

Cape Town Consensus on Posttraumatic Stress Disorder

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ABSTRACT

The association between traumatic events and psychopathology has long been recognized, and the literature on posttraumatic stress disorder (PTSD) has burgeoned since this entity was introduced into the diagnostic nomenclature. This literature has been characterized by a range of clinical controversies about the optimal diagnosis and treatment of PTSD. In response, several systematic reviews of treatment, clinical guidelines, and consensus statements about PTSD have been generated, but their conclusions are not always consistent. Our aim here is to provide a concise overview of the literature on PTSD, focusing in particular on recent investigations and publications, with the objective of summarizing practical clinical implications and suggesting future research opportunities. We consider, in turn, the diagnosis and evaluation, psychobiology, pharmacotherapy, psychotherapy, and prevention of PTSD.

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OVERVIEW

Posttraumatic stress disorder (PTSD) is a prevalent and disabling disorder that although associated with a range of traumatic events, receives particular attention from clinicians, researchers, and the lay public during times of military combat, terrorist attacks, and natural disaster. There are ongoing clinical controversies about the optimal diagnosis and treatment of PTSD, and the relevant research literature has burgeoned in recent decades. Partly in response, several systematic reviews of treatment, clinical guidelines, and consensus statements about PTSD have been generated by expert clinicians, professional organizations, and health care institutions.¹⁻¹⁰

Perhaps not surprisingly, there have been important differences in the conclusions of these publications, both with regard to the relevance of the diagnosis of PTSD, and with regard to optimal prevention and treatment. These differences may have substantial impact on patients, particularly when they emerge from authorities that have a regulatory role, such as the National Institute on Clinical Excellence. They may also lead to a lack of clarity in the minds of practicing clinicians. Our aim here is to provide a concise overview of the literature on

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PTSD, focusing in particular on recent investigations and publications, with the objective of summarizing practical clinical implications and suggesting future research opportunities.

DIAGNOSIS AND EVALUATION

There are ongoing debates about the optimal thresholds and boundaries for PTSD, and about its position in the diagnostic classification system. Although the concept of PTSDs has been recognized for centuries, the idea of a specific disorder called PTSD was only introduced into the official psychiatric nomenclature in 1980. Its status continues to be debated; there are some who still argue that responses to trauma can readily be characterized in terms of other mood and anxiety disorders, while others hold that a distinct category of posttraumatic responses is needed to characterize the broad and partly unique array of posttraumatic psychiatric phenomena. Certainly, the experience of trauma can be associated with a range of subsequently evolving psychopathological symptoms and syndromes, which is highlighted by the finding that PTSD itself is typically characterized by high rates of comorbidity with many other psychiatric disorders. Diagnostic issues can further be complicated by forensic and legal issues, such as adequate compensation of survivors, whether veterans or civilians, in some countries.

Fortunately, ongoing research provides new insights into the question of the validity of PTSD, and into critical issues in its definition and diagnostic criteria. In their review, Wittchen and colleagues¹¹ emphasize that PTSD (as defined by *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria) occurs at relatively high rates after exposure to certain traumatic event patterns, with some consistency in its sociodemographic and clinical correlates and associations. Certainly, rates of exposure to these traumatic events vary from region to region (they are higher in certain parts of the United States than in many European and developing countries) and by gender. Nevertheless, exposure to trauma is quite common throughout the world and, importantly, despite different rates of trauma, there seems to be a similar conditional risk for developing PTSD in response to particular traumatic events across countries and studies.

