Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges

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Post-traumatic stress disorder (PTSD) is arguably the most common psychiatric disorder to arise after exposure to a traumatic event. Since its formal introduction in the DSM-III in 1980, knowledge has grown significantly regarding its causes, maintaining mechanisms and treatments. Despite this increased understanding, however, the actual definition of the disorder remains controversial. The DSM-5 and ICD-11 define the disorder differently, reflecting disagreements in the field about whether the construct of PTSD should encompass a broad array of psychological manifestations that arise after trauma or should be focused more specifically on trauma memory phenomena. This controversy over clarifying the phenotype of PTSD has limited the capacity to identify biomarkers and specific mechanisms of traumatic stress. This review provides an up-to-date outline of the current definitions of PTSD, its known prevalence and risk factors, the main models to explain the disorder, and evidence-supported treatments. A major conclusion is that, although trauma-focused cognitive behavior therapy is the best-validated treatment for PTSD, it has stagnated over recent decades, and only two-thirds of PTSD patients respond adequately to this intervention. Moreover, most people with PTSD do not access evidence-based treatment, and this situation is much worse in low- and middle-income countries. Identifying processes that can overcome these major barriers to better management of people with PTSD remains an outstanding challenge.

Key words: Post-traumatic stress disorder, trauma, DSM-5, ICD-11, cognitive behavior therapy, definition, evidence-based treatment, access to treatment

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Although traumatic stress has been known for over 100 years by a number of terms, including "shell shock", "battle fatigue", or "soldier's heart"[1], it was only in the 1980s that persistent stress reactions were recognized in psychiatric nosology. In the wake of the mental health problems evident in many troops returning from deployment in Vietnam, the DSM-III introduced the diagnosis of post-traumatic stress disorder (PTSD).

Since that time, our knowledge about PTSD has grown significantly. However, in spite of this, the field of traumatic stress has often been dogged with controversy over the very definition of PTSD, its etiology, and optimal means for treatment. This situation has not changed today, since our conceptualization of psychological responses to trauma continues to be a matter of debate.

In this context, this review outlines our current understanding of PTSD, including diagnostic definitions, prevalence and risk factors, conceptual models, treatment approaches, and some of the major challenges currently facing the field.

DIAGNOSTIC DEFINITIONS

There are currently two major diagnostic definitions of PTSD.

The DSM-5 requires that a person experience or witness a major traumatic event (exposure to actual or threatened death, serious injury or sexual violence) (Criterion A). If one has experienced or witnessed such an event, there are four symptom clusters that he/she should manifest. First, one needs to have at least one of the following re-experiencing symptoms: intrusive distressing memories, recurrent distressing dreams, dissociative reactions (e.g., flashbacks), intense or prolonged psychological distress at exposure to reminders of the trauma, marked physiological reactions to internal or external cues symbolizing or resembling an aspect of the traumatic event (Criterion B). Second, one is required to have active avoidance of internal (e.g., thoughts, memories) and/or external (e.g., situations, conversations) reminders of the trauma (Criterion C). Third, at least two "alterations in cognitions and mood" symptoms are needed, including inability to remember an important aspect of the traumatic event, persistent and exaggerated negative thoughts about oneself or the world, persistent distorted cognitions about the cause or consequences of the event, pervasive negative emotions, markedly diminished interest, feeling detached or estranged from others, persistent inability to experience positive emotions (Criterion D). Finally, one has to present at least two of the following arousal symptoms: irritable behavior and angry outbursts, reckless or self-destructive behavior, hypervigilance, exaggerated startle response, problems with concentration, sleep disturbance (Criterion E). People are required to manifest these symptoms for more than one month after trauma exposure, in order to minimize pathologization of normal stress reactions.

It is worth noting that the DSM-5 definition has broadened the scope of PTSD from its traditional focus on fear responses to also include other emotional reactions to trauma. In fact, many PTSD patients, especially from military and first responder populations, present with non-fear emotional responses[2].

Many areas of the world operate on the World Health Organization's International Classification of Diseases (ICD) to guide psychiatric diagnoses, rather than the DSM-5. The ICD typically adopts a simpler approach to psychiatric diagnoses than the DSM, because of the need to impose less burden on diagnosticians in poorly resourced settings, who often cannot allocate lengthy assessments to each patient.

The recently approved ICD-11 diagnostic guidelines for PTSD strategically adopt a narrow focus on fear circuitry symptoms, comprising re-experiencing of the traumatic event, avoidance of reminders, and a perception of heightened current threat (reflected by various forms of arousal)[3]. Central to this definition is the proposition that a core component of PTSD is re-experiencing the memories of the traumatic event in the present.

