate that was half that of the host Australian-born population (Steel, Silove, Phan, & Bauman, 2002).

This large discrepancy in CMD prevalence rates between Vietnamese and Cambodian refugees cannot be readily explained by a difference in the resettlement environment alone. Moreover, there is evidence that Cambodians are not exceptional in being more prone to developing disorders such as PTSD and depression (Mollica, Brooks, Tor, Lopes-Cardozo, & Silove, 2014). By far the most compelling reason for the striking variation in mental disorder prevalence rates between the Vietnamese and Cambodians observed across studies is the difference in the nature and quantum of traumatic events experienced by each of these populations. In relation to the Vietnamese population resettled in Australia, a large number of refugees originated from the south of the home country, a region in which armed conflict was sporadic and localized. The consequence was that many refugees recorded relatively low rates of exposure to traumatic events, particularly those of the most severe kind, for example, torture, sexual abuse, and exposure to combat. In comparison, the Khmer Rouge autogenocide exposed almost the entire Cambodian population to forced displacement, traumatic loss of family, and conditions of persecution, in which torture, exposure to murder and other forms of gross human rights violations, and other abuses, were common. The extent of this exposure is clearly recorded in the California study. These historical differences in both the quantum and type of exposure to traumatic events across the two populations offer the most plausible explanation for the observed differences in the prevalence of PTSD and other common mental disorders observed across the two populations.

In summary, a comparison of studies among the Cambodians and Vietnamese suggests that the epidemiological method, if rigorously applied, can detect veridical differences in prevalence rates of PTSD and other common mental disorders across cultures, based on differences in exposure to traumatic events and related major stressors. The corollary is that caution needs to be exercised in applying averaged prevalence rates of mental disorder derived by combining data from refugee communities to attempt to predict the needs of any newly displaced refugee population. Instead, the literature indicates the need to conduct fresh studies in each individual refugee population in order to obtain an accurate assessment of mental health needs. The capacity to undertake these studies is greatly enhanced by progress in epidemiological methods in the transcultural field, including in the cultural adaptation and testing of measures; in training and monitoring indigenous field personnel; and in the use of electronic data collection systems. These advances lower the cost and logistic challenges in conducting epidemiological studies and ensure the capacity to produce data in a timely manner in order to guide service planning.

RELATIONSHIP OF THE RAPC FIELD WITH GLOBAL MENTAL HEALTH

The fields of RAPC and global mental health share a common goal of identifying and addressing the needs of populations living in settings where mental health services are poorly developed (Patel & Prince, 2010). Although a large number of refugees remain confined in camps, a high proportion now reside in urban locations intermingled with the host society, living under conditions of protracted insecurity, deprivation, and marginalization. The principle of equity therefore dictates that any new services developed for refugees should be extended to the local host population in general. In that sense, refugee mental health initiatives can drive a process of service reform and modernization for the host community at large. That approach requires a shift in thinking in the

refugee mental health field from a singular focus on traumatic stress to a broader-based community mental health service model that includes a wider range of both low- and high-prevalence mental disorders. Refugee populations benefit from this wider focus by ensuring care for persons within their ranks with severe disorders, for example, the psychoses such as schizophrenia and bipolar and other mood disorders. During mass conflict, it is common for mental health facilities to close, leaving many of these persons without medications and often resulting in relapse of severe illnesses (Silove, Ekblad, & Mollica, 2000). These persons are at risk of abandonment, exploitation, assault, and physical illness as they attempt to navigate unstable and insecure conditions during the process of mass displacement. Lack of treatment increases the risk that some persons with severe mental disorders will manifest disruptive and at times aggressive behaviors, adding to the difficulties that families and the wider community confront in achieving social stability. For all these reasons, there is a need for a broad-based community approach to mental health care in which specialist services for trauma-related disorders are embedded.

SUBPOPULATIONS AT RISK

Subpopulations at heightened risk of trauma-related mental disorder within the general RAPC grouping include survivors of torture and politically motivated sexual abuses; single mothers; and unaccompanied minors. Survivors of torture often present with complex problems relating to head and other injuries, chronic pain, and sexual dysfunction. Cultural taboos may inhibit survivors of sexual violence from discussing the abuses they have experienced; women in particular may fear being blamed or ostracized by their families or wider communities for the abuse they have experienced. Tortured militants often adopt a stoical stance in which they have become disciplined to subjugate personal needs to their overweening focus on the wider political cause. As a consequence, they are reluctant to acknowledge or engage in psychological interventions focused on their individual traumatic stress reactions. Militia commonly compel abducted child soldiers to commit atrocities against their own communities and families. Such acts leave long-lasting impacts on character development, complicating the process of rehabilitation (Schauer & Elbert, 2010).

Asylum seekers are a high-risk group for mental health problems because of the chronic nature of the postmigration living difficulties they encounter. This subgroup of refugees lives under conditions of chronic insecurity imposed by policies aimed at deterring their entry into Western countries. Provisions adopted by governments (for e.g., prolonged detention; restrictions on those living in the community) affect access to work, health care, education and contact with family (Silove, Steel, & Watters, 2000). Applications for permanent residency can be a prolonged and arduous process, involving intrusive interviews aimed at verifying claims of torture and sexual abuse. Such a procedure can provoke flashbacks and nightmares. All these factors tend to exacerbate and prolong symptoms of PTSD and depression (Silove et al., 1997). Mental health personnel working in this field confront daunting ethical issues, including the risk of provoking PTSD symptoms by conducting detailed assessments to support refugee claims; maintaining professional independence when working in detention centers governed by prison-like protocols; and engaging in research and advocacy without breaching principles of professional impartiality (Silove & Mares, 2018).

PSYCHOPATHOLOGY: RANGE AND COMORBIDITY OF DIAGNOSES

As indicated, the adoption of PTSD in DSM-III coincided with the early period of development of services for torture survivors in Western countries. As multidiagnostic assessments were developed, many refugee patients were found to qualify for comorbid diagnoses, most commonly involving mood, anxiety and somatic disorders. In some communities, drug and alcohol problems complicated the clinical picture. In addition, some categories of mental disturbances relevant to the RAPC field remained contentious in relation to their status in formal psychiatric classification systems. Those of particular interest were complex PTSD, now included in the 11th revision of the *International Classification of Diseases* (ICD-11), and a disorder of prolonged or complicated grief, now adopted with some definitional variations in ICD-11 and the fifth edition of the DSM (DSM-5). Two other categories that have received relatively little attention as trauma-related disorders relevant to RAPC communities are the adult form of separation anxiety disorder and intermittent explosive disorder. Research into these diagnostic categories in the RAPC field has a wider significance to the fields of traumatology and mental health classification in general; relevant studies offer a test of the universality of novel diagnostic categories; provide the opportunity for examining cultural variations in the expression of symptoms; and allow more detailed examination of how context and types of traumas influence the prevalence and manifestations of disorders.

Prolonged Complex Bereavement Disorder

Refugees commonly experience a multiplicity of losses of close others and property; such experiences impact their sense of belonging and identity, particularly among persons from collectivist cultures. Moreover, traumatic losses invariably occur in the context of gross human rights violations. This confluence of factors may lead to persisting feelings of injustice, which in turn may generate lasting feelings of anger.

The delay in investigating prolonged and/or complex forms of grief in RAPC mental health may be attributable to the singular focus on PTSD in the early evolution of the field. The first study in this area was conducted among Bosnian refugees, focusing on the overlap of complicated grief and PTSD. Factor analysis revealed that the symptom domains of each disorder were largely independent, supporting the construct validity of both categories (Momartin, Silove, Manicavasagar, & Steel, 2004). The only area of overlap related to intrusive images of the deceased person. Consistent with wider literature, complicated grief was strongly associated with depression.

A further study among West Papuan refugees living under impoverished conditions in the Papua New Guinea capital of Port Moresby investigated the newly established and overlapping categories of prolonged complicated bereavement disorder (PCBD) and prolonged grief disorder (PGD) as defined in DSM-5 and ICD-11, respectively (Tay, Rees, Kareth, et al., 2016). Symptoms from these two classifications were supplemented by items nominated by community members and Melanesian psychiatrists familiar with the culture. Confirmatory factor analysis identified a unitary higher-order construct of prolonged complicated grief, supporting the diagnostic coherence of the category in this transcultural setting (Tay, Rees, Kareth, & Silove, 2016). Six symptom subdomains were identified in which anger/negative appraisal and confusion/diminished identity were prominent dimensions. A sense of injustice was strongly associated with complicated grief. In a further study among West Papuan refugees living in a remote border town in Papua New Guinea (Tay, Rees, Tam, Kareth, & Silove, 2019), four classes

of refugees were identified: a majority with low grief symptoms (67%); a complicated bereavement class (11%); a PTSD class (11%); and a combined PTSD and complicated bereavement class (10%). Compared to the other classes, members of the combined PTSD and complicated bereavement class reported higher rates of exposure to traumatic losses; greater disruption of interpersonal bonds and social networks; and severe feelings of identity confusion.

These findings offer preliminary evidence that a prolonged/complicated grief constellation occurs among refugees with a Melanesian background. Moreover, the data suggest that among a population that has experienced prolonged persecution and displacement, the sense of injustice associated with the loss may be instrumental in prolonging a grief reaction in which anger and identity confusion are prominent features.

Separation Anxiety in Adults from RAPC Backgrounds

Separation anxiety disorder refers to a state of extreme and overwhelming fear for the safety, health, and whereabouts of close attachments, usually family members. Long regarded as a childhood disorder, separation anxiety disorder is now recognized as a diagnosis that can manifest across the lifespan, commonly occurring in early to mid-adulthood, and particularly among women in the childbearing age (Manicavasagar & Silove, 2020). Separation anxiety disorder differs conceptually from grief in that in the separation reaction, fear and anxiety are directed toward the living rather than the deceased. Separation anxiety disorder is common, manifesting in 5% of the general population over the course of a lifetime. Research suggests that the disorder is more common in low-socioeconomic environments and is associated with exposure to traumatic events, characteristics that are relevant to RAPC populations (Silove et al., 2015).

There is growing evidence of overlap of adult separation anxiety disorder with PTSD among adult refugees, a convergence of symptoms that reflects the observation that persons exposed to mass conflict commonly experience traumatic events, such as atrocities, that involve simultaneous threat to the self and close others. Moreover, refugee families often are separated, generating fear for the safety of close others; or they live in insecure settings, where threat of violence, for example to children, represents a major stressor for parents. Research has confirmed the expected pattern of overlap between PTSD and separation anxiety disorder, including in studies among Bosnians (Silove, Momartin, Marnane, Steel, & Manicavasagar, 2010) and West Papuans (Tay, Rees, Chen, Kareth, & Silove, 2016). In the latter population, one-fifth of refugees manifested a comorbid pattern, and these persons reported the most severe forms of psychosocial disruptions of mass conflict and displacement.

Complex PTSD

Critics of the PTSD construct have asserted that the category fails to encompass the full range of symptoms and maladaptive responses manifested by survivors of "complex" traumas such as torture, sexual abuse, and exposure to other forms of intentional abuses and violence (Herman, 1992). Although several attempts have been made to formulate a complex form of PTSD, early research failed to provide unequivocal support for the separate nosological status of the category. More recently, however, a category of complex PTSD has been included in the ICD-11, represented as a variant of PTSD characterized by the core characteristic of a disturbance of self-organization (see Friedman et al., Chapter 2, this volume). Given the types of repetitive interpersonal abuses that

refugees encounter, including torture, mass violence, and other forms of human rights violations, there are reasons to expect high rates of complex PTSD among these populations. A limited number of studies have examined whether complex PTSD occurs across cultures (Ho et al., 2020; Knefel et al., 2020), and a subset of these inquiries have been conducted among refugees. In our own study among West Papuan refugees (Tay, Rees, Chen, Kareth, & Silove, 2015b, 2018), the prevalence of complex PTSD exceeded that of PTSD alone. However, factor analysis was unable to separate the two categories, raising questions regarding whether elements of both are best regarded as part of one syndrome among refugees. Nevertheless, when a hierarchical model was examined, complex PTSD was found to occur in those refugees reporting the most extreme exposure to life-long traumatic experiences, encompassing events occurring in childhood and in later life, in addition to severe stressors experienced during the migration and resettlement process. In the next tier of the hierarchy were persons with other common mental disorders, and on the lowest level were those with no mental disorders. Considered as a whole, this small body of studies has produced somewhat equivocal findings concerning the status of complex PTSD among refugees, suggesting the need for further research to clarify the nosological and clinical status of this putative diagnosis.

Explosive Anger and Intermittent Explosive Disorder

Growing attention has been given to manifestations of anger among survivors of traumatic events in the RAPC field, given that in clinical practice, problems of anger and aggression are common presenting complaints. Uncontrollable and repetitive episodes of anger are disturbing to the survivor and impact adversely on family and social relationships, at times attracting the attention of external agencies because of the threat involved to others. The aggregated expression of trauma-induced anger across the population may play a role in generating social instability and hence may prolong the fragile status of countries emerging from prolonged periods of conflict and persecution.

Our team has pursued a 20-year program of research into explosive anger in postconflict Timor-Leste. In a longitudinal study of an adult population living in an urban and a rural village, the prevalence of explosive anger remained more or less consistent over 6 years, involving two-fifths of the community (Silove, Mohsin, et al., 2017). Both qualitative and quantitative inquiries revealed a number of risk factors associated with explosive anger, including exposure to human rights abuses related to traumatic losses of family, persistent conditions of poverty, and an overall sense of injustice associated with grief arising from the violent death of family and extended networks (Silove, Tay, et al., 2017). There was an aggregation of anger within couples in families exposed to high levels of conflict-related traumatic events, suggesting that these families were at high risk of a range of mental health and psychosocial problems (Silove, Tay, et al., 2017). If this pattern is replicated in other postconflict societies, there may be grounds to focus preventive interventions on these families with a high risk of transgenerational transmission of mental health problems—mediated by children's exposure to intrafamilial conflict and violence.

CULTURAL EXPRESSIONS OF TRAUMATIC STRESS

A key tenet of transcultural psychiatry is that cultural factors play a central role in the pathogenesis, subjective experience, and expression of mental distress. The so-called

'emic' position asserts that each culture has its own distinctive way of manifesting and making sense of mental distress; the implication is that no one system of diagnosis or treatment can be applied to all cultures. The contrary 'etic' or universalistic position argues that core experiences of mental distress are common to all humanity and that if there are cultural variations in manifestations of mental disorders, they relate to surface features and not the essential features of the relevant syndromes. For example, persons from traditional cultures may tend to emphasize somatic complaints in the first presentation of PTSD, but careful inquiry will identify the features of the underlying disorder. Less controversial is the issue that the attribution of causation of mental disturbance varies by culture; it is common, for example, for persons from traditional cultures to ascribe symptoms to supernatural or animistic causes (Lim, Hoek, & Blom, 2014).

Culture-bound syndromes offer evidence in support of the emic position in that they represent unusual states of abnormal behavior that are distinct to one cultural group or, at most, a particular region—and the pattern of behavior has no clear counterpart with mental disorders observed in other societies (Kohrt et al., 2014). Exposure to traumatic events or severe stressors may be implicated in the psychogenesis of a number of these syndromes, for example, *susto* or "soul theft," which is widely recognized in Latin American societies and manifests as an exaggerated flight or startle response (Nogueira, de Jsus Mari, & Razzouk, 2015). The overlapping category of *ataque de nervios* appears to be a more general anxiety response also related to stressors (Nogueira et al., 2015). Nevertheless, much controversy persists about the causes, nature, and significance of culture-bound syndromes. For example, some authorities argue that the culture-bound syndrome of *pibloktoq* that occurs among the Inuit, described as a state of frenzy in which the individual exhibits bizarre behavior, including echolalia and coprolalia, may not be culture bound but rather may represent a reaction to sexual exploitation by colonialists (Kirmayer, 2007). As such, rather than an emic manifestation of mental disorder, *pibloktoq* may be a reaction to cultural intrusion.

The meaning and significance of cultural syndromes can also evolve and change. For example, West Papuan refugees subjected to a long period of persecution and displacement experience a condition known as *sakit hati,* in which the person becomes preoccupied, resentful, and withdrawn, culminating in episodes of explosive anger that can be expressed as aggression toward close others. The West Papuan explanation for this condition is that it expresses feelings of frustration and anger arising from the sense of helplessness that the refugee feels in not being able to address the ongoing human rights violations occurring in the homeland (Rees & Silove, 2011). This adaptation of the syndrome to the local context derives from the wider usage of the term *sakit hati* throughout the Malay-Indonesian region as a state of resentment or jealousy arising from disappointment in a romantic relationship. Moreover, *sakit hati* appears to have more serious consequences among West Papuans in that it can lead to bouts of ill-directed violence reminiscent of another well-known regional syndrome, *amok* (Saint Martin, 1999).

In general, although exposure to traumatic events may be instrumental in provoking some cultural syndromes, systematic evidence is often lacking, primarily because of the small and selective samples included in most reports describing these reaction patterns. Many cultural syndromes (e.g., spirit possession) are suggestive of dissociative states, which in some instances are triggered by traumatic events, but again, data tend to be limited to case studies. Therefore, more systematic research is needed to examine whether and to what extent cultural syndromes overlap with Western categories of traumatic stress such as PTSD or prolonged complex bereavement disorder. In clinical practice in the RAPC field, a balanced approach is needed in considering both emic

(or within culture) and etic (universalist) perspectives, with the aim of constructing a shared understanding of the problem and ensuring a common foundation for therapy in the therapist–patient relationship.

INTERVENTIONS

Context and Delivery

In high-resourced Western countries, comprehensive services for refugees with PTSD and related disorders have been developed based on the cardinal principles of cultural sensitivity, respect for human rights, and the embedding of clinical treatment for traumatic stress within a broader psychosocial model. The overarching objective is to ensure a nonstigmatizing and receptive environment for patients who may lack trust in institutions, including health care services, based on their adverse experiences in their homelands.

Interventions draw on a range of components tailored to meet the needs of individuals, including psychopharmacology, psychological therapies of various types, and physical therapies including physiotherapy and massage. Psychosocial interventions range from general psychoeducational courses, lifestyle and physical activity programs, and initiatives designed to meet the needs of specific groups such as refugee children, adolescents, survivors of torture, and the elderly. The use of bicultural counsellors or interpreters is vital to the success of the service. Careful attention is needed to provide training and support for these personnel to ensure high standards of translation and the protection of confidentiality and privacy.

Pharmacology and Somatic Therapies

Psychopharmacological agents used in the RAPC field are drawn from the range of medications applied in the general field of psychotraumatology (see Davis et al., Chapter 23, this volume). In low-resource settings, the range of medications available may be limited to first- generation antidepressant/antianxiety and antipsychotic drugs. Based on knowledge gained in ethnopsychopharmacology, dosages need to be reduced for some ethnic groups, and special consideration needs to be given to risk of serious adverse effects, including potentially lethal outcomes when first-generation medications are taken in overdose (Lin & Poland, 1995; Lin & Smith, 2000). Special care also needs to be exercised in treating the elderly and those with comorbid medical conditions.

Many patients from diverse cultures are accustomed to traditional healers offering single-dose remedies as treatment and may require additional education to ensure the regular use of psychotropic medications on a daily basis over a prolonged period of time. Inquiring into sexual side effects of drugs requires special care in societies where discussion of the topic of intimacy remains highly sensitive, and especially so when the therapist and patient are from opposite genders.

Brief Psychotherapies

A wide range of psychological interventions have been devised to treat states of distress, PTSD, and other trauma-related mental disorders in RAPC populations. The

principle of task shifting is widely applied in which lay counsellors or generic health workers such as nurses are trained to implement brief, structured, manualized psychological programs, either individually or in groups (Silove et al., 2017). Trainees are then provided supervision by visiting professionals or by remote communication, for example, by telehealth. The driving principle is to design and implement treatments that are both economical and suitable for rolling out with cultural adaptation across a range of RAPC communities. Positive short- and medium-term outcomes have been documented in randomized controlled trials (RCTs) for a range of therapies, including narrative exposure therapy (NET; Lely et al., 2019; Neuner, Schauer, Klaschik, Karunakara, & Elbert, 2004); the common-elements treatment approach (CETA; Murray et al., 2014); cognitive-behavioral therapy (CBT), for example, for women survivors of sexual abuse (Bass et al., 2013, see Galovski et al., Chapter 19, this volume); and problem management plus (PM+; Dawson et al., 2015) and its variants. Available therapies draw on evidence-based components of trauma-focused therapies (see Chapter 19, this volume) for treating PTSD and related CMDs in Western settings.

The depth and extent of the work undertaken to adapt therapies to each culture vary across modalities. In a minority of instances, extensive ethnographic work has been conducted prior to the development or adaptation of a therapy to ensure its congruence with the belief systems, explanatory models, and traditional practices of the relevant community (Hewage et al., 2018; Hinton & Jalal, 2019; Hinton, Rivera, Hofmann, Barlow, & Otto, 2012; see Galovski et al., Chapter 19, this volume). More recently, integrative ADAPT therapy (IAT) based on the ADAPT model was shown to be superior to a CBT intervention in achieving short-term improvement in a range of symptoms among refugees from Myanmar (Tay et al., 2020).

A number of issues remain to be clarified, however, prior to the widespread adoption of brief manualized psychotherapies in the RAPC field. These include the cost and logistics of implementing these approaches in an equitable way across refugee populations at a global level, given that the majority of communities are distributed across low-resource settings where access, logistic constraints, and available skills present major challenges to implementation. Questions also remain as to whether the community service systems in these contexts are capable of sustaining psychotherapy programs by ensuring ongoing supervision, peer support, and strategies to update knowledge and skills for counsellors who otherwise are at high risk of burnout if left to work in isolation (Silove, 2020). Longer-term follow-up studies are needed to ensure that the short- and medium-term gains achieved from these therapies are sustained over time and indeed assist refugees to withstand future traumatic events and stressors. There is also a risk that a singular focus on brief psychotherapies may obscure the need to provide a range of other interventions for refugees with complex and highly disabling forms of traumatic stress disorders that are resistant to time-limited interventions. This minority may require longer programs of psychosocial rehabilitation (Buhmann, Nordentoft, Ekstroem, Carlsson, & Mortensen, 2016).

Services also need to be competent to deal with the low-prevalence but severe mental disorders that occur in all societies, including psychoses such as schizophrenia and related disorders, bipolar disorder, and other severe mood disorders, organic brain conditions, and, in some settings, drug and alcohol problems. Comorbidity is common; for example, someone with a psychotic illness such as schizophrenia may also experience PTSD. It therefore is vital to ensure that within RAPC communities, the full range of mental health problems is treated in a culturally sensitive manner.

CONCLUSIONS

Much progress has been made in the modern RAPC mental health field since its inception over four decades ago. Specialist services have been established worldwide and increasingly apply the principles of ecological models specifying a multilevel approach in assessing and responding to the range of mental health and psychosocial challenges experienced by these populations. These models may have wider application across other domains of psychiatric traumatology, for example among indigenous and other minority populations exposed to high levels of traumatic events and abuse. Major advances have been made in refining methodologies for conducting cross-cultural epidemiological studies in the field, offering an important tool in determining the mental health needs of conflict-affected and refugee populations. The pattern of heterogeneity in prevalence rates of PTSD and related disorders found across studies attests to the importance of assessing each new refugee community afresh, given that they differ substantially in their histories of exposure to trauma and stressors, and hence to their risk of adverse mental health outcomes. Reconciling Western concepts regarding the pathogenesis and expression of traumatic stress responses with indigenous constructs and belief systems remains an ongoing challenge, given the process of rapid cultural change occurring worldwide.

Although progress has been made in developing brief structured psychotherapies for RAPC populations, these interventions derive largely from principles of Western psychiatry and psychology. Attention to the cultural aspects of therapies and their congruence with the lived experience of refugees may increase both the receptivity and meaning-making aspects of interventions. There also is a minority of complex cases that require tailored, multimodal interventions and that may benefit more from longer-term rehabilitation approaches than from short-term psychotherapies. More generally, further work is needed in integrating indigenous concepts of mental health into systems of diagnosis and treatment. Engaging with these issues at the clinical and programming level, though challenging, remains a constant source of stimulation and engagement for practitioners in a field in which, like no other, consideration needs to be given in every case to the intricate intersection of culture, history, human rights, and political injustice in shaping the traumatic stress response.

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CHAPTER 27

PTSD and the Law
FORENSIC CONSIDERATIONS

Dean G. Kilpatrick, Alexander C. McFarlane, and Lucy A. Guarnera

Posttraumatic stress disorder (PTSD) has always generated controversy, in large part because the contours of the diagnosis bear directly on a variety of forensic contexts. The considerable confusion and debate surrounding the diagnosis have only intensified due to major differences in the PTSD definitions in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association [APA], 2013) and the 11th edition of the *International Classification of Diseases* (ICD-11; World Health Organization [WHO], 2018).

One reason PTSD has drawn particular attention and criticism in forensic situations is that the boundaries of its stressor criterion have a direct effect on whether PTSD can be diagnosed. Kilpatrick, Resnick, and Acierno (2009) described historical arguments about the PTSD stressor criterion as disputes over whether to define this gatekeeper broadly or narrowly. PTSD cannot be officially diagnosed unless an individual has experienced a qualifying potentially traumatic event (PTE) as defined by the operative DSM or ICD classification system. Therefore, the stressor criterion is highly relevant in forensic situations because it sets the boundaries of the types of PTEs that qualify as capable of supporting a PTSD claim in court.

PTSD is extremely important in many civil litigation and compensation cases. In the former, plaintiffs bring civil lawsuits, alleging that they suffered physical, psychological, or economic harm due to deliberate or negligent acts of another party and seek monetary redress. In compensation cases, litigants seek monetary compensation from governmental programs or agencies due to traumatic events such as military combat, violent crime, or accidents at work (i.e., veterans' compensation, crime victims' compensation, and workers' compensation, respectively). In some jurisdictions, establishing liability requires that an individual have a disability resulting from a diagnosable disorder such as PTSD. On one hand, then, less restrictive diagnostic criteria may make it more likely for individuals with little or no impairment to improperly receive awards. On the other hand, research has repeatedly shown that even subthreshold or partial

PTSD—defined as meeting most but not all criteria required for the full diagnosis—is associated with significant impairment and need for treatment (McFarlane, Lawrence-Wood, van Hooff, Malhi, & Yehuda, 2017; Pietrzak, Goldstein, Malley, Johnson, & Southwick, 2009). Thus, if diagnostic criteria for PTSD are more restrictive, this has the potential to reduce liability and disadvantage litigants with legitimate claims (Vermetten, Baker, Jetly, & McFarlane, 2016).

PTSD is also relevant in criminal cases (Berger, McNeil, & Binder, 2012). Those accused of committing violent crimes may use PTSD as a defense (i.e., as part of an insanity defense or diminished capacity defense). For example, a woman charged with attacking an intimate partner who battered her in the past may argue that PTSD from previous attacks produced a heightened perception of impending threat, leading her to use force in self-defense. Conversely, a claim of PTSD can also be used *against* a criminal defendant. For example, a defendant accused of sexual violence may argue that the sexual contact proven by DNA evidence was consensual; in this case, the prosecutor may present evidence that the alleged victim has rape-related PTSD and argue that the event was therefore not consensual.

After guilt has already been determined, PTSD or PTE exposure may also be invoked in criminal cases to mitigate criminal penalties. For example, in the sentencing phase of a death penalty case, mental health and mitigation experts may present evidence of PTSD symptoms or lifetime exposure to PTEs such as child abuse, sexual assault, domestic violence, or military combat. The hope is that such information might incline the jury to assign a penalty less than death.

Another forensic context in which PTSD is becoming increasingly relevant is immigration court, as claims for asylum have increased in all industrialized nations across the last quarter-century (UN High Commissioner for Refugees [UNHCR], 2018). Under United States law, for example, an asylum seeker must demonstrate "credible fear" of returning to their home country because of persecution or fear of persecution due to nationality, religion, or membership in another designated class (U.S. Citizenship and Immigration Services, 2015). Immigration courts often operationalize "credible fear" as PTSD or related symptoms, meaning that an asylum case may hinge entirely on a PTSD diagnosis.

All of these types of forensic cases typically occur in adversarial settings, where opposing parties vigorously debate the evidence for or against PTSD in a particular case. Understanding the scientific literature on PTSD is crucial to inform these debates. Many publications address PTSD in forensic settings (e.g., Young, 2016, 2017a, 2017b), so this chapter will not provide a comprehensive review of the literature. Instead, the focus is on the following questions: What are the forensic implications of the PTSD criteria in DSM-5 and ICD-11? How do the diagnostic criteria affect the types of forensic cases described above? How much emphasis should be placed on malingering? How is emerging biomarker research changing forensic assessment of PTSD? Are there potential ways to improve PTSD assessment and expert witness testimony in adversarial legal settings?

IMPACT OF DSM-5 AND ICD-11 CRITERIA ON FORENSIC CASES

While the definition of PTSD can have a tremendous impact on civil, compensation, criminal, and immigration cases, the primary purpose of the DSM and ICD systems is not to simplify matters for the legal system. The primary purpose, rather, is to define

mental disorders in order to promote reliable diagnoses and useful clinical information. However, given the role of the PTSD criteria in forensic settings, any diagnostic features that could impact legal proceedings require careful monitoring to minimize unintended consequences.

Overall, there are substantial differences in the PTSD diagnostic criteria in the DSM and ICD classification systems—differences that likely have significant forensic implications. The biggest difference is that ICD-11 splits PTSD into two separate disorders: PTSD and complex PTSD. Accordingly, the two systems also include quite different PTSD symptoms, with some revised DSM-5 symptoms now split between ICD-11's PTSD and complex PTSD diagnoses. This has generated considerable controversy and confusion, as critics (e.g., Resick et al., 2012; Vermetten et al., 2016) have raised major questions about the conceptual coherence and empirical support for the complex PTSD construct. As ICD-11 will not be formally adopted until 2022, it is still unknown how the new complex PTSD diagnosis will affect forensic cases (e.g., whether individuals claiming complex PTSD will demand or receive greater monetary awards compared to those with "simple" PTSD).

As was the case with PTSD as defined in DSM-IV (APA, 2000) and ICD-10 (WHO, 2004), the two systems also differ in their approach to defining the types of traumatic events that can result in PTSD. In DSM-5, the stressor criterion (criterion A) is defined quite explicitly both in the criterion itself (see Friedman et al., Chapter 2, this volume, Table 2.1) and in the accompanying text, which provides many specific examples of qualifying and excluded events. In contrast, ICD-11 only lists exposure "to an extremely threatening or horrific event or series of events" without any more specific language or examples. These differences will affect which PTEs can support claims of PTSD in court.

Overall, given that PTSD is defined quite differently in DSM-5 and ICD-11, employing different diagnostic systems will likely result in some variation as to whether or not an individual is identified as having the disorder. Reviewing the evidence on these discrepancies is beyond the scope of this chapter but can be found elsewhere (see Friedman, Chapter 2, this volume, and Young, 2017b). However, this issue has forensic relevance for two reasons. First, should someone qualify for a PTSD diagnosis using one set of diagnostic criteria but not the other, this may open the door for savvy litigators to argue that the PTSD construct itself is insufficiently reliable to meet the standards for admissibility into court. For example, in the United States, the *Daubert* evidentiary standard used in the federal system and many states specifies that the "known or potential rate of error" of any scientific technique be established before it can be admitted in court (*Daubert v. Merrell Dow Pharmaceuticals,* 1993, p. 580). Second, some forensic experts may cherry-pick which set of diagnostic criteria to use, depending on whether or not they wish to diagnose PTSD (i.e., in order to benefit the retaining party). Even without such an intention, a forensic expert diagnosing PTSD may be required to justify their choice of diagnostic system in court, particularly if the alternative system would be more favorable to the opposing party.

The remainder of this section focuses primarily on how DSM-5 revisions impact forensic cases, given that more is known about DSM-5 since it has been in effect since 2013, while ICD-11 will not be adopted until 2022. There are three general ways by which the diagnostic revisions in DSM-5 can influence forensic cases: (1) changes to criterion A, (2) changes to PTSD symptoms, and (3) potential changes to diagnostic reliability or validity.

DSM-5 Changes to Criterion A

Changes to criterion A affect forensic cases because criterion A is a gatekeeper that defines the type of PTEs eligible for assessment using the remaining PTSD criteria. Even before DSM-5 was released in 2013, critics argued that it broadened the range of qualifying PTEs compared to DSM-IV, with this "bracket creep" increasing the pool of individuals in a position to malinger PTSD (e.g., First, 2010; McNally, 2006). The controversy about revisions to criterion A has only continued in the years since, with others (e.g., Levin, Kleinman, & Adler, 2014) arguing that eliminating the DSM-IV requirement of experiencing intense fear, helplessness, or horror at the time of the traumatic event "appears to increase the potential for malingering" by allowing individuals to claim PTSD long after a seemingly benign response to a PTE (p. 152). Such concerns clearly imply that forensic considerations should be primary in defining criterion A. However, there are several problems with this approach.

First, as will be discussed subsequently, the bulk of available research does not indicate that malingering is a particularly grave problem for PTSD. Second, excessive concern over perceived broadening of criterion A is misguided because experiencing a PTE is a necessary but not sufficient condition for PTSD to develop. Just because a PTE is included in criterion A does not mean that a person who experiences it *will* develop PTSD, only that they *might* develop PTSD depending on numerous risk and protective factors. In fact, most people do not develop PTSD even following extreme stressors (Kilpatrick et al., 2013), so expanding criterion A will not necessarily prompt a deluge of civil, compensation, and asylum claims.

Third, even the PTEs associated with the highest levels of conditional risk for PTSD (e.g., military combat, interpersonal violence; Karam et al., 2014) are not easy to verify using official records. For example, a National Research Council report (NRC, 2007) on PTSD compensation and military service noted that military records are inadequate to document many types of PTEs that occur in war zones. Similarly, fewer than one in five rapes is reported to police (Kilpatrick, Resnick, Ruggiero, Conoscenti, & McCauley, 2007), making it impossible to verify the occurrence of most rapes using police records. Thus, even the types of traumatic events all clinicians agree ought to be included in criterion A are typically disputed in adversarial legal proceedings. The PTEs now included in DSM-5 that were not included in DSM-IV will be similarly subject to rigorous vetting in forensic contexts, in contrast to characterizations that the revised criterion A opened the "floodgates" to easy malingering of PTSD claims in court (Young, 2016, p. 243). This underscores the importance of forensic experts making good-faith efforts to obtain as much objective verification of a PTE as possible, as well as communicating to the court their assumptions and the limitations of the quality of information before them.

Even though revisions to criterion A have had less drastic effects than critics feared, criterion A as defined in DSM-5 does directly impact forensic cases by redefining the types of events considered capable of producing PTSD. Overall, DSM-5 revisions to criterion A arguably did not *expand* the range of PTEs as critics charged, since some new types of events not covered by DSM-IV are now included, while other types of events previously covered by DSM-IV are now excluded. Regarding new exclusions, criterion A as written in DSM-5 excludes nonviolent, nonaccidental deaths from qualifying PTEs, as well as some potentially life-threatening physical illnesses or experiences that were included in DSM-IV. DSM-5 also makes clear that vicarious observation of traumatic events via media does not qualify unless the exposure is work-related. In other words,

a person who views upsetting events via television news, movies, or Internet videos cannot claim PTSD in court.