What counts as a traumatic event, however, is difficult to define. The *DSM* provides specific criteria for determining whether or not a traumatic event qualifies to be associated with PTSD. These definitions of trauma have changed over time; ini-

tially the emphasis was on events that most would consider distressing, while more recent editions have attempted to delineate both the objective (eg, life-threatening) and subjective (eg, associated with fear and horror) aspects of the trauma.¹² However, it is possible that neither necessary nor sufficient features of trauma can always be defined in such a way that differentiates them from other distressing life events. Instead, traumatic events that are widely recognized as prototypical for severe trauma (eg, rape) have a high conditional probability for PTSD, while those that are more atypical and that require more contextual information to determine their impact (eg, car accidents) have a low conditional probability for PTSD. Critical issues that make it difficult to provide an essentialist definition of traumatic events include variations in the timing (eg, childhood versus adulthood) and duration (eg, brief versus chronic) of exposure. It is notable that even for the most prototypical severe traumatic events, the conditional probability of developing PTSD is 40% to 50% at most; thus, a range of factors, other than the trauma itself, are needed to account fully for the pathogenesis of the disorder.

The natural course of PTSD is increasingly researched, with data now available from both clinical studies of traumatized patients and from longitudinal epidemiological studies. Many data suggest that PTSD can be understood as the pathological lack of resolution of acute stress symptoms that are almost universally expressed in the aftermath of exposure to psychological trauma. At the same time, there is growing awareness that this picture is complex, and that vulnerabilities that pre-exist the trauma, or factors in the aftermath of the trauma, also influence the course. In the context of multiple traumatic events, a relatively common or minor stressor may trigger PTSD. In addition, PTSD may occur with considerably delayed onset, with delays up to decades. Longitudinal studies have clarified specific patterns of comorbidity associated with PTSD, have helped identify relevant risk factors for both trauma and PTSD, and have identified the relative lack of spontaneous and complete remission once PTSD occurs. Such work has, however, also highlighted important differences across trauma types, gender, and study cohorts, which complicate the prediction of persistent PTSD.

Clinical Directions

Although there is some disagreement in the literature on the value of screening for trauma and common mental disorders, in view of the high prev-

absence of PTSD and the efficacy and cost-efficiency of certain treatments, we argue for the importance of community screening—particularly the screening for clinical symptoms ~1 month after trauma. The feasibility of such large-scale screening efforts in the general population has been well demonstrated by recent efforts.¹³ Although the optimal screening time and method are unknown, it is known that screening high-risk individuals too early after the trauma may result in a large number of false positives. In primary-care settings the prevalence of PTSD is higher than in the community, as people in the early stages of PTSD may more readily seek help for non-specific symptoms. Thus it is important to screen for the presence of anxiety symptoms in general and major traumatic events in particular. In more specialized clinical settings, eg, mental health practices, routine screening for both PTSD and traumatic events seems reasonable. In the aftermath of trauma, those who are already receiving mental health services may in addition develop PTSD or a range of other psychiatric conditions. Screening for comorbid disorders and key symptoms (eg, suicidality) in this context is therefore important.

Research Directions

It is difficult to delineate necessary and sufficient criteria for defining those events that precipitate PTSD. There is surprisingly little evidence for the value of criterion A2 (ie, the person's response to the traumatic event involved intense fear, helplessness, or horror) in predicting progression to PTSD. It might be worth referring to a range of potentially traumatic events, some of which are more prototypic for developing PTSD (eg, sexual assault), and some of which are more commonly associated with developing other stress-related conditions (eg, adjustment disorder after motor vehicle accident). More research is needed on what traumatic events to screen for and when, but guidelines on this may need to vary by place and time. More work is needed to understand particular subtypes and spectrums of PTSD (eg, PTSD associated with aggression, PTSD associated with suicidality, disorders of extreme stress not otherwise specified), heterogeneity in natural course (eg, delayed-onset PTSD), and the thresholds for meeting the core diagnostic criteria for PTSD (ie, re-experiencing, avoidance/numbing, and hyperarousal). There are many studies of the prevalence of trauma and PTSD, and re-analysis of existing datasets may be helpful in defining more sharply optimal PTSD criteria, subtypes, and spectrums. The forthcoming

revision of *DSM-IV* and *International Classification of Diseases*, tenth edition, and the need to reconcile differences in the two systems, makes this a timely exercise. This revision also offers a useful opportunity to include formally both categorical and dimensional approaches to PTSD assessment. Future epidemiological studies would benefit from more expansive interviews, and additional psychological measures.