In addition to PTSD, the DSM-5 also includes the diagnosis of acute stress disorder, which describes stress reactions occurring in the first month after trauma exposure. This diagnosis was initially introduced in the DSM-IV as a means for describing severely distressed people who could not be diagnosed with PTSD in the initial month, and also as a way to identify people who were at high risk for later PTSD. Subsequent longitudinal studies indicated that this diagnosis is only a modest predictor of PTSD: at least half of people who develop PTSD do not initially meet the criteria for acute stress disorder[4].

Initial conceptualizations of acute stress disorder placed much emphasis on dissociative responses immediately after trauma exposure (including depersonalization, derealization, reduced awareness of one's surroundings)[5], resulting in the DSM-IV requirement that dissociative symptoms be present to meet the criteria for the disorder. In contrast to this position, convergent findings indicated that, despite the relationship between peri-traumatic dissociation and later PTSD[6], many people who develop PTSD do not display dissociative responses in the acute phase after trauma[4]. As a result, in the DSM-5, the diagnosis of acute stress disorder does not require specific symptom clusters to be present, but, in recognition that people can experience acute stress in diverse ways, requires at least 9 of 14 potential acute stress reactions to occur in the initial month after trauma[7]. Importantly, this diagnosis is not intended to predict subsequent PTSD, but rather to describe people with elevated distress in the initial month who may benefit from mental health services[7].

A major reason for the inclusion of the category of acute stress disorder in the diagnostic system was that, in the US context, it is easier for many people to receive mental health care under local health insurance rules if they have a diagnosis. It was argued that the requirement that PTSD can only be diagnosed if the symptoms persist for more than one month after the trauma can result in many distressed individuals not receiving mental health care.

Another diagnostic construct that is worth noting is complex PTSD, which has been introduced in the ICD-11. To receive this diagnosis, one needs to present the core PTSD symptoms, and in addition experience disturbances in self-identity (e.g., negative self-concept), emotional dysregulation (e.g., emotional reactivity, violent outbursts), and persistent difficulties in relationships[3]. Although most commonly seen in the wake of prior prolonged childhood abuse, this disorder can also occur in survivors of other severe traumas, such as torture[8].

Complex PTSD has been the focus of many studies in recent years. A significant number of factor analytic studies tend to converge on the proposed factor structure of the disorder, with evidence of two overarching factors of PTSD symptoms and disturbances in self-organization[9-12]. Furthermore, latent class analyses have consistently documented that there is a class of individuals with high PTSD symptoms and high disturbances in self-organization, and another class with high PTSD symptoms and low disturbances in self-organization[12-16]. Importantly, there is also evidence that complex PTSD identifies a distinct class from borderline personality disorder[14]. Consistent with the proposal that complex PTSD emerges after prolonged childhood trauma, there are higher rates of childhood abuse in people with complex PTSD than in those with PTSD[13,14,17].

PREVALENCE

Although many people are exposed to traumatic events at some point in their lives, most of them rebound to enjoy pre-trauma levels of psychological functioning[18]. Epidemiological studies have reported lifetime PTSD prevalence rates of 13.0-20.4% for women and 6.2-8.2% for men[19,20]. The World Mental Health Surveys have observed higher 12-month prevalence rates in high-income (Northern Ireland: 3.8%; US: 2.5%; New Zealand: 2.1%) than in low- and middle-income countries (Colombia: 0.3%; Mexico: 0.3%)[21].

There is evidence that some features of a traumatic event are more likely to trigger PTSD. For example, there are markedly lower rates of PTSD following natural disasters (typically 5-10%) relative to sexual assault (>40%)[20,22]. Overall, interpersonal violence typically leads to higher rates of PTSD[23,24]. In fact, the World Mental Health Surveys found that organized, physical or sexual violence increased the risk for PTSD[25]. Adjusting for methodological factors, reported torture is the strongest factor associated with PTSD, followed by cumulative exposure to potentially traumatic events[26].

In studies that have focused on individual countries (which is methodologically sounder, because it allows greater consistency of potential contextual confounding influences), there is evidence that the prevalence of PTSD is higher in certain ethnic groups, such as Hispanics and African Americans in the US[27,28]. The finding that Hispanics are more at risk of PTSD has been confirmed in military samples[29]. Of course, these differences may be ascribed to differential access to health resources, ethnic discrimination, or socio-economic factors, so that their interpretation remains uncertain.

Epidemiological studies suggest that most people with PTSD have comorbid disorders, particularly depression, anxiety disorders, and substance use disorder[20,30,31]. These high rates of comorbidity may be explained by psychiatric disorders predisposing people to experience traumatic events[31], or by traumatic events or PTSD itself triggering the development of other psychiatric conditions. Indeed, depression may result from prolonged learned helplessness, and substance use disorder may be due to self-medication[32]. Greater exposure to traumatic events is likely to result in greater comorbidity[21].

COURSE

For many years it was believed that PTSD followed a linear course after trauma exposure, with a trend for symptoms to be highly prevalent in the days and weeks after exposure and to remit over the following months in most people. This view was supported by much evidence that rates of PTSD diminished by 6 months after trauma with respect to rates in the weeks after the event[33,34]. The exception to this trend was delayed-onset PTSD, which the DSM has traditionally defined as the onset of PTSD occurring at least 6 months after the traumatic event.