Conversely, DSM-5 includes types of sexual violence that may not have counted as PTEs in DSM-IV. DSM-IV limited qualifying sexually violating events to "sexual assault" (p. 463), while DSM-5 uses the more inclusive term *sexual violence,* which the U.S. Centers for Disease Control and Prevention (Basile, Smith, Breiding, Black, & Mahendra, 2014) defined as including forced sexual contact, alcohol/drug-facilitated sexual contact, abusive sexual content, noncontact sexual abuse, sexual trafficking, and some types of sexual harassment. Ample research indicates that a range of sexually violent experiences are potent risk factors for PTSD (Brown, Testa, & Messman-Moore, 2009; Kilpatrick et al., 2003; Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993). Furthermore, there is some evidence that more extreme types of sexual harassment increase risk of PTSD, even after controlling for exposure to other types of PTEs (Willness, Steel, & Lee, 2007). In any case, the stressor criterion in DSM-5 does not include *all* types of sexual violating experiences. Furthermore, the DSM-5's inclusion of less extreme forms of sexual violence within criterion A has permitted many victims of historical sexual abuse by religious institutions to qualify for PTSD—thus making it easier to sue the offending institutions for damages—whereas these individuals would not have qualified under prior DSM definitions (Wright, Swain, & McPhillips, 2017). The current formulation of criterion A thus clarifies that these forms of sexual abuse are PTEs and encourages assessment of PTSD even if the sexual violence was less extreme.

Another revision to criterion A that is particularly likely to affect litigation in civil and compensation cases is the addition of PTEs involving repeated or extreme exposure to aversive details of traumatic events. A variety of professionals repeatedly exposed to disturbing content are now included in criterion A; these professionals include paramedics, battlefield medical staff, or mortuary technicians who are repeatedly exposed to gruesome injury and death, as well as child protective service workers, law enforcement officers, or therapists who repeatedly hear accounts of child victimization or other types of violent crimes. DSM-5 also allows for such exposure via media as long as the exposure was work-related, such as a military service member who operates drones and repeatedly witnesses video feeds of death and destruction occurring thousands of miles away. While this revision does expand the types of events that might lead to civil damages or compensation for PTSD, a study using a large national sample of adults found that the conditional risk of PTSD given this type of repeated traumatic exposure was less than 1% (Kilpatrick et al., 2013). Thus, it seems unlikely that including these individuals within criterion A will result in a meaningful increase in the number of PTSD cases on a population level. Conversely, the inclusion of this class of PTE does provide coverage for employees who have to contend with these very difficult work-related traumatic exposures.

DSM-5 Changes to PTSD Symptoms

Moving on from criterion A, we find that four PTSD symptom revisions in DSM-5 have particular relevance to forensic cases. First, reckless or self-destructive behavior is a new DSM-5 PTSD symptom that has generated considerable attention in forensic settings. For example, Young (2016) argued that the addition of reckless or self-destructive behavior to the DSM-5 symptom list "opens a Pandora's Box of improper forensic use" (p. 239). Specifically, Young (2016) expressed concern that a savvy litigant or attorney could use these "relatively open-ended criteria" to argue that a variety of

substance-abusing, harmful, or antisocial behaviors—nonspecific signs of impairment or distress in which a person might engage for any number of reasons—now represent a PTSD symptom (p. 243). Likewise, a criminal defendant might argue that the act constituting the offense resulted from PTSD-related recklessness or aggression rather than from full-fledged criminal intent (Levin et al., 2014). Courts have increasingly shown a willingness to consider such arguments about criminal responsibility, particularly when the defendant is a veteran (Grey, 2012).

Second, at least one of the two active avoidance symptoms in criterion C are now required to obtain a PTSD diagnosis, thus excluding individuals experiencing only passive avoidance (i.e., emotional numbing). In fact, several studies (Kilpatrick et al., 2013; O'Donnell et al., 2014), including one with a veteran sample (Hoge, Riviere, Wilk, Herrell, & Weathers, 2014), found that the active avoidance requirement was a main reason people met DSM-IV but not DSM-5 criteria for PTSD (although, of note, a subsequent study with a veteran sample did not replicate this finding; Weathers et al., 2018). Given the overall thrust of this research, some experts have expressed concern that the requirement for at least one active avoidance symptom has the potential to particularly disadvantage military and emergency services personnel seeking compensation (Hoge et al., 2016). Their work roles require them to function in dangerous environments and confront unpleasant thoughts and feelings that most people would avoid. Such individuals must learn to override avoidance behaviors to function on a daily basis; hence, thresholds for avoidance may be higher among these individuals and occur only when they can no longer suppress fear or horror evoked by their duties (Adler, Wright, Bliese, Eckford, & Hoge, 2008). Thus, military and emergency services personnel may wait longer after the onset of symptoms before seeking treatment, compensation, or removal from the aversive work environment. For example, a study utilizing the National Epidemiological Survey on Alcohol and Related Conditions–III found that male veterans who sought treatment for PTSD waited an average of over 10 years after the onset of symptoms, in comparison to less than 5 years for male civilians seeking treatment (Lehavot, Katon, Chen, Fortney, & Simpson, 2018). These kinds of delays can lead to further risk of injury due to continued PTE exposure and may also present risks to the organization and wider community if these personnel continue to work while suffering from extremely impairing symptoms (Sanderson & Cocker, 2013).

Relatedly, military and emergency services personnel may engage in reckless behavior when avoidance is not possible, and such recklessness may indicate a numbing response to their hyperarousal (Borders, McAndrew, Quigley, & Chandler, 2012). For example, a police officer may take excessive risk in the face of danger, in a state akin to depersonalization, rather than avoid the situation. Thus, those conducting forensic assessments in such cases must take a broad view of responses to fear that incorporates a range of behaviors people use to adapt to trauma-related stimuli, situations, thoughts, and feelings, which can range from reckless denial of risk to overt avoidance.

Third, DSM-5 explicitly requires that PTSD symptoms must have either begun or worsened after exposure to a traumatic event or events. This means that symptoms such as reckless or self-destructive behavior or sleep difficulties do not count as PTSD symptoms *unless* they began or worsened after a PTE. This new standard is more conservative than that in the DSM-IV, but it is consistent with the legal standard in tort or compensation cases requiring that a psychological injury must have been caused or aggravated by the event in question. Accordingly, forensic evaluators should assess exposure to *all* lifetime PTEs to help determine which PTE caused or aggravated PTSD symptoms.

A final revision to DSM-5 PTSD diagnostic criteria that may have some impact in criminal forensic cases is the addition of a new "with dissociative symptoms" specifier, in which the person with PTSD also has persistent and recurrent symptoms of depersonalization or derealization. While dissociative symptoms may seem like a likely path to a criminal defense by negating *mens rea* (i.e., the "guilty mind" required for criminal responsibility), Berger and colleagues (2012) note that this defense is rarely used in criminal cases and tends to succeed only when there is a clear link between the situation in which the crime was committed and the circumstances that resulted in the PTSD. For example, a veteran might argue that he is not legally responsible for committing a violent crime because an antecedent threat was extremely similar to his battlefield experiences, triggering a dissociative flashback during which he responded with violence that was rational within the context of the flashback. Furthermore, as Moskowitz (2004) noted, it can be difficult to distinguish whether dissociation preceded a violent act or whether it developed as a consequence of the violence—a fact that shrewd prosecutors may raise to attempt to rebut a *mens rea* defense based on dissociation.

Potential Changes to Diagnostic Reliability or Validity

Another crucial question regarding the DSM-5 PTSD diagnostic criteria is whether the diagnosis is sufficiently reliable to be admissible in forensic settings. Studies published around the release of DSM-5 in 2013 contained some encouraging data about the reliability and validity of the revised PTSD diagnosis. The DSM-5 field trials found that PTSD was one of the most reliable of any psychiatric diagnosis assessed, with a test–retest reliability of kappa = 0.67 (Regier et al., 2013). Kilpatrick and colleagues (2013) also found that the new DSM-5 criteria had limited impact on PTSD caseness or prevalence. Since then, research has consistently found good interrater reliability and test–retest reliability for the DSM-5 versions of the structured instruments most commonly used to assess PTSD in practice, such as the Clinician Administered PTSD Scale for DSM-5 (CAPS-5; Weathers et al., 2018), PTSD Checklist for DSM-5 (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015; Bovin et al., 2016); Posttraumatic Stress Disorder Symptom Scale Interview for DSM-5 (PSSI-5; Foa et al., 2016), UCLA PTSD Reaction Index for DSM-5 (PTSD-RI-5; Kaplow et al., 2020), and Child PTSD Symptom Scale for DSM-5 (CPSS-5; Foa, Asnaani, Zang, Capaldi, & Yeh, 2018). All of this evidence indicates that, as long as a clinician uses appropriate methods for diagnosing DSM-5 PTSD, the diagnosis should be able to withstand a *Daubert* or similar evidentiary challenge in court.

Regarding the reliability of ICD-11 PTSD or complex PTSD, much less research has been conducted as ICD-11 has not yet been formally adopted. Recent international field trials found that the interrater reliability of ICD-11 PTSD (kappa = 0.49) was less than that of ICD-10 PTSD (kappa = 0.62) and as the second-lowest out of 14 diagnoses assessed when using an unstructured diagnostic protocol (Reed et al., 2018). Interrater reliability was higher but still only "fair" (Krippendorff's alpha = 0.76) when using a more structured approach to assess ICD-11 PTSD and complex PTSD (i.e., the International Trauma Interview [ITI]; Bondjers et al., 2019). More research on the reliability of ICD-11 PTSD and particularly the new complex PTSD diagnosis is needed as ICD-11 moves closer to its 2022 adoption date, especially given the high bar already set by the reliability of the DSM-5 diagnosis.

A final issue of forensic relevance that neither DSM-5 nor ICD-11 addresses sufficiently is the increasing body of evidence regarding cumulative risk of developing

PTSD with repeated trauma exposures (Karam et al., 2014; Kilpatrick et al., 2013; Reger, Bourassa, Smolenski, Buck, & Norr, 2019). The impacts of these repeated exposures, particularly in military and emergency services personnel, are not independent of each other (Harvey et al., 2016). Thus, forensic experts should consider the potential impact of PTEs that occurred *prior* to the PTE in question, to determine whether prior traumas either aggravated an existing case of PTSD or increased vulnerability to develop PTSD after exposure to a new PTE. Unfortunately, some civil litigation and compensation claims require the plaintiff to define a particular event that caused or aggravated the PTSD, as is required by the diagnostic criteria. In reality, given research evidence on the cumulative impact of multiple exposures, many individuals may not be able to identify a single traumatic event causing their PTSD symptoms. Thus, in litigation settings, strict application of the stressor criterion for PTSD (as defined in both DSM-5 and ICD-11) likely excludes many individuals with legitimate claims, especially military or emergency services personnel.

MALINGERING AND PTSD

DSM-5 defines malingering as "the intentional production of false or grossly exaggerated physical or psychological symptoms motivated by external incentives" (APA, 2013, p. 726). Miller (2015) described four types of malingering as it relates to PTSD: (1) total fabrication without any real symptoms, (2) exaggeration of symptoms as much worse than they really are, (3) feigned "extension" of symptoms that have improved or remitted entirely, and (4) false linkage of genuine symptoms to a negligible or compensable act, when in fact there is no connection. Individuals malingering PTSD may fabricate the traumatic event itself or may have genuinely experienced a PTE and subsequently feign symptoms (Resnick, West, & Wooley, 2018).

The allegation that malingering is a more prevalent problem for PTSD than for other disorders is frequently made (e.g., First, 2010; McNally & Frueh, 2012). Such concerns are not new. After World War I, suggestibility and secondary gain were seen as the key determinants of postcombat symptoms and impairment (Bailey, 1918). This belief led to the abolishment of military pensions prior to World War II in the United Kingdom (Jones, Palmer, & Wessely 2002). Patients that would now unequivocally be diagnosed with PTSD were once labeled as possessing "compensation neurosis" (Trimble, 1981). A lingering consequence of this historical backdrop is the ongoing preoccupation with the concern that PTSD is easily and frequently malingered in forensic settings, which continues to attach stigma to the psychological impact of traumatic stress (McFarlane, 2015).

Within adversarial legal contexts, individuals asserting PTSD and their attorneys have incentives to view malingering as a minor problem that should not raise doubts about claims of PTSD. Conversely, the opposing parties have incentives to view malingering as a major problem that calls a PTSD diagnosis into serious question. As Rogers and Cruise (1998) aptly noted over 20 years ago, both overstating and understating the frequency of malingering have negative consequences: "The devastation to defendants or plaintiffs of being falsely accused of malingering by forensic experts is unimaginable. Conversely, undetected cases of malingering wreak their own havoc" (p. 281). So should forensic mental health professionals take a skeptical approach toward all claims of PTSD, or should they treat claims of PTSD as legitimate absent a specific reason for doubt? The answer depends on the true base rate of malingering in PTSD cases, as estimated by the best available science.

An important overarching point about the state of the science is that conclusive, ecologically valid malingering research is very difficult to conduct effectively. As the NRC (2007) report concluded, "[I]n the research literature on malingering for PTSD, there are no ecologically valid studies that have carefully ascertained pure malingering status criterion groups (that is, malingering cases versus true cases) using real world assessment situations" (p. 100). This is because, in real-world forensic situations, there is rarely definitive, unquestioned information about either the exact details of the PTE in question or the nature of the claimant's symptoms. No "magic bullet" can conclusively divide claimants into malingerers and nonmalingerers, with the unfortunate corollary that much existing research on malingered PTSD is of poor quality (Guriel & Fremouw, 2003; NRC, 2007; Young, 2017b).

With these caveats in mind, the preponderance of high-quality research suggests that rates of malingered PTSD are not exceptionally high; nor is there evidence that malingering is a greater concern for PTSD than other disorders. Much of this research concerns disability evaluations (particularly for veterans' compensation), since these forensic contexts commonly feature PTSD diagnoses and present a strong incentive to feign. In a recent authoritative review, Young (2017b) found that the mean, median, and modal rates of feigning on disability evaluations fell around 10–11%, which is substantially lower than the rate claimed in a previous review that included poor-quality malingering studies (i.e., 40% ± 10% in Larrabee, Millis, & Meyers, 2009). Of note, Young's (2017b) estimate included disability evaluations covering a wide range of conditions, not just PTSD. This is relevant because there is some evidence that persistent postconcussive symptoms following mild traumatic brain injury might be particularly prone to malingering and thus raise the global base rate across all disability evaluations (Institute of Medicine, 2015; Young, 2015). In that vein, the two studies reviewed by Young (2017b) that included participant groups with *only* PTSD diagnoses reported malingering rates of 7% (Lindley, Carlson, & Hill, 2014) and 5% (Wrocklage et al., 2016).

As another approach to estimating base rates of malingered PTSD, many researchers have investigated how seeking or being awarded veterans' compensation affects treatment utilization and outcomes. Regarding treatment utilization, if many veterans seeking compensation are malingering PTSD, then it would be expected that large numbers of veterans would drop out of mental health treatment after being awarded compensation. However, research consistently shows that receiving veterans' compensation for PTSD results in *greater* subsequent use of mental health care (Laffaye, Rosen, Schnurr, & Friedman, 2007; Sripada et al., 2018), an effect that holds up to 12 years after the compensation was awarded (Murdoch & Jonk, 2019).

Regarding treatment outcomes, if many veterans seeking compensation are malingering PTSD, then it would be expected that compensation seekers would have worse treatment outcomes than those not seeking compensation (i.e., because malingerers have no incentive to "get better" in treatment). In contrast to this supposition, research has consistently found no relationship between veterans' compensation status and PTSD treatment outcomes (Cook, Thompson, Harb, & Ross, 2013; Laffaye et al., 2007; Monson et al., 2006; Schnurr et al., 2007). In studies that appear to show worse treatment outcomes for veterans seeking compensation, this effect may disappear when partialing out the influence of baseline PTSD symptoms, since veterans with more severe symptoms may be more likely to seek compensation *and* more likely to have poor treatment outcomes (Belsher, Tiet, Garvert, & Rosen, 2012).

Overall, malingering of PTSD symptoms should be carefully considered in individual cases, but the evidence for its widespread existence appears to be overstated.

This is important because a low base rate for malingered PTSD decreases the positive predictive value of the various psychological assessment instruments used to detect malingered PTSD (Young, 2017b). In other words, as the true base rate of malingering decreases, a test result suggesting malingering becomes more likely to be a false positive. This underscores the importance of conducting comprehensive forensic evaluations for PTSD that are not overly reliant on any one test result (Resnick et al., 2018).

PTSD BIOMARKERS IN FORENSIC ASSESSMENT

Many forensic issues regarding PTSD would be simplified if there were biomarkers with high predictive value for PTSD status to improve diagnostic accuracy. Prior research has identified voluminous candidate biomarkers for PTSD across the full range of body systems, including heart rate, skin conductance, inflammation, neuroendocrine function, gut microbiome, mitochondrial function, protein levels, anatomic brain regions (e.g., those associated with fear, memory, and learning), and genes and gene expression (e.g., those associated with regulation of neurotransmitters, especially serotonin and norepinephrine). (For some recent comprehensive reviews, see Bersani et al., 2020; Lebois et al., 2016; Michopoulos, Norrholm, & Jovanovic, 2015; Young, 2017a.)

Unfortunately, while previous research has identified many candidate biomarkers that show statistically significant mean differences within a sample, none of these individual biomarkers has shown sufficient sensitivity and specificity to predict PTSD status with high accuracy as required for forensic applications (Young, 2017a). Potential genetic markers, in particular, have typically failed to replicate in later genome-wide association studies (see, e.g., Ashley-Koch et al., 2015). The tremendous heterogeneity of PTSD phenotypes, as well as the high comorbidity characteristic of the disorder, likely complicate the search for biomarkers (Michopoulos et al., 2015).

Given these setbacks, the future of forensic biomarker assessment for PTSD likely lies with "multi-omic" approaches that combine many different markers from a variety of biological fields (e.g., genomics, proteomics, metabolomics). To that end, Dean and colleagues (2019) recently unveiled a promising multi-omic PTSD assessment developed by collecting blood samples and physiological data from male combat veterans to assess for hundreds of candidate biomarkers. They then used sophisticated machine learning techniques to narrow the candidates down to approximately two dozen biomarkers with the greatest predictive values. The resulting assessment boasted good sensitivity (85%) and specificity (77%), although a critic noted that the test's positive predictive value decreases precipitously when the percentage of true PTSD cases drops from 50% in the Dean and colleagues (2019) sample to the lower base rates typically observed among combat veterans (Baethge, 2020). Thus, further validation with more ecologically valid samples (with lower PTSD base rates, female patients, and a preponderance of moderate cases) is necessary before this kind of biomarker assessment is ready for forensic use.

Should a valid PTSD biomarker assessment become available, it could have unintended consequences for forensic cases. Young (2017a) expressed concern that an overemphasis on biomarkers—many of which are evident before any triggering PTE—may divorce PTSD from the traumatic event in question and thus weaken the legal argument for compensation or civil liability. Even now, defense experts frequently identify an alleged victim's prior vulnerabilities (such as preexisting PTSD, other psychopathology, or other risk factors for PTSD) and argue that the PTE in question is therefore

not responsible for causing the current symptoms. However, preexisting vulnerabilities to PTSD—whether biological or psychosocial—cannot be used as a legal defense, even though they make a PTE more likely to cause harm. Specifically, according to the "eggshell skull rule" of tort law, "you take your victim as you find them," meaning the at-fault party cannot rely on the victim's frailty (such as an eggshell-thin skull) to limit liability. Should biomarker assessments expand the range of known vulnerabilities to PTSD, forensic experts should likewise expand their evaluation procedures to include a careful assessment of both biological and psychosocial preexisting risk factors for PTSD to address the eggshell skull rule in court.

ADDRESSING BIAS IN FORENSIC ASSESSMENT AND TESTIMONY

Legal professionals have long expressed concerns about the objectivity of forensic experts in court (e.g., Hand, 1901), and this concern extends to clinicians diagnosing PTSD. Indeed, the few early studies on PTSD claims in adversarial contexts noted a tendency for experts' opinions to align with the party retaining their services. For example, Zusman and Simon (1983) examined claims of psychological trauma following a 1972 flood in West Virginia and observed a systematic pattern in how plaintiff and defense experts differed regarding their conclusions on the plaintiffs' trauma symptoms. The authors suggested that one cause of discrepancies might be "forensic identification" of experts with the retaining party, such that initially neutral experts "emphasize findings and patterns that support 'their side' " (p. 1304). In approximately the past decade, this tendency for experts to shift their opinions in line with the retaining party—known as "adversarial allegiance"—has become better understood (Murrie & Boccaccini, 2015). Three principles of adversarial allegiance as they apply to forensic assessment of PTSD are discussed briefly below.

First, multiple factors can contribute to adversarial allegiance—including, at minimum, attorney selection effects, expert selection effects, and cognitive bias (Murrie & Boccaccini, 2015). In the context of forensic assessments of PTSD, all three of these sources of adversarial allegiance may be present; for example, (1) an expert with a well-established pro-victim orientation may be sought out by an attorney representing an alleged trauma victim (attorney selection effects), (2) an expert skeptical of PTSD claims may decline referrals from plaintiffs and accept referrals from organizations being sued for emotional damages (expert selection effects), and (3) an expert may disproportionately seek out or emphasize information that confirms the retaining party's account due to well-established cognitive biases that affect individuals across a variety of decision-making contexts (Neal & Grisso, 2014).

Second, the interrater reliability of psychological test scores, diagnoses, and expert opinions is generally lower in adversarial contexts as compared to neutral contexts (Guarnera & Murrie, 2017). As previously discussed, the gold-standard instruments used to assess DSM-5 PTSD in practice (e.g., CAPS-5, PTSD-RI-5) all boast high interrater reliability in published studies. However, no existing studies have investigated the interrater reliability of PTSD diagnoses or scores on PTSD instruments specifically within adversarial contexts (e.g., how often plaintiff-retained and defense-retained experts agree). Thus, it is currently unknown how much PTSD diagnostic reliability may be influenced by adversarial pressures.

Third, less structured expert opinions are more vulnerable to adversarial allegiance than opinions based on more structured assessment procedures (Guarnera,

Murrie, & Boccaccini, 2017). For example, psychological instruments requiring clinicians to intuit ambiguous personality traits show greater reductions of interrater reliability in adversarial settings as compared to instruments requiring simple counts of life events (Murrie, Boccaccini, Guarnera, & Rufino, 2013). This finding is directly applicable to forensic evaluations of PTSD, which typically require experts to integrate various strands of evidence regarding multiple, complex symptoms for a disorder with diverse phenotypes. Because many PTSD symptoms (e.g., intrusive thoughts, dissociative experiences) are difficult to directly observe, unstructured assessments of such symptoms may be particularly prone to allegiance effects.

Given these concerns, how can forensic clinicians assessing PTSD reduce the impact of adversarial allegiance to arrive at more objective conclusions? A prime option is to conduct more structured trauma evaluations, most notably by using gold-standard instruments on which experts have been extensively trained. Clinicians can also intentionally engage in simple debiasing techniques with proven efficacy (e.g., systematically considering all evidence counter to one's initial opinion; Mussweiler, Strack, & Pfeiffer, 2000; see also, generally, Larrick, 2004). Experts might also consider blinding themselves to the referral source before conducting the initial stages of trauma assessment to avoid unconscious influences of the referring party. Although blinding requires considerable advanced planning and infrastructure, research suggests that blinded experts are viewed as more credible in forensic contexts (Robertson & Yokum, 2012). Use of multiple independent trauma experts by the courts can also combat unreliability by decreasing the impact of any one evaluator's error. Of course, clinicians need to calibrate their allegiance interventions according to the resources available in any particular case.

On a broader level, some legal systems have introduced codes of conduct for expert witnesses to minimize the risk of bias. For example, New South Wales Uniform Civil Procedure Rules (2005) require experts to clearly state the material facts and assumptions on which their opinions are based, as well as the reasons for choosing the supporting literature. Experts are also required to stipulate their impartiality. While the impact of these codes of conduct has not been systematically assessed, such procedures may help give judges the information they need to assess the quality of expert opinions, including potential bias. On the other hand, persuasive research on the "bias blind spot" indicates that experts rarely believe themselves to be biased, since many of the cognitive processes that produce biased opinion are outside of conscious awareness (Pronin, Lin, & Ross, 2002). Thus, allowing experts to stipulate their own impartiality may be misleading.

SUMMARY

No other diagnosis is subject to such scrutiny by judicial and legislative processes. PTSD is a disorder that brings into stark focus the rights of individuals in a civil society to be protected from foreseeable harm. There will always be a tension between those who advocate for the rights of the individual who may have experienced harm and those who advocate for the rights of the state, employers, or others who are alleged to have caused harm. This struggle underlies some of the tensions in the field regarding the appropriate boundaries of the PTSD diagnosis. As a consequence, the traumatic stress field is a domain where opinions abound but evidence is critically important. There is now an invaluable body of research evidence to address many of the previous

assumptions and questions about PTSD in forensic settings. The legal domain is a critical test of the validity and utility of this body of knowledge.

The introduction of revised sets of PTSD diagnostic criteria in DSM-5 and ICD-11 bring many of these enduring controversies and debates to the surface. This chapter highlights that, while revisions in DSM-5 have created some challenges in forensic settings, the impact has not been substantial and can be addressed. The impact of ICD-11 revisions is far less certain, particularly given the new complex PTSD diagnosis. Although most legal jurisdictions have chosen to use DSM criteria, it remains to be seen whether litigants may attempt to invoke the ICD-11 definition in forensic settings should those criteria benefit a particular legal argument.

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CHAPTER 28

Technology-Based Interventions for PTSD

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New technologies offer significant opportunities to improve the assessment and treatment of mental health problems, including posttraumatic stress disorder (PTSD). These technologies can be used to provide information, conduct assessments, deliver interventions, and mobilize social support, strengthening self-management and facilitating in-person mental health treatment. Technologies can be used to provide standalone self-help tools for those people who do not need or want in-person care or care that is integrated with human support via coaching or professional treatment. A primary strength of technologies is their potential to greatly increase the reach of services. They might help reach those who do not seek help because of social stigma, lack of awareness of services, or disbelief in their usefulness. They might reduce logistical challenges in locating and getting to services, and barriers due to cost. In principle, they can expand reach by reducing or eliminating the need for in-person contact. Those technological interventions that are entirely self-administered are "nonconsumable" (Muñoz et al. 2018), Unlike in-person treatment, costs of delivery do not increase per patient; instead, marginal costs decrease until they approach zero.

There is increasing interest in technology-facilitated interventions to improve the well-being of individuals experiencing PTSD and other trauma-related problems. This chapter focuses on three technology tools—the Internet, mobile phones, and virtual reality—in terms of their capacities to improve, or even transform, assistance for those exposed to traumatic events.

EFFECTIVENESS OF INTERVENTION TECHNOLOGIES

Internet Interventions for PTSD

Internet interventions vary greatly and can include a range of written, audio, and video content, including educational information, assessment and feedback, self-monitoring, goal setting, cognitive restructuring, therapeutic exposure, and skills training. As has

been found with anxiety disorders generally (Andrews et al., 2018), reviewers of the effectiveness of Internet interventions for PTSD have concluded that they are significantly more effective than passive (i.e., wait-list) controls, with medium to large effect sizes (Kuester, Niemeyer, & Knaevelsrud, 2016; Lewis, Roberts, Bethell, Robertson, & Bisson, 2018; Sijbrandij, Kunovski, & Cuijpers, 2016; Simblett, Birch, Matcham, Yaguez, & Morris, 2017). For example, Kuester and colleagues (2016) reviewed 20 randomized controlled trials (RCTs) of Internet interventions for PTSD in adults and observed moderate to large effect sizes for PTSD global symptom severity and avoidance, intrusion, and hyperarousal symptom clusters, when compared to passive control conditions. Internet PTSD interventions did not perform significantly better than active comparison treatments, possibly due to the low number of studies using active controls. Sijbrandij and colleagues (2016) drew similar conclusions, and noted that effects were strongest when interventions were therapist-assisted, but that self-guided interventions also showed a moderate effect size. Simblett and colleagues (2017) included 39 papers evaluating "e-mental health" interventions (i.e., including *both* Internet and phone app interventions). The number of participants in the studies ranged from 25 to 1,292, with 14 that included sample sizes ≥100. Research was carried out in the United States, the Netherlands, Australia, Sweden, Germany, Switzerland, Canada, Poland, and China. Findings were consistent with other reviews, but the authors also reported a significant between-group difference when comparing e-mental health interventions with active control conditions. In a Cochrane review of 10 studies, Lewis and colleagues (2018) found beneficial effects of Internet-based PTSD interventions, but concluded that the quality of the evidence was very low due to the small number of trials, study heterogeneity, and risk of bias in some of the studies.

Results from RCTs indicate good acceptance of PTSD Internet programs, but rates of dropout are significant. Kuester and colleagues (2016), defining dropout as the percentage of participants not completing a whole course of treatment, found rates to be 23% for cognitive-behavioral therapy (CBT) Internet interventions and 16% for expressive writing Internet interventions. Few studies include longer-term follow-up, so that maintenance of effects cannot be adequately assessed, despite observation of large effects at 1.5-year follow-up in some nonrandomized studies (Wagner & Maercker, 2007). Because of wide variation between interventions in content and amount of human support, and heterogeneity between studies, it is difficult to compare interventions (Kuester et al., 2016) or studies (Simblett et al., 2017).

The most investigated Internet intervention for PTSD is *Interapy,* with seven RCTs (e.g., Kersting et al., 2013; Knaevelsrud, Brand, Lange, Ruwaard, & Wagner, 2015). It is a therapist-supported, narrative writing intervention; participants engage in writing exercises over a 5-week period that include elements of exposure, cognitive reappraisal, and farewell rituals. Therapists provide email feedback after each writing assignment. Across the seven studies of Interapy, large effect sizes (g = 0.81–0.84) were observed for overall PTSD as well as for avoidance and intrusion symptoms, with medium effects on hyperarousal. Broadly, Internet PTSD research has included a range of populations, including veterans and military personnel (e.g., Hobfoll et al., 2016), war-traumatized civilians (e.g., Knaevelsrud et al., 2015), older adults with childhood war trauma (Knaevelsrud, Böttche, Pietrzak, Freyberger, & Kuwert, 2017), sexual assault survivors (e.g., Littleton, Grills, Kline, Schoemann, & Dodd, 2016), disaster survivors (e.g., Ruggiero et al., 2012), and mixed groups (e.g., Titov et al., 2014).

In addition to reducing PTSD symptoms, Internet interventions are being designed to increase support of family members of those with PTSD (Owen et al., 2017) and to

address concurrent problems experienced by trauma survivors, such as prolonged grief (Kersting et al., 2013) and alcohol abuse (Brief et al., 2013). For example, *VetChange,* a self-administered intervention, uses motivational interviewing, CBT, and self-control training to address co-occurring problem drinking and PTSD. Brief and colleagues (2013) found that use of *VetChange* reduced drinking and PTSD symptoms significantly more than a wait-list control.

Finally, Internet interventions are potentially important in the context of disaster mental health response to assist survivors in managing PTSD symptoms and other problems (Ruggiero et al., 2012; Ruzek, Kuhn, Jaworski, Owen, & Ramsey, 2016). For example, *My Disaster Recovery* is an Internet intervention that includes modules on social support, self-talk, relaxation, trauma triggers, unhelpful coping, and professional help. A Mandarin language variant of the program (Wang, Wang, & Maercker, 2013) was tested with Chinese rural survivors of the 2008 Szechuan earthquake; PTSD symptoms improved significantly more for those using the tool than among wait-list controls. Another promising area of research focuses on interventions for trauma survivors in low- and middle-income countries (LMICs; Ruzek & Yeager, 2017). Arjadi, Nauta, Chowdhary, and Bockting (2015) located three RCTs of Internet interventions conducted in LMICs. Two studies of *Ilajnafsy,* an adaptation of Interapy, suggested that such interventions can be helpful (Knaevelsrud et al., 2015; Wagner et al., 2012). Knaevelsrud and colleagues (2015) showed that the intervention reduced PTSD symptoms in war-traumatized Arab residents in Iraq, suggesting that, even in unstable settings with ongoing human rights violations (e.g., torture, killings, disappearances, and rape), technology-facilitated interventions may benefit trauma survivors. As noted above, Wang and colleagues (2013) found that Internet intervention effectively reduced PTSD symptoms among Chinese trauma survivors.

Mobile Interventions for PTSD

Mobile apps have some important features that are not shared by interventions delivered on a computer. They are available at all times to most users and thus are better able to provide "just-in-time" support. They can potentially improve situational coping, offer as-needed supports, facilitate self-monitoring, and remind users of therapeutic content. Potentially, the data gathered with phone sensors can help assess individual needs, individualize content, and evaluate services. Insel (2017) noted that, by offering a passive, ubiquitous device that can capture behavioral and cognitive information continuously, the mobile phone could become a potential path to measurement-based care, allowing care managers to more easily monitor well-being.

Wickersham, Minas Petrides, Williamson, and Leightley (2019) reviewed five RCTs of app-based PTSD interventions. Within-group comparisons suggested improvements in PTSD symptoms immediately following intervention, with small to moderate effect sizes, but there was little evidence for greater reductions in PTSD symptoms compared to control conditions. The study with the longest follow-up period reported a partial rebound in PTSD symptoms at 6 and 12 months (Roy et al., 2017). Three of the five studies investigated the *PTSD Coach* app (see below); the other two investigated apps that were not specifically designed for PTSD (Kahn, Collinge, & Soltysik, 2016; Roy et al., 2017). Studies of *PTSD Coach* have produced promising results (Kuhn et al., 2017; Miner et al., 2016; Possemato et al., 2016), but a small RCT indicated that self-managed use was not more effective than usual care in reducing posttraumatic stress symptoms or pain among acutely injured medical patients (Pacella et al., 2019). Wickersham and

colleagues (2019) concluded that there was little evidence that apps produce strong long-term improvement in PTSD or greater improvements than those receiving active comparisons or no intervention.

PTSD Coach is the most used PTSD app, with over 639,000 downloads in 96 countries as of May 2020. It was originally designed not to reduce PTSD symptoms, but to help users manage acute distress by educating them about PTSD, enabling self-assessment of symptoms, improving self-management of symptoms by providing coping tools, and promoting use of social support and community resources. In addition to the few apps that have received research attention, a "plethora of Android and iOS PTSD-specific apps" are available to the public (Rodriguez-Paras et al., 2017), with most offering at least one element of CBT (e.g., psychoeducation, self-monitoring; Livingston, Shingleton, Heilman, and Brief, 2019). Despite lack of an evidence base at the present time, there are indications that apps are both feasible and acceptable interventions for PTSD (Gould et al., 2019). Veterans and partners in the Kahn and colleagues (2016) study used *Mission Reconnect* for over one hour per week throughout the intervention period and were highly likely to recommend it to a friend. Miner and associates (2016) reported that participants opened *PTSD Coach* between two and three times per week, and only 1 of 43 participants reported not using the app at all. Apps are being developed for use in LMICs. *Step-by-Step* is based on an evidence-based treatment (EBT) for depression, anxiety, and PTSD (Carswell et al., 2018), and interviews with Syrian refugees suggest that users will react positively to such a tool (Burchert et al., 2019).