PSYCHOBIOLOGY

PTSD is characterised by particular kinds of disruption of homeostasis, and the relevant phenomenology (eg, altered mechanisms of learning and extinction, sensitization to stress, hyperarousal, avoidance) and psychobiology of this disruption appear to be universal. Basic work on the neuroanatomy and neurochemistry of the stress response has provided an important foundation for exploring these disruptions. Some of the neurobiological changes accompanying PTSD may reflect the consequences of trauma, but others may comprise pre-existing vulnerability factors. There is growing interest not only in factors that increase vulnerability to PTSD, but also in the correlates of resilience.

"Top down" research has explored the cognitive-affective processes involved in mediating PTSD.^{14,15} For example, PTSD research has documented abnormalities in memory, disruption of normal fear extinction, and hypervigilance and avoidance in this condition. Functional and structural brain imaging studies have been particularly useful in establishing the brain correlates of these phenomena. Thus, there is consistent evidence from a range of work that PTSD is associated with amygdala hyperactivity, reduced hippocampal volume, and decreased activity in medial prefrontal cortex (including anterior cingulate).^{16,17}

"Bottom up" research has explored the molecular underpinnings of the symptoms and disruptions seen in PTSD.^{14,18} From a molecular perspective, neuronal circuits involved in mediating PTSD symptoms and cognitive-affective disruptions are comprised of multiple neurotransmitter systems and interactions with other neurochemical and neuroendocrine systems. Thus, there is evidence that PTSD is associated with specific disruptions in monoaminergic systems, various other neurotransmitter systems (eg, glutamate, gamma-aminobutyric acid, substance P, neuropeptide Y), and the hypothalamic-pituitary-adrenal axis (HPA axis). The latter has been the most intensively scrutinized and shows clear evidence of dysregulation—corticotrophin-releas-

ing factor (CRF) hypersecretion and adrenocortical hypoactivity. Importantly, early adversity is similarly associated with later abnormalities in these systems, such as persistent hyperactivity of the HPA axis, and chronic overactivity of CRF-containing neurons in limbic and hypothalamic brain regions.¹⁹

A full understanding of the pathogenesis of PTSD will require a comprehensive understanding of gene-environment interactions. Recently, single nucleotide polymorphisms of the FKBP5 gene were reported to interact with levels of child abuse to predict severity of adult PTSD symptoms.²⁰ FKBP5 expression is induced by glucocorticoids as part of an intracellular negative feedback loop; the protein acts on glucocorticoid receptors (GR) to reduce their binding affinity and increase their nuclear translocation. FKBP5 variants that predicted PTSD severity have been associated with increased cortisol-induced FKBP5 mRNA expression in peripheral blood mononuclear cells, and they showed less dexamethasone suppression and thus more GR resistance. Consistent with this, Segman and colleagues²¹ found that increased FKBP5 mRNA expression in PBMCs after trauma predicted later PTSD.

Clinical Directions

PTSD is not simply a normal reaction to an abnormal stressor.^{22,23} The psychobiological findings that emphasize the significance of individual vulnerability to PTSD are consistent with the epidemiological findings, indicating that in many, but not all, cases posttraumatic symptoms may remit spontaneously without professional intervention. Although it is important not to pathologize normal stress responses (given that most people adjust after even severe traumatic events), it is also important to diagnose PTSD (given the suffering and morbidity associated with this disorder). The fact that PTSD is associated with specific alterations of psychobiological systems provides clinicians with a target for intervention. Understanding the relevant psychobiological mechanisms, and how they unfold over time is important for understanding how best to identify risk, promote resilience, and treat where necessary, as well as how to tailor interventions optimally.