Apart from their role as direct interventions, mobile apps are also thought to hold promise for increasing engagement in and adherence to in-person EBTs for PTSD. For example, *PE Coach* facilitates delivery of prolonged exposure (PE) therapy; it is designed to strengthen client and provider adherence to PE and to help clients understand treatment, complete homework, master breathing retraining, and measure symptom change. Kuhn and colleagues (2015) investigated 271 PE clinicians' actual use of *PE Coach*. Half of the sample reported using it, with 93.6% intending to continue; 77.6% of those not using it intended to use it in the future. Impact on client adherence and outcomes has not yet been investigated.

Virtual Reality Exposure Interventions for PTSD

Virtual reality (VR) is a technology that allows delivery of exposure therapy through simulation of real-life situations in an interactive computer-generated environment. VR and real objects are similar, creating an illusion that the user is encountering objects in the real world. VR provides an opportunity to expose the client to feared sensory (visual, auditory, tactile, and olfactory) stimuli that are being avoided and causing distress in safe, controllable situations that may be more acceptable to participants than approaching them in the real world. VR treatment of PTSD has focused on VR exposure (VRE) because of these capabilities. Note that, compared to Internet and mobile interventions, VRE requires more therapist time because VRE is an adjunct to individually delivered in-person care, although this may change as technology platforms become easier to use (Lindner et al., 2017).

Carl and colleagues (2019) reviewed 30 RCTs of VRE for anxiety disorders and found a large effect size for VRE versus wait list ($g = 0.90$) and a medium to large effect size for VRE versus psychological placebo ($g = 0.78$), with effects maintained at follow-up. VRE was not significantly different from conventional *in vivo* exposure. Five studies comparing VRE for PTSD to placebo or wait-list conditions yielded a medium effect

size (g = 0.59). Two other meta-analyses of VRE for PTSD have concluded that VRE is an effective medium for delivery of exposure therapy for PTSD (Botella, Serrano, Baños, & Garcia-Palacios, 2015; Goncalves, Pedrozo, Coutinho, Figueira, & Ventura, 2012), but a recent trial found that, while both VRE and in-person exposure resulted in improvement at posttreatment with no significant differences between groups, in-person exposure demonstrated greater improvement than VRE at 3- and 6-month follow-ups, suggesting that VRE may result in less sustained symptom recovery after treatment ends (Reger et al., 2016). As with Internet interventions, VR interventions have shown low rates of symptom worsening (4%; Fernández-Alvarez et al., 2018), Surveys indicate that many people would prefer VRE to traditional in-person exposure (García-Palacios, Botella, Hoffman, & Fabregat, 2007; Maples-Keller, Bunnell, Kim, & Rothbaum, 2017). Potential limitations of VR include significant costs of VR technologies and the need to develop a range of trauma-specific VR interventions because of the specificity of trauma memories and experience.

METHODOLOGICAL CONSIDERATIONS

Research on technologies for PTSD is in an early stage of development, especially with regard to mobile and VRE interventions. Reviewers have identified a need for more large-scale trials that incorporate active control conditions, given that superiority over another active treatment is more meaningful than superiority over a wait-list condition (e.g., Kuester et al., 2016; Wickersham et al., 2019). Also recommended are increased systematic manipulation of particular program components (e.g., therapeutic support) and parameters (e.g., number of sessions) to test for efficacy, and more investigation of who benefits under which circumstances from which Internet-based interventions and elements (Kuester et al., 2016). Lewis and colleagues (2018) concluded that further research is required to establish noninferiority for Internet interventions, explore mechanisms of change, establish optimal levels of guidance, explore cost-effectiveness, measure adverse events, and determine predictors of efficacy and dropout.

Overall, evidence for the efficacy of mobile interventions for treating PTSD is much weaker than Internet interventions. While several studies have shown some reductions in PTSD symptoms, improvements have not been consistently significant or sustained, or more substantial than improvements seen in control conditions. The very few extant studies should be seen as evidence of "promise" rather than of effectiveness or ineffectiveness. While some have included a wait-list comparison (Kuhn et al., 2017; Miner et al., 2016), others have not included any control group (Possemato et al., 2016; Roy et al., 2017). Methodological limitations include reliance on self-report measures of PTSD, possible sampling bias due to participant self-selection, small sample sizes, use of very brief interventions, and brief follow-up periods. Wickersham and colleagues (2019) recommended that future RCTs should include adequately powered larger samples, clinician-administered diagnostic interviews to measure PTSD outcomes, control groups to enable comparison with existing standards of care, and longer intervention and follow-up periods.

As with mobile interventions for PTSD, few studies have evaluated VRE for PTSD. Page and Coxon (2016) noted that, compared to VR research in other clinical areas, the literature on VRE for PTSD has used small sample sizes and has been less likely to use a control group or RCT design. Only 8% of all studies regarding PTSD used a sample size greater than 30; 25% used a control group and 25% used an RCT design.

RCTs comparing technology-facilitated PTSD care with in-person services are much needed, and no conclusions may be made about the long-term effectiveness due to the limited availability of follow-up data. Studies that systematically vary single elements of intervention are important to better understand and improve these interventions. As an example of such a study, Spence and colleagues (2014) conducted an RCT to compare the efficacy and safety of an online PTSD intervention that included psychoeducation, stress management, and cognitive restructuring, with and without an exposure component. Both interventions were associated with significant reductions in PTSD symptoms, with no differences between groups in outcomes or adverse events.

In the broader Internet and VRE intervention literatures, rates of treatment worsening have been relatively low and comparable to those seen with in-person interventions (Karyotaki et al., 2018; Fernández-Alvarez et al., 2018; Rozental, Magnusson, Boettcher, Andersson, & Carlbring, 2017), but this must be established with regard to PTSD. There is little evidence about the potentially adverse effects of app-based interventions. One PTSD-focused study has found self-directed app use to be associated with worsening social quality of life (Possemato et al., 2016). Wickersham and colleagues (2019) noted that no studies of apps for PTSD have specifically sought to identify negative outcomes and that future trials should aim to capture possible adverse effects. Such an approach is also important for Internet and VRE studies. Generalizing from research on anxiety and depression, because significant percentages of those receiving Internet interventions fail to show improvement following intervention, nonresponse should also be actively investigated, since it might prolong an ongoing problem or prevent engagement in in-person treatment (Rozental, Andersson, & Carlbring, 2019). Experts in the field of Internet interventions have put forward recommendations that provide researchers with guidelines for monitoring and reporting negative effects (Rozental et al., 2014).

IMPLEMENTATION OF TECHNOLOGY-FACILITATED INTERVENTIONS

The public health promise of technological interventions lies in their dissemination potential (Bennett & Glasgow, 2009). But despite strong research support for the effectiveness of Internet interventions, accomplishing their implementation in routine care remains an enormous challenge. Technology barriers (e.g., costs and unfamiliarity), in addition to a limited evidence base, have presented challenges to spread VRE PTSD interventions, but new forms of VR hardware are making it easier to develop and implement user-friendly software in clinical settings (Lindner et al., 2017). In the absence of evidence for effectiveness, mobile app interventions are spreading rapidly, so that it will be increasingly important to ensure that clinicians use them effectively and that clients are guided to efficacious apps. An overarching need is to operate from an implementation conceptual framework during all aspects of intervention development and research (see Stirman, Chapter 32, this volume, on implementation of best practices). Such a framework is present in an important suggestion put forward by Mohr, Weingardt, and colleagues (2017) that mental health technologies should be seen as "technology-enabled services" rather than "products." They argued that viewing technologies as products has led to development of technology tools without understanding how they fit with services, and that the goals of services, the roles of the provider, and the technologies must all be designed and evaluated simultaneously as an integrated

effort. Such an approach suggests that evaluation should be conducted in the settings where it is intended for use and that research should simultaneously examine both effectiveness and implementation using hybrid trial designs.

In order to benefit clients, technology-based interventions must be shown not only to be efficacious in controlled trials, but also to be feasible and effective when delivered under real-world conditions. Recognition of this has led some to express concern about overselling technologies before adequate demonstration of ability to achieve outcomes at scale (Tomlinson, Rotheram-Borus, Swartz, & Tsai, 2013). In fact, some studies have suggested that PTSD Internet interventions can be effective when delivered in real-world settings at scales larger than those seen in most research trials. Ruwaard, Lange, Schrieken, Dolan, and Emmelkamp (2012) reported on outcomes for 1,500 patients treated for depression, panic disorder, posttraumatic stress, or burnout in a Dutch clinic using Internet-based, therapist-assisted CBT. The study included 478 patients with clinically significant PTSD symptoms, and its purpose was to assess the external validity of seven previous RCTs of the Interapy intervention by examining its effectiveness in routine clinical practice. Results indicated that 40% of PTSD patients demonstrated recovery (i.e., reliable improvement from a pretest score above cutoff to a posttreatment score below cutoff), 20% showed improvement, 40% showed no change, and 0% deteriorated. Effect sizes (Cohen's *d*) were large: 1.6 for intrusion symptoms and 1.3 for avoidance symptoms. Treatment adherence, defined as the percentage of patients completing every step of the treatment program, was highest in the posttraumatic stress sample (76%); 89% of patients indicated that they would recommend the treatment to others. As noted earlier, the Interapy intervention includes significant human support, and in this study, PTSD clients were treated by a group of 65 therapists with master's degrees in clinical psychology.

Titov and colleagues (2017) similarly reported outcomes for the Australian MindSpot clinic, an online service for adults with anxiety and depression. Between January 2013 and June 2015, 25,469 people completed assessment and were eligible for analysis. In this study, 82% of users were not in contact with other mental health services. Most patients used the program for assessment, information, or referral. Of those completing an assessment, 24% started MindSpot treatment, and 137 of 6,149 clients using the courses had PTSD as their primary problem. Across problems, large clinical effects were found on all outcome measures; effect sizes for PTSD were 1.5 and 2.4 at posttreatment and 3-month follow-up, respectively. Deterioration was very low (2.9% for PTSD). Overall, these data suggest that MindSpot was effective in improving access to and providing effective interventions

Client Engagement

Across the field of technology interventions for mental health, there is a challenge of motivating clients to engage with the interventions and to use them sufficiently in order to gain potential benefits. Individual studies of Internet interventions for PTSD show variation in dropout rates, but many users stop using the programs before they might be expected to receive a "therapeutic dose." For example, in the study of *VetChange* reported by Brief and colleagues (2013), less than 40% of participants completed all eight intervention modules. Rates of uptake and engagement with mental health apps also vary widely (Fleming et al., 2018). One possible strength of VRE is its potential for reducing dropout from exposure therapy (Botella et al., 2015), but this capability remains to be demonstrated.

Generally, reviewers have concluded that guided technology-facilitated interventions are more likely to be effective than unguided interventions, in part because they generate greater engagement (Mohr, Cuijpers, & Lehman, 2011). More studies of aspects of guidance are needed, and conceptual models should inform the design of support methods and research on support. Mohr and colleagues (2011) proposed a "supportive accountability" model as a helpful step toward understanding how human support enhances adherence to technology use. Another model, the Schueller, Tomasino, and Mohr (2016) "efficiency model of support," focuses on support "efficiency," which is defined as "the ratio of the outcome of an intervention relative to the human resources required to deliver it" (p. 2). This is an important concept in that aspects of human support represent trade-offs between devoting additional resources and improving engagement and outcomes. Note that engagement with technologies encompasses more than reduction of dropout. Perski, Blandford, West, and Michie (2017) defined technology engagement in terms of "(1) the extent (e.g. amount, frequency, duration, depth) of usage and (2) a subjective experience characterized by attention, interest and affect" (p. 258). More studies of ways of increasing engagement (e.g., Titov et al., 2014), guided by theoretical models (e.g., Yeager & Benight, 2018), are needed. In addressing obstacles to engagement with technologies, it will be important to keep in mind that dropout from in-person interventions is also high; the challenge is to engage individuals in mental health care.

Provider Factors

A stakeholder survey conducted with 175 organizations and providers in eight European countries showed greater acceptability of blended treatment (integrated in-person and Internet sessions) compared to stand-alone Internet treatments (Topooco et al., 2017). But while providers report high levels of interest in using websites and mobile apps, and some evidence suggests that practitioners will actively use mobile technologies (Kuhn et al., 2015), very few are doing so (Schueller, Washburn, & Price, 2016). Clinicians will only adopt technologies if they are perceived to add clear value to clinical care (i.e., if they make offering patient care easier and improve quality of services), so that developers of interventions will need to understand the needs of clinicians who will use them (Schueller et al., 2016). In fact, use of technologies is likely to involve both drawbacks and benefits for clinicians. Drawbacks may include the need to learn about intervention content and process and master new skills, and providers may have questions about security and privacy concerns (Schueller et al., 2016). Potential benefits include ability to address additional problems experienced by clients in addition to what can be made the focus of in-person discussions, ability to offer more between-session assistance to clients, and greater ease in scheduling and homework review.

An important concern for many is likely to be that use of technologies may interfere with development of a strong therapeutic relationship or alliance. Two PTSD-related studies bear on this issue. Knaevelsrud and Maercker (2007) found that use of Internet-based treatment for PTSD (Interapy) was associated with establishment of strong, stable therapeutic alliances. In a study of Interapy with Arabic-speaking traumatized patients in Iraq, Wagner, Brand, Schulz, and Knaevelsrud (2012) found high ratings of therapeutic alliance early in treatment that remained stable from across sessions, despite the unstable setting and ongoing exposure to violence. As with PTSD, the few studies of technologies for depression and anxiety that have investigated it have all showed a high level of client–therapist alliance (Pihlaja et al., 2018).

One key element of implementation is the training of clinicians. To date, few providers have received any kind of formal training related to technology use, and the need for training models is slowly becoming recognized. For example, Slovensky, Malvey, and Neigel (2017) argued that mHealth is a major technological phenomenon that deserves significant educational reform in professional training and that practitioners cannot be assumed to easily make the transition to incorporating technologies. They proposed a set of core competencies: digital communication skills, technology literacy and usage skills, mHealth products and services, regulatory and compliance issues, and the technology business case (uses of technology in private practice and commercial enterprises). Note that training must also encompass mastery of the intervention-specific content and methods found in Internet and mobile programs. Despite the widespread adoption of mobile health apps by consumers, the curriculum for instruction in technology-facilitated care has not yet been well defined, although instructional materials and courses are being developed (e.g., American Psychological Association's "Using Technology in Clinical Practice").

Organizational Considerations

Adoption of technology-facilitated interventions by organizations will be affected by many factors, including evidence base, cost-effectiveness, and treatment philosophy and resources. Change in clinical outcomes may not be the primary adoption consideration for many settings. Bennett and Glasgow (2009) recommended that academic investigators should form research partnerships with delivery settings to better understand adoption considerations.

More attention to the development and evaluation of models of technology-integrated service delivery is required. Especially needed are examples of the design and evaluation of stepped care systems in which lower cost, simpler services are made available first, followed by more expensive interventions, depending on outcome. In the systems envisaged here, self-guided technologies would be the initial services. Gilbody and colleagues (2017) recommended that unsupported Internet interventions should be offered as a form of treatment for nonclinical populations, although the expected benefits are likely to be small. Similarly, Muñoz and associates (2018) noted that small effects can be clinically useful, especially in LMIC countries where mental health services are scarce or inaccessible. Karyotaki and colleagues (2018) reviewed research on CBT Internet interventions across problems and found that self-guided interventions had low rates (5.8%) of clinically significant deterioration and lower risk of deterioration than control conditions (including regular care). They suggested that self-guided Internet interventions could be an alternative to watchful waiting in general practice and could be disseminated at scale in countries where mental health resources are limited.

CHALLENGES FOR THE FUTURE

Managing Rapid Proliferation: Consumer and Clinician Guidance

More than 10,000 smartphone apps have been developed to address mental health problems (Torous et al., 2018) and the supply is rapidly expanding. Livingston and colleagues (2019) noted that the availability of these technologies constitutes a new kind of "research-practice gap." Those mobile interventions with the strongest research

support are largely inaccessible to the general public; those most easily accessible on iTunes and Google Play platforms generally lack research support. Because it is relatively easy, technically, to develop and disseminate apps, the gap is not only between researchers and clinicians, but also between researchers, industry software developers, and consumers. Consumers use informal means to locate apps, based on web searches, social media, and word of mouth; they do not concern themselves greatly with research results (Schueller, Neary, O'Loughlin, & Adkins, 2018). Given the proliferation of apps, ways must be found to direct users (consumers, clinicians, and organizations) to effective interventions that have been developed based on knowledge and evidence. Some organizations have developed systems for evaluating and rating mobile tools (e.g., Torous et al., 2018). For example, One Mind PsyberGuide (*www.onemindpsyberguide.org*) is a nonprofit initiative that helps individuals and organizations identify the best mental health mobile apps using expert ratings that take into account research evidence, user experience, and privacy policy.

Intervention Design

Currently, many PTSD technology interventions are composed largely of written information and attempt to place the content of in-person EBTs on the Internet and phones. High dropout and low engagement suggest that more innovation and attention to human–computer interaction is needed to create products that are more acceptable to users (Gilbody et al., 2017). The content of apps (i.e., aesthetics, features, and functionality) is a strong determinant of use (Schueller et al., 2018). Titov and colleagues (2014) speculated that improved content of Internet interventions will enable increasing proportions of the population to benefit from them, but they argued that technologies must be improved through a process of repeated clinical evaluation and quality assurance cycles rather than assuming that they can be easily developed and delivered.

There is a special challenge associated with reinventing the ways in which mobile phone interventions might assist individuals with PTSD. Schueller, Muñoz, and Mohr (2013) argued that mobile mental health will need to avoid simply replicating in-person interventions on technologies and, more fundamentally, rethink intervention methods to better fit the ways users engage with their phones. Similarly, Kazdin (2015) noted that, in addition to being used to develop novel ways of delivering what we have available now (i.e., improving EBT reach), technologies should lead to a reconsideration of all facets of mental health treatment. Individuals use mobile phones differently than computers and websites (Mohr, Tomasino, et al., 2017). Apps are used for short amounts of time, sometimes frequently, in simple interactions that support a single or limited set of tasks (e.g., searching for restaurants, communicating with friends). By contrast, the content of Internet interventions is presented on large screens, includes extensive didactic information, and requires longer engagement times. This thinking led to the design of the *IntelliCare* suite of apps, each supporting a single skill related to depression or anxiety (e.g., goal setting, cognitive restructuring, exposure) and emphasizing in-the-moment practice of new skills rather than taking a more traditional educational approach. For most apps, there is no explanation prior to engagement. Thus, these apps are designed for brief, frequent interactions, consistent with the ways people use their mobile phones. Mean app session lengths are 1 minute, and mean use frequencies are 21–29 uses per week, with no dropoff over time (Mohr, Tomasino, et al., 2017).

Other approaches may also improve engagement and effectiveness. Ecological momentary interventions (EMIs; Schueller, Aguilera, & Mohr, 2017) refer to

"momentary health treatments provided via hand-held mobile technologies that deliver psychological interventions while people are engaged in their typical routines in their everyday life" (Heron & Smyth, 2010, p. 2). When EMIs include learning models, the outcomes for each specific individual are optimized, and no single treatment is given to all individuals. Also important for engagement are game mechanics and multimedia presentations of content that can enhance the intervention experience (Sardi, Idri, & Fernanedez-Aleman, 2017); phone-based sensors and passive data collection that can be used to predict mental well-being and guide service delivery (Mohr, Zhang, & Schueller, 2017b); and the social connection functions of apps that can be used to mobilize support from providers, supportive others, or communities of others with similar experiences (Morris, Schueller, & Picard, 2015).

Innovation is also needed in the design of preventive interventions. Technologies offer potential to overcome many limitations of traditional prevention programs, such as limited resources and availability of evidence-based interventions, especially in rural areas and LMICs (Ebert, Cuijpers, Muñoz, & Baumeister, 2017). Technologies could be made available throughout the acute posttrauma period (Price, van Stolk-Cooke, Brier, & Legrand, 2018), for example, in hospital trauma centers (Mouthaan et al., 2013) and following disasters (Ruggiero et al., 2012). Ennis, Sijercic, and Monson (2018) reviewed seven, primarily pilot, studies of preventive Internet interventions for those exposed to trauma and found mixed results: Indicated interventions (provided to those with subthreshold symptoms of disorder or subclinical diagnosis) produced significant improvements over other active control conditions, but selected interventions (targeted at individuals with risk factors for PTSD who may or may not be experiencing symptoms) did not produce significant symptom improvement. While the quality of studies was rated as fair to good, study heterogeneity (e.g., in outcome measures) and other methodological limitations mean that conclusions should be seen as preliminary.

Evolution of Technology Research

Potentially, research on technology-facilitated interventions offers significant advantages compared with research on in-person treatments and can facilitate a more rapid pace of clinical innovation (Andersson, Titov, Dear, Rozenthal, & Carlbring, 2019). Studies can often be conducted with less cost and faster recruitment than ordinary clinical trials, with data gathered via telephone interviews and online questionnaires. Large sample sizes can be obtained, creating the possibility of using factorial research designs and investigating two or more main effects and possible interactions between conditions. But the rapid evolution of technologies itself creates major challenges for research (Patrick et al., 2016). Increasingly, the adequacy of traditional RCTs for studying effectiveness is being challenged by more rapid "agile science" approaches seeking to speed up ability to determine which elements of interventions work, as well as rapidly and iteratively improve those that do (Hekler et al., 2016; Mohr et al., 2013).

Technologies also make possible other innovations in research methods. Microrandomized trials are sequential factorial designs that randomly assign an intervention component to each individual at relevant points in time (Klasnja et al., 2015). Each individual is randomized multiple times in order to better understand the dynamic nature of interventions and how their effectiveness corresponds to various contextual factors. This design might be helpful because traditional RCTs show which treatments are effective, but not when and how much of an intervention to provide (Schueller et al., 2017).

Technologies offer up the capacity to focus on entire populations and conduct population-based research. Oldenburg, Taylor, O'Neil, Cocker, and Cameron (2015) argued that digital technologies offer several advantages for managing public health in populations: They can reach large numbers at relatively low cost; reduce the amount of human contact needed for program delivery; address multiple elements of effective behavior change programs simultaneously (e.g., education, coaching, social support), with high fidelity; and generate large amounts of data to guide programs. Taylor and colleagues (2018) argued that taking a population-based approach could enable going beyond a focus only on outcomes to permit simultaneous attention to effectiveness, adoption/engagement, and reach.

Infrastructures: Technological and Human

If the contribution of technologies to PTSD treatment is to be optimized, new technology platforms and online collaboration environments will be needed. Many researchers are facing a new type of obstacle to implementation: lack of funding for technical support and maintenance of smartphone and Internet applications (Livingston et al., 2019). Most health care or nonprofit organizations will not have the technological resources to maintain and upgrade the technological platforms on which interventions depend. Bennett and Glasgow (2009) suggested that it might be helpful to create a federally supported Internet intervention infrastructure that could be leveraged by investigators to disseminate interventions. Similarly, Muñoz and associates (2018) proposed the development of "digital apothecaries," that is, online repositories where multiple technology interventions could be easily accessed.

Perhaps as important as technological platforms are the human infrastructures for implementation and collaboration during the research process. Some evidence suggests that researchers in different countries are motivated to collaborate and build off each other's work, as illustrated by the shared development of the *PTSD Coach* app across countries (Kuhn et al., 2018). Because diverse specialist expertise is needed to create technology interventions and broaden conceptual models, it is important that collaboration includes input from multiple disciplines (e.g., computer science, anthropology, education, psychology). And as interventions are developed, it is not clear what organizations or professional groups might undertake to implement technologies for trauma survivors, unless they are made available within a specific health care organization or individual practice. Therefore, implementation teams will need to be created to deliver technology-facilitated interventions and engage in continuous process improvement. This is especially important if technologies are to be made available on a population-wide basis with elements of unguided as well as guided interventions.

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CHAPTER 29

Treating PTSD Using Telemental Health Technology

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In the short space of a few decades, the infrastructure connecting our world has experienced a seismic shift. The pervasiveness of connected technology has enabled changes in how people all over the world accomplish tasks of daily living ranging from banking and shopping to maintaining intimate relationships. It is therefore no surprise that this same technical infrastructure has inspired clinicians and patients to seek technological solutions to circumvent some of the most intractable barriers which limit delivery of efficacious psychotherapy for posttraumatic stress disorder (PTSD) (e.g., barriers such as work schedules, family responsibilities, travel costs, transportation, shortage of well-trained providers, and beliefs about help-seeking; e.g., Hundt, Harik, Thompson, Barrera, & Miles, 2018).

Novel, sophisticated technologies and broad availability of wireless communications networks have given rise to *telehealth*–the use of electronic communications and information technology to provide and support health care when distance separates the provider from the patient (Field, 1996). *Telemental health* (TMH) refers specifically to the use of telehealth to provide psychological, psychiatric, and other behavioral health services. The most widely studied TMH modality is *clinical videoteleconferencing* (CVT), which allows a therapist and patient in separate locations to see each other and interact in real time ("synchronously").

In this chapter, we discuss the common barriers faced by individuals with PTSD that can be mitigated with technology and outline research on the use of TMH to deliver evidence-based PTSD care. This chapter also identifies clinical considerations when implementing TMH with a trauma population, discusses challenges to TMH implementation, and highlights opportunities for future research in this domain. Although this chapter focuses predominately on the use of CVT, it will also address ongoing innovations in TMH technology that can support the provision of evidence-based

psychotherapy (EBP) for PTSD alone or in combination with other technologies. A more expansive review of Internet-based interventions and mobile applications (apps) for PTSD can be found in Josef Ruzek's review of technology-based interventions in Chapter 28, this volume.

COMMON BARRIERS TO TRADITIONAL PTSD CARE

Despite the establishment of a number of evidence-based therapies (EBTs) for PTSD, certain critical barriers prevent patients from accessing these interventions. These barriers largely fit into four categories: geographic, privacy-related, schedule-related, and motivational. Any of these barriers alone can significantly impact an individual's ability to obtain an EBT for PTSD. Often, however, individuals experience multiple barriers across several domains, making it extremely difficult to access and engage in treatment. When combined with PTSD-related avoidance, participating in evidence-based PTSD treatment becomes an even greater challenge.

Geography and distance pose major barriers to receiving effective care for PTSD, with rural communities frequently having few mental health providers and limited access to specialized care for PTSD (President's New Freedom Commission on Mental Health, 2004). Approximately 40% of the veterans served by the U.S. Department of Veterans Affairs (VA, 2012) reside in rural areas. Unsurprisingly, veterans and military personnel living in sparsely populated areas report significantly lower service acquisition rates compared to nonrural areas (Seal et al., 2010; Teich, Ali, Lynch, & Mutter, 2017). Even in a developed country like the United States, 55% of its counties (all rural) do not have a licensed mental health care provider (psychologist, psychiatrist, or social worker; Substance Abuse and Mental Health Services Administration, 2011). The proportion of older Americans insured by Medicare who received health care via telemedicine due to mobility and distance issues increased 12-fold between 2005 and 2017, and the fastest increase was in counties that had no psychiatrists (Barnett, Ray, Souza, & Mehrotra, 2018).

Even in geographic locations with mental health providers, transportation and travel time can be barriers to regular treatment attendance. Where relevant, advanced age and/or mobility-limiting injuries can make travel itself difficult. Notably, symptoms of PTSD (e.g., trauma-related fears of driving, fears of crowded public transportation, or trauma-related cues in the clinical care setting) may themselves diminish the likelihood of initiating and maintaining attendance (Gilmore et al., 2016).

Privacy and stigma concerns represent another significant barrier to seeking mental health treatment. Patients often worry that others will find out about their condition. Fear of being identified in a therapist's waiting room or through physical artifacts of therapy such as signed consent forms or therapy notes can be sufficient to keep individuals from needed care. This may be especially impactful in professions that are at elevated occupational risk for PTSD, including law enforcement, firefighters, military personnel, and prison guards, who may also fear that a documented mental health diagnosis will harm their career.

Increasingly, consumers expect on-demand services or flexible availability, and therapy is not excluded from these expectations. Traditional face-to-face evidence-based PTSD treatment usually requires that patients have one or two interactions per week with their therapist during clinic hours. Given that many clinics operate during normal business hours, this significant time commitment often overlaps with patients'

work schedules and other responsibilities. Enabling patients to complete some of their treatment outside of the clinic can make scheduling easier, as it eliminates added commute times and offers opportunities to schedule sessions at times when patients might otherwise be unable to attend an appointment (e.g., during one's lunch hour). Additionally, for some patients who are avoidant or highly reactive to stressors during the week, standard once-a-week contact may be insufficient. To adequately engage in therapy, such patients may need higher levels of interaction, accessibility, and clinician reinforcement via secure messaging, phone support, or brief video chats. Treatment models that allow for more flexible scheduling and additional on-demand support can thus potentially enhance patient engagement and improve retention in PTSD care.

Finally, individuals with PTSD are often ambivalent about seeking treatment, which affects their motivation to navigate the barriers discussed previously. They may believe medications have too many side effects, that family members or friends are more helpful than a professional, that a "strong" person can handle problems on his or her own, that some of their PTSD-related behaviors are adaptive, that they don't deserve to get better, or that they are unfixable (e.g., Stecker, Fortney, Hamilton, & Ajzen, 2007; Tanielian & Jaycox, 2008). When people are able to overcome these barriers and seek help, they may lose momentum or give up if they face delays in starting treatment or if the logistics become too frustrating. By reducing logistical barriers and allowing for between-session check-ins, telehealth may lower the motivational barriers to treatment entry and reduce risk for dropout.

Additional barriers to accessing traditional mental health care are circumstances in which in-person contact is not permitted or may even be dangerous or prohibited. For example, in the case of national disasters (hurricane, flood, mass shooting), local providers themselves may be directly impacted and unable to meet the local mental health needs. In such instances, providers from another, less impacted community can be available to satisfy the mental health needs virtually. Or in another case, a global pandemic such as COVID19 may occur in which social distancing to reduce the risk of contagion can sharply limit traditional in-person mental health care contact. These circumstances can create significant barriers to accessing traditional in-person mental health care, often at a time of great need.

TECHNOLOGY AS A SOLUTION

Delivery of mental health services through CVT directly addresses several of these barriers while improving patient access to evidence-based PTSD care. Originally, CVT was typically delivered from a provider or specialist located at a large medical facility, often in an urban location, to a patient situated at a smaller local clinic (i.e., office-based CVT), referred to as the hub-and-spoke model. This structure eased some of the barriers associated with accessing mental health treatment including access to specialty providers, travel distance, time, and costs (Morland, Poizner, Williams, Masino & Thorp, 2015). Nonetheless, obstacles including travel burden, concerns about stigma and privacy, and rigid and inconvenient clinic hours remained as patients were still required to go to clinics. Furthermore, the dual scheduling requirements inherent in this structure proved inconvenient for patients and providers alike as it necessitated synchronous availability at both facilities.

In response to these ongoing barriers, there has been a broad shift toward providing CVT services directly in patients' homes (Morland, Poizner, et al., 2015; Yuen

et al., 2015). Recent advances in technology have made home-based care an easy and appealing option for many consumers ad providers alike. The ubiquity of video chat applications (e.g., Zoom, Skype, FaceTime, Duo, Facebook Messenger) has increased comfort levels with this type of communication across all segments of the population. Furthermore, improvements in broadband technology and high-speed networks have made high-quality video chats possible from the average household, often without any added equipment. Using home-based CVT, patients connect to a provider using their computer, tablet, or smartphone. Patients may be located in their home, at another facility (e.g., a library), or even in their car during a work lunch break while the clinician may be located at the office or his or her own home. Home-based CVT eliminates travel burden, provides significantly greater scheduling flexibility beyond typical office hours, and, when appropriate, enables family members to participate in care, which can give providers important insight into the patient's home environment. The VA has been an early adopter in the use of TMH technologies, using CVT for psychiatric medication management, general supportive counseling, and, most recently, the delivery of EBTs. In 2019 alone, VA providers delivered TMH services to more than 230,000 veterans over more than 786,000 sessions using synchronous TMH (*www.telehealth.va.gov*).

Reducing timing and travel burdens can potentially improve patients' retention in care. A recent study found that patients who received telehealth video tablets had more psychotherapy and medication management visits and better continuity of care than matched controls (Jacobs et al., 2019). Similarly, preliminary findings from two recent studies reported that home-based PTSD treatment options show lower treatment dropout than traditional office-based PTSD treatment options with no difference in treatment efficacy (Medellin et al., 2019; Morland et al., 2019).

The addition of mobile applications (apps), texting, and Internet-based (e.g., online, self-directed) tools to the TMH landscape has further potential to improve engagement and reduce barriers to PTSD care, allowing for a completely virtual model of care (see Ruzek, Chapter 28, this volume, on technology-based interventions). Although research supporting the efficacy of stand-alone apps, texting, and Internet-based interventions is less developed, these modalities can be available on demand 24/7 and can be integrated with virtual CVT provision of care. Individuals with PTSD can also use e-health tools to get information, communicate with providers, and coordinate care (Whealin, Seibert-Hatalsky, Howell, & Tsai, 2015). In the VA Healthcare System, veterans with a PTSD diagnosis are more likely than other psychiatric patients to use the VA's online portal (My HealtheVet) to refill medications or send secure messages to their providers. However, the majority of veterans surveyed with mental health diagnoses do not yet use the online VA portal or CVT services (Abel et al., 2018). Overall, there has been little research to date on best practices for integrating self-management tools or online communication tools with CVT care, but in clinical day-to-day practice their utility is established.

With the development and refinement of CVT technology, this modality has become increasingly ubiquitous across a variety of health care systems and among individual community providers, giving an unprecedented number of individuals with PTSD access to evidence-based care. Furthermore, marketing campaigns for Teladoc, Talkspace, and other TMH platforms have expanded the perceptions and expectations of mental health care to include more flexible, technology-based modalities. Both office- and home-based CVT have become established, and patient-demanded, routes of delivering clinical care in spite of the challenges of sufficiently evaluating constantly advancing technologies.

CURRENT STATE OF THE ART

Effectiveness

Randomized controlled trials (RCTs) of interventions delivered via CVT have repeatedly demonstrated the non-inferiority of CVT in delivering EBTs for PTSD when compared to traditional in-person in-office care (e.g., Acierno et al., 2016, 2017; Morland et al., 2014, 2015a; Yuen et al., 2015). Numerous RCTs comparing CVT and in-person psychotherapy modalities for the treatment of PTSD confirm that services over a CVT modality are clinically "as effective" as traditional in-person services.

Office-Based CVT

In 2010, Tuerk, Yoder, Ruggiero, Gros, and Acierno published the first study examining the use of office-based CVT. Patients traveled to a local clinic and were connected to a remote therapist to provide an EBT specifically for PTSD via CVT. The nonrandomized trial demonstrated the feasibility and acceptability of the CVT modality in a group of veterans with combat-related PTSD and found significant improvements in PTSD symptoms at posttreatment following prolonged exposure therapy (PE) delivered via office-based CVT. One year later, another pilot study reported preliminary data from 13 male veterans showing no difference in therapeutic alliance or outcomes between patients receiving CVT or in-person delivery of group cognitive processing therapy (CPT; Morland, Hynes, et al., 2011). When that trial was completed with 125 male veterans, full study results established the non-inferiority of CVT when compared to in-person CPT at posttreatment and 6-month follow-up (Morland et al., 2014). These findings would later be replicated among female civilians and veterans with PTSD, further confirming the non-inferiority of CVT for the delivery of EBTs for PTSD and extending these findings to female and civilian populations (Morland, Mackintosh, et al., 2015). These studies established the non-inferiority of office-based CVT when compared to in-person modalities across diverse populations.

Home-Based CVT

With the effectiveness of office-based CVT established, several studies shifted to examining whether home-based CVT would yield similar findings. Yuen and colleagues (2015) compared PE delivered via home-based CVT to an in-office in-person condition with a group of veterans. Clinician-reported PTSD and anxiety symptoms at posttreatment did not differ between CVT and in-office care. Non-inferiority for PE delivered via home-based telehealth compared to in-person modalities was later established for PTSD symptoms among a large group of veterans immediately after treatment and six months later (Acierno et al., 2017). This study also reported non-inferiority for depression symptoms, but only at 6-month follow-up. A final study also compared home-based CVT and in-person delivery of a combination of behavioral activation and exposure therapy for PTSD (Acierno et al., 2016). CVT was non-inferior to the in-person modality for both PTSD and depression symptoms at posttreatment and at 3- and 12-month follow-ups. Taken together, these studies established office- and home-based CVT as effective ways of delivering both individual and group trauma-focused therapies for PTSD.

Additional studies demonstrated the efficacy of CVT for PTSD-related symptoms. Morland and colleagues (2010) found group-based anger management therapy (AMT)

delivered via CVT was non-inferior to in-person group AMT in reducing anger symptoms among veterans with PTSD and dysregulated anger. Interestingly, the CVT group reported a stronger group therapy alliance. Holmqvist, Vincent, and Walsh (2014) compared an office-based CVT modality to a self-directed web-based cognitive-behavioral therapy for insomnia (CBT-I) program for chronic insomnia. Both interventions resulted in significant improvements in insomnia symptoms.

Despite most studies showing the non-inferiority of CVT-delivered EBTs for PTSD, a minority of studies found traditional in-person modalities to be more effective. One RCT that compared CPT delivered to veterans via CVT to in-person delivery found that individuals in the in-person condition experienced significantly greater improvements in PTSD symptoms when compared to those in the CVT condition at the end of treatment (Liu et al., 2019). However, the group differences declined over time, and CVT was non-inferior at follow-up, which is consistent with prior studies.

Psychotherapy Process Variables

A common concern arising with virtual care through CVT is whether therapy "process" factors such as satisfaction, therapeutic alliance, attendance, and treatment compliance are impacted when the patient and the provider are not in the same room. When CVT has been used to treat PTSD, most studies report "as good as" effects on process variables and, in some cases, better effects. For example, several studies reported comparable attrition between CVT and in-person care (Acierno et al., 2016, 2017; Morland et al., 2019). Most recently, Morland and colleagues (2019) compared attrition rates among individuals with PTSD who received office-based CVT, home-based CVT, or in-home in-person PE therapy for PTSD. The lowest dropout rate was reported for the in-home in-person therapy condition followed by the in-home CVT condition. This is consistent with a recent CPT study that found the lowest dropout for home-based therapy options (CVT and in-home-in person) with no differences in treatment efficacy (Medellin et al., 2019). Finally, attendance rates (Frueh, Monnier, Yim, et al., 2007; Shore & Manson, 2005), information retention (Morland, Pierce, & Wong, 2004), and patient and clinician satisfaction and alliance (Germain, Marchand, Bouchard, Guay, & Drouin, 2010; Gros, Lancaster, Lopez, & Acierno, 2018) for CVT are also comparable to in-person care.

Contrary to the expressed concerns of some treatment developers, research indicates that the use of CVT does not affect therapist adherence (Frueh, Monnier, Grubaugh, et al., 2007; Morland, Greene, et al., 2011) or the therapist's ability to maintain treatment fidelity (e.g., Acierno et al., 2016) in the delivery of PTSD EBTs. Therapist competence (i.e., developing rapport, conveying empathy) and adherence (i.e., structuring sessions, providing feedback) to a manualized group CBT have been found to be similar in both delivery modalities (Frueh, Monnier, Yim, et al., 2007). Importantly, it is estimated that up to half of treatment providers may not use manuals regularly in their practice (Addis & Krasnow, 2000; Cook et al., 2020). Although there is not much specific evidence regarding the use of CVT for non-CBT PTSD interventions, the current findings do suggest that the integrity of specialized treatments can be maintained over CVT.

Patient Preferences

Successful use of CVT to treat PTSD begins with the willingness of patients and providers to use this modality. For the past decade we have known that patients, including

individuals with PTSD, are highly receptive to receiving medical and psychiatric services using a technology modality (Grubaugh, Cain, Elhai, Patrick, & Frueh, 2008). Research has also demonstrated the acceptability (Shore, Brooks, & Novins, 2008) and use of TMH services (Shore et al., 2012) among populations underserved by conventional mental health programs such as Native American and Alaskan Native veterans. Beyond the United States, a recent study by Ashwick, Turgoose, and Murphy (2019) indicated that TMH was acceptable to veterans with PTSD in the United Kingdom, with many veterans reporting overall positive experiences and improvements in their health.

As the use of CVT to deliver psychological care becomes more commonplace, research must shift from examining the *willingness* to receive CVT to the *preference* for receiving care through telehealth. The availability of video sessions is already a clear "selling point" for therapists in private practice who are advertising their services. This is especially attractive to millennials and young professionals, who increasingly expect flexibility in both time and location of services rendered across all commercial and medical domains. However, patient preference is hardly uniform. In a study of veterans receiving PE via home-based CVT, office-based CVT, or in-home in-person care, Morland and colleagues (2019) found that home-based teleconferencing was preferred by almost half of the participants, while a third preferred in-home in-person care, and a quarter preferred to drive to the hospital for office-based care. These findings suggest that a range of treatment modalities must be offered to patients with PTSD, as each option was preferred by at least a quarter of participants. Clinicians should routinely ask their patients how they want to receive their care, and, when possible, provide them with the preferred modality.

Patient Experience with CVT

Given the criticality of comfort and the therapeutic alliance to clinical success, these common factors of care have been extensively studied in CVT. Notably, the technological landscape has meaningfully changed, enabling a culturewide increase in comfort with novel technologies. A decade ago, ownership of mobile phones, especially smartphones, was limited to financially comfortable individuals. Now, mobile phones are ubiquitous even among the indigent. Similarly, both video chats and social media were only used by small segments of the population. Now there are multiple video-based media platforms, such as Skype, FaceTime, Instagram, and Zoom video, which consumers use regularly to communicate in their professional and personal lives.

A systematic review conducted in 2014 examined patient perceptions of TMH (87% CVT, 13% telephone; 43% PTSD focused) across 14 RCTs that directly compared telehealth to in-person therapy (Jenkins-Guarnieri, Pruitt, Luxton, & Johnson, 2015). Although some studies have reported higher levels of comfort and alliance for in-person therapy when compared to telehealth (e.g., Ertelt et al., 2011; Frueh, Monnier, Grubaugh, et al., 2007; Morland et al., 2004), the systematic review determined that patient ratings of therapeutic alliance and satisfaction for CVT and in-person therapy were comparable (Jenkins-Guarnieri et al., 2015). This confirms findings from an earlier review that did not find differences between in-person and CVT therapy for PTSD (Germain et al., 2010). Importantly, Jenkins-Guarnieri and colleagues (2015) noted that differences between in-person and telehealth modalities were primarily found in studies that used group therapy or reported technological factors that weakened CVT technology (e.g., low bandwidth). Furthermore, these studies are now almost a decade old; both technology and familiarity with CVT have improved dramatically since then.

Authors of the systematic review also suggested that treatment preferences and personality attributes may also be important contributors to alliance, comfort, and satisfaction with telehealth treatment, suggesting there is a strong need for more research on the influence of these factors on patient experience with CVT (Jenkins-Guarnieri et al., 2015).

In general, research has found that patient satisfaction with CVT (e.g., Gros et al., 2018; Yuen et al., 2015), and engagement in it (e.g., Fortney et al., 2015; Morland et al., 2015) is similar to, and potentially better than, in-person therapy. Overall, research indicates that patients with PTSD have a positive impression of CVT prior to use, although willingness to engage in CVT may be reduced among rural populations (Whealin et al., 2015). A recent study conducted among veterans with PTSD living in rural areas examined patient perceptions before and after receiving CPT via home-based CVT using a tablet. While veterans began the study with neutral or positive feelings toward home-based CVT, after treatment they were notably much more positive: They preferred it, felt comfortable with it for PTSD treatment, and would recommend it to others (Whealin, King, Shore, & Spira, 2017). Negative feedback from a minority of veterans in the study pertained to safety and privacy concerns or technical problems experienced during CVT therapy that reduced their treatment satisfaction (Whealin et al., 2017). These concerns can, and should, be routinely addressed by providers throughout the provision of CVT services. More information on how to navigate and ameliorate these concerns can be found later in this chapter.

Provider Experience with CVT

Ultimately, clinician comfort is a key driver in the uptake and success of CVT. Patients may be readier for CVT than their providers. Various logistical and clinical protocols are necessary for the successful delivery of services via CVT, and these extra preparatory steps can be challenging. Equipment may need to be purchased; rooms and lighting will need to be arranged. Low-cost Health Insurance Portability and Accountability Act (HIPAA)–compliant platforms will need to be obtained to facilitate communication between patient and clinician. Although these differences can be managed and implications minimized, clinicians may find themselves uncomfortable with these changes when they first begin to deliver treatment through CVT.

Beyond logistics, CVT delivery of treatment poses a number of limitations and clinical concerns for providers, including uncertainty about legal issues (e.g., differing state regulations around use of telehealth, privacy and risk related to different technology platforms, ability to respond to a crisis virtually, and limited personal connection) (Gershkovich et al., 2016). Interestingly, these issues were endorsed by a third of providers who had never used telehealth, but they were also endorsed by providers with CVT experience.

The remote delivery of trauma-focused treatment may pose unique safety issues. Providers commonly express the concern that a patient will become dysregulated during the session and that being alone without a clinician in this situation could be dangerous. Gilmore and Ward-Ciesielski (2019) identified three common perceived risks reported by mental health care providers when working with clients at risk for suicide: lack of control over patients when dysregulated, challenges with escalating care when necessary (e.g., triage), and difficulty obtaining accurate clinical assessments. For example, nonverbal cues and signals (e.g., the smell of alcohol) may be more difficult or impossible to perceive and assess over CVT (Thorp, Fidler, Moreno, Floto, & Agha,

2012). Interestingly, despite these concerns, both younger and more experienced clinicians are more likely to use TMH with high-risk patients (Gilmore & Ward-Ciesielski, 2019).

It is important to recognize that clinicians who regularly utilize CVT report that emergencies and dangerous incidents are very rare. In fact, a case study of home-based CVT to manage the suicidality of veterans with PTSD indicates that CVT is safe and useful in detecting both PTSD and symptoms indicating risk (Gros, Veronee, Strachan, Ruggiero, & Acierno, 2011). Typical and appropriate precautions include provider collection of releases of information, contact information for a trusted patient contact, and the patient's physical location at the start of each session. Providers should also research local hospitals, psychiatrists, and emergency resources near the patient's location.

Taken together, these findings suggest that many providers, even those who use telehealth, might benefit from telehealth-specific preparation and coursework, ethics guidance, and continuing education to increase their comfort and confidence in using this modality. Maheu and colleagues (2018) suggested that the core telehealth competencies clinicians need to develop are ability to evaluate patients' suitability for telehealth, "telepresence" in interacting via video, comfort with the technology, knowledge of legal/regulatory issues, evidence-based practice, the ability to integrate mobile health tools, and telepractice development (accurate and effective online marketing).

Publicly funded organizations such as telehealth resource centers and trade organizations (e.g., the American Telemedicine Association) provide an enormous array of such resources but have not effectively disseminated them to mental health providers. The American Psychological Association (APA, 2011), the American Psychiatric Association, the American Telemedicine Association, and the Veterans Health Association (VHA) have all published guidelines for the practice of TMH. Unfortunately, these guidelines may not be comprehensive enough to instill confidence in the average provider, who is not comfortable with using this technology and has limited professional or tech support. Furthermore, these providers—many of whom are not psychologists or part of the VHA system—may not even be aware that these guidelines exist. Information that addresses legal issues (e.g., interstate delivery of care), clinical considerations (e.g., provider comfort, safety), and logistics (e.g., HIPPA-compliant consenting and software options) is also difficult to find from reputable sources. In reality, these barriers likely prevent many providers from adopting TMH practices, despite an interest in the flexibility and capabilities of the technology. A centralized source—whether through the APA or an independent organization —with a focus on the development and dissemination of clinical, legal, and professional information to all mental health care providers would serve to expedite the uptake of these practices among clinicians.

GENERALIZABILITY: IMPLEMENTATION OF CVT INTO CURRENT HEALTH CARE MODELS

The clinical effectiveness of CVT is now well established, and some c-CBT interventions possess efficacy. Technologies for secure video and secure messaging are widely available and are continually advancing rapidly. Currently, the primary factors that will fuel or limit the uptake of CVT and other potentially transformative TMH technologies are not clinical or technological; rather, they are regulatory and economic.

Regulatory Limitations

By overcoming barriers of distance, telemedicine technologies could enable clinicians to provide care anywhere in the world. However, licensing and regulations are determined by geography, so clinicians are limited to the jurisdictions in which they are approved to practice. In the United States, mental health professional licenses are issued at the state level. In large states such as California, there are large numbers of clinicians in big cities who could provide services to patients in rural areas. In smaller, underserved states, however, TMH will have limited ability to increase access because there are an insufficient number of clinicians within the state. This problem is compounded when considering challenges in finding a clinician trained in evidence-based treatments for PTSD and other trauma-related conditions. The VA and other federal agencies have exceptions to these regulations, which allow for interstate delivery of therapy; perhaps accumulating data on the safety and efficacy of such practices will promote changes in regulations on interstate care. Countries that handle licensing at a national level allow for wider provision of care within their borders and yet face the same challenges internationally. Although a PTSD specialist in Sydney has the technical capacity to treat clients in Singapore and Karachi, they lack the regulatory frameworks to enable such cross-national care.

Economics

Insurance payors in the United States would certainly advocate for the expansion of TMH services to a broader market. A recent study of three insurance companies in the United States (Wilson, Rampa, Trout, & Stimpson, 2017) found a dramatic increase in telehealth insurance claims for mental health and substance abuse treatments. A number of private insurance companies are incentivizing patients to use telehealth for simple visits by offering reduced co-pays. The availability of telehealth visits is seen as a competitive advantage for providers and health care companies in the marketplace. However, payors in the United States tend to reimburse telehealth visits at substantially lower rates than in-person visits (Wilson et al., 2017). Thus, although demand for these visits is clearly increasing, provider enthusiasm will grow more slowly—and providers may be unable to meet increasing demands on the health care system—unless financial incentives shift. Currently, providing telehealth visits may be attractive for providers who need to increase their patient load or to those who value working from a home office. On the other hand, the majority of providers who have already invested in operating an office may be less inclined to introduce CVT modalities into their clinical practice. The economics of online therapy are still being developed; it is unclear how attractive this approach will be to many providers.

The economic impetus for uptake of telemedicine may be strongest in government-run systems that are responsible for care of an entire population. The VA is rapidly increasing its use of CVT to expand reach of care (*www.telehealth.va.gov*). The British National Health Service is a pioneer in integrating computer-based interventions into mental health services (Bennion, Hardy, Moore, & Millings, 2017).

Recent shifts in the capabilities and ubiquity of web-based technologies serve to increase convenience in virtually every consumer product or service. Consumers have come to expect on-demand, convenient services. The mental health care system's use of technology lags far behind standards set by nearly every other sector. Furthermore, research on the effectiveness of these interventions is occurring much slower

than advances in the marketplace. Ultimately, consumer forces will drive practices, but patients who remain unable to access mental health treatment will pay for the costs of delays in the implementation of TMH.

FUTURE DIRECTIONS AND CHALLENGES

Despite the strong body of empirical research demonstrating that CVT is a highly effective medium for remote delivery of EBPs, there are challenges to fully realizing the potential of this medium. In this section, we review several areas for potential growth: using CVT to augment conventional in-person practice; integrating live video into e-health interventions; describing virtual PTSD specialty practices; and setting up virtual partnerships with local organizations to expand the reach of PTSD care.

Expansion of a Provider's In-Person Practice

For providers who are primarily delivering in-person care, CVT can enable expansion of their client base and geographic service area. Clinicians can also use CVT to continue care for established patients who are physically unable to travel to a scheduled in-person session or who move away and would otherwise require a referral to a new provider.

Therapists and patients can extend the therapeutic window through use of messaging software between sessions to ask and answer questions, transmit homework, or identify items to be discussed in the following session. Treatment companion apps for specific psychotherapies (e.g., CPT Coach, PE Coach, CBT-I Coach) support these treatments with features for reinforcing key concepts, tracking homework completion, and monitoring symptoms. Furthermore, clinicians can assign self-management tools that provide in-the-moment support during times when a clinician might not be available. Examples of apps offering such skills include PTSD Coach (Kuhn et al., 2017), AIMS for Anger Management (Greene et al., 2014), and Virtual Hope Box for suicidal ideation (Bush et al., 2015). These self-management tools may address specific problems that are within the domain of the primary problem being treated (e.g., PTSD Coach), or they could support the patient in a co-occurring problem that is outside of the therapist's domain (e.g., parenting). The current publicly available versions of VA and U.S. Department of Defense apps are self-contained and do not share data with providers or the medical system. Some newer apps have secure data sharing, which allows patients to share their homework and symptoms with their clinicians in real time, enabling the clinicians to intervene if patients are getting off-track. These systems can also be used to track provider adherence and offer appropriate supervision, when necessary.

Video Augmentation of Other Digital Technologies

Video contact can be used to enhance treatment that is primarily delivered through a different modality such as apps or online programs. Patients using these tools benefit from having live human support (Lewis, Roberts, Simon, Bethell, & Bisson, 2019). While support is most commonly delivered via text or messaging, it could also be delivered via video. For example, therapist-supported Internet treatments, such as Interapy, could offer the option of synchronous video contact in cases where patients are not improving as expected. In other online interventions, coaches, paraprofessionals, or

peers may be able to fill a role previously assigned to licensed PTSD specialists. CVT contact could also be used as a "step-up" from self-directed care. For example, a patient who initiated an online program with minimal support from a peer counselor could be stepped up to CVT psychotherapy and/or psychiatric management if more intensive intervention is required.

Virtual Specialty Psychotherapy and Psychiatry Clinics

The quality of PTSD care available to trauma survivors is usually limited by the local availability of resources. Development of virtual PTSD specialty clinics that utilize CVT could expand the reach of EBP-trained providers, getting expert care where it is most needed. Virtual PTSD clinics could have a limited scope, specializing in the delivery of EBPs for PTSD or providing psychiatric consultation to patients' local physicians who may feel uncomfortable prescribing medications for PTSD. In contrast, a virtual clinic could also be staffed with an interdisciplinary team, providing EBP and psychiatric management via secure video, with paraprofessional coaches or techs helping with tasks such as initial screening, ongoing symptom monitoring, and between-session support via video or text. Interdisciplinary teams have been used successfully to improve treatment outcomes among rural veterans with PTSD who were being managed in primary care clinics (Fortney et al., 2015). Alternatively, virtual PTSD subclinics could also be integrated into larger online networks of CVT psychotherapy providers. Behavioral health networks that offer in-person care might choose to subcontract with a virtual specialty clinic to provide PTSD services in areas where local network providers lack specialized PTSD expertise.

Virtual Partnerships to Expand Access to PTSD Care

Taking the point above a step further, not all trauma survivors need PTSD treatment, but when they do, there may be limited local staff with the requisite expertise. CVT technology offers a platform for building partnerships between PTSD specialists and local organizations that are serving trauma-exposed populations. Stewart, Orengo-Aguayo, Wallace, Metzger, and Rheingold (2019) described a school-based program that delivers trauma-focused CBT to African American teens affected by community violence. The school facilitated referrals and provided a convenient location with a secure CVT connection; remote providers delivered the psychotherapy. A consortium of schools or colleges could potentially contract for virtual PTSD specialty services to augment their campus health services. CVT could also be used to expand PTSD care and consultation to settings like prisons, which have limited mental health expertise but high rates of PTSD, especially among female prisoners (Baranyi, Cassidy, Fazel, Priebe, & Mundt, 2018).

CVT can also support programs to provide culturally competent mental health services in underserved areas by linking distant providers with local outreach workers. Goss and colleagues (2017) describe such a program serving Native American veterans in tribal areas. If the cross-national regulatory issues could be resolved, there is also potential for using CVT to mobilize a geographically dispersed global network of providers who can respond to acute needs. Networks of CVT providers, working in partnership with local disaster outreach workers, could provide psychotherapy to people affected by disasters or refugees. For example, an international network of Arabic-speaking providers with expertise in trauma could potentially use telemedicine to help

address the mental health needs of Syrian refugees displaced to other countries (Abdul-Hamid, Hughes, & Morgan, 2018).

CONCLUSION

PTSD is a high-prevalence condition for civilians and veterans alike and takes a tremendous human and economic toll on those who experience traumatic events. Luckily, we are living in an age of unprecedented opportunity to resolve symptoms and sequelae of PTSD, given both the clarity around effective models of care and the availability of technologies that can enable their efficient dissemination. TMH solutions benefit from the ubiquity of technologies capable of supporting synchronous communication between skilled specialty providers and prospective patients, who may otherwise succumb to well-known barriers to effective care related to geography, transportation, convenience, cost, privacy, and motivation. While maintaining the credibility and effectiveness of gold-standard EBTs, TMH can enable increased privacy and efficiencies that limit access challenges for providers and patients alike. Research on TMH suggests that this modality shift is not only feasible, but in many cases preferable, and it provides the foundation for scalable solutions that may reduce the significant impact of undertreated PTSD on patients around the world.

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CHAPTER 30

Psychoneurobiology of Resilience

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> Although the world is full of suffering,
> it is also full of the overcoming of it.
> —Helen Keller

Resilience is an "ordinary magic"—the norm rather than the exception following exposure to stress or trauma (Masten, 2014b). Despite its prevalence, the empirical study of resilience is relatively underdeveloped, as the majority of work in stress and trauma response has focused on the deleterious effects of these experiences—namely, the onset or worsening of psychopathology. There is great interest and great importance in studying factors that promote a protective, buffering, or *resilient* response to stress. To date, this work has included developing conceptualizations of resilience; understanding neurobiological mechanisms that underlie individual variability in stress response; learning how psychosocial factors influence, or are influenced by, these neurobiologically based mechanisms and stress-induced alterations; designing scales to measure and assess resilience both broadly and more specifically; and developing methods to enhance or promote resilience both as a preventative measure prior to stress/trauma exposure and as an intervention following exposure. This chapter provides a selective and abridged discussion of the current evidence concerning these factors as well as some of the inherent challenges in this work and areas for future investigation.

DEFINING RESILIENCE

The American Psychological Association (2014) defines resilience as "the process of adapting well in the face of adversity, trauma, tragedy, threats or even significant sources of stress." Although this is a solid conceptualization, we believe that a more encompassing definition of resilience is the one offered by Ann Masten. She defines resilience as the capacity of a dynamic system to adapt successfully to disturbances that threaten the viability, function, or development of that system (Masten, 2014a, 2014b;

Southwick, Bonanno, Masten, Panter-Brick, & Yehuda, 2014). This definition highlights many important aspects of resilience as well as some of the challenges we have had as a field in agreeing upon a unified definition.

Masten's definition applies to any manner of stressors or traumatic events spanning from a single one-time stressor experienced by an individual organism to a global stressor such as the 2020 COVID-19 pandemic occurring at the time of preparing this chapter, affecting millions worldwide. It applies to development across the lifespan and to individuals, families, organizations, cultures, and societies. Furthermore, this "adaptive dynamic system" definition applies not only across species but also across content domains as it holds relevance for the resilience of economies and so forth (Southwick et al., 2014). This definition additionally accommodates challenges and considerations like the significant within and between individual variability, such as an individual demonstrating an impressive level of resilience in one domain of their life but struggle in another (e.g., family versus work), or during one phase of life but not another (e.g., adolescence versus midlife; Averill, Averill, Kelmendi, Abdallah, & Southwick, 2018; Feder, Fred-Torres, Southwick, & Charney, 2019). External factors associated with resilience, such as caregiver support, may have different effects that are dependent on timing—for example, enhancing resilience in early childhood and yet potentially hindering individuation and self-confidence in adolescence or young adulthood (Feder et al., 2019; van Rooij et al., 2017).

METHODOLOGICAL CONSIDERATIONS AND CHALLENGES

The empirical study of resilience presents some significant methodological considerations and challenges, one of the most important of which is the dearth of prospective evidence, as resilience is not generally tested until there is exposure to a stressor. Measuring aspects of resilience—whether emotional, cognitive, behavioral, or neurobiological in nature—before exposure to a stressor or in the absence of stress and adversity is highly different from measuring these factors during or after exposure. Baseline levels of pre-exposure resilience are rare unless there is some control over the likely exposure, such as when there is a planned combat deployment (Baker et al., 2012) or when baseline data collected for another purpose are then leveraged following an unexpected stressor (Mercer et al., 2012). Both the timing and context of evaluation are critical. Cross-sectional and case control study designs can easily conflate or overlook important factors and can associate trajectories to resilience or chronic stress pathology, depending on when the assessment is conducted (Galatzer-Levy, Huang, & Bonanno, 2018). The lack of prospective data poses a significant threat to how data is interpreted and must be considered carefully when interpreting most of the evidence we review in this chapter.

While most research in resilience has focused on the individual, it is important to remember that the human existence does not take place in a vacuum. Rather, the human experience occurs in the context of social and interpersonal interactions—family, friends, neighborhoods, cultures (including work and academic settings), religions, organizations, communities and societies, each of which may itself be more or less resilient (Walsh, 2011). Mounting evidence supports the importance of investigating the influence of these factors and contexts and learning how they help, or hinder, an individual's capacity to respond to stress or adversity (Reeck, Ames, & Ochsner, 2016). Furthermore, individual responses to stress are shaped by environmental and intrapersonal factors. During or following a disaster, for example, individual survivors may be dependent on the coping skills of other survivors and on the ability of their

families, organizations, and communities to prepare for and respond to adversity (Norris, Sherrieb, & Pfefferbaum, 2011; Walsh, 2011).

Not surprisingly, given the role of resilience in buffering against the onset or worsening of psychopathology subsequent to stress or trauma exposure, there has been considerable interest in resilience as a protective factor in suicidal thoughts and behaviors. In a nationally representative sample of military veterans, greater purpose in life, curiosity, and optimism (Kachadourian, Tsai, Harpaz-Rotem, Southwick, & Pietrzak, 2019; Pietrzak, Pitts, Harpaz-Rotem, Southwick, & Whealin, 2017), as well as social support (Pietrzak et al., 2017; Pietrzak, Russo, Ling, & Southwick, 2011), acceptance-based coping (Pietrzak et al., 2017), spirituality, and self-determination (Elbogen et al., 2019), were negatively associated with suicidal ideation and attempts. This important research highlights a challenge in this work, for it is not perfectly clear whether these factors reflect resilience, are the cause of resilience, or perhaps are both.

Assessment of resilience in empirical studies presents a considerable challenge because there is significant variability with respect to how people operationalize and thus measure it and relatively few measures have been carefully validated. In many studies, rather than specific measures of resilience, the construct is simply conceptualized as low symptoms/high functioning following exposure to a stressor. Multiple measures of resilience are currently available, but we will focus on only two (see Southwick, Pietrzak, & White, 2011, for a more comprehensive discussion of available measures). First, the Connor–Davidson Resilience Scale (CD-RISC) was originally developed as a 25-item self-report measure assessing an array of resilient characteristics, including personal competence, tolerance of negative affect, acceptance, control, spirituality, and hardiness (Connor & Davidson, 2003). Second, the Response to Stress Experiences Scale (RSES) was originally developed by the National Center for PTSD as a 22-item self-report scale with five primary factors: meaning-making and restoration, active coping, self-efficacy, cognitive flexibility, and spirituality (Johnson et al., 2011). While both of these measures assess resilience, they have different, and perhaps complementary, applications. For example, the CD-RISC may be most useful as an outcome measure, whereas the RSES may be best used in evaluating characteristics of resilience (Southwick et al., 2011). Finally, another construct that has received considerable attention and is sometimes confused with resilience is posttraumatic growth (PTG). Evidence suggests that resilience and PTG are inversely related, such that high levels of resilience are associated with low levels of PTG (Levine, Laufer, Stein, Hamama-Raz, & Solomon, 2009). However, PTG is associated with better functioning in individuals with posttraumatic stress disorder (PTSD) (Tsai, El-Gabalawy, Sledge, Southwick, & Pietrzak, 2015) and may help foster resilience to later traumatic events and so may be considered a salutogenic construct (Levine et al., 2009; Tsai, Mota, Southwick, & Pietrzak, 2016).

EARLY LIFE DEVELOPMENT

Early life experiences and developmental environment play a critical role in vulnerability or resilience to stress across the lifespan (Averill et al., 2018; Feder et al., 2019; Malhi, Das, Bell, Mattingly, & Mannie, 2019; Masten, 2014a). Evidence from both animal and human studies demonstrates that stress, when perceived to be unpredictable, unmanageable, overwhelming, or otherwise out of one's control, often leads to impaired stress response modulation, including significantly exaggerated or dampened neurobiological (e.g., sympathetic nervous system [SNS] and hypothalamic–pituitary–adrenal (HPA) axis), emotional, cognitive, and behavioral responses to future stressors, in addition

to impaired stress-related coping and sense of competence (Anacker, O'Donnell, & Meaney, 2014; Averill et al., 2018; Frodl & O'Keane, 2013; Wu et al., 2013). These compromised responses are related, in part, to the effects of early life stress on the structure and function of brain regions implicated in stress response, including the hippocampus, prefrontal cortex (PFC), and amygdala (Averill et al., 2018; Heim, Shugart, Craighead, & Nemeroff, 2010; Wu et al., 2013). In contrast, stress exposure that is perceived to be predictable, controllable, and manageable can have a "steeling" or "inoculating" effect, which promotes adaptive responses to future stress and boosts one's sense of mastery and confidence over managing stressful circumstances (Lyons, Parker, Katz, & Schatzberg, 2009; Southwick, Pietrzak, Tsai, & Krystal, 2015).

These differences in response to the perception or interpretation of stress are seen across species. For example, developing animals exposed to mild to moderate stress that they can control or master are more likely to become stress-inoculated and are better able to deal with stressors in the future relative to animals exposed to either very minimal or overwhelming stress (Parker, Buckmaster, Justus, Schatzberg, & Lyons, 2005). Infant monkeys that have experienced brief, intermittent separations from their mother tend to have lower basal plasma levels of adrenocorticotropic hormone (ACTH) and cortisol, lower stress-induced cortisol levels, superior prefrontal cortical function, and fewer anxiety-like behaviors compared to monkeys that have not been stress inoculated (Parker et al., 2005). Enhanced tolerance to stress has also been found in animals reared in nurturing environments, including brief periods (i.e., 15 minutes) of handling for 3 weeks early in life. As adults, these animals tend to be less fearful in novel environments and less reactive to stress compared to animals that have not been handled (Ladd, Thrivikraman, Huot, & Plotsky, 2005). Although there is less stress inoculation research in human infants and children, the existing body of work shows similar findings. For example, positive early life experiences with relatively brief parental separation has been associated with less hospitalization stress among pediatric inpatients, and mild to moderate manageable stress during childhood has been associated with reduced heart rate and blood pressure responses to distressing laboratory tests in adolescents (Southwick, Douglas-Palumberi, & Piertzak, 2014). As individual characteristics such as genetic inheritance, age, gender, intelligence, timing/type/chronicity of trauma, family functioning, community social support, and culture interact in complicated ways, it is important to use caution in interpreting the role and experience of stress exposure in inoculation and not assume that it is protective in all cases, particularly when it is experienced or interpreted as unmanageable, unpredictable, or something that cannot be mastered (e.g., Masten & Narayan, 2012).

Early development of effective self-control also appears to be an important foundation for resilience across the lifespan. Adaptive self-control includes the capacity to delay gratification through controlling impulses, regulating emotions and behaviors, and employing self-discipline and willpower. In an important series of studies that include prospective and longitudinal data, investigators following more than 1,000 children from birth to their early 30s as part of the Multidisciplinary Health and Development Study (Moffitt et al., 2011), found that childhood self-control predicted psychosocial outcomes in adulthood, with greater self-control predicting increased wealth, less substance dependence, fewer criminal convictions, and better physical health. To isolate the role of self-control relative to other environmental and genetic factors, a separate cohort of 500 sibling-pairs who grew up in the same family were followed from birth to 32 years of age (Moffitt et al., 2011). Those siblings with poor self-control as children had poorer psychosocial outcomes in adulthood (Moffitt et al., 2011).

SELECT NEUROBIOLOGICAL UNDERPINNINGS OF STRESS RESPONSE MODULATION

Coordinated activation of various neurotransmitter systems and brain regions allows an individual to evaluate and respond to stress and potential threat (Averill et al., 2018; McEwen, 2016, 2017; Pitman et al., 2012; Popoli, Yan, McEwen, & Sanacora, 2011; Wu et al., 2013). Based on a highly individualized process of recognition and appraisal of internal and external stimuli, the nervous system rapidly controls the intensity and temporal dynamics of the SNS response and, when deemed appropriate, normalizes back to baseline. The temporal dynamics of the neurobiological responses are critical. Based on the interplay between the neurobiological systems, genetics, and other individual and environmental characteristics, some individuals may have an unusually robust and/or prolonged stress response and thus "overshoot" or overreact.

During these situations, the SNS releases epinephrine and norepinephrine (NE), which trigger the protective actions of "fight or flight"; that is, whether to actively confront or flee/retreat from the threat/danger. Neuropeptide Y (NPY), one of the most abundant peptides in the mammalian brain and a primary SNS modulator with neuroprotective and anxiolytic effects, is released in parallel with NE when the SNS is robustly activated (Enman, Sabban, McGonigle, & van Bockstaele, 2015; Kautz, Charney, & Murrough, 2017; Sah & Geracioti, 2013; Schmeltzer, Herman, & Sah, 2016; Wu et al., 2011). NPY serves as a "physiological brake," helping to modulate the SNS within an adaptive level of activation while inhibiting the continued release of NE (Averill et al., 2018; Wu et al., 2013). Recent evidence suggests that dopaminergic neurons may also help regulate the stress response by providing safety signals to block or "brake" response to fear (Lee, Wang, & Tsien, 2016). Robust increases in NPY mirroring elevated NE during extreme training exercises have been associated with enhanced performance among Special Forces military personnel demonstrating high resilience (Morgan et al., 2000, 2002). Other studies involving combat veterans with chronic PTSD have reported low baseline NPY as well as blunted NPY response to challenge with the $alpha_2$ receptor antagonist yohimbine (Rasmusson et al., 2000).