Research Directions

Although some progress has clearly been made in understanding the psychobiology of PTSD, given the public health importance of this condition it is important to undertake appropriately powered stud-

ies (current psychobiological studies most often have small sample sizes) to better understand the genetic, environmental, and neuroimaging correlates of normal stress responses and of PTSD, and their interactions across the life span. Current genetic and imaging tools are potentially powerful, and with sufficient investment into PTSD research it will be possible to better integrate data from different methods, and to better delineate endophenotypes associated with PTSD vulnerability. There is growing awareness of the interface between mood disorders and general medical conditions, and additional attention to understanding medical comorbidity in PTSD is needed. It is crucial to identify and employ appropriate control groups (eg, traumatized patients without PTSD, trauma survivors with depression). In addition, is it important to explore the subtypes and spectrums of PTSD, including early versus late onset PTSD, single trauma versus multiple trauma PTSD. Validated laboratory animal models should allow a translational approach to understanding risk and resilience after trauma, and may also shed light on the heterogeneity of PTSD.

PHARMACOTHERAPY

Recent clinical guidelines and expert reviews have emphasized the value of pharmacotherapy in PTSD.^{3,5,24-28} On the other hand, two influential reviews have recently concluded that much of the evidence-base for the efficacy of pharmacotherapy in PTSD is weak.^{6,10} This reflects disagreement, in part, about whether data showing statistical significance in various clinical trials (eg, selective serotonin reuptake inhibitors [SSRIs] and venlafaxine) can be extrapolated to predict a clinically meaningful response in real-world treatment settings.

The numbers needed to treat (NNT) with medication in PTSD are, in fact, acceptable. There is a large database of trials of SSRIs and venlafaxine that demonstrates not only their efficacy but also their safety and acceptable tolerability. Psychotherapeutic interventions have an advantage in meta-analytic comparisons with pharmacotherapy given that the active intervention is often compared with waiting list rather than with placebo. Furthermore, results obtained with expert psychotherapists in specialized centers may not generalize to other settings. Nevertheless, there is marked heterogeneity of response to pharmacotherapy, and the placebo response is surprisingly robust; these phenomena need to be better understood. Indeed, many important questions about the optimal pharmacotherapy of PTSD remain unanswered.

A particularly vexing issue is the management of the patient who is refractory to SSRIs or serotonin-norepinephrine reuptake inhibitors. An initial trial of these medications should last for ≥ 12 weeks. Switching between agents may prove useful, although there is little supporting evidence.²⁵ Similarly, although there is little evidence for the value of higher doses of SSRIs in PTSD, individual patients may benefit from an increase.²⁵ A small database of randomized controlled studies suggests a role for new generation antipsychotic agents in refractory patients.²⁹ However, because the adverse event profile of these agents, particularly with chronic use, is of concern, these must be considered carefully. When faced with a patient with PTSD, clinicians may feel the need to use pharmacotherapy to resolve symptoms completely. However, the literature suggests that in many cases, pharmacotherapy provides relief rather than a cure.

Clinical Directions

There are good reasons for using pharmacotherapy in PTSD. As Stein and colleagues³⁰ emphasize in their review, there is a large database of trials of SSRIs/venlafaxine showing efficacy and tolerability.³¹ Although the National Institute for Clinical Excellence guidelines chose 0.5 as a clinically meaningful effect size,⁶ it is not clear that such a definition is valid for PTSD. When one calculates the NNT, these provide good comparative justification for the pharmacotherapy of PTSD with SSRIs.³¹ There are now also a number of pharmacotherapy relapse prevention trials in PTSD; these underscore the importance of continuing pharmacotherapy once a therapeutic response is obtained.²⁷

Work on other psychiatric disorders such as depression suggests that switching to a different medication in treatment-resistant patients may be useful. Augmentation with second-generation antipsychotics can be considered in patients refractory to first-line agents. On the one hand, it is important to preserve even small gains with initial therapy, and augmentation therefore has a role.²⁶ On the other hand, we would caution against the excessive use of polypharmacy. Similarly, general principles of pharmacotherapy emphasize the importance of selecting agents with the safest possible profiles, and of discontinuing medication if there is no associated benefit.