While the SNS serves a cardinal role in the initial response to stress, the HPA axis serves a restorative role in stress modulation (Averill et al., 2018; Pervanidou & Chrousos, 2010; Pitman et al., 2012; Wu et al., 2013). Stress-related HPA activation results in transient elevation of cortisol both peri- and post-stress exposure. Cortisol is released in response to a cascade of events: The hypothalamus releases corticotropin-releasing hormone (CRH), which stimulates the pituitary gland and ACTH release; ACTH then stimulates the adrenal gland and release of cortisol along with the neurosteroid dehydroepiandrosterone (DHEA; Pervanidou & Chrousos, 2010; Pitman et al., 2012). Cortisol is thought to be involved in a number of processes, including: replenishing and mobilizing energy stores, contributing to hypervigilance and increased arousal, focused attention and memory formation, and inhibiting growth and reproductive systems (McEwen, 2019; Pitman et al., 2012). When cortisol release is exaggerated and remains elevated for too long, it can have deleterious effects, including neurotoxic effects in the hippocampus, a brain region central to stress response and resilience, given its critical role in regulating the HPA axis and acting as a foundation for both learning and memory. Evidence suggests that DHEA may serve a protective role in relation to cortisol modulation and stress tolerance, and it can improve performance under conditions of high stress (Morgan, Rasmusson, Pietrzak, Coric, & Southwick, 2009). Furthermore, DHEA has antidepressant, anxiolytic, and procognitive effects (Sripada et al., 2013; Sripada,

Welsh, Marx, & Liberzon, 2014; Wolkowitz et al., 1999), which may relate, at least in part, to DHEA's positive effect on glial and neuronal survival through antiglutamatergic and antiglucocorticoid activity (Southwick, Vythilingam, & Charney, 2005). It is important to consider the neurobiological aspects of stress response modulation carefully, as studies in this area often lack prospective evaluation, thus making it hard to be certain if these factors underlie and give rise to resilience, are the result of it, or a combination of both.

GENETIC VARIABILITY IN STRESS RESPONSE

Mounting evidence suggests that a range of genetic factors may influence stress reactivity and resilience. In fact as much as 46% of the variance in risk for developing PTSD has been attributed to genetic factors (Wolf, Mitchell, Koenen, & Miller, 2014). Through the study of epigenetics, researchers understand that genes can be "turned on" or "turned off" by biochemical reactions (e.g., methylation, acetylation, or phosphorylation) that are triggered by a host of interacting, external and internal environmental events (social support, stress, etc.). Depending on the specific gene and mechanism involved, turning genes on or off (and subsequent transcriptional activity) may be adaptive or maladaptive for the organism (see McEwen & Getz, 2013av; Nestler, 2012). Important gene by environment considerations relevant to resilience include functional variants of the serotonin transporter gene, the alpha$_{2C}$-adrenergic receptor gene, and glucocorticoid, mineralocorticoid, HPA-axis-related genes. An example is *CRHR1,* a CRH receptor 1 gene implicated in the activation of signal transduction pathways that regulate physiological processes such as stress, reproduction, and immune response, with major expression in the cortex, hippocampus, amygdala, and cerebellum, Another example, *FKBP5,* is an FK506-binding protein gene implicated in immunoregulation and expressed in multiple polyadenylation sites (Averill et al., 2018).

Evidence also suggests that polymorphisms in dopaminergic and noradrenergic genes (e.g., *COMT* Val^{158}Met) are associated with stress reactivity and the pathogenesis of stress-related psychopathology (Armbruster et al., 2012; Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010). Furthermore, the met allele of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism has been implicated in reduced BDNF release, elevated HPA-axis reactivity, and impaired fear extinction (Felmingham et al., 2018; Pitts et al., 2019). Through interactions with the environment, variants of genes that help to regulate these and other stress-related neurobiological systems contribute to an individual's vulnerability or resilience in the face of stressful and traumatic experiences (Feder, Charney, & Collins, 2011; Wu et al., 2013). Two recent reviews of the genetics of resilience discuss (1) implications for genome-wide association studies and candidate genes implicated in the stress response system, PTSD, and depression (Maul et al., 2020) and (2) the role of DNA methylation and gene expression (Mehta, Miller, Bruenig, David, & Shakespeare-Finch, 2020), particularly highlighting the potential benefit of focusing on resilience and well-being rather than pathological phenotypes. Caution is warranted when interpreting the role of candidate genes, as there is concern that (1) the results seen may not survive at the genome-wide level (Johnson et al., 2017) and (2) in most cases, data is collected following stress exposure, and thus we cannot be certain if results indicate a lack of chronic stress pathology, the presence of—or result of—existing resilience, or perhaps another associated phenomenon.

FEAR AND REWARD CIRCUITRY

It has been suggested that resilience is associated with adaptive extinction and limited overgeneralization of fear (LeDoux, 2014; Quirk & Mueller, 2008; Shin & Liberzon, 2010). Brain regions such as the PFC, hippocampus, amygdala, nucleus accumbens, hypothalamus, and select brainstem nuclei (Quirk & Mueller, 2008; Shin & Liberzon, 2010) play a role in various components of fear processing, including perception of threat, initial fear response, fear learning/conditioning, potential generalization of fear to other stimuli, and modulation of fear response (LeDoux, 2014; Quirk & Mueller, 2008; Shin & Liberzon, 2010). A robust reward system (i.e., anterior cingulate cortex, nucleus accumbens, and ventral tegmental areas responsible for dopamine signaling relating to motivation, mood, and reward processing) helps to protect against the deleterious effects of stress (Nikolova, Bogdan, Brigidi, & Hariri, 2012).

Although some of these factors and systems may have relatively little impact on stress vulnerability and resilience when considered in isolation, their interaction and additive effects may be profound. Just as McEwen and Stellar described allostatic load as a cumulative measure of physiological dysregulation of multiple neurobiological systems (McEwen & Stellar, 1993), Charney (2004) applied a similar model to resilience and speculated that resilient individuals might be those with relatively low CRH, HPA axis, and locus coeruleus–norepinephrine (LC/NE) activation, as well as relatively high stress-induced NPY, galanin, DHEA, and testosterone.

EMOTION REGULATION AND COGNITIVE REAPPRAISAL

Stress exposure is an inherently emotional experience and an individual's ability to *regulate* their emotional responses plays an essential role in their susceptibility or resilience to adversity (Troy & Mauss, 2011). Evidence from empirical investigations and clinical interactions have repeatedly demonstrated that a particular emotional reaction to a stressor is dependent on each individual's unique and subjective interpretation and appraisal of the event (Troy & Mauss, 2011). Theories underlying cognitive emotion regulation, with emphasis on cognitive reappraisal and attention control, highlight the considerable variability in personal significance, meaning, and relevance of any given situation. Author Anais Nin (1961) described this phenomenon well, noting, "We do not see things as they are—we see them as we are." Two primary aspects of cognitive emotion regulation that have been identified as important in adaptive and resilient reactions to stress are cognitive reappraisal and attention control (Ochsner & Gross, 2005; Troy & Mauss, 2011). In all circumstances, regardless of stress level, an initial appraisal and interpretation is almost instantaneous. Using cognitive reappraisal, an individual reevaluates their initial reaction, considers additional relevant information, and ideally is able to reframe their original negative or extreme reaction into a more positive or moderate one (Ochsner & Gross, 2005). Attention control is the process of actively directing one's attention away from certain aspects of a situation (including both internal and external stimuli) and toward other aspects—ideally away from overly negative or stressful aspects and toward more positive ones—to change the overall emotional impact (Ochsner & Gross, 2005; Troy & Mauss, 2011). Similar to other factors associated with resilience described in this review, we cannot be certain that adaptive and effective use of cognitive reframing and attention control produce resilience, are the result of it, or perhaps are part of a cycle of both promotion and consequence. A

classic neuroimaging study of deliberate emotion regulation in resilience and PTSD reported that trauma exposure appears to impair successful downregulation of emotional reactions to negative stimuli, whereas the ability to effectively upregulate emotional responses to negative stimuli may be associated with resilience, serving as a protective factor (New et al., 2009).

PSYCHOSOCIAL AND HEALTH FACTORS

A great deal of research has been published on psychosocial and health factors associated with resilience to stress and trauma. Commonly cited factors include positive emotions and realistic optimism, moral code and altruism, meaning and purpose, supportive social networks, religion and spirituality, exercise and physical fitness, mindfulness, a flexible coping style, and a resilient personality (Averill et al., 2018; Bonanno, Westphal, & Mancini, 2011; Wu et al., 2013). Realistic optimism, for example, has been shown to promote mental and physical well-being and health, heightened mood and increased hopefulness, greater meaning in life, and improved social support networks. Functional magnetic resonance imaging (MRI) studies examining the neurobiology of optimism have identified the ventral striatum and PFC as being central to adaptive cognitive reappraisal, attention control, and, in turn, improved mood and enhanced resilience (Kuzmanovic, Jefferson, & Vogeley, 2016; Speer, Bhanji, & Delgado, 2014). Optimism is also associated with increased capacity for adaptive coping (Carver, Scheier, & Segerstrom, 2010), a flexible stress management style that implements variable coping strategies based on situation factors of the stressor at hand (Bonanno & Burton, 2013). In the "broaden-and-build" model of positive emotions, Fredrickson posited that negative emotions, such as anger, fear, and disgust, each heighten autonomic arousal and narrow attention as preparation for specific actions, such as escape or attack (Fredrickson, 2001). In contrast, positive emotions have been shown to reduce physiological arousal and to broaden focus of attention, allowing for more creative, inclusive, flexible, and integrative thinking.

Personality factors are thought to underlie a large portion of one's resilience, or lack thereof, as some personality types cope and adapt better than others when faced with adversity (see Bonanno et al., 2011, for a review). In addition to optimism, personality factors, including emotional stability, extraversion, dispositional gratitude, and decreased openness to experiences, have been associated with increased resilience (e.g., Bonanno et al., 2011; Isaacs et al., 2017). The issue of lacking prospective data noted above is especially relevant to personality characteristics. Extreme stress and trauma can significantly influence worldview and long-held beliefs about the self, others, and the world and thus could affect personality characteristics such as optimism, gratitude, and emotional stability. Measuring personality as it relates to resilience in retrospective analyses has significant threat for biases and problems with interpretation, as it cannot account for any potential changes from pre- to post-stressor (Bonanno et al., 2011).

Physical activity and exercise support resilience through psychological and physiological mechanisms. For example, physical activity protects against the repercussions of emotional and physical stress by helping to regulate the HPA axis, enhancing expression of NPY, and promoting neurogenesis (Silverman & Deuster, 2014). A number of neurobiological mechanisms have been proposed (Erickson et al., 2011) to explain the positive effects of exercise on mood, behavior, and cognition: (1) exercise increases concentrations of compounds that affect mood (e.g., dopamine, serotonin, endorphins);

(2) regular aerobic exercise tends to dampen SNS and cortisol responses to psychological laboratory stress; and (3) exercise promotes the growth and repair of neurons by "turning on" relevant genes that increase the production of nerve growth factors. Exercise also appears to offset genetic risk for stress-related psychopathology (Choi, Zheutlin, et al., 2019), including moderating the deleterious effects of the Val66Met BDNF polymorphism (Pitts et al., 2019).

Considerable evidence suggests that having a strong and supportive social network enhances resilience, whereas lower levels have been linked to increased rates of depression, anxiety, and PTSD (Kaniasty & Norris, 2000, 2008; Mota et al., 2019; Pietrzak et al., 2017; Platt, Lowe, Galea, Norris, & Koenen, 2016). Numerous factors contribute to the association between positive social support and resilience. It is important to consider the dynamic interplay between social support and resilience, such as the quality versus quantity of support (Shang et al., 2020), the perception of support relative to actual received support, and the roles of social causation (e.g., positively correlated social support and resilience) and social selection (e.g., increased psychopathology leading to decreased social support; Kaniasty & Norris, 2000, 2008). High social support has been associated with self-confidence, less engagement in risky behaviors, and the use of effective coping strategies during stressful situations. There is even evidence that positive social support may foster resilience by moderating the genetic risk (likely through epigenetic changes in gene expression) for a variety of illnesses, including depression related to maltreatment (Kaufman et al., 2004; McEwen & Getz, 2013). Positive social support is also associated with increased release of the hormone oxytocin, which is believed to play an important role in regulation of social attachment, sexual behavior, social communication, maternal behavior, classification of facial expressions as positive or negative, feelings of trust, and positive social interactions (e.g., Sippel et al., 2017). Oxytocin reduces anxiety and fear by inhibiting the amygdala and by dampening the cortisol response to stress (Olff, 2012).

GENERALIZABILITY OF RESEARCH FINDINGS

Generalizability and reproducibility are continual challenges in most empirical research with human participants, given the extreme heterogeneity among individuals. Thus, understanding whether research findings associated with one cohort of individuals can be generalized to other groups and then replicated is often challenging. Though other factors are also likely relevant, here we briefly review five primary variables that may influence the generalizability of findings focused on the psychoneurobiology of resilience: the individual, family, or community; the culture; the phase of life; characteristics of the stressor/trauma; and timing of evaluation and data collection.

As above, most resilience research to date has focused on individuals, overlooking critical social and interpersonal variables. Whether and the degree to which findings related to resilience in the individual can be generalized to resilience in broader social settings is not yet known. In fact, it may not be possible to differentiate meaningfully the complex and intertwined factors associated with individual, family, and community resilience (Norris et al., 2011).

Much of the research on resilience and related constructs has also focused on Western cultures. Because culture influences many vulnerability and resilience factors, Western-conducted resilience research may not generalize adequately to non-Western cultures. For example, some (but not all) non-Western cultures tend to be

more collectivistic in their approach to what constitutes adaptive individual functioning (Southwick et al., 2014). For those individuals, interdependence and harmony among extended kinship systems and the larger community are highly valued. Social support, for example, is expressed differently in different cultures, and care must be taken to recognize the considerable heterogeneity that exists (e.g., among non-Western individuals of separate local cultures within a common, larger culture). Furthermore, for some individuals and groups, optimal coping with adversity may include non-Western cultural healing practices or a combination of Western and non-Western approaches (Southwick et al., 2014). Factors associated with stress vulnerability and resilience can also differ depending on age and stage of development (Feder et al., 2019). For example, some of the parenting skills needed to foster resilience and protect infants/young children from adversity are different from those needed to raise hardy teenagers and young adults.

While a number of protective and resilience factors appear to cut across a range of stressful and traumatic situations, some resilience factors and skills are more useful and effective for specific challenges. For example, some of the resilience-promoting skills that a soldier needs to succeed in combat are different from the skills needed to hold together a marriage and a family during times of financial hardship. Similarly, some resilience skills needed to live with chronic mental illness differ from those needed to fight a fire or survive a natural disaster. The type of stressor also appears to affect outcomes (Santiago et al., 2013). Other variables may also affect outcomes, for example, potential sex differences. Relatively little research in resilience has investigated sex differences in stress response modulation. This important line of inquiry may generate critical information to advancing our understanding of resilience and our ability to build resilience and adaptive stress responses (Fallon, Tanner, Greenwood, & Baratta, 2019).

As discussed above, the study design and related timing of evaluation and measurement are important considerations for generalizability. The opportunity to examine characteristics of resilience before and after exposure to a trauma may provide different information and thus lead to different interpretations than is possible with data collected postexposure only. Variability in data collection and interpretation of findings has significant implications for generalizability.

INTERVENTIONS TO ENHANCE RESILIENCE

Although numerous training programs have been developed to increase resilience and the ability to cope with stress, particularly for individuals with high-risk occupations (e.g., firefighters, police, soldiers), very few of these programs have been subjected to rigorous scientific evaluation. Programs or interventions designed to enhance resilience, or constructs associated with resilience, such as social support, can be directed toward communities, organizations, families. or individuals, and they can be delivered prior to, during, or after stressful events. Some of these interventions involve bolstering individual factors associated with resilience such as optimism, physical fitness, and social support. For example, learned optimism is a cognitive-behavioral therapy that teaches the practitioner to recognize and challenge inaccurate negative perceptions and appraisals. As another example, social-emotional training programs have been developed to teach children and adults skills needed to enhance social competence and to build and maintain supportive social networks (Durlak, Weissberg, Dymnicki,

Taylor, & Schellinger, 2011; McKay-Jackson, 2014). Other interventions with mounting, yet somewhat inconsistent, empirical support are designed to modify appraisals of threat and adversity. Examples include training in attention control (Badura-Brack et al., 2015; Naim et al., 2015; Paulus & Aupperle, 2015), which teaches participants to filter out irrelevant negative information while still attending to positive as well as relevant negative information; mindfulness training, where trainees are taught to direct their attention to the present moment (Hilton et al., 2017; Hopwood & Schutte, 2017; Muller-Engelmann, Wunsch, Volk, & Steil, 2017; Paulus & Aupperle, 2015); and training in cognitive reappraisal, which is typically associated with cognitive behavioral therapies and involves learning to cognitively reframe adverse events in a more positive light (Cutuli, 2014; Denny & Ochsner, 2014; Moyal, Henik, & Anholt, 2013).

Comprehensive resilience training programs that focus on skill building in general emphasize management skills (e.g., meditation, cognitive reframing, relaxation training, breathing practices) such as the Comprehensive Soldier Fitness program (Cornum, Matthews, & Seligman, 2011; Fravell, Nasser, & Cornum, 2011), the Battlemind Training System (Adler, Bliese, McGurk, Hoge, & Castro, 2009), hardiness training, and the Penn Resiliency Program (Horowitz & Garber, 2006) have been modestly to moderately successful, though significantly more empirical research is needed to evaluate these programs (for reviews, see Horowitz & Garber, 2006; Leppin et al., 2014). The Battlemind program has the most rigorous empirical evidence relative to other programs with two randomized trials; however, this body of literature remains lacking. One randomized controlled trial of an adapted Battlemind for members of the armed forces in the United Kingdom reported no significant differences in aspects of mental health and alcohol use between those who received Battlemind relative to those who received the standard debriefing with the exception of lower binge drinking in the Battlemind group (Mulligan et al., 2012). A second study compared Battlemind debriefing, small- and large-group Battlemind training, and standard postdeployment stress education (Adler et al., 2009). They found that soldiers receiving one of the iterations of Battlemind reported fewer depressive, posttraumatic stress, and impaired sleep symptoms as well as a reduced sense of stigma regarding mental health compared to those who received the standard stress education (Adler et al., 2009). As discussed earlier in the chapter, without positive results from randomized prospective studies, Battlemind cannot, currently, be considered an effective resilience-building intervention.

Resilience training programs may also focus on the development of job- or task-related skills (e.g., survival skills for soldiers, specialized training for police and firefighters). These programs are often designed to increase coping self-efficacy, with the goal of helping trainees view stressors as challenges that they can manage and from which they can recover. The programs typically include scenario-based training, which entails repetitive exposure with feedback to realistic and challenging scenarios that trainees are likely to face in the future (e.g., (Andersen, Pitel, Weerasinghe, & Papazoglou, 2016). A sense of mastery and coping self-efficacy may increase perceptions of predictability and control, shift a perceived threat into a perceived challenge, increase motivation and perseverance, enhance active problem-focused coping, modify neurobiological and emotional responses to stressors, and help to protect against stress-related medical and psychological disorders (reviewed in Southwick et al., 2011).

A meta-analysis by Leppin and colleagues (2014) highlights some of the challenges in this line of research, including (1) how the programs are classified (e.g., are they intended to ameliorate or prevent stress-related psychopathology, to enhance or promote new or improved resilient coping skills, to be used in a single setting/situation

like scenario-based training or across all experiences, and to address routine stressors or catastrophic tragedies); (2) the outcomes measured (e.g., resilience, coping skills, well-being, confidence, stress level, and psychopathology, such as depression or anxiety); (3) the tools used to measure the selected outcomes (e.g., self-report, clinician-administered, performance-based); (4) research bias (e.g., randomization, blinding, missing or not reported data, conflicting interests); and (5) study design (e.g., often limited to cross-sectional and observational data collection that does not assess change/improvement based on the intervention; Horowitz & Garber, 2006; Leppin et al., 2014). Given the significant variability across all of these factors, the related lack of consensus regarding defining and measuring resilience, and the paucity of well-controlled, randomized trials, it is important to use caution in interpreting the results of these studies. Despite this, most programs appear to have some benefit in reducing symptoms of stress and/or enhancing resilience (Horowitz & Garber, 2006; Leppin et al., 2014). Continued research in this area is critical.

Potential pharmacological agents would target neurobiological systems involved in fear, learning, emotion regulation, reward, extinction, and social behavior that may play a role in enhancing resilience. Examples include agents that help to regulate the SNS (e.g., NPY) and the HPA axis (e.g., DHEA, CRH antagonists); agents that affect fear learning and extinction (e.g., ketamine (Amat et al., 2016; Bagot et al., 2017; Brachman et al., 2016; Price, 2016), agents that may buffer against anhedonia, anxiety, fear, and persistent negative memories (e.g., endocannabinoids (Hillard, 2014; Lutz, Marsicano, Maldonado, & Hillard, 2015)); and agents that impact social recognition and attachment (e.g., oxytocin; Milaniak et al., 2017; Sippel et al., 2017). It is critical to emphasize that much of this work is in very early stages and must be tested in randomized, controlled studies.

FUTURE DIRECTIONS

As research on resilience progresses, a number of issues should be considered. First, future research should work toward a consensus regarding how to define, operationalize, and measure resilience, in both quantitative and qualitative studies, as well as in cross-sectional, prospective, and longitudinal studies. Throughout the chapter, we have mentioned the importance of timing of assessment and the lack of prospective data in the empirical literature. We do not, in any way, intend to minimize or invalidate the importance of the evidence discussed herein. Rather, we want to stress the need for cautious consideration of findings (a good skill for all topics of study) given the somewhat unique nature of resilience, in that it is hard to fully "know" or carefully examine resilience until one is faced with adversity. Furthermore, as discussed, there is significant within- and between-subject variability in response to stressors based on myriad factors, and resilience will never be an "all or none" phenomenon.

Methods such as latent growth mixture modeling can identify resilience and other trajectories following trauma exposure, which may not otherwise be detected using classification methods (Pietrzak et al., 2014; Pietrzak, van Ness, Fried, Galea, & Norris, 2013). Future research should also endeavor to obtain pre-event measures of trauma-related psychological symptoms (e.g., PTSD), as well as risk and protective determinants of resilience (Mancini & Bonanno, 2010). Furthermore, research should consider that trajectories of resilience and other psychological outcomes (e.g., chronic or delayed-onset symptoms) may differ as a function of trauma type (e.g., traumatic loss, military

combat, natural disaster). A recent study on the trajectory and course of PTSD symptoms in a nationally representative sample of military veterans found, among many important things, that modifiable correlates such as social connectedness may be vital in mitigating a symptomatic PTSD trajectory (Mota et al., 2019). Population-based studies on predominant trajectories of psychopathology and functioning after exposure to different types of trauma will be useful in understanding prototypical psychological symptom courses, including resilience, that are linked to specific traumatic events.

Future research will benefit from attempts to address multifactorial biopsychosocial determinants of resilience in longitudinal studies. To date, most research has focused on characterizing sociodemographic, trauma-related, and a limited set of psychosocial factors associated with resilience. However, considerably less is known about how these factors might interact with biological factors to foster resilience to trauma (see Southwick & Charney, 2012). A recently published research agenda provides a useful framework to approach genetically based studies on resilience (Choi, Stein, Dunn, Koenen, & Smoller, 2019). It is anticipated that a better understanding of the biopsychosocial underpinnings of resilience will lead to interventions designed to mitigate or prevent trauma-related psychopathology and functional impairment.

Resilience is a highly complex construct, with stress response modulation at its core. The neurophysiological, psychological, cognitive, and social-emotional elements discussed above all relate to an individual's capacity for adaptive regulation of the stress response. It is an exciting time in the field of resilience where a great deal of research has established a firm foundation for continued efforts to advance our knowledge about biopsychosocial components related to resiliency and about effective approaches to build resilience before and after stress exposure.

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CHAPTER 31

Public Mental Health Interventions Following Disasters

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DISASTERS AND PUBLIC HEALTH

Disasters may be climate-related, human-generated, or a combination of both. Human-generated disasters that are intentional, such as mass violence and acts of terrorism, can result in extreme adverse psychological and behavioral effects (Ursano, Fullerton, Weisaeth, & Raphael, 2017). Some disasters are abrupt, unfolding over minutes or hours (e.g., earthquakes, mass shootings, plane crashes), while others are slow-moving events that span days, weeks, or months (e.g., terrorist events, pandemics, floods). Climate-related disasters are occurring with increased frequency and severity (see Figure 31.1), in large part due to a changing global climate (Intergovernmental Panel on Climate Change [IPCC], 2018). These disasters result in profound disruption through damage to property, physical injury and death, displacement of individuals and families, and prolonged disruption to a broad range of services on which communities rely.

Episodes of mass violence, particularly mass shootings, are also increasing in frequency, primarily in developed nations. While mass violence typically does not create the same degree of death and widespread damage and disruption as climate-related disasters, these events undermine perceptions of safety and create extremes of fear within affected communities and nationally (Institute of Medicine Committee on Responding to the Psychological Consequences of Terrorism, 2003). They also bring attention to issues related to personal safety and firearm ownership as well as the role of mental illness in violence, topics that are increasingly divisive for communities and nations.

Disasters strike at the fault lines of communities, exacerbating sociocultural divisions within the unique contextual factors of a community. Various factors impact the community experience of response to and recovery from disasters, such as previous exposure to disaster events, economic resources, cultural values, community perception

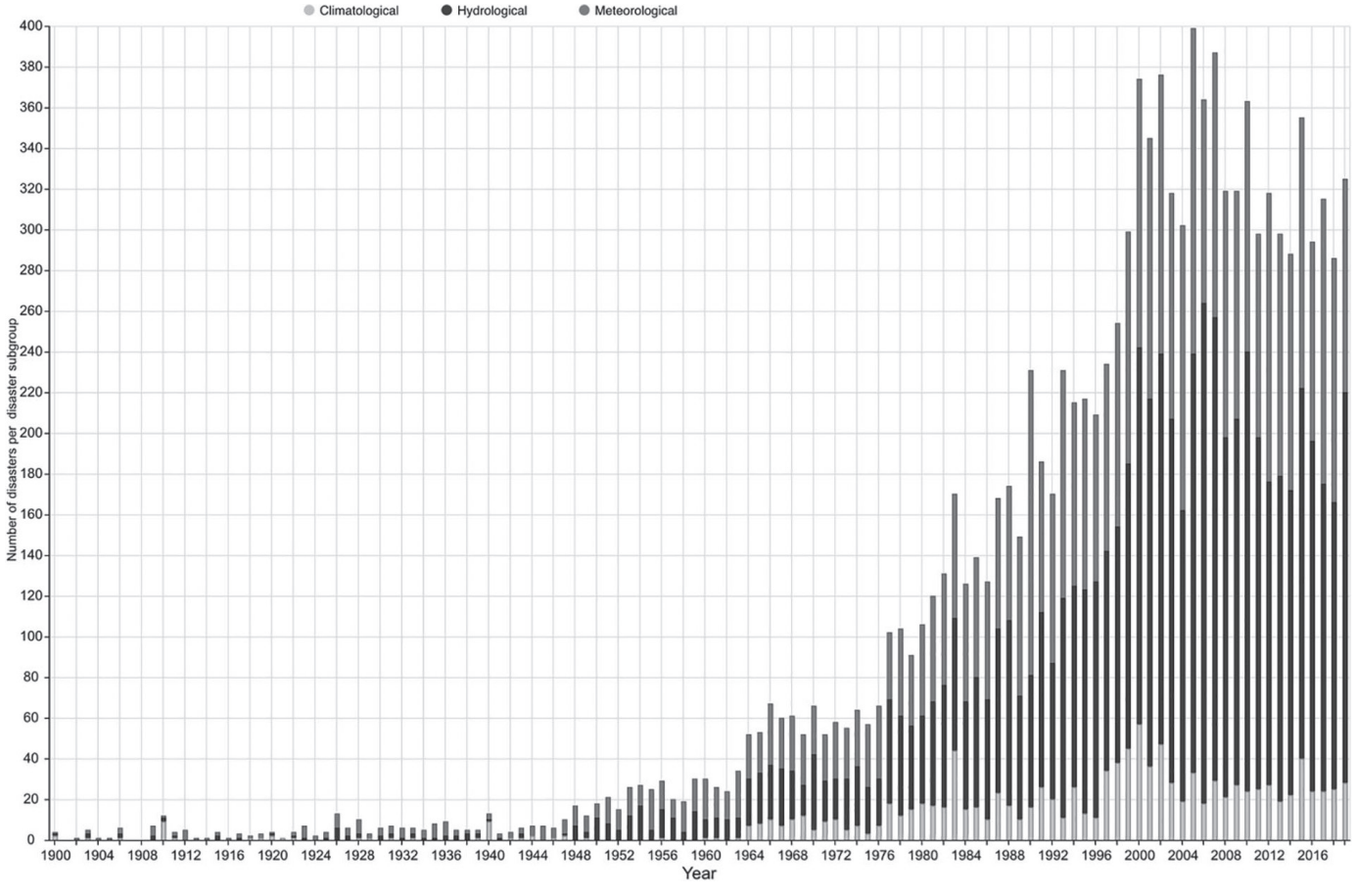

FIGURE 31.1. Frequency of global climate-related disasters. SOURCFE: EM-DAT: The Emergency Events Database—Université catholique de Loubain (UCL)—Cred. D. Guha-Sapir—*www.emdat.be*. Brussels, Belgium.

and meaning of the event, and trust in institutions responsible for managing the disaster. These create a disaster ecology in which various forces of harm impact individuals, communities, and societies (Shultz, Espinel, Galea, Zelde, & Reissman, 2017). Cultural and contextual factors informed community response in (1) Japan following the Fukushima triple disaster in 2011, where mistrust of the government utility company led to widespread outrage and refusal of citizens to comply with recommended public health interventions (Miller, 2016); (2) the Flint, Michigan, lead water crisis in 2015 in which community members perceived systemic racial inequities that further eroded public trust (Cuthbertson, Newkirk, Ilardo, Loveridge, & Skidmore, 2016); and (3) Hurricane Maria in Puerto Rico in 2017, after which perceptions of inequity in resource distribution created animosity between the public and government officials (Santos-Lozado, 2018). Each of these events, as with all disasters, was informed by the sociocultural and contextual factors unique to the communities in which they occurred.

Advanced disaster planning reduces errors or omission of critical factors during high- stress crisis response (United Nations Office for Disaster Risk Reduction, 2015). Use of an established framework, such as the Haddon matrix, helps ensure that preparedness activities are structured and comprehensive. The Haddon Matrix is a framework for risk analysis and mitigation that considers the agent, vector, and population across the pre-event, event, and postevent time periods.

"Tipping points" occur when events, actions, or perceptions strongly influence psychological reactions or social behaviors at the group level. A variety of factors may provoke tipping points, including belief that resources are unfairly distributed; the inciting event was intentional; conspiracy theories; restriction of civil liberties; stigma or blame; and loss of faith in institutions or community leaders. The result is reduced adherence to recommended health behaviors, increased strain on public health systems, suboptimal utilization of health care resources, greater distress, and diminished well-being among community members, all of which ultimately prolong recovery.

COMMUNITY PHASES OF RECOVERY FOLLOWING DISASTER

Following a disaster, particularly one that involves a single acute event (such as an extreme weather event or an incident of mass violence), affected communities can progress through phases of psychosocial recovery (see Figure 31.2). This model has particular relevance for understanding community response as well as consideration of disaster planning and resource allocation.

The *honeymoon phase* coincides with an influx of government, volunteer, and international assistance. Community bonding occurs through a shared catastrophic experience as well as giving and receiving of assistance. Survivors feel hopeful and optimistic that their lives will be restored to wholeness. Disaster mental health workers can develop a foundation to provide assistance in subsequent, more difficult, phases.

The *disillusionment phase* is characterized by disappointment as disaster assistance diminishes and attention on recovery efforts fades from the media cycle. The sense of community is weakened as people increasingly focus on unmet needs. Resentment surfaces as survivors receive unequal monetary compensation for what is perceived as similar damage and loss. Survivors have growing demands, including financial pressures, relocation or living in damaged homes, family strife, bureaucratic hassles, and limited time and energy for recreation or self-care. Health problems and exacerbation of preexisting conditions emerge. The disaster anniversary provides an important opportunity

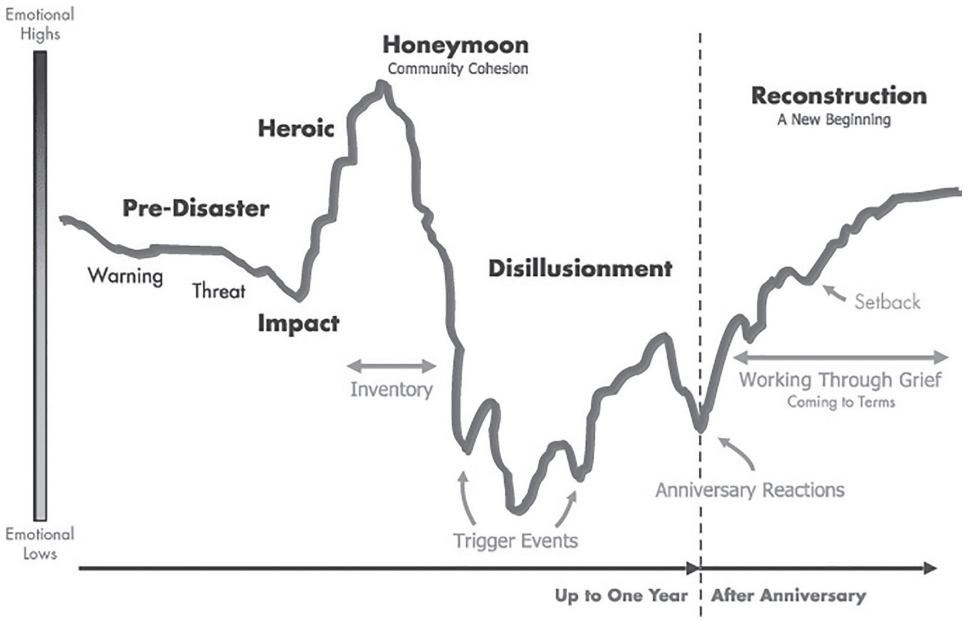

FIGURE 31.2. Psychosocial community phases of disaster.

for leaders to support community well-being through memorializing, making meaning of the event, and "building back better."

The *reconstruction phase* may last for years, particularly after large ecological disasters. Survivors attempt to rebuild their lives as well as their social and occupational identities by returning to old jobs or finding new work, rebuilding homes, and establishing new social support systems. Some are able to accept new circumstances, grieve losses, and manage changes. Individuals may find meaning and emerge with an increased sense of personal strength and belief in their ability to manage future adversity.

Disaster planners and service providers should recognize that community members manifest psychological and behavioral symptoms over different timelines in response to the same event. Moreover, depending on the severity of the experience, resources available during and after the event, and individual coping skills, some will develop persistent symptoms that may require extended treatment. Anger can be directed at community leaders if psychological and medical and disaster response plans do not sufficiently account for these factors.

ADVERSE MENTAL HEALTH CONSEQUENCES

Most people will do well and recover promptly to previous levels of function following a disaster, with some experiencing an increased perception of efficacy and ability to handle future challenges. However, others may experience adverse mental health effects. Psychological and behavioral effects of disasters begin immediately after the event and may persist for extended periods of time. Disasters can impact people far beyond the geographic region of the event and are experienced within cultural and contextual factors unique to each community.

Psychological and Behavioral Effects

Psychological disorders, such as posttraumatic stress disorder (PTSD), depression, and anxiety, can occur after disasters, resulting in considerable morbidity and mortality, warranting prompt assessment and evidence-based interventions. In addition to disorders, earlier and more common responses are distress reactions and risky health behaviors (see Figure 31.3; Ursano et al., 2017). Sleep disruption, anxiety, and increased substance use are most commonly identified in emergency and primary care settings.

Distress reactions are common, early manifestations following traumatic events, comprising the largest portion of the early public mental health burden following disasters. Insomnia is highly prevalent and increases risk for other psychosocial difficulties (Zhen, Quan, & Zhou, 2018). Anger is common following disasters and is associated with increased likelihood of negative mental health outcomes (Forbes et al., 2015). Decreased perception of safety is common following intentional acts of mass violence and increases risk for developing psychological disorders. Fullerton and colleagues surveyed local residents following the 2002 Washington, D.C., sniper shootings and found that decreased perceptions of safety were associated with increased probabilities of PTSD, depression, and alcohol use (Fullerton, Mash, Benevides, Morganstein, & Ursano, 2015). Health risk behaviors represent coping strategies to manage distressing emotions and include increased use of tobacco and alcohol. Some people may even begin using substances for the first time. Individuals may also isolate themselves, reducing access to available health care and social support resources. Education of health care personnel and public health messaging can articulate high-risk health behaviors to avoid, alternative coping strategies, and where to get help when needed.

Psychological disorders may develop following disasters, resulting in significant morbidity and mortality, and warranting formal treatment. The most studied of these disorders is PTSD, along with anxiety and depression. Previous psychological disorder also increases risk of recurrence following a disaster. Screening of the affected population and prompt initiation of evidence-based interventions reduce long-term adverse effects.

FIGURE 31.3. Psychological and behavioral impact of disasters.

The recovery period following disasters can be prolonged and stressful. As stressors mount (e.g., health, financial, occupational and family), coping resources are often exhausted and suicidal thoughts, and behaviors increase (Kolves, Kõlves, & De Leo, 2013). Some research suggests that suicidal thoughts and behavior diminish moderately from baseline in the early weeks and months following a community disaster, then increase from baseline during the following months and years (Kessler et al., 2008). Interpersonal violence increases, with women being most affected (Harville, Taylor, Tesfai, Xiong, & Buekens, 2011). Additional disaster-specific factors that increase adverse mental health outcomes include population displacement and migration, breakdown of community infrastructure, food scarcity, loss of employment, and poor sense of social connectedness (Ursano et al., 2014).

Exposure and Contamination

Disasters involving exposure and contamination by chemical, biological, radiological, or nuclear (CBRN) material result in unique psychological and behavioral effects that benefit from tailored public mental health preparedness and response measures (National Academies of Sciences, Engineering, and Medicine, 2019). Extreme ecological disasters may damage CBRN facilities and local infrastructure. Following the earthquake and tsunami in 2011, damaged reactors in Fukushima, Japan, exposed soil, water, and community members to nuclear material. The resulting fear and uncertainty about nuclear contamination led to ostracism and hostility toward displaced individuals most severely affected (Maeda & Oe, 2017). CBRN materials are often novel and fear-inducing for citizens, disaster managers, and health care workers. Uncertainty about the site of exposure, nonspecific symptoms, fears of prophylactic medication and treatment shortages, and concerns about isolation and quarantine fuel distress and increase risk for panic.

CBRN events result in significant increase in presentation to health care with somatic symptoms. During CBRN events, the population will respond based on perception of risk, which can be higher than actual risk. Public health messaging is critical to educate the community about actual risks, steps taken to mitigate risks, and when and where to get help. Health care facilities should be prepared for surge emergency care demands on resources for citizens with somatic or other concerns related to their fear of exposure or their belief that they already have been exposed. Mental health personnel trained in the effects of mass trauma and evidence-based interventions, embedded in primary care and emergency settings, can provide assessment and initiate early interventions.

Infectious outbreaks of SARS, MERS, H1N1, Ebola, and Zika virus created unique challenges for public health planning (Morganstein, Fullerton, Ursano, Donato, & Holloway, 2017). The SARS-CoV-2 (COVID-19) global pandemic of 2020 resulted in unprecedented social, economic, and health impacts with over 124.5 million people infected and 2,740,877 dead as of March 24, 2021 (*Washington Post* Staff, 2021). Communities around the world experienced the adverse psychological effects of physical distancing requirements, stay-at-home orders, and mandatory quarantines (Brooks et al., 2020). At the outbreak epicenter in Wuhan, China, a significant number of health care workers experienced distress (71.5%), insomnia (34%), anxiety (44.6%), and depression (50.4%), with women, nurses, and front-line workers being most severely impacted (Lai et al., 2020). During infectious disease outbreaks, absenteeism among health care personnel is a public health concern as it further diminishes needed resources during

times of increased care demand. Health care personnel concerns are fueled by fears of contracting illness, coping with inadequate protective equipment, bringing illness home to their families, and experiencing illness stigma from community members. The factors found to improve well-being in health care workers include timely and thorough training; functioning equipment in adequate supply; ongoing camaraderie with colleagues and managers; regular and updated communication from leaders; adequate preparation about the range of exposures; education about normal psychological reactions and helping resources; access and availability of support resources; and an organizational culture that promotes a growth mindset, acknowledging present challenges while seeking opportunities and looking to the future (Brooks, Dunn, Amlôt, Rubin, & Greenberg, 2018).

The Role of Media

Increased exposure to disaster-related media is associated with adverse outcomes (Pfefferbaum et al., 2014), including the COVID-19 global pandemic (Bendau et al., 2020), suggesting that media can serve as a vector for transmitting distress throughout a population. Media also plays an important role in disseminating information following disasters and may serve to alleviate anxiety in those already experiencing high levels of distress related to the disaster. Partnering with media is crucial since it can help disaster-affected communities by broadly disseminating information on risks, recommended health behaviors, the time to get help, and the way to access resources.

The media will understandably expect to receive information from those involved in disaster management. It is helpful to work collaboratively to ensure that accurate information is conveyed and that important public health information is disseminated. Encouraging the media to provide warnings before showing graphic material and indicating the date of material being shown can reduce unnecessary exposure to traumatic material or concerns about recurrence of the event that could increase community distress.

Social media are increasingly being used following disasters, and patterns have been observed in both the mechanisms by which information is shared across networks

TABLE 31.1. Mobile Apps for Disasters

FEMA	Access to weather services and disaster preparedness and response tips, local shelters, location of FEMA disaster recovery centers; also allows submission of photos of disaster damage.
SAMHSA Disaster Behavioral Health	Information and resources on disaster behavioral health issues relevant to preparedness, response, and recovery. Information sheets can be downloaded directly to the device, allowing access during cellular signal disruption.
WISER	First responder Hazmat incident resource; helps identify substances, containment and suppression advice, medical treatment information
Nextdoor	Allows users to indicate they are in distress, and any local users will be provided their location to come provide assistance.
GasBuddy	Provides information on closest gas stations that are operational and able to provide gas.

and the focus of information sought by users during different phases of disaster, which should guide disaster communication and messaging (Niles, Emery, Reagan, Dodds, & Danforth, 2019). In addition to use of social media for information following disasters, an increasing array of online and mobile resources are available to enhance disaster preparedness, response, and recovery for responders and community members impacted by disasters (see Table 31.1). They can be used to provide critical guidance on sheltering in place, evacuations, where and when to access available resources, as well as preparedness and response guidance for specific disasters, such as hurricanes or hazardous material spills. Mobile apps can be used to crowd source data about the direct impact of disaster events down to the individual level, such as home damage and physical injury, as well as to make information about services that remain operational accessible for those in need. Extreme weather events often adversely impact access to electricity as well as Internet and mobile device connectivity. Thus, reliance solely on these devices for needed resources should be avoided.

CONSIDERATIONS FOR SPECIAL POPULATIONS

Certain populations warrant special consideration in disaster planning and response. These include certain gender-specific vulnerabilities, children and adolescents, older adults, the socioeconomically disadvantaged, minority and marginalized groups, those with preexisting conditions, those exposed to the higher doses of disaster trauma, and disaster responders. Some of these populations may be particularly vulnerable to negative mental health outcomes and account for a disproportionate share of a community's postdisaster mental health burden, especially in the absence of advance planning considering their unique needs.

Gender-Specific Vulnerabilities

Both female and male disaster survivors have certain gender-specific vulnerability factors, which may interact with each other across multiple interpersonal domains, such as within couples, families, and communities, to impact recovery.

Women, at times and in certain situations, are more likely than men to experience adverse mental health outcomes following disasters, including PTSD, and depression (Norris et al., 2002). In many cultures, women assume a primary caregiving role, and this role may be significantly expanded in the postdisaster period as they assume responsibility for others impacted by the disaster. This role, combined with the loss of financial, social, and material support, can adversely impact women's well-being.

Men also have specific postdisaster areas of vulnerability, such as increased substance use after disasters. The increased socialization of men to assume providing and protecting roles may increase risk of injury or death associated with disaster rescue and recovery activities, as well as greater self-esteem loss if they perceive themselves to have "failed" their loved ones or community as providers and protectors in the context of a disaster.

Children and Adolescents

Children and adolescents possess unique vulnerabilities that place them at increased risk of poor mental health outcomes following disasters. A child's stage of cognitive,

emotional, and language development may limit the extent to which they understand the disaster, regulate their feelings, and express their needs. These factors, however, do not necessarily lead to psychological harm, especially if trusted caretakers are available, responsive to the child, and able to model adaptive coping mechanisms. On the other hand, parental distraction, family discord, disrupted schedules and routines, and separation from primary attachment figures increase the vulnerability of children and adolescents. In addition, the posttraumatic reactions experienced by parents and caregivers can also shape the reactions of their children, as well as impact the care that parents and caregivers provide.

Behavioral and psychological responses in children and adolescents may appear different from those of adults and can be overlooked or misinterpreted as "acting-out" behavior when observed by stressed and distracted parents, educators, and school administrators. Behaviors unique to children and adolescents indicating adverse responses following disasters can include diminished academic performance, aggression, and regression. Ensuring adequate care for parents, as well as education for teachers and school personnel regarding possible changes in a child's behavior following a disaster experience, can help to identify distress reactions, facilitating effective and timely interventions. Finally, children are particularly vulnerable to experiencing the consequences of failed public safety infrastructures in the wake of disasters, including rape, violence, child trafficking, and other forms of exploitation, all of which can result in severe and long-standing mental health consequences.

Older Adults

Studies have linked older age with increased risk of adverse outcomes following disasters. Given that the population of older adults is expected to rise substantially over the next few decades and that emergency preparedness among older adults has been found to be inadequate across demographic, social, and economic strata (Killian, Moon, McNeill, Garrison, & Moxley, 2017), there is a clear rationale for specifically considering this population's needs in disaster response planning.

However, older age in and of itself does not directly translate to increased vulnerability. Older adults comprise a highly heterogeneous segment of the population. In fact, there is some evidence of greater resilience to disasters with increased age, thought to be mediated in part by prior experience with such events (Norris et al., 2002). Therefore, when considering the postdisaster needs of older adults, it is important to recognize that a range of physical and mental health, social, economic, and environmental factors converge to influence an individual older adult's level of vulnerability, which may differ from that of another older adult.

Socioeconomically Disadvantaged and Other Marginalized Groups

Lower socioeconomic status is often associated with adverse outcomes following disasters (Norris et al., 2002). Those who are poor are disadvantaged in a number of ways, including fewer financial resources, limited access to transportation that would enable them to heed evacuation warnings, and housing that may be poorly built, inadequately maintained, or situated in a geographically vulnerable area. Individuals who are homeless are especially vulnerable to the above risk factors. In addition, with few exceptions, studies in the United States have found that individuals who belong to minority ethnic groups, including African Americans, Asian Americans, Native Americans, and

Latinos, tend to do worse in the aftermath of disasters compared to those from majority ethnic groups (Norris & Alegria, 2005). A broader definition of minority groups also includes other historically or currently marginalized groups, regardless of whether they belong to a visible minority (e.g., LGBTQ people, people with mental illness and substance use disorders, and migrants and refugees).

Beyond other risk factors to which minority groups are disproportionately exposed (e.g., lower socioeconomic status and chronic adversity), ethnicity and culture may also factor into the differential impact of disasters on minority populations. Ethnic disparities in access to health care, including mental health care, are well documented and may result from reluctance to seek help among individuals from minority groups; insufficient insurance coverage; inadequate detection of health problems due to communication barriers; and lack of cultural competency among health care providers and institutions (Norris & Alegria, 2005). Consideration of the broad spectrum of minority and marginalized populations during disaster preparedness planning can facilitate service use and promote both individual and community recovery.

Preexisting Conditions

Most people with mental health conditions will typically rise to the occasion and participate in response activities immediately after a disaster. However, damaged infrastructure and systems of care increase risk that individuals with preexisting health conditions will experience adverse outcomes (Norris et al., 2002). These outcomes include preexisting physical health conditions, mental health conditions such as PTSD and depression, and other risk factors associated with poor health such as hospitalization. Risk arises largely from dependence on medical equipment, pharmaceuticals, human resources, and facilities that may be unavailable in the aftermath of disasters. Adequate planning to ensure access to resources and systems of care during disaster response and recovery is particularly important to meet the needs of this population.

Exposure Characteristics

The characteristics of disaster exposure, including severity, duration, frequency, and type of exposure, can impact postdisaster mental health outcomes. In particular, a robust literature supports the notion that more severe and direct disaster exposure, including experiencing personal loss or injury and witnessing the injury or death of others, increases the risk of adverse mental health outcomes (Norris et al., 2002). Other specific markers of disaster severity associated with this increased risk include bereavement, life threat, financial loss, property damage, relocation, and experience of horror or panic during the disaster.

A longer duration of disaster exposure also correlates with an increased risk of adverse postdisaster mental health outcomes. The frequency with which disasters occur can impact the level of psychological distress, with the occurrence of multiple serial or simultaneous disaster events being associated with greater distress (Shultz, Espinel, Galea, Zelde, & Reissman, 2017). Finally, the type of disaster also shapes subsequent psychological responses. A review of studies indicated that while the rates of PTSD resulting from nonintentional trauma decreased over the first 12 months posttrauma, the rates of PTSD resulting from intentional trauma (including human-generated disasters deliberately designed to inflict harm) increased over the same time frame (see Santiago et al., 2013).

Disaster Responders

Disaster responders can be defined as public health, safety, and service workers who have an integral role in response and recovery efforts following disasters. In addition, hospital and medical staff, including physicians, nurses, ancillary staff, and other personnel, including truck drivers and heavy equipment operators, can also have an important role in postdisaster response. Disaster responders are, to some extent, a self-selected group, many of whom chose to work in first responder occupations in the predisaster setting (e.g., police, paramedics, firefighters) or to volunteer assistance in postdisaster response and recovery efforts (e.g., Red Cross volunteers). As such, they may show high levels of resilience during and after disasters. Their resilience can be further fostered by disaster response training.

Due in part to their more severe and more frequent exposure to disasters relative to the general population, however, disaster responders are at risk of developing adverse mental health outcomes. Exposure to violent death and human remains puts disaster responders at risk for psychological stress and psychiatric disorders (McCarroll & Biggs, 2017). In addition, role conflict may present a unique stressor for disaster responders who are both responders to the disaster and victims of the disaster and may struggle between their concern for the safety of family members and their sense of duty and dedication to work. Finally, disaster responders may be at increased risk of mental distress if they psychologically identify with victims (e.g., a child victim may well remind the disaster responder of his or her own child; Mash et al., 2018).

INTERVENTIONS

Interventions developed to address disaster exposure are typically evidence-informed and guided by expert recommendations and case studies. Brief and population-based interventions address the logistical constraints of the postdisaster environment (Morganstein & Flynn, in press).

Public Health Response: Physical and Psychological Needs

Mental health needs should be incorporated into the initial emergency response, both at the disaster site and in hospital emergency rooms. Prompt postdisaster interventions should address distress reactions (e.g., sleep disturbance) and health risk behaviors (e.g., increased alcohol and tobacco use). Tailored community education can decrease postdisaster distress and mental and physical health-related issues. Early intervention provides an opportunity to screen for additional high-risk adverse trauma effects (e.g., family and community violence and suicidal behaviors). Evidence-based mental health interventions, including trauma-focused therapies and medications, are available from trained mental health clinicians (see Galovski et al., Chapter 19, this volume). Early attention should be given to posttraumatic distress and psychiatric symptoms which may develop into disaster-related psychiatric disorders (e.g., PTSD) and comorbid psychiatric sequelae (e.g., generalized anxiety disorder, depression, alcohol and substance use disorders). Additional factors may contribute to the trajectory of postdisaster distress and disorders, including preexisting medical and mental health conditions, access and use of health care, and degree and type of exposure (e.g., exposure to death, injury and loss of property).

Disaster-exposed individuals present at emergency departments and primary medical care for somatic symptoms, depression, and health risk behaviors (e.g., increased alcohol or drug use, sleep difficulties, accidents) and not necessarily for mental health treatment. For those with posttraumatic symptoms, referral should be made to mental health clinicians. Collaborative care provides an opportunity for disaster-affected individuals who do not meet mental disorder criteria to receive additional support and care. Informal resources such as family members, peers, workplace support, community leaders, and faith organizations are important sources of social support.

Intervention at Individual and Community Levels

Postdisaster interventions should address disaster-related distress, psychiatric disorder, and functional impairment, as well as protective factors that reduce the risk of adverse consequences and promote healthy functioning, including perceived safety, individual and community collective efficacy, and disaster preparedness (see Azad et al., Chapter 18, this volume, on early intervention). Furthermore, community resilience, which acts to prevent disaster-related health problems and promote disaster management and organizational behavior within the community, is critical to effective postdisaster interventions.

The perception of safety is an important aspect of disaster response and should be a focus of public health intervention by community leaders and health care providers. During disasters and terrorist events, perceived safety may vary across individuals and differ based on event circumstances. These events can also be characterized by perceived uncontrollability and uncertainty, which influence perceived safety and well-being. Lower feelings of safety in Washington, D.C., residents during the 2002 sniper attacks were associated with greater posttraumatic stress and depression, and increased alcohol use (Fullerton et al., 2015). When developing programs to enhance perceived safety, individual differences, including gender, mental disorders, prior trauma exposure, and personality characteristics, should be considered. Messaging by leadership and credible health care providers provides timely, accurate information and readily available assistance both in person and through media sources.

Collective efficacy, defined as social cohesion among neighbors along with their willingness to intervene for the common good (Sampson, Raudenbush, & Earls, 1997), mitigates the impact of longer-term psychological consequences of disaster exposure. Collective efficacy is both an individual-level perception and a community-level capacity (Fullerton et al., 2015). Social resources, that is, perceived collective efficacy and social support, had buffering effects on psychological distress under conditions of high resource loss after a forest fire and flood within a 2-month period (Benight, 2004). In contrast, lower perceived collective efficacy was associated with a greater likelihood of mental distress, PTSD, and depression in Florida Department of Health workers after multiple hurricanes (Fullerton, Mash, Wang, Morganstein, & Ursano, 2019; Ursano et al., 2014). Thus, efforts to promote social cohesion among community members may mitigate the mental health consequences of community disasters.

Community leaders, law enforcement, community organizations, and health care providers have a significant impact on individual and community disaster preparedness. These efforts can be promoted through traditional and social media and direct communication, and include developing emergency plans, stockpiling necessary resources, communicating information about potential risks, and developing disaster responses. A primary strategy involves building formal and informal integrated communication

networks and developing effective and efficient communication strategies for before, during, and after a disaster, with well-established plans for potential technological disruptions.

Health Risk and Crisis Communication

Educating the public by providing knowledge and guidance in managing disaster-related stressors and engaging in self-care is an important population-based intervention approach (Reynolds & Seeger, 2012). Furthermore, risk communication by community leaders that provides information regarding disaster preparation and response fosters community cohesion and prosocial behaviors. Disaster-related communication should be accurate, clear, consistent, and timely. Engaging in language that community members understand, providing accurate information, and acknowledging concerns are important to building trust and public confidence. Communication that involves reassuring nonverbal behavior, imagery, rituals, and symbols can enhance community efficacy and social cohesion.

Innovative intervention strategies provide tools for disaster responders, mental health care providers, and disaster-exposed individuals. Tools designed specifically for clinicians include mobile apps (e.g., tips for applying psychological first aid [PFA] in the field, recommending strategies for assessing and tracking victims' needs, and providing local referrals; *www.ptsd.va.gov/professional/materials/apps/pfa_mobile_app.asp*; *www.nctsn.org/resources/pfa-mobile*). The National Child Traumatic Stress Network offers free online PFA training for clinicians for continuing education credit (*www.nctsn.org/resources/psychological-first-aid-pfa-online*). The Department of Veterans Affairs also provides self-help apps for individuals who are managing PTSD symptoms or helping a family member with PTSD and provides brief mindfulness training (*www.ptsd.va.gov/appvid/index.asp*). The Substance Abuse and Mental Health Services Administration's Behavioral Health Disaster Response app provides resources to assist with pre-event preparation, on-the-ground assistance, and postevent resources, among other tools (*http://store.samhsa.gov/apps/disaster*).

The Role of Leadership

Leaders play a central role in mitigating traumatic event outcomes. They maintain the social cohesion of the community and foster resilience, while acknowledging and addressing the psychological and health risk consequences of disaster exposure.

Effective communication with the community is a critical leadership skill and serves as a behavioral health intervention. Communication marked by active listening, empathy, support, and a desire to help reduces fear and isolation that may emerge postdisaster. Understanding the community's needs and how to appropriately verbalize these needs, together with appreciating the importance of listening, strengthens the community and instills trust in leadership. Leaders are also in unique positions to provide public education related to traumatic stress and grief responses, emphasizing that individuals are expected to recover from event-related reactions, including distress, acute stress disorder, and PTSD. Acknowledging the need for care and support following disasters and addressing barriers to care are important ways in which leaders can help reduce stigma associated with psychiatric illness, encourage positive health-related behaviors, and promote recovery.

Another important leadership skill, "grief leadership," involves supporting a community through their loss, mourning, and recovery postdisaster (Ursano & Fullerton, 1990). A difficult but necessary responsibility of leaders is knowing when to shift from survivor rescue to body recovery and how to effectively communicate this transition to the community. Resources are specifically available to serve as guidelines and means of consultation for leaders. For example, the Center for the Study of Traumatic Stress developed a series of fact sheets tailored to issues important to leaders who are helping to support neighborhood and work communities following trauma exposure, including stress management, interaction with the media postdisaster, safety, recovery, and grief leadership (*www.cstsonline.org/fact-sheet-menu/leadership*).

Leaders must pay attention to their own distress responses and health risk behaviors following disasters. For example, reduced sleep, overdedication to work leading to exhaustion, and/or withdrawal from their leadership role can compromise efforts to manage distress and coping. In some cases, seeking support is necessary. Leaders who are able to acknowledge when they need help are better able to continue leading and caring for others and to serve as positive role models for community members. Mental health providers are also ideally positioned to attend to leaders' mental health and serve as trusted advisors for leaders, providing formal and informal consultation and encouraging them to engage in self-care.

Psychological First Aid

Psychological First Aid (PFA) is a framework for delivering interventions to promote recovery for individuals and communities immediately following disaster exposure. Reduced distress and improved well-being are associated with the five "essential elements," including (1) establishing a sense of safety, either through evacuation or identifying or developing a physically safe environment; (2) promoting social connectedness to family and other sources of social support; (3) maintaining community and individual self-efficacy through emergency response guidance and policies and self-care (e.g., through healthy nutrition, adequate sleep, rest, and exercise), respectively; (4) increasing calmness by using methods to reduce arousal symptoms (e.g., relaxation training); and (5) fostering optimism and hope in the context of ongoing disaster-related risks (Hobfoll et al., 2007). Various resources have been developed to expand education and utilization of the PFA framework following different types of disasters, including a protocol to support healthcare workers' well-being and sustainment during the COVID-19 pandemic (Sulaiman et al., 2020). Although PFA represents a robust evidence-informed intervention in the acute disaster aftermath, the limited number of controlled studies of PFA provide insufficient evidence to develop actual clinical practice guidelines.

While most disaster-exposed individuals do not develop psychiatric disorders, PFA addresses the distress that most people experience following disasters. PFA assesses immediate basic needs and provides early psychological support after a trauma. By providing access to essential resources, including water, food, shelter, health-related support, and sanitation, and promoting safety, PFA aids in decreasing disaster-related distress. PFA is typically conducted within public and mental health, medical, and emergency systems. Importantly, PFA is also conducted by laypersons who are not trained mental health professionals and can be administered in diverse settings made available to affected communities (e.g., shelters, schools, service centers, and workplaces). For

those who do not seek formal health care intervention, PFA can effectively manage postdisaster distress and functioning.

Here is a possible PFA case scenario: A Category 5 hurricane made landfall in a densely populated urban area. The city suffered extensive damage, with over 500 casualties reported so far. While a significant proportion of the city's inhabitants evacuated to shelters or other temporary residences, some individuals remained trapped in the area. Some were looking for family members, and those who evacuated sought information about when they could return home. Those who remained trapped awaited rescue and struggled through stifling heat without electricity, clean water, or medical assistance. Disaster workers, ranging from volunteers to military detachments, were being deployed to the area in support of the disaster response mission, and community leaders were trying to rally the city in the wake of the disaster.

Table 31.2 illustrates how disaster workers and community leaders can employ PFA principles to respond effectively to the needs of affected communities.

Collaborative Care Model Postdisaster

Early combined collaborative care interventions treat medical and mental health conditions following disasters. Efficacy trials indicate that early collaborative care interventions that address mental and physical health needs can be effectively administered in acute care settings following trauma (Petrie & Zatzick, 2010). This approach allows for coordinated treatment delivery from health care providers in trauma centers, including primary care providers, nurses, and mental health professionals, that address medical, pharmacological, alcohol and substance use/misuse, and psychotherapeutic needs, while preparing patients for transition from inpatient to outpatient services. Collaborative care interventions also include shared patient-provider treatment planning and follow-up care emphasizing continuity of care.

TABLE 31.2. PFA Interventions by Disaster Workers and Community Leaders

PFA principle	Disaster worker intervention	Community leader intervention
Safety	Ensure immediate physical safety by removing hazards whenever possible.	Broadcast accurate, clear, and timely messages about the current level of danger and ongoing disaster relief efforts.
Calming	Provide psychoeducation about common psychological responses to disasters and normalize short-term distress reactions.	Conduct "walking rounds" at evacuation centers to provide information and reassurance.
Efficacy	Help survivors identify adaptive responses and use them.	Distribute factsheets with anticipatory guidance for both survivors and disaster workers.
Connectedness	Facilitate survivors' communication with their loved ones and existing support networks.	Consult with other leaders to establish a unified community recovery plan.
Hope	Emphasize survivors' strengths and ability to recover from previous challenges.	Identify the community as resilient and promote a vision of recovery.

Psychological Debriefing

Psychological debriefing is one component of critical incident stress management, a framework for brief interventions following crisis events that employs psychoeducation and group interaction with the goal of reducing adverse outcomes. Debriefing involves individuals discussing their trauma experiences, with the goal of emotionally processing the event and normalizing responses. Debriefings are typically administered as a single session within one month of trauma exposure and conducted in a group setting composed of participants who have had limited or no interaction prior to the disaster. Although psychological debriefing was developed for use in numerous settings, empirical review of its efficacy indicated that it did not reduce psychological distress, depression, or anxiety, or prevent the onset of PTSD and may in some cases increase PTSD or depression risk (see Rose, Bisson, Churchill, & Wessely, 2002). Thus, psychological debriefings or single-session strategies are not recommended as treatments following traumatic events (American Psychiatric Association Workgroup on ASD and PTSD, 2004; Department of Veterans Affairs & Department of Defense, 2017). An extensive discussion of effective early intervention strategies can be found in Azad et al., Chapter 18, this volume.

CONCLUSION

Disasters impact large and diverse populations. Management of postdisaster distress, disorder, and health risk behaviors, as well as community disaster preparedness and response, are important for individual and community recovery. Leadership is critical, particularly knowledge of community resilience and vulnerability as well as cultural and contextual factors that impact how community members respond to the event. Effective interventions must be rapid, coordinated, and sustained. Coordinated response across medical, emergency, and public health optimizes mental health care for the disaster-affected population. All hazards planning addresses preparedness measures across the full range of threats for communities, including natural and human-generated events for all affected populations. Incorporating mental health into all aspects of health-related preparedness, response, and recovery planning ensures that interventions are comprehensive and that they adequately address critical psychological and behavioral responses at the individual and community levels.

DISCLAIMER

The views expressed are those of the authors and do not necessarily reflect the views of the Department of Defense, the Uniformed Services University, the Department of Health and Human Services, or the United States Public Health Service.

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CHAPTER 32

Dissemination and Implementation of Best Practices in Prevention and Treatment of PTSD

Shannon Wiltsey Stirman

As best practices in the prevention and treatment of posttraumatic stress disorder (PTSD) are identified (American Psychological Association, 2017; Department of Veterans Affairs & Department of Defense [VA/DoD], 2017; International Society for Traumatic Stress Studies [ISTSS], 2018), the field has increasingly recognized the importance of ensuring that these interventions are integrated into care and made accessible to individuals who need them. Significant efforts have been made to implement evidence-based interventions (EBIs) across mental health systems, including the VA (Karlin & Cross, 2014), the DoD (Borah et al., 2013; Finley et al., 2015; Wilk et al., 2013), and the Improving Access to Psychological Therapies program (IAPT; Clark, 2018) in the United Kingdom. Additionally, many organizations and local health care systems have begun to implement treatments for individuals with PTSD and trauma-related disorders (Bruns et al., 2015; Lang, Franks, Epstein, Stover, & Oliver, 2015). This chapter will review factors that are associated with implementation and identify promising and established strategies for implementing EBIs.

MULTILEVEL INFLUENCES ON IMPLEMENTATION

Understanding the context in which EBIs are provided is critical to increasing the likelihood of successful implementation. Over 60 different frameworks for implementation have been developed to identify implementation determinants, processes, or outcomes (Tabak, Khoong, Chambers, & Brownstein, 2012), and the frameworks and research that informed or was informed by these frameworks indicate that factors at multiple levels can influence implementation outcomes. Key outcomes that are assessed in implementation research include reach, effectiveness, implementation fidelity, adoption, and maintenance or sustainability, as well as factors such as feasibility and acceptability (Glasgow, Vogt, & Boles, 1999; Proctor et al., 2011).

Implementation frameworks reflect the reality that individuals who work with individuals who have or are at risk for PTSD provide interventions in contexts that are likely to influence their perceptions and experiences when delivering them, as well as their ability to deliver them effectively (Stirman, Gutner, Langdon, & Graham, 2016). Frameworks that are commonly used to guide assessment of the contextual factors and processes that can influence implementation outcomes in mental health settings include the Exploration, Planning, Implementation, and Sustainment framework (EPIS; Aarons, Hurlburt, & Horwitz, 2011) and the Consolidated Framework for Implementation Research (CFIR; Damschroder et al., 2009). These frameworks describe a variety of potential determinants of implementation in the outer and inner context (see Figure 32.1). Additionally, they include individual factors and characteristics of the innovation that may influence the fit and acceptability of the intervention within a specific setting.

The *outer context,* which comprises broad sociopolitical influences, includes policy, social norms, political considerations, and broad cultural influences on implementation. Social factors such as stigma associated with seeking mental health treatment can influence decisions to adopt EBIs. Conversely, consumer and policymaker advocacy for health equity and the availability of EBIs can influence mental health agencies, court

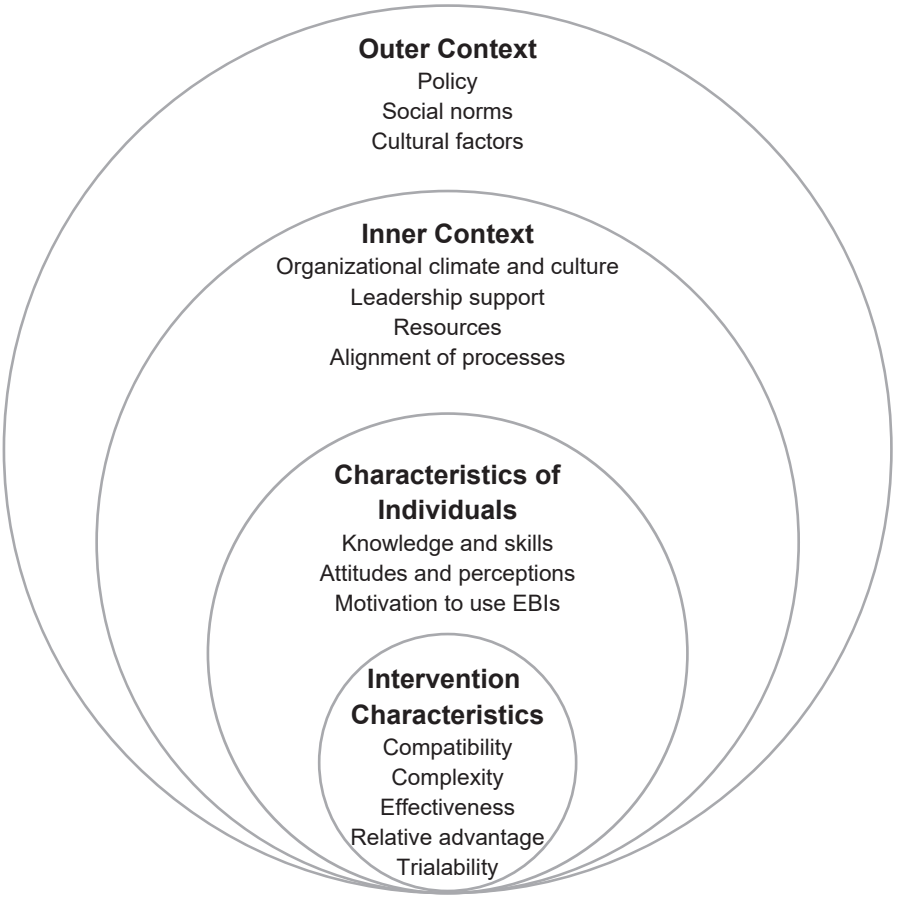

FIGURE 32.1. Multilevel implementation factors in implementation of EBIs for PTSD.

systems, legislatures, and politicians to issue policies or mandates to support implementation (Stirman et al., 2016). Examples related to PTSD treatment include mandates and policy regarding the availability of EBIs (Karlin & Cross, 2014) and publication of practice guidelines that recommend specific interventions for PTSD (American Psychological Association, 2017; VA/DoD, 2017; ISTSS, 2018).

The practice setting itself, or the *inner context,* comprises factors such as leadership support, availability of resources, organizational structure, climate, and culture. Both the organizational social context (culture and climate) and factors such as resource allocation and staffing have been associated with implementation success (Stirman et al., 2016). Organizational factors can have a substantial influence on implementation success (Aarons et al., 2011; Cook et al., 2015; Damschroder et al., 2009; Sayer et al., 2017). PTSD programs with higher EBI reach within the VA were characterized by a culture that values EBIs and aligned processes such as scheduling appointments, patient referral processes, workflow and staff time, and resource allocation to support EBI implementation (Cook et al., 2015; Sayer et al., 2017). Clinic leaders may create climates that are favorable to implementation by selectively hiring individuals who are open to or experienced in providing EBIs, allowing time for training, and offering rewards for EBI delivery (Aarons, Ehrhart, Farahnak, & Hurlburt, 2015).