Research Directions

A great deal of additional pharmacotherapy research is needed in PTSD. In particular, we need

large effectiveness (real-life) studies, and we need studies that address the optimal sequencing and combination of pharmacotherapy and psychotherapy. Several clinical populations, particularly PTSD with comorbid substance use disorders, and children and adolescents with PTSD, are understudied. Different kinds of traumatic events, and different subtypes need to be more intensively studied.^{32,33} Methodological improvements to study design are needed. For example, data on non-included patients is often unavailable, and raters are not always sufficiently blind.¹⁰ Additional research to develop predictors of response to pharmacotherapy, including genomic or neuroimaging markers, may be useful. More work is needed to better understand the psychometrics of PTSD scales used in pharmacotherapy trials, to understand the nature of the placebo response, and to determine appropriate definitions of response and of remission, including measures of functional outcomes, and of early onset versus late onset of response.

PSYCHOTHERAPY

As Cloitre notes in her review,³⁴ there have been more than two dozen randomized, controlled trials of cognitive-behavioral psychotherapy (including prolonged exposure), a dozen studies of eye movement desensitization and reprocessing (EMDR), and very few or no good studies of a range of other psychotherapy interventions. We know little about applicability of CBT to a range of different settings (eg, post-disaster, refugees), and more work is needed on the long-term efficacy of the different psychotherapies (given that PTSD is a chronic disorder) and on real-world effectiveness (given that many patients drop out during CBT). Although some guidelines have emphasized the use of exposure as the primary intervention for victims of childhood abuse,¹⁰ the evidence base, in fact, does not support this view. The treatment of childhood abuse and other complex forms of PTSD (eg, domestic violence, ethnic violence) is likely to be enhanced by consideration of the multiple additional emotional, interpersonal, and social difficulties that are recognized as resulting from these experiences.

Indeed, ongoing research is attempting to delineate the active components of psychotherapy. Early work on the comparison of cognitive therapy and prolonged exposure suggested that each was effective. More recent work has suggested that particular components may be helpful in specific populations; for example, subjects with a history of childhood abuse may substantially benefit from specific skills

training prior to embarking on exposure. There is little research showing that the combination of pharmacotherapy and psychotherapy are more effective than either treatment modality alone, but there is ongoing interest in the addition of psychotherapy to patients refractory to medication, or the use of psychotherapy during medication tapering.

Clinical Directions

There is substantial evidence that CBT is effective in the treatment of PTSD.^{4,35} However, there is uncertainty about the durability of its effects, and after treatment, ongoing assessment and maintenance treatment may be needed. It is premature to make definitive conclusions about the relative benefits of cognitive therapy and exposure therapy, and there is uncertainty about whether data from trials are generalizable to the context of routine care. Some evidence suggests that optimal intervention is dependent upon the stage of the disorder—social support may be effective early, but chronic PTSD may require multimodal intervention to address impairment.

EMDR, a trauma-focused therapy, also appears effective in a smaller set of studies. However, the extent to which it overlaps with CBT is unclear, and dismantling studies are required. It is important to emphasize that not all psychotherapies are effective; supportive therapy may, for example, be associated with symptom exacerbation in PTSD patients with histories of child abuse. There is little empirical data on the effects of psychodynamically-oriented psychotherapy or psychoanalysis in PTSD patients. Nevertheless, arguments that careful attention is required to understand the meaning of traumatic events for their survivors are reasonable.