Additionally, *characteristics of individuals* who provide and receive the intervention must be considered. Factors such as motivation, knowledge, skill, and beliefs and attitudes about the EBI can influence therapists' decisions to adopt EBIs and offer them to their clients. Research suggests that a potential reason for lower rates of use of trauma-focused treatments may be that some providers may believe that their clients will not be receptive to the protocol or that they might be unsuitable for the protocol due to low readiness for change, difficulty understanding concepts in the treatments, or possibility of symptom worsening (Cook, Dinnen, Simiola, Thompson, & Schnurr, 2014; Osei-Bosnu et al., 2016; Zubkoff, Carpenter-Song, Shiner, Ronconi, & Watts, 2016). Individual characteristics and attitudes have also been associated with treatment fidelity. In a study with therapists who had received training to provide cognitive processing therapy (CPT) in practice settings across Canada, therapists' educational degree type and willingness to adopt an EBI if required to do so by their organization were associated with early fidelity to CPT (Sijercic, Lane, Gutner, Monson, & Stirman, 2020).

Finally, *characteristics of the intervention* (Damschroder et al., 2009), such as its level of complexity, its compatibility with the setting and individuals who will participate in the intervention—whether it is noticeably effective or whether it can be tried and de-adopted—and its relative advantage over current practice can all influence implementation success. For example, Cook, Thompson, and Schnurr (2015) examined perceptions of two trauma-focused treatments and found that perceptions of compatibility with providers' prior practice, the EBI's observable impact, and perceptions of relative advantage were associated with self-reported use of these treatments.

Several studies have identified both organizational factors and individual perceptions of the interventions that can influence use of EBIs (Borah, Holder, & Chen, 2017; Patterson, Dulmus, & Maguin, 2013). For example, both individual and organization-level factors that influence training have been associated with training success and subsequent EBI delivery (Beidas et al., 2014; Garner, Hunter, Godley, & Godley, 2012; Henggeler et al., 2008). Leadership support and leader characteristics (such as transformational leadership) are associated with more positive attitudes toward EBIs (Aarons, 2006; Aarons et al., 2015; Aarons & Sommerfield, 2012), which can in turn influence whether and how providers deliver EBIs. In a quantitative examination of a framework

that included multilevel influences on implementation in 38 VA PTSD residential programs, Cook and colleagues (2015) found that for prolonged exposure (PE), a supportive organizational context (dedicated time and resources, and incentives and mandates) and overall positive perception of the PE were associated with implementation. For CPT, the supportive organizational context was significantly associated with implementation. In another study that identified both individual and organizational factors associated with the use of trauma-focused psychotherapies in outpatient treatment settings (Couineau & Forbes, 2011), lack of skills and confidence, along with therapist expectations about treatment outcomes, were identified as barriers to therapist adoption of trauma-focused interventions. Among therapists in outpatient PTSD clinical teams within the VA (Finley et al., 2015), perceived effectiveness of PE and CPT treatments were associated with self-reported use of EBIs and adherence. Additionally, the amount of supportive care (rather than EBIs) that these therapists provided was associated with perceptions that the clinic was understaffed. Self-reported adherence to PE was also associated with endorsement of emotional support from colleagues. Importantly, implementation theory and research indicate that variables across different levels can interact with one another to influence use of EBIs (Becker-Haimes, Williams, Okamura, & Beidas, 2019; Shelton, Cooper, & Stirman, 2018).

IMPLEMENTATION STRATEGIES

In light of the numerous factors that can interact and influence the success of efforts to implement EBIs, a variety of strategies have been developed to promote implementation. Currently, the field is working to develop effective approaches for selecting the most appropriate strategies to address the unique needs of the settings where implementation occurs (Lewis et al., 2018; Powell et al., 2017). A good understanding of the context can guide the identification of appropriate strategies to support implementation. Typically, this understanding is developed through a needs assessment that solicits multiple stakeholder perspectives and practice-level data. Once factors that may facilitate or complicate implementation are identified at the individual (provider, patient), organizational, system/outer context, and intervention levels (Figure 32.1), they can be mapped onto strategies that have been developed to address those particular issues (Lewis et al., 2018; Powell et al., 2017). A recent example of an exercise to identify appropriate implementation strategies is the application of an intervention mapping approach to address challenges to evidence-based psychotherapy (EBP) implementation and fidelity (Crowe, Collie, Johnson, & Stirman, 2020). Table 32.1 lists some strategies that have been used to support implementation of EBPs for PTSD. The effectiveness of some implementation strategies is still being investigated, but it is likely that multifaceted packages of implementation strategies are needed to implement EBIs in the complex systems where service delivery occurs.

System-Level Strategies

Some national systems have issued policies that mandate availability of treatments for PTSD. Some, like the United States Department of Veterans Affairs, require that all facilities make specific psychotherapies for PTSD available (Rosen et al., 2016). In the United Kingdom, the Improving Access to Psychological Therapies (IAPT) program includes recommendation of cognitive-behavioral therapy (CBT) in treatment

TABLE 32.1. Selected Strategies to Support Implementation of EBIs

Level	Strategy
System/outer context	Mandates Block grants to support EBP implementation
Organizational/inner context	Needs assessment/solicit stakeholder input Organizational change strategies Learning collaboratives Quality improvement Incentives Participatory system dynamics modeling
Low-resources settings/countries	Task shifting Cascade/train the trainer strategies
Individual provider	Training Consultation Fidelity support and feedback
Patient/consumer	Engagement strategies Education Co-creation
Intervention	Adaptation (tailoring, simplifying, adding components)

guidelines and a requirement for ongoing collection of evaluation data, which is summarized for the public (Clark, 2018). Other policy-level strategies can include block grants, preferential contracting, or insurance reimbursement for EBI use. However, while mandates and policies are often the impetus for implementation of EBIs within mental health systems (Bond, 2018), they are generally accompanied by other implementation strategies, such as investments in training and consultation, increases in staffing, or changes to organizational processes to facilitate implementation, audit and feedback, and incentives. For example, among the 25 or more states that have policies to promote the delivery of EBIs, many include resources to provide training in EBIs that target PTSD and other disorders (Bruns et al., 2015). Public awareness campaigns are another form of outer-context strategy that can educate consumers about treatment options and address stigma associated with treatment seeking.

Strategies That Target Organizational Barriers

Addressing Organizational Context

In the past two decades, interventions have been developed to improve the organizational context to facilitate EBI delivery. Interventions such as the Availability, Responsiveness, and Continuity organizational strategy have been shown to change organizational culture and improve EBI outcomes (Glisson et al., 2010; Williams, Glisson, Hemmelgarn, & Green, 2017). A multifaceted intervention to develop a supportive implementation climate and to prepare clinic leaders to support and promote EBIs (Aarons et al., 2015) has also shown promise in increasing the use of EBIs for some mental health disorders. While these strategies have not yet been tested with EBIs for PTSD, they represent a promising direction for efforts to implement interventions in complex organizations and systems.

Learning Collaboratives

Tailoring training and implementation processes to address organizational and individual barriers and drawing from theories of behavior change have been associated with a significant increase in the use of imaginal exposure in the treatment plans of individuals diagnosed with PTSD (Couineau & Forbes, 2011). Due to the need to address the need for both individual training and support to address organizational barriers, some researchers have begun to evaluate the use of learning collaboratives, which provide opportunities for both consultation and technical support in addressing organizational barriers to implementation. The National Child Traumatic Stress Network has used learning collaboratives for many years to expand the availability of trauma-focused CBT (Ebert, Amaya-Jackson, Markiewicz, & Fairbank, 2012; Ebert, Amaya-Jackson, Markiewicz, Kisiel, & Fairbank, 2012; Stirman et al., 2017). Program evaluation data suggests that they may be effective in promoting implementation of trauma-focused treatments for children and adults, (Lang et al., 2015; LoSavio et al., 2019) and in expanding professional networks to support implementation (Bunger et al., 2016).

Other Promising Approaches

Quality Improvement and pay-for-performance approaches have been the subject of recent investigations, with preliminary results suggesting improved patient-level outcomes and delivery of collaborative care models (Unützer et al., 2012). Recent research suggests that participatory system dynamics, a process by which teams identify and simulate potential solutions to barriers to EBI delivery before identifying a solution, has the potential to increase EBI reach and may confer advantages over traditional quality improvement in light of the ability to simulate the impact of improvement plans before implementing them (Zimmerman et al., 2016). Efforts are underway to test these strategies with EBIs for PTSD and other diagnoses that are common among trauma-exposed individuals.

Strategies for Low-Resource Settings

Implementation in low- and middle-income countries requires adaptation of treatments to fit with local culture and address lower levels of literacy. In settings where there are few trained mental health professionals, lay health workers or paraprofessionals have been trained to provide EBIs and have become important partners in tailoring interventions for local contexts. Studies on task shifting have indicated that it is possible for lay health workers to effectively implement interventions such as narrative exposure therapy (NET; Neuner et al., 2008), CPT (Bass et al., 2013; Bolton et al., 2014), and trauma-focused CBT (Murray et al., 2015) with training and support. Fortunately, studies have indicated that the use of a cascade, or train-the-trainer model, can be an effective strategy for training local providers to deliver treatments for PTSD such as NET (Jacob, Neuner, Maedl, Schaal, & Elbert, 2014). Due to additional constraints in funding, lack of infrastructure, and sociopolitical instability (Chen, Olin, Stirman, & Kaysen, 2017), more flexible, or less intensive, public health approaches may also be considered as a strategy to reach more individuals, albeit with a lower impact on outcomes (Martin, Murray, Darnell, & Dorsey, 2018; Zatzick, Koepsell, & Rivara, 2009).

Strategies That Address Individual Determinants of Implementation

Training

As EBIs are identified, it is critical that the mental health workforce receive training and support in providing the interventions. Substantial research has determined that traditional strategies for training, such as review of a manual, web-based training, or attendance at a workshop increase knowledge about the intervention but do not result in the ability to deliver the intervention at the level of skill with which it was delivered in the initial studies (Herschell, Kolko, Baumann, & Davis, 2010). In a review of training strategies, Hepner, Holliday, Sousa, and Tanielian (2018) determined that effective training typically includes didactic elements such as workshops or web-based training. However, to improve EBI fidelity (adherence to the manual and skill of delivery), multiday workshops, with integrated written materials (e.g., training manuals, handouts), are typically necessary (Hepner et al., 2018). Interactive elements, including skill demonstrations, feedback, and role plays, have been associated with greater adherence and competence to the EBI, although typically, after a workshop, skill levels do not reach benchmarks for competence that are required for clinical trials (Herschell et al., 2010).

To reduce financial and practical burdens associated with in-person training, web-based trainings have been developed. Asynchronous online training has the advantage of being convenient and self-paced, and can produce gains in knowledge (Beidas, Edmunds, Marcus, & Kendall, 2012; Dimeff et al., 2015; Ruzek et al., 2014), although there is some evidence that workshops may lead to greater self-efficacy (Dimeff et al., 2015). Other studies have examined live, web-based trainings over video conferencing or on avatar-based e-learning platforms (Mallonee, Phillips, Holloway, & Riggs, 2018; Paxton et al., 2018). While these platforms resulted in similar increases in knowledge, satisfaction with in-person workshops appears to be greater (Mallonee et al., 2018).

Consultation

There is considerable evidence that initial didactics are not sufficient to develop levels of skill that are seen in clinical trials and that some form of follow-up support and consultation is necessary (Hepner et al., 2018; Herschell et al., 2010; Nadeem, Gleacher, & Beidas, 2013). Consultation provided following initial workshop training increases the skill or competence with which EBIs are delivered (Herschell et al., 2010) and also improves provider attitudes toward EBIs (Barnett et al., 2017; Ruzek et al., 2016). Consultation typically involves discussion of individual cases and may also include active learning strategies and feedback on work samples (Monson et al., 2018; Nadeem, Gleacher, & Beidas, 2013). However, there is some evidence that neither role play nor review of work samples is necessary to produce good outcomes (Edmunds, Beidas, & Kendall, 2013; Monson et al., 2018), although there is some evidence that role plays may be more beneficial for clinicians who are more highly engaged in the consultation process (Edmunds, Kendall, et al., 2013). Furthermore, consultation has been shown to lead to better patient outcomes (Monson et al., 2018), and greater use of the EBI in practice (Charney et al., 2019).

In combination, training and consultation can improve therapist skill, regardless of their theoretical orientation, baseline level of skill, or organizational context in which they practice (Creed et al., 2016; Kolko, Iselin, & Gully, 2011). Clinicians who participated in the VA's training programs for PE and CPT developed more positive

views of these treatments after they completed their first supervised training cases (Chard, Ricksecker, Healy, Karlin, & Resick, 2012; Ruzek et al., 2016). Furthermore, training and consultation can lead to clinical improvements that are similar in magnitude to those found in clinical trials (Eftekhari et al., 2015; Monson et al., 2018). However, despite these benefits, programs that focus largely on training and consultation may not lead to levels of EBI reach that are as high as desired (Maguen et al., 2018). Some research has indicated that programs with higher EBI reach have organization-level conditions and missions that are more favorable to EBI use (Sayer et al., 2017). Thus, there is increasing recognition that implementation efforts must address organizational barriers in addition to providing training and support.

Fidelity Support

Fidelity comprises adherence to the EBI protocol and skill or competence of delivery**.** Some studies have indicated a link between treatment fidelity to CPT and symptom improvement (Farmer, Mitchell, Parker-Guilbert, & Galovski, 2017; Holder, Holliday, Williams, Mullen, & Surís, 2017; Marques et al., 2019). Despite this emerging evidence, providers do not always provide all elements of the treatments of the training (e.g., Thompson, Simiola, Schnurr, Stirman, & Cook, 2018; Wilk et al., 2013). Thus, some form of fidelity support may be instrumental in maintaining adequate levels of fidelity. Research suggests that integrating feedback on fidelity into training or ongoing consultation is associated with therapists' achievement of certification in an EBI (Lu et al., 2012). Furthermore, when fidelity is monitored through supportive consultation, reduced turnover of trained providers has been observed (Aarons, Sommerfeld, Hecht, Silovsky, & Chaffin, 2009). Particularly if more scalable strategies for assessing fidelity are identified (Stirman et al., 2018), ongoing fidelity support may be an important way to support clinicians and maintain competence over time (Stirman et al., 2017).

Strategies to Address Patient-Level Barriers

Much of the research on strategies to address patient-level barriers to implementation of treatments for PTSD have focused on treatment engagement and selection. For example, shared decision making using tools that outline options for evidence-based PTSD treatment can improve patient engagement and retention in evidence-based treatments (EBTs; Mott, Stanley, Street, Grady, & Teng, 2014; Watts et al., 2015). Psychoeducational orientations that briefly outline evidence-based treatment options have been associated with selection of EBIs over other treatment options in VA PTSD clinics (Lamp, Maieritch, Winer, Hessinger, & Klenk, 2014; Schumm, Walter, Bartone, & Chard, 2015). Some evidence suggests that individuals who select EBIs after attending brief orientation groups are more likely to complete treatment than those who engage in treatment as usual (DeViva, Bassett, Santoro, & Fenton, 2017).

Addressing Intervention Characteristics through Adaptation

EBIs are often adapted to accommodate setting constraints, reimbursement policies, patient needs, or therapeutic style (Aarons, Miller, Green, Perrott, & Bradway, 2012), and planned adaptation is recognized as an important strategy to promote sustained implementation (Shelton et al., 2018; Stirman, Baumann, & Miller, 2019). In some settings, EBIs have been integrated into intensive treatment programs with massed

delivery in order to meet patient needs to complete treatment in shorter periods of time (Held et al., 2019). Studies have also shown that adapting treatment or session length (Nacasch et al., 2015) or including sessions to address emergent life events can result in significant symptom change despite differences from the original protocol (Galovski, Blain, Mott, Elwood, & Houle, 2012).

Other forms of adaptation target the content of the intervention to improve fit with client needs or the practice setting. Because some forms of adaptations, particularly those made in a more improvised manner in routine practice, may not preserve key aspects of the EBIs themselves (Stirman et al., 2015), researchers have begun to develop and investigate processes and strategies to adapt EBIs to meet local needs and to promote health equity while preserving fidelity. For example, Valentine and colleagues used a multiphase process to pilot CPT in a community setting with Spanish-speaking clients and to make adaptations based on stakeholder feedback (Valentine et al., 2017). To improve the fit with the individual served by the clinic, some of the CPT terminology was changed, worksheets were simplified, and case examples reflected the types of trauma and concerns that were commonly faced within the community. Most recently, in the final phase of the program described by Valentine and colleagues (2017), an evaluation determined that when delivering a protocol that had been tailored to the population in a manner that preserved core CPT components, both the level of fidelity and the amount of fidelity-consistent adaptations made to the protocol were associated with subsequent improvements in PTSD and depression (Marques et al., 2019).

Until more is known about which forms of adaptation yield good outcomes, it is important that adaptation is accompanied by careful documentation of any changes that are made and by collection of data to ensure that they are having the desired effect (Stirman et al., 2019). Such efforts can inform the field about how best to flex EBIs without reducing their effectiveness and may result in adaptations that improve engagement, access, or outcomes.

CONCLUSION

Interventions to prevent and treat PTSD are complex, and implementation into complex systems requires a multifaceted approach that leverages the strengths of the organization and individuals, and that also addresses the barriers that are identified (Stirman et al., 2016). When possible, evaluation of focused, well-documented efforts should be employed to determine that implementation efforts are feasible and effective before a broader rollout. Iterative approaches that use practice-level data can be instrumental in ensuring that all barriers are identified and successfully targeted. Practice-based research and amplification of successes can further inform the field about successful approaches to implementing EBIs for PTSD.

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CHAPTER 33

Key Questions and an Agenda for Future Research

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Remarkable progress has been made in advancing our conceptual and clinical understanding of posttraumatic stress disorder (PTSD) since the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III) was published (American Psychiatric Association [APA], 1980). This volume attests to the depth and breadth of scientific research on psychological and psychobiological mechanisms that mediate or moderate the processing of trauma-related stimuli. It also documents the many significant advances in the development and testing of evidence-based psychosocial and pharmacological treatments for PTSD that are now available to clinicians. In this chapter, we review 19 key crosscutting questions with important implications for science and practice.

QUESTION 1. *Looking beyond DSM-5, what can we expect regarding the PTSD diagnosis in the future, and how will this affect science and practice?*

DSM-5 (APA, 2013) has been criticized because with 20 symptoms it is one of the most complicated DSM-5 diagnoses. It also has one of the highest levels of potential diagnostic combinations, permitting an extraordinarily high number of potential ways to meet diagnostic criteria. As a result, the criticism continues. DSM-5 creates the potential for extremely high levels of heterogeneity in PTSD samples, which in turn could thwart efforts to identify biological markers and other risk factors, causal mechanisms, and effective treatments (Galatzer-Levy & Bryant, 2013; Young, Lareau, & Pierre, 2014; see Friedman et al., Chapter 2, this volume).

These short-sighted critics fail to realize that posttraumatic psychopathology is complex and that there are probably a number of distinct biological endophenotypes, each preferentially associated with a smaller number and different pattern of clinical symptoms, that may result from exposure to a criterion A event. DSM-5 moved PTSD

out of the Anxiety Disorders category and into a category of its own because it was recognized that, based on phenomenology alone, there were different clinical presentations than the fear-based anxiety disorder of DSM-III (e.g., adrenergic/hyperaroused, dysphoric/anhedonic, dissociative, and externalizing; Friedman, 2016; Friedman et al., 2011b). The emerging evidence that a number of different psychobiological abnormalities may underlie DSM-5 PTSD (see Question 10) raises the possibility that several different PTSD clinical phenotypes and biological endophenotypes will be identified in the future. This suggests that DSM-6 (or DSM-7, etc.) may no longer have a single overarching PTSD diagnosis, but rather a family of posttraumatic syndromes, each characterized by a different pattern of symptom expression and/or a different underlying pathophysiology. In other words, the heterogeneity and large number of symptoms in DSM-5 may be a necessary prelude to the identification of specific phenotypes that, with the help of biomarkers, will make it much easier to diagnose, distinguish, and treat posttraumatic psychopathology in the future (see Questions 10 and 16).

QUESTION 2. *What is a traumatic event?*

The most impactful life-changing events are not always traumatic, as defined by criterion A. One of us recalls asking a three-tour Vietnam veteran, "What was the worst thing that ever happened to you?" Instead of describing the battle of Hamburger Hill or some other horrific war-zone encounter, he replied, "When my wife left me." Indeed, events such as rejections in love, public humiliations, financial setbacks, and academic failures can be the worst events in a person's life. And following such experiences, it is not uncommon to experience distressing memories, avoidance of reminders of the event, negative thoughts and feelings, and arousal symptoms (especially insomnia). Some studies have shown that individuals who do not meet criterion A may otherwise meet all other PTSD diagnostic criteria (Boals & Schuettler, 2009; Mol et al., 2005). So, this raises the question of whether the person actually has PTSD and the related question of whether the DSM definition needs to be broadened. What follows is mostly speculative at this point, but it does suggest a potentially productive area for future research.

To address this question, it is useful to begin with Horowitz since the DSM PTSD construct is based on his original conceptualization of how people process adverse experiences. According to Horowitz (1986, p. 241), "The signs and symptoms of response to a stressful life event are expressed in two predominant phases: the intrusive state, characterized by unbidden ideas and feelings and even compulsive actions, and the denial state, characterized by emotional numbing and constriction of ideation." Given that DSM originally embraced (and continues to retain the essence of) this model when it created the diagnostic criteria for PTSD, and given that Horowitz includes both criterion A-type events and other significant stressful events in this conceptualization, it should come as no surprise that many people who are trying to cope with major (non-criterion A) life setbacks could endorse criteria B–E symptoms.

There are two ways of looking at this issue: from the perspective of the event itself and from the perspective of the response to the event. An event can be defined as "traumatic" based on its inherent properties, as in DSM-5's criterion A: "actual or threatened death, serious injury or sexual violation." An event also can be defined as traumatic *to an individual*, based on the individual's appraisal of and reaction to the event. It has always been difficult to know where to draw the line between traumatic events that meet criterion A and significant adverse events that do not. This is because

of individual differences in resilience versus vulnerability, past experiences, preparation, training, and other factors.

PTSD has been criticized since DSM-III because the traumatic–nontraumatic dichotomy has seemed arbitrary to some (e.g., Brewin, Lanius, Novac, Schnyder & Galea, 2009). The DSM-IV (APA, 1994) work group recognized this problem and tried to address it by adding criterion A2, a subjective component to the criterion, so that an individual did not meet criterion A unless the individual experienced "fear, helplessness, or horror" (DSM-IV; APA, 1994, p. 428) during exposure to a criterion A1 event. Unfortunately, the particular responses stipulated in criterion A2 were not sensitive or specific enough to provide a reliable subjective indicator that the individual had been unable to cope with the overwhelming stress of a criterion A1 event. There was also clear evidence showing that A2 failed to improve our ability to diagnose PTSD and that it was superfluous since people rarely met the symptom criteria without meeting A2 (Friedman, Resick, Bryant & Brewin, 2011a). That is why A2 was eliminated in the DSM-5. Lacking reliable indicators of posttraumatic subjective distress, the line DSM-5 has drawn between traumatic and nontraumatic events is probably the best we can do at this time, but it is a temporary solution that is clearly not the best way to address this question.

We believe that DSM-IV had the right idea but lacked the necessary data to know how subjective responses should be characterized and considered in the diagnostic criteria. Given what we are learning about altered neurocircuitry, neurobiology, and gene expression associated with PTSD (see Averill et al., Chapter 9; Rasmusson et al., Chapter 10; and Bustamante et al., Chapter 11, this volume), we can now measure a variety of acute psychobiological as well as psychological responses to traumatic events (see Averill et al., Chapter 9, this volume). Integrating this with Horowitz's (1986) initial formulation, it is clear that the human response to stressful situations is a multilayered process consisting of cognitive, emotional, and biological components. It remains necessary to identify which of those components are psychological or psychobiological indicators of a failure to cope with traumatic stress.

It is tautological to state that an event is traumatic if it causes PTSD. But it is reasonable to define a traumatic event as one that overwhelms the normal robust mechanisms for coping and adaptation. And, as we know, individuals will differ greatly in how they experience stressful events. The challenge for diagnosis is to find a way to preserve the integrity of what the PSTD diagnosis is intended to capture while systematically incorporating critical personal reactions into the diagnostic process. A potential strategy would be to use psychological and/or biological markers indicative of a significant stress reaction, in the spirit of, but better than, A.2's "fear, helplessness, or horror" distinction. There are many precedents for this in medicine; for example, although one may experience a variety of intense and debilitating cardiovascular symptoms (e.g., chest pain and shortness of breath), one has not had a heart attack unless, immediately afterward, there is an abnormal rise in the level of troponin (a cardiac protein).

Let us be clear: We are not there yet. An expanded definition of critical posttraumatic reactions would need to be developed, and we currently have no PTSD analogues of troponin. But once we have identified reliable and valid markers of subjective response, we can finish the job started by DSM-IV. This approach would give us a consistent conceptual way to identify when a person has experienced an event as traumatic, since one person's traumatic event may be another person's stressful challenge. Whereas everyone will likely perceive rape, torture, combat, and the like as traumatic, other events may or may not elicit such uniform responses, at least for some individuals.

Furthermore, for some individuals, certain events currently classified as nontraumatic may be reclassified as traumatic based on that person's specific response to that event at that specific time.

QUESTION 3. *How can we understand the great differences between DSM-5 and ICD-11?*

The *International Classification of Diseases* (ICD)-11 sought to develop a set of PTSD criteria that were much less complicated and much easier to utilize, especially in resource-poor nations where most mental health services are delivered by paraprofessionals (Maerker et al., 2013). While we sympathize with this pragmatic objective, we have three strong criticisms of the ICD-11 process and results. First, decisions were made by consensus compared with DSM-5, which was based on a careful review of published peer-reviewed scientific results. Second, ICD-11 eliminated DSM-5's B4 and B5 criteria (that exposure to traumatic reminders increases psychological distress and physiological activation, respectively), thereby removing the link between classic psychological learning and cognitive theory and PTSD (see Bryant, Chapter 6, this volume). Traumatic stimulus-driven emotions and cognitions are crucial for understanding not only the underlying psychological abnormalities in PTSD but also the rationale for designing our most effective treatments such as prolonged exposure (PE) and cognitive processing therapy (CPT). Third, ICD-11 eliminated DSM-5's criterion D symptoms (negative cognitions and mood) and relegated them to a lower-tier "associated symptoms" category that has no relevance for making ICD-11's PTSD diagnosis per se. In this regard, findings from the World Mental Health Survey have shown that, in some respects, criterion D symptoms perform better as predictors of PTSD severity, trajectory, functional burden, and suicidality than core ICD-11 symptoms (Koenen, Stein, & Karam, 2018).

Several studies have shown that the majority of individuals with PTSD were identified by one but not the other system: Only 33% met the criteria of both systems in the World Mental Health Survey (Koenen at al., 2018) and only 42% in an Australian cohort (O'Donnell, 2014. Thus, ICD-11 may be detecting posttraumatic psychopathology among a significant group of patients who do not meet DSM-5 diagnostic thresholds and vice versa. Although it is possible that ICD-11 is more sensitive to a specific posttraumatic phenotype than DSM-5, it is clearly another indication that we should no longer try to fit all posttraumatic psychopathology under a single tent, labeled PTSD. This is an important challenge for future research.

QUESTION 4. *Is there a complex PTSD diagnosis, or isn't there?*

ICD-11 has included complex PTSD, whereas DSM-5 has concluded that there is not sufficient scientific evidence for the validity of this diagnosis. Instead, DSM-5 has added a dissociative subtype of PTSD to the diagnostic menu, based on many sources of evidence (e.g., predictive validators, brain imaging, confirmatory factor analysis, and treatment research; see Friedman et al., Chapter 2, and DePrince et al., Chapter 8, this volume). Future research needs to clarify how much these two diagnoses do or do not overlap. Specifically, it is unknown whether people with DSM-5's dissociative subtype also exhibit the disturbances in self-regulation (i.e., impaired affect regulation, integrity of the self, and interpersonal relationships) that characterize ICD-11's complex PTSD. As Friedman has argued (2013), if future research finds a strong association

between DSM-5's dissociative subtype and ICD-11's disturbances in self-regulation, it would strongly suggest that the dissociative subtype is, in fact, complex PTSD.

QUESTION 5. *What is the evidence for subsyndromal PTSD as a distinct diagnostic entity? Should PTSD be considered a dimensional rather than a categorical disorder?*

When the findings from the National Vietnam Veterans Readjustment Study (NVVRS; Kulka et al., 1990) were first published, results were reported with respect to both full and "partial" PTSD. The rationale for this procedure was that veterans with partial PTSD exhibited significant posttraumatic distress that often required clinical attention. Since that time, other investigators have also identified partial/subsyndromal cohorts and have often found that individuals with partial/subsyndromal PTSD are significantly more impaired than healthy comparison individuals and significantly less impaired than subjects with full PTSD (Breslau, Lucia, & Davis, 2004; Friedman et al., 2011a; Pietrzak, Goldstein, Southwick & Grant, 2012; Schnurr et al., 2000). Unfortunately, because different partial/subsyndromal definitions were used in these studies, it is not possible either to aggregate or to interpret these data. What all of this suggests is that PTSD is a spectrum disorder in which posttraumatic stress symptoms are distributed along a mild-to-severe continuum. According to this argument, people who meet PTSD diagnostic criteria generally represent those affected most severely, but the line separating full and partial/subsyndromal PTSD is arbitrary at best.

There is a precedent in DSM-5 for the addition of a subsyndromal entity as a recognized diagnosis in its own right. For example, cyclothymic and persistent depressive disorders are subsyndromal bipolar and major depressive disorder, respectively. Therefore, the argument goes, addition of partial/subsyndromal PTSD to DSM-5 would acknowledge the dimensional nature of posttraumatic distress and provide a diagnostic niche for people requiring clinical attention who do not meet full PTSD diagnostic criteria.

Clearly, much more research is needed to address this issue. To begin with, we should attempt to validate differing definitions of partial/subsyndromal PTSD to determine what criteria optimize clinical significance. Once identified, the best case definition for partial/subsyndromal PTSD should be adopted, so that all research on this putative disorder is conducted on people who meet the same diagnostic criteria. Next, research is needed to demonstrate that partial/subsyndromal PTSD is clinically significant in terms of symptom severity and functional impairment. Furthermore, it would be important to know whether partial/subsyndromal PTSD is associated with the same psychobiological abnormalities as full PTSD. Finally, it would be important to determine whether partial/subsyndromal PTSD responds to treatments shown to be effective for full PTSD or whether better results might be achieved from different therapeutic approaches.

QUESTION 6. *What are the major challenges in research on memory and dissociation, and how might such findings influence both clinical and forensic practice?*

Among other things, PTSD is a disorder of memory. On the one hand, some people with PTSD cannot escape intolerable, intrusive recollections of their traumatic experiences. On the other hand, some survivors of such experiences cannot retrieve memories

of part, or all, of such events. These clinical observations have spawned a great deal of research on fundamental mechanisms of cognition and memory and on how such mechanisms may be altered among individuals exposed to traumatic events who have developed PTSD (see Brewin & Vasterling, Chapter 7, this volume).

It is generally accepted that different cognitive and neurobiological mechanisms underlie the acquisition, encoding, and retrieval of emotionally charged information compared to more neutral input. It also appears that such cognitive processing is altered among people with PTSD. Such abnormalities in cognition and memory appear to be implicated in expression of clinical symptoms such as reexperiencing, fragmented thoughts, amnesia, and dissociation (see Brewin & Vasterling, Chapter 7, this volume). Furthermore, trauma-related dissociation and dissociative amnesia have become topics of renewed interest because of their prominence in PTSD and other trauma-related disorders (see DePrince et al., Chapter 8, this volume). Indeed, advances in this area of research have led to adoption of the new dissociative subtype of PTSD in DSM-5 (see Friedman et al., 2011a, and Chapter 2, this volume, and DePrince et al., Chapter 8, this volume).

Questions about PTSD-induced memory alterations and dissociation have prompted innovative basic and clinical research. Investigators utilizing sophisticated cognitive psychology paradigms and/or functional brain-imaging protocols designed with these questions in mind have begun to enlarge our understanding of fundamental mechanisms that mediate and moderate information processing, encoding, and memory retrieval. Much more research is needed to help us understand how such mechanisms are altered in PTSD and explicate the psychopathology and pathophysiology of this disorder.

A proposed manipulation of the memory process for therapeutic purposes is to activate traumatic memories and then block their reconsolidation with propranolol. Proponents of this approach have published preliminary data suggesting that eliminating traumatic memories in this way can significantly reduce the severity of PTSD symptoms (Brunet et al., 2018).

QUESTION 7. *What new directions in developmental issues should be considered with respect to children, adolescents, and older adults?*

In recent years, there has been increased attention to the impact of traumatic exposure on younger and older individuals. We have learned not to generalize from findings with 30-year-old adults to children, adolescents, or older adults. Each age group appears to respond differently to exposure to traumatic events. Thus, a developmental perspective is needed to inform theory and practice across the lifespan.

Many of the cognitive, emotional, and behavioral challenges associated with normal development mediate or moderate the impact of trauma exposure in the young (see Brown et al., Chapter 14, this volume). Key trajectories influencing this process include neurobiological maturation, affect regulation, cognitive-emotional development, coping capacity, beliefs about oneself and the environment, social embeddedness, safety and security at home, and prior and ongoing exposure to severe or traumatic stress. Such developmental differences may not only influence the appraisal, cognitive processing, encoding, and retrieval of traumatic material but also affect the posttraumatic psychological, emotional, and behavioral expression of such experiences. Thus, treatments must be developmentally sensitive and appropriate since effective interventions for preschoolers may be very different for school-age children, adolescents, or adults

In addition, as noted by Brown and colleagues (Chapter 14, this volume), we should reach the point where all child-serving systems, including medical, mental health, child welfare, juvenile justice, and educational systems, become aware of and sensitive to the needs of traumatized youth and families, and are able to meet those needs both consistently and effectively.

The good news is that an emerging body of clinical research shows that there are effective, evidence-based treatments for children and adolescents from among psychodynamic/attachment, child and parent cognitive-behavioral, and group school-based treatments. The best treatments include, respectively, child–parent psychotherapy, trauma-focused cognitive-behavioral therapy (TF-CBT), and cognitive-behavioral interventions for trauma in schools (CBITS). Research on pharmacotherapy for children, however, remains at an early stage, with few published randomized controlled trials (RCTs; Cohen & Mannarino, Chapter 20, this volume). More research is critical to improve treatment for children who have PTSD with comorbid psychiatric conditions, to clarify the place of psychotropic medications in the treatment of traumatized children, and to improve implementation of evidence-based treatments though dissemination initiatives.

At the other end of the age continuum are the young-old, middle-old, and old-old adults, all of whom receive much less attention either conceptually or with respect to basic or clinical research. Indeed, medication trials generally exclude older adults as participants, and what we know about the treatment of PTSD in older adults is affected by this limitation. Studies that possess a sufficient sample of older adults might analyze treatment findings as a function of age to systematically address this important void in the literature. Some of the unique challenges regarding older adults with PTSD concern the impact of retirement, reduced physical capacity, concurrent physical illnesses, impaired cognition and memory caused either by normal aging or neurodegenerative processes, loss of social support through death and illness, and metabolic changes affecting pharmacotherapy. Furthermore, different stages in the later-life aging process itself are often ignored because 65- and 85-year-olds are frequently thrown into the same "older adult" category (Cook & Simiola, Chapter 15, this volume). Finally, because the processing of traumatic material is often carried out within the context of life review, therapy with older adults presents exciting challenges and opportunities for the development of age-specific components in psychological treatments.