Research Directions

There is a need for randomized studies of CBT against an active comparator for effectiveness studies of psychotherapy and for longer-term studies. Larger samples and a broader range of outcome measures may help delineate the specific effects of particular interventions. There is a strong need to develop therapies that may be more appropriate in particular contexts, eg, group therapy in the aftermath of disaster, or specific interventions for patients in whom PTSD is secondary to domestic violence. More data is needed on the comparison of psychotherapy with pharmacotherapy, and on the optimal ways of combining these modalities (for example, CBT plus D-cycloserine).³⁶

PREVENTION

The occurrence of natural disasters and ongoing situations of conflict, and the need for allocating resources as efficiently as possible, dictate that prevention is a key area of clinical and research interest. Again, however, there has been a good deal of controversy in this area. For example, work suggesting that debriefing and benzodiazepines are ineffective for the prophylaxis of PTSD (and perhaps even increase vulnerability to PTSD) requires many practitioners to change the way in which they prescribe.³⁷

As Zohar and colleagues³⁸ emphasize in their review, there is a growing body of psychobiological research that can be used to inform our thinking about prevention in the aftermath of trauma. This work suggests that ultimately we may be able to develop better interventions in this context, particularly in the critical period immediately after a traumatic event. This is a common approach in other medical emergencies, such as myocardial infarction and cerebro-vascular accident.

In the interim, however, it is important to remember the principal of “*primum non nocere*”—whether in ordinary clinical practice or in extraordinary disaster medicine. Several guidelines have emphasized factors that can be summarized as the four Ps—do not pathologize, do not psychologize, do not pharmacologize, do not push for professional contact. It is important to create an expectation of recovery. In addition, it is key to help the helpers by empowering first responders.^{9,39} These principles are also key in children and adolescents, but different approaches may be needed to ensure their application.¹

Clinical Directions

In the immediate aftermath of a traumatic event, debriefing and benzodiazepines should be avoided.³⁷ Acute stress management may be important early on, but this should be distinguished from acute stress treatment. Hobfoll and colleagues⁹ identify five empirically supported intervention principles that should be used to guide and inform early prevention efforts. These are promoting: 1) a sense of safety, 2) calming, 3) a sense of self- and community efficacy, 4) connectedness, and 5) hope. Later on, the expectation of recovery needs to be balanced with a willingness to provide care to those suffering from PTSD (should this occur).⁴⁰

It is crucial that we provide education about PTSD. In the aftermath of a disaster, only a minority will develop PTSD. Rather than using clinical

resources at this early stage, we should reserve them for those who do in fact develop PTSD. At this stage, the focus should clearly be on the expectation of recovery and on community resilience.⁴¹ Once PTSD is diagnosed, then robust intervention may be useful in preventing chronic PTSD. In countries with few resources and high prevalence rates of trauma it is important to put trauma on the public health agenda, to attempt to address inequalities in access to treatment, and to ensure implementation of existing knowledge.

Research Directions

Further work is needed to investigate optimal screening, particularly after mass exposure to trauma,^{13,42} and to understand the psychobiology of preventive interventions. Ultimately an understanding of the factors predicting PTSD, and the development of key targets (eg, via physiological or gene expression studies) may be crucial for producing innovative interventions. Animal studies can be useful for understanding memory consolidation immediately after trauma and for exploring early interventions. A range of pharmacological agents (modulators of the stress response, memory consolidation drugs, neurotrophic/neuroprotective agents) require study. Beta-blockers may be important in altering arousal. SSRIs are currently being explored in prophylaxis trials.

In the future it will be important to demonstrate the effectiveness, and assess the cost-efficacy, of interventions in the aftermath of trauma. Given the relative lack of such studies, there are important opportunities for the field. A range of sampling and design issues must be considered.¹³ Reluctance to seek help is an important issue that needs to be addressed, perhaps by increasing the desirability of treatment. Targeting high-risk individuals (perhaps by neurophysiological measures, gene expression, etc) is a key goal for the future. School-based interventions do not have a strong record. However, parenting interventions, eg, programs for at-risk children and adolescents, may be useful.⁴³ **CNS**

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