QUESTION 8. *What are the major questions about gender differences with respect to posttraumatic reactions, and how should they be addressed in research and practice?*

Recognizing that *gender* refers to the social context and psychological experience of a male or female individual in a given society and culture, gender issues (compared to biological sex differences) are best conceptualized as an interaction between sex-based biology and the individual's social context (Kimerling et al., Chapter 13, this volume). We agree that such a "gender-interactional" model is needed in PTSD research to identify social contextual factors that may moderate the extent to which sex differences are observed in PTSD. Social contexts and social roles, such as those defined within a given culture (e.g., traditional vs. nontraditional gender roles), family structure, or military service, are also important potential moderator variables. We also agree with Kimerling and colleagues (Chapter 13, this volume) that application of a gender-interactional model to PTSD research requires examination of the extent to which relationships

among trauma variables differ as a function of gender. Because these designs conceptualize gender as an elemental basis for difference, they have the greatest power to organize data on gender into gender-informed models of traumatic stress. Such an approach is needed to understand how traumatic experiences may differ for men and women, and whether such differences might inform different gender-based approaches to treatment.

QUESTION 9. *What new directions in research and practice will advance our understanding of PTSD within a cross-cultural context?*

PTSD has been identified in traumatized individuals around the world, despite ethnic, cultural, and other differences across countries and cultures. The World Mental Health Survey has shown that PTSD occurs in low- as well as high-income countries and that, although prevalence may differ, the symptom characteristics, risk factors, clinical course, associated features, and burden of PTSD appear to be consistent from one country to the next (Koenen et al., 2018; Silove & Klein, Chapter 26, this volume). For example, in an early study, North and colleagues (2005) compared Africans and European Americans exposed to the embassy bombing in Nairobi and the Murrah Federal Building bombing in Oklahoma City, respectively. They found remarkably similar outcomes for the individuals exposed to these events with regard to morbidity, PTSD symptoms, and functional impairment. Therefore, the question is no longer whether PTSD is solely a European American, culture-bound syndrome with no relevance for other people, but whether PTSD is the best posttraumatic idiom of distress for individuals from traditional cultures.

It is at present an unanswerable question given that few investigators have addressed this issue systematically. Mexican men and women exposed to a variety of traumatic events reported both PTSD and culture-specific idioms of distress (e.g., *ataques de nervios*; Norris, Murphy, Baker, & Perilla, 2003). Among Puerto Rican survivors of the 1985 floods and mudslides, 17% of those reporting *ataques de nervios* also met the criteria for PTSD (Guarnaccia, Canino, Rubio-Stipec, & Bravo, 1993). Much more research is needed to investigate the degree of overlap between PTSD and a variety of culture-specific posttraumatic idioms of distress.

Such speculations lead inevitably to questions about ethnocultural differences in psychobiological reactivity associated with either PTSD or culture-specific idioms of posttraumatic distress. Two questions merit attention in this regard. First, do people diagnosed with PTSD from industrialized and traditional cultures exhibit the same pattern of biological alterations? Second, do Mexicans, for example, exposed to the same traumatic event, diagnosed either with PTSD or *ataques de nervios*, exhibit similar or different patterns of biological alterations? Designing experiments to address such questions is straightforward. The challenge is to implement such designs in settings that deepen our understanding of posttraumatic reactions in different ethnocultural settings.

From a clinical perspective, a more important question is whether individuals with PTSD from traditional cultures will respond to treatments shown to be effective in industrialized settings. Few clinical trials have addressed this question, although Hinton and colleagues have reported impressive success with culturally adapted CBT protocols for Cambodian refugees and Latinas (Hinton et al., 2005). Bass and colleagues (2013) had positive results with a culturally adapted form of CPT without exposure in a group format, with individual support for Congolese survivors of sexual violence. We look forward to continued developments in this area.

QUESTION 10. *What are the major questions regarding the identification of biomarkers for PTSD?*

As noted by Rasmusson and colleagues (Chapter 10, this volume), there has been an enormous accumulation of information about the many neurobiological abnormalities associated with PTSD. We have moved well beyond research focusing on monoaminergic, synaptic, and neuroendocrine alterations to consideration of abnormalities in other systems. Most notably, recent research on the amino acid pathway has focused attention on glutamatergic and gamma-aminobutyric acid (GABA)-ergic mechanisms (see Averill et al., Chapter 9, this volume). In addition, we have expanded our focus to include corticotropin-releasing factor (CRF), neuropeptide Y (NPY), cannabinoids, allopregnenalone/pregnenalone (Allo), and immunological mechanisms. Despite these impressive advances, we agree with Rasmusson and colleagues (Chapter 10, this volume) that we still lack a comprehensive model that identifies key components underlying the complex, maladaptive biopsychosocial responses that lead to PTSD in order to develop effective preventive or therapeutic interventions for the disorder.

Our technological capacity to address this challenge has increased greatly in recent years, with more traditional and brain-imaging approaches bolstered by genetic (see Question 11) and neuropathological capabilities. Indeed, establishment of the Department of Veterans Affairs National PTSD Brain Bank (see Girgenti et al., Chapter 12, this volume) is enabling investigators to look at the brain tissue itself in order to understand what differences in tissue morphology as well as genomic and epigenetic expression distinguish PTSD patients from nonaffected individuals and from people with other psychiatric disorders such as major depressive disorder.

Furthermore, such research is likely to help us distinguish between different PTSD endophenotypes that are associated with different pathophysiological abnormalities, each of which may require a different therapeutic intervention. As noted previously (see Question 1), the likelihood that a number of different psychophysiological abnormalities may underlie DSM-5 PTSD, raises the possibility that several different PTSD endophenotypes will be identified in the future and that DSM-6 (or DSM-7, etc.) may no longer have a single overarching PTSD diagnosis, but rather a family of posttraumatic syndromes, each characterized by a different pattern of symptom expression and/or a different underlying pathophysiology. For example, Mehta and colleagues, investigating genome-wide gene expression and DNA methylation in peripheral blood cells among patients with PTSD, found that methylation patterns were almost completely different among those whose PTSD was due to childhood maltreatment versus those whose PTSD was due to trauma exposure during adulthood (Mehta et al. (2013). Furthermore, there is evidence that an effective genomic pharmacological target for "postchildhood maltreatment" PTSD is different from that for "adult-trauma-related" PTSD (Pape et al., 2018; see Question 16).

QUESTION 11. *What new directions should be considered with respect to the genetics of PTSD?*

Interest in the genetics of PTSD is a major component of the search for biomarkers for PTSD. As discussed by Bustamante and colleagues (Chapter 11, this volume), a number of identified candidate genes regulate key components of the human stress response. From both clinical and public health perspectives, the identification of genes that distinguish between people at high and low risk of developing PTSD following

trauma exposure is a major research priority. The ability to identify people at high risk of developing PTSD would enable providers to target evidence-based interventions to high-risk groups and to improve our understanding of the pathophysiology of PTSD. Genetic variants associated with PTSD are promising biomarkers of risk because they remain unchanged throughout life, and DNA can be obtained noninvasively and assayed reliably. Most studies to date have used DNA from peripheral samples. In addition to genetic assays, epigenetic studies are also needed to advance our understanding of what factors might promote the expression or suppression of genes that mediate key stress-related mechanisms. Establishment of a National PTSD Brain Bank enables us to see how well peripheral biomarkers reflect PTSD-related genomic and epigenetic alterations in different regions of the brain (see Girgenti et al., Chapter 12, this volume). Although genotype exerts a major influence on behavior, emotional expression, resilience, and so forth, it is not the only important factor in this regard. Epigenetic research on how nurturing, learning, preparation, cognitive appraisal, emotion regulation, coping strategy, social support, and so forth might affect gene expression or exert genetic influence is a key area for future research.

Finally, genetic research will eventually help us select optimal treatments for PTSD and other disorders. The most obvious example is how medical research on pharmacogenetics will help physicians choose the best medications for their patients. Such findings will certainly extend to pharmacotherapy for PTSD. There is no reason why genetic research should not also focus on optimizing choice of psychotherapy (or various therapy combinations) in the future.

QUESTION 12. *What are the top priorities for research on enhancing resilience?*

Resilience may be expressed variously in genetic, molecular, behavioral, social, and other domains (see Averill et al., Chapter 30, this volume). For example, research with depressed children suggests that vulnerability in the genetic domain (e.g., homozygosity for the short allele of the 5-hydroxytryptamine [5-HT] transporter gene) may be offset by resilience elsewhere (e.g., social support; Kaufman et al., 2004). Our understanding of resilience among people exposed to traumatic stress is at an early stage. A crucial imperative of such research is to move beyond traditional approaches in identifying risk and protective factors to discover dynamic biopsychosocial mechanisms that mediate or moderate resilience, sometimes through gene × environment interactions. We agree with Averill and colleagues (Chapter 30, this volume) that future research on resilience will benefit from attempts to address multifactorial biopsychosocial determinants of resilience in longitudinal studies. Furthermore, research that has traditionally restricted its focus to sociodemographic, trauma-related, and a limited set of psychosocial factors associated with resilience needs to broaden its scope and investigate how the interaction between these and biological factors can foster resilience to trauma.

In addition to basic research, it is necessary to investigate promising directions for enhancing resilience. Such potential approaches include psychoeducational interventions, skills acquisition with respect to cognitive reappraisal and coping strategies, as well as psychotherapy, when indicated. We look forward to this new direction in research to identify specific or combined approaches that will ultimately prove to have the greatest effect on promoting and maintaining resilience to trauma and significant sources of stress.

QUESTION 13. *What new directions should be considered with respect to psychosocial treatments?*

Trauma-focused psychotherapies, especially cognitive-behavioral therapies such as CPT and PE, as well as eye movement desensitization and reprocessing (EMDR), have proven to be very effective treatments for PTSD (see Galovski et al., Chapter 19, this volume). Practice guidelines for PTSD all recommend trauma-foucsed therapy at the highest level, and those that make recommendations about treatment sequencing recommend trauma-focused therapy as the initial offering (Hamblen et al., 2019). The success of these treatments has led to the general belief that the theoretical underpinning for the most effective psychosocial treatments is the processing of traumatic material (see Bryant, Chapter 6, on psychological theory, and Galovski et al., Chapter 19, on psychosocial treatments, both in this volume).

Some treatments that do not focus on trauma are also effective, though less so than trauma-focused approaches (e.g., Belsher, 2019). The most evidence is for present-centered therapy (PCT). Other effective treatments include stress innnoculation training and interpersonal therapy. All three are suggested as second-line treatments in the Department of Veterans Affairs and Department of Defense (VA/DoD) PTSD guideline (see Hamblen et al., 2019). Given the promising findings, it is important to know whether there are additional effective non-trauma-focused approaches, and more about how these treatments compare with trauma-focused treatments. Other treatments needing additional study are "third-wave" cognitive-behavioral and mindfulness approaches, such as dialectical behavior therapy, mindfulness-based cognitive therapy, and acceptance and commitment therapy (see Bryant, Chapter 6, this volume). Evidence supporting their effectiveness for PTSD is mixed. Larger and more rigorous trials are needed in order to determine the effectivenss of these approaches as a primary treatment for PTSD.

Because comorbidity is the rule in PTSD, not the exception, treatment studies have included patients with a range of comorbidities. Particular progress has been made in the area of treating PTSD and comorbid substance abuse using concurrent treatment of PTSD and substance use disorders using PE (COPE; Back et al., 2015), which combines PE with relapse prevention skills (Norman et al., Chapter 24, this volume). However, more research is needed to determine whether specific comorbid conditions moderate treatment outcome (e.g., Clarke, Rizvi, & Resick, 2008) or whether a given treatment is effective in a given comorbid population (e.g., van Minnen, Harned, Zoellner, & Mills, 2012).

Despite the significant progress made in developing and refining treatments, many patients do not achieve an adequate response. Optimizing treatment outcome is the most important topic for future research. One strategy in need of further investigation is treatment matching. Although single studies have identified predictors of treatment outcome, there is little consistency across studies, and therefore, we have no clear answer to the question of what works best for which patients. There also is almost no information about what to do if a patient does not respond to treatment: Change the treatment? Add more sessions? Combine treatments? More systematic study of how to address inadequate treatment response is needed. Systematic operationalization of response categories (Larsen, Sippel, & Schnurr, 2020) and treatment refractoriness (Sippel, Holtzheimer, Friedman & Schnurr, 2018) is needed in order to move this research forward.

Since the first edition of this book in 2007, significant advances have been made in knowledge about techonological strategies to deliver psychotherapy (see Question 15).

These advances include apps, web-based treatments, virtual reality, and clinical videoteleconferencing (see Ruzek, Chapter 28, and Morland et al., Chapter 29, this volume, on Internet and telehealth approaches, respectively). This is a very exciting area, particularly as the need for telehealth care has increased due to the COVID-19 pandemic of 2019–2020. To varying degrees, research has found these strategies to be effective, but more information is needed to understand optimal ways to use these technologies and to ascertain for whom and in which settings they are most effective.

Other important questions concern dissemination and implementation. After studies conducted in academic settings began to identify effective treatments for PTSD, researchers began to ask whether the findings translated to practice settings and how best to disseminate and train practitioners in evidence-based treatment (see Question 19). In 2005, Foa and colleagues (Foa et al., 2005) published a pivotal study showing that nondoctoral-level rape crisis counselors could be trained to deliver PE and achieve comparable efficacy with expert clinicians in an academic setting. Much progress has been made since this study appeared, but questions of dissemination and implementation are still relevant today. The field of implementation science, itself expanding significantly in parallel with the rsearch on PTSD, has provided strategies for studying the barriers and facilitators to treatment, as well as to enhance implementation and implementation fidelity (see Stirman, Chapter 32, this volume). More needs to be done, however, to understand optimal strategies to implement effective treatment.

QUESTION 14. *Can neuroimaging inform us of the mechanisms of action for CBT?*

An intriguing and conceptually rich area concerns the explication of biological mechanisms underlying successful psychosocial treatments. Several (but not all) investigators have found that PTSD is associated with greater activation in emotional processing centers (e.g., amygdala, insula, and anterior cingulate cortex) and underactivation of emotion modulation centers (e.g., prefrontal cortex [PFC]; Fitzgerald et al., 2017; Garfinkel et al., 2014; see Averill et al., Chapter 9, on neurocircuitry, this volume). (Inconsistent findings may, in part, be ascribed to heterogeneity due to different PTSD endophenotypes; see Question 10.) Furthermore, a number of studies have found that normalization of PTSD-related alterations in neurocircuitry are associated with a positive response to trauma-focused psychosocial treatments. For example, successful treatment has been associated with reduced amygdala and increased PFC activation (Fonzo et al., 2017; Zantvoord, Diehle, & Lindauer, 2013) and stronger connectivity between emotion processing and modulation regions (Duval et al., 2020). Such research could also focus on network analyses regarding the salience, central executive, and default mode networks (see Averill et al., Chapter 9, this volume, on the triple-network model).

A major question that could be investigated by this approach is whether all effective psychosocial treatments are associated with the same alterations in neurocircuitry or whether there are notable differences between PE, CPT, EMDR, non-trauma-focused treatments such as PCT, and mindfulness-based approaches? A related question is whether successful pharmacotherapy works through a similar or different mechanism. For example, in their research on major depressive disorder (MDD), Mayberg and associates found that CBT effects change through "top-down" actions on PFC and other cortical target areas, while medication has a "bottom-up" subcortical locus of action (Goldapple et al., 2004).

An additional question that might be addressed by such research concerns alterations in brain function associated with successful treatment of comorbid PTSD and

MDD. Because the two disorders frequently occur simultaneously, comparisons of pre- and posttreatment functional brain imaging might help us understand whether comorbid PTSD/MDD represents the co-occurrence of two distinct DSM-5 disorders or whether PTSD/MDD is really a depressive subtype of PTSD.

Investigating EMDR in this way would be particularly interesting. If altered functional brain imaging following successful EMDR treatment resembles that observed following successful PE or CPT, it would suggest that EMDR's mechanism of action is similar to these other CBT approaches. If, on the other hand, successful EMDR treatment is associated with different alterations in neurocircuitry, it would support claims by EMDR advocates that it is a unique therapeutic approach with a different mechanism of action.

A related opportunity concerns the use of brain-imaging techniques to map treatment outcomes for individuals with the dissociative subtype of PTSD (see DePrince et al., Chapter 8, this volume, on dissociation). Because the dissociative subtype is associated with a unique pattern of excessive frontal and reduced amygdala activity, it will be of great interest to see whether successful treatment is associated with normalization of such neurocircuitry abnormalities. Also, comparing neurocircuitry outcomes among successfully treated dissociative and nondissociative individuals with PTSD should advance our understanding of the mechanism of action of treatment and determine whether such therapeutic mechanisms affect dissociative and nondissociative PTSD in the same way.

QUESTION 15. *How will advances in technology influence treatment engagement and participation?*

Rapid innovations in technology have opened the door to creative therapeutic approaches and have also facilitated the dissemination of evidence-based care. The Internet has served as a vehicle for providing treatment to patients with PTSD. Telemental health technology has overcome many barriers to care and has made evidence-based treatment available to patients who live in remote areas. And efforts to disseminate best practices have utilized web-based and mobile phone applications to promote the adoption of evidence-based treatments by clinicians.

As discussed by Ruzek (Chapter 28, this volume), an emerging body of research indicates that Internet-based psychotherapy provides a cost-effective and time-sensitive means for diagnostic screening and treatment that decreases therapist time and health care costs throughout the treatment process. Another major advantage is the relative anonymity afforded by Internet-based treatments; this is an effective way to reduce the stigma of seeking mental health treatment, which is especially important to military personnel who may fear that receipt of treatment will damage their careers. There is also evidence (see Ruzek, Chapter 28, this volume) that increased anonymity promotes disclosure more than face-to-face therapy contexts. Research testing the efficacy and possible advantages of Internet therapy has been generally positive but is still at an early stage.

On the other hand, there are very few published rigorous clinical trials with mobile app approaches, since, as with self-help books, there is currently neither a mechanism for controlling the quality of mobile apps nor any credentialing of authors of content. In addition, some mobile apps were developed to be used with a clinician; however, there is no way to stop patients from using a mobile app without clinical guidance. It remains to be seen whether mobile phone-based (or Internet) self-help tools for PTSD can be used independently or are best combined with some coaching contacts via telephone, text message, or e-mail to augment face-to-face treatment.

Clinical video teleconferencing (CVT) delivery of CBT has been shown to be as effective as face-to-face CBT (Morland et al., Chapter 29, this volume). It has been especially useful for providing evidence-based treatments to patients living in remote areas.

Given the growth and accessibility of telemental health and Internet options (including the use of web-based social media such as Facebook or Twitter), a relevant question is how best to orchestrate these technological options for psychoeducation, self-assessment, therapeutic engagement, and treatment. There are as many answers as goals, since the optimal strategy for a public health campaign against domestic violence will differ from that for self-identification and engagement in evidence-based treatment for a disaster survivor with PTSD.

QUESTION 16. *What new directions should be considered with respect to pharmacotherapy?*

We agree with the consensus statement by the PTSD Psychpharmacology Working Group (Krystal et al., 2017) who have raised the alarm about the crisis in pharmacotherapy for PTSD because (1) there have not been any significant discoveries about effective medications since sertraline and paroxetine, both selective serotonin reuptake inhibitors (SSRIs), received Federal Drug Administration (FDA) approval nearly 20 years ago; (2) the limited efficacy of these medications has necessitated polypharmacy for most patients treated; and (3) research and drug development has stalled, with very few industry or other-sponsered clinical trials. The Working Group recommends that current and future research focus on five, greatly unexplored, classes of medications: "rapid acting antidepressants (ketamine-like drugs, scopolamine), cannabinoid drugs, glucocorticoids, non-SRI antidepressants/monoamine transporter antagonists (trazadone, vortioxetine, cyclobenzaprine, etc.), opioids (buprenorphine, kappa opioid receptor antagonists), riluzole," and medications with other mechanisms of action (Krystal et al., 2017, pp. e54–e55). We would add that other neurobiological PTSD-related neurobiological abnormalities reviewed by Rasmusson and colleagues (see Chapter 10, this volume), such as NPY, CRF, Allo, and immunological alterations, should also be considered in this regard.

Clinical practice guidelines for PTSD currently recommend four medications for PTSD, three SSRIs (sertraline, paroxetine, and fluoxetine) and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. Remission rates after a 12-week trial are approximately 30% (see Davis et al., Chapter 23, this volume). Unfortunately, such rates compare unfavorably with results from CBT (see Galovski et al., Chapter 19, this volume). There are at least two reasons for the relatively poor performance of SSRI and SNRI medications. First, these are relative nonspecific medications that indiscriminately potentiate action at all of the many different kinds of serotonin receptor sites in the brain (sometimes with opposing effects). Second, given the heterogeneity of PTSD (see Questions 1 and 10), it is likely that these medications are only effective for a limited number of PTSD endophenotypes in which the pathophysiology is related to abnormalities in the monoaminergic pathway. As noted previously (see Averill et al., Chapter 9, this volume, and Question 10), one would not expect SSRIs or SNRIs to be effective if the pathophysiology is related to alterations in the amino acid pathway rather than the monoaminergic pathway. Instead, one might shift the therapeutic focus to ketamine or other medications, such as topiramate, that act on glutamatergic and gamma-aminobutyric acid (GABA)-ergic mechanisms.

The lion's share of medication trials so far have exemplified an empirical rather than a conceptually driven approach, and have utilized agents with established efficacy

for other disorders, such as antidepressants, antiadrenergics, anticonvulsants, and atypical antipsychotics rather than for PTSD, specifically. What is needed are medications designed to target the unique abnormalities associated with PTSD. In this regard, two specific possible approaches might target specific endophenotypes or specific genetic/epigenetic abnormalities associated with PTSD. For example, although the alpha-adrenergic antagonist, prazosin, was not effective in a large heterogeneous PTSD cohort, Raskind and colleagues found that it was effective for individuals with elevated blood pressure, whose PTSD, presumably, was due to a specific endophenotype associated with dysregulated adrenergic activity (Raskind et al., 2013). A second example is the work of Pape and colleagues (2018) who found that women with the unique epigenetic PTSD endophenotype associated with childhood maltreatment (see Mehta et al., 2013; and Question 10) responded to a medication that blocked CRF's type 1 receptor (CRF_1), whereas this medication was ineffective for individuals whose PTSD was due to traumatic exposure during adulthood. Both examples exemplify the current emphasis on "precision medicine," a treatment approach that goes beyond observable symptoms and clinical phenomenology to consider individual variability in genes, pathophysiology, environment, and lifestyle.

Because medication has achieved full remission in only a minority of cases, there has been considerable interest in adjunctive medications. As reviewed (see Davis et al., Chapter 23, this volume), there is currently little evidence supporting any specific augmentation strategy. Most notably, a large multisite trial showed that risperidone augmentation of antidepressants is ineffective (Krystal et al., 2011); as a result, atypical antipsychotics are no longer recommended as adjunctive agents for PTSD. Frankly, a more successful augmentation strategy for partial responders might be with CBT because monotherapy trials have shown greater success with this approach than with additional medications. In short, until we can identify more effective medications, systematic exploration of augmentation with other medications or CBT is a top priority. On the other hand, research testing medications, such as d-cycloserine (DCS) or hydroxycortisone, to augment CBT is an exciting development, with a rich body of animal research (e.g., DCS facilitation of fear extinction) to support it, despite some recent unsuccessful clinical trials with PTSD (see Davis et al., Chapter 23, this volume).

Finally, research on pharmacological interventions for acute posttraumatic reactions and prevention of PTSD is extremely important and inconclusive. A handful of studies with propranolol, hydrocortisone, and imipramine have suggested that early pharmacological intervention might be effective, but recent results with prophylactic propranolol treatment have been disappointing (see Davis et al., Chapter 23, this volume); additional studies with other agents are needed. From both a clinical and a public health perspective, designing such a "morning after pill" (Friedman, 2002) is a major priority that should focus on CRF, NPY, adrenergic, glucocorticoid, glutamatergic, and other agents.

QUESTION 17. *How should our emerging understanding of the association between PTSD and physical disorders influence research and practice?*

Evidence continues to indicate that PTSD appears to mediate the relationship between trauma exposure and poor health. Such evidence comes from several sources: self-report, objective indicators, clinical utilization, and mortality data. When comorbid psychiatric disorders are taken into account, PTSD still appears to have a specific impact on poor health (Schnurr & Green, 2004; see Schnurr et al., Chapter 25, this volume). The mechanisms underlying this association are unclear, but a variety of

psychological (e.g., depression, hostility), behavioral (e.g., risky behaviors, substance abuse), and biological alterations (e.g., adrenergic, hypothalamus–pituitary–adrenal [HPA], and immunological dysregulations) have been proposed (Friedman & McEwen, 2004; Friedman & Schnurr, 1995; Schnurr & Jankowski, 1999).

Given this relationship, it would seem that the best treatment for an individual with comorbid PTSD and (for example) hypertension would be aggressive PTSD treatment, in addition to treatment as usual for the medical disorder. As Schnurr and colleagues (Chapter 25, this volume) point out, the few attempts to test this hypothesis have had negative results because symptom reduction in PTSD was not associated with better medical outcomes. Clearly, this is an important area for future research. Such research should also identify those specific medical disorders with the strongest association with PTSD because they are most likely to benefit from conjoint PTSD/medical treatment. Methodologically, Schnurr and colleagues caution that such studies should have sufficiently long follow-up periods to observe changes in health. Another important question regarding treatment is whether interventions designed to improve physical health affect PTSD and other clinically significant distress reactions.

In addition to research questions, Schnurr and colleagues (Chapter 25, this volume) emphasize that the association between PTSD and health has important implications for the provision of health care. First, mental health professionals need to pay more attention to the physical health needs of trauma survivors. Second, because the majority of individuals with PTSD do not seek mental health care, the major area in which to implement this approach is the primary care setting. In recent years, there has been a paradigm shift within military, veteran, and private-sector health care, such that screening for PTSD is routinely done in primary care settings. Along with screening, diagnostic assessment and treatment has been moved into primary care as well. A number of practice models have been proposed to provide integrated primary/mental health care. Such approaches require an enduring culture change within the primary care setting, so that beliefs about traditional primary care roles expand to embrace such an integrated paradigm. Adopting implementation science approaches to study this critical transformation of the primary care setting is a fruitful area for future research (see Stirman, Chapter 32, this volume).

QUESTION 18. *What are the major priorities for research and practice concerning prevention and public health interventions following mass casualties and disasters?*

Epidemiological research indicates that the vast majority of the population is resilient and will develop neither PTSD nor some other psychiatric syndrome following exposure to a mass casualty or disaster (see Korte et al., Chapter 4, and Copeland & McGinnis, Chapter 5, this volume, on epidemiology of PTSD among adults and children, respectively). It is also apparent that almost everyone will be upset during the immediate posttraumatic aftermath, so that distinguishing between vulnerable and resilient individuals during the immediate postimpact phase is very difficult (see Azad et al., Chapter 18, this volume). Thus, a "wellness" public health approach needs to focus on resilience, prevention, identification of populations at risk, early intervention, community (societal) interventions, and traditional clinical approaches for individual patients (Friedman, 2002, 2005; see Morganstein et al., Chapter 31, this volume).

The goal of such a wellness-oriented preventive public health approach is twofold. First, such a strategy is predicated on the expectation that since most people are resilient, psychological recovery from the impact of traumatic events can be accelerated by

both enhancement of people's natural resilience and promotion of new strategies for coping with traumatic stress. The second preventive public health goal is to identify individuals who may have serious deficiencies in resilience. Such individuals might benefit from acquisition of skills that compensate for deficiencies identified in advance. For example, genetic vulnerabilities (Bustamante et al., Chapter 11, this volume) might be offset by behavioral (e.g., reduced conditionability), social (e.g., increased capacity to obtain and utilize social support), or pharmacological (e.g., NPY enhancers) interventions (see Averill et al., Chapter 30, this volume, on resilience).

Psychoeducation for the public at large may be an important preventive mental health strategy for resilient and vulnerable individuals alike. As with national smoking cessation initiatives, such an approach would provide the public with key information about what to anticipate following exposure to traumatic stress, how to distinguish between normal and abnormal posttraumatic reactions in themselves and in loved ones, what to do if such events occur, and what mental health resources might be available (see Azad et al., Chapter 18, and Morganstein et al., Chapter 31, this volume). Such information could be made available and accessible on the Internet, in naturalistic settings (schools, churches, workplaces, etc.), through public service announcements, and so forth.

The wars in Iraq and Afghanistan have spawned a number of initiatives within the U.S. military to promote resilience through predeployment stress inoculation and other strategies that incorporate well-established findings about psychological toughening, fear conditioning, and trauma-induced erroneous cognitions. Unfortunately, such approaches have not proven to be effective in the few reports published to date (see Azad et al., Chapter 18, and Averill et al., Chapter 30, this volume on early intervention and resilience, respectively). When, and if, effective interventions can be demonstrated, we will need to know for whom they are effective and how they are working. Demonstration of effectiveness in military settings should set in motion similar tests of stress inoculation among civilian cohorts. A good place to start might be with children at risk for exposure to urban or domestic violence, or with people who live in geographic areas where the probability of natural disasters is high. It is a very hopeful sign of the times that the trauma field has shifted from an exclusive interest in diagnosis and treatment of chronic PTSD to an interest in resilience and prevention.

Even with the best prevention in the world, natural or human-made traumatic stressors will continue to occur, so a comprehensive public mental health strategy needs to extend beyond resilience building and prevention to early detection and intervention for people at risk to develop chronic posttraumatic problems. Providing CBT for severely affected people (e.g., those with acute stress disorder) several weeks after traumatic exposure appears to be very successful (Bryant, Moulds, & Nixon, 2003; see Azad et al., Chapter 18, this volume). There remain unanswered questions about timing (how soon after the traumatic event?), dosage (how much treatment?), developmental, cultural, and other differences that need to be addressed systematically. Future research might address the issue of how to engage people in early intervention programs when their strong inclination will be to escape or avoid any reminders of the traumatic event and hope that they can forget or "just get over it."

Confronting such issues within a traditional clinical conceptual or therapeutic context is inadequate preparation for public mental health interventions for the population at large. As noted elsewhere (Friedman, 2005; Ritchie, Friedman, & Watson, 2006; see Morganstein, Chapter 31, this volume), intervention strategies need to be embedded within the existing social and community infrastructure, and institutions

such as neighborhoods, schools, religious communities, workplace settings and different ethnocultural enclaves. The tools for implementing such approaches include social procedures and activities such as legislation, public safety, public education, family self-help networks, community outreach, web-based information, smartphone applications, public service announcements, and the media (including social media).

Elsewhere, we have suggested that key measurable public health outcomes should be available to the general population; be relatively inexpensive; have a many-pronged pre- and posttraumatic public education component; ameliorate widespread distress through effective posttraumatic risk communication; accelerate the timetable for normal recovery among resilient individuals who experience transient posttraumatic distress; provide effective outreach, especially to communities at greatest risk; empower families and communities to achieve recovery; and provide screening, referral, and therapeutic services for those requiring clinical intervention (Friedman, 2005).

Implementation of the developmentally sensitive psychological first aid (PFA) manual during the immediate aftermath of Hurricane Katrina was an important public health milestone as a strategy to prevent the later development of PTSD among traumatized survivors of the hurricane (Ritchie et al., 2006; see Morganstein et al., Chapter 31, this volume). This approach, developed jointly by the National Center for PTSD and the National Child Traumatic Stress Network, is predicated on the consensus opinions of leaders in both civilian and military settings, and extrapolation from RCTs with psychosocial interventions (see Watson et al., 2003). Unlike psychological debriefing, which promotes emotional processing of very recent traumatic events and which is ineffective or potentially harmful (see Azad et al., Chapter 18, this volume), PFA is a pragmatic approach that emphasizes safety, security, communication, reunification with loved ones, psychoeducation, and information about available resources should clinical evaluation seem warranted. Although this approach appears to be a reasonable one, its effectiveness must be evaluated by empirical trials. Acknowledging that rigorous research on acute disaster mental health interventions can be a daunting challenge, a number of methodological approaches, such as dismantling studies, paired cohort comparisons, utilization of ongoing surveillance databases (for quasi-prospective studies), and other strategies might be easier to implement than randomized controlled designs to evaluate the effectiveness of PFA (see Norris, Galea, Friedman, & Watson, 2006). In short, we agree with Morganstein and colleagues (Chapter 31, this volume) that an aggressive research program on prevention and public health interventions is needed.

QUESTION 19. *What are the best ways to implement best practices for PTSD?*

Although we have developed a number of evidence-based practices for PTSD, we have not succeeded in implementing these treatments so that the majority of clinicians utilize best practices on a routine basis. As described by Stirman (Chapter 32, this volume), implementation of best practices for PTSD is a multilevel process that must address (1) the outer context (e.g., policy, norms, and social factors; (2) the inner context (e.g., organizational context and culture, leadership support, resources, and alignment of processes); (3) characteristics of individuals (e.g., knowledge and skills, attitudes and perceptions, and motivation to use evidence-based treatments); and (4) intervention characteristics (e.g., compatibility, complexity, effectiveness, relative advantage, and trialability). Such a multilevel implementation involves identification of potential barriers that operate at different systems levels, such as skills deficits, perceptions that

trainers have limited experience in delivering interventions in real-world settings, limited access to supervision, requirements for increased documentation, the time or emotional burden of delivering a treatment, inadequate funding to support training and implementation, and a lack of systems in organizations for identifying and prioritizing best practices.

Research on implementation suggests that if trauma survivors are to receive best practices, implementation models should be utilized as an organizing framework for those concerned with service improvement. We agree with Stirman (Chapter 32, this volume) that achievement of these objectives will require an unprecedented degree of collaboration between policymakers, managers, and clinicians in the trenches—all groups concerned. Both top-down and bottom-up mechanisms will be needed. First, policymakers and managers must improve communication with their clinicians. But such a unidirectional approach is unlikely to succeed by itself because clinicians are very independent and tend to rely more heavily on their own judgment rather than on clinical practice guidelines. Successful implementation can only be achieved with a change in the clinical culture in which frontline practitioners embrace evidence-based treatment approaches and their practice setting facilitates and provides ongoing support for their adoption of best practices. To help practitioners develop their knowledge and master evidence-based treatments, training methods must themselves become more evidence-based. The emerging perspectives of implementation science can provide ways of thinking and methods of changing practice that better anticipate the complexities of change.

As we utilize implementation science methodology to help us understand the many components of this complex process, it is important to remember that two outcomes need to be measured. First, we need to test various implementation strategies to determine which ones will change clinicians' behavior, so that they are more likely to utilize best practices. But we also need to find out whether the adoption of evidence-based treatments will improve clinical outcomes with respect to symptom severity and functional status. It is a daunting challenge but one that we must accept.

FINAL THOUGHTS

Forty years of research and clinical experience support the validity of PTSD as a unique, prevalent, and potentially disabling psychiatric diagnosis. PTSD also provides a valuable scientific heuristic within which to understand the impact of traumatic stress at genetic, molecular, neurobiological, cognitive, behavioral, and sociocultural levels. In addition, current research has advanced to understand how such alterations influence gene expression, brain function, psychological processes, and clinical abnormalities. The ultimate goal, however, is to translate such scientific findings into effective and widely disseminated evidence-based practices for people with PTSD and, whenever possible, to intervene early or even prevent onset of the disorder.

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