The understanding that PTSD follows a linear course has been challenged in recent years by evidence that the severity of the disorder fluctuates over time, that it can worsen or remit, and that this pattern can keep recurring, with the result that one's PTSD status is not static[35]. Recent studies have used latent growth mixture modelling to map the trajectories of the course of PTSD, reliably demonstrating a resilient class which consistently shows few PTSD symptoms, a recovery class with initial distress followed by gradual remission, a delayed reaction class with initial low symptom levels but increased symptoms over time, and a chronic distress class with consistently high PTSD levels[36-39].

Using network analysis, which considers the strength of relationships between symptoms, there is also evidence that the PTSD syndrome develops over time. In the acute phase after trauma, PTSD symptoms appear more loosely interconnected, while they become more closely related with the known factors (e.g., re-experiencing, active avoidance) as time progresses[40].

These convergent findings emphasize the challenges of predicting subsequent PTSD from acute reactions. Although there is evidence of an association between elevated symptoms in the acute phase and development of later PTSD[41-45], we do not have adequate cut-offs to reliably identify who will develop PTSD. One way of improving early detection comes from a consortium that recently pooled 2,473 trauma survivors from ten longitudinal studies using a likelihood estimate approach[46]. This study found that, in a patient with elevated early symptom severity, the concomitance of female gender, less than secondary level education, and exposure to past interpersonal trauma was associated with a 34% greater likelihood of developing PTSD.

RISK FACTORS

What predisposes only a small proportion of trauma survivors to develop PTSD? Many of the risk factors are in fact the same observed across several psychiatric disorders: female gender, low socio-demographic background, prior mental disorder, family history of mental disorders, and traumatic childhoods[47]. In terms of vulnerability factors more specific to PTSD, the disorder is more likely to occur after prolonged trauma or interpersonal traumatic events[47].

The subjective response to the trauma is also predictive, with acute dissociative reactions[48,49] and catastrophic appraisals[50-52] about the outcome of the event being strongly associated with later PTSD severity. The post-trauma environment is also important, with low social support and ongoing stressors contributing to risk for PTSD development[47].

MODELS OF PTSD

Neurobiological models

Most theories of PTSD invoke processes involving fear conditioning. This model posits that at the time of trauma the surge of stress hormones released in association with the fear experienced by the individual results in strong associative learning between cues present at the time of trauma and fear responses. The associated cues assume the property of predicting future threat, thereby resulting in a re-experiencing of fear when the individual is exposed to internal and external reminders of the trauma[53]. This model also posits that recovery from initial stress reactions usually involves extinction learning, in which one is repeatedly exposed to reminders of the trauma but on these occasions there is no adverse consequence; accordingly, there is new learning that the previously conditioned cues now signal safety[54].

There is evidence of neural changes in people with PTSD that are consistent with circuitry known to be implicated in fear conditioning: the amygdala, prefrontal cortex, and the hippocampus. Many studies indicate that PTSD is associated with a smaller size of the hippocampus, with meta-analyses reporting that this finding is observed bilaterally[55]. A recent consortium study including 1,868 participants (794 with PTSD) found an average smaller size of the hippocampus in those with the disorder[56]. The extent to which a smaller hippocampus is a consequence of PTSD or a risk factor has yet to be definitively addressed. One study compared monozygotic co-twins who either did or did not serve in Vietnam[57], and found that veterans with PTSD had smaller hippocampi than Vietnam veterans without PTSD, but the co-twins of those with PTSD who had not served in Vietnam had hippocampi that were just as small. There is also much evidence of reduced volume of prefrontal regions in PTSD[58], consistent with proposals that PTSD patients have problems with extinction learning.

Other studies have used fear provocation tasks to activate the threat network in PTSD patients. The most replicated finding is evidence of underactivation of medial prefrontal cortex regions, consistent with the notion of an impairment of the regulatory processes that promote extinction[59]. There is also evidence of dysfunctions in threat detection, executive functioning, emotion regulation, and contextual processing[60,61].

Noradrenergic dysregulation is well-documented in PTSD, and has been postulated to be key to the development of intrusive re-experiencing of trauma memories[62-65]. This notion is supported by evidence that prazosin (a noradrenergic receptor inhibitor) is efficacious in reducing nightmares and re-experiencing symptoms of PTSD[66,67]. Further support is from evidence

that administration of propranolol (a beta-adrenergic antagonist) in the hours after trauma exposure limits subsequent reactivity to reminders[68], although it does not prevent overall PTSD[69,70].

The PTSD field has also focused on the glucocorticoid system. Although increased cortisol levels are typically associated with chronic stress, PTSD is often linked with *lower* cortisol levels[71]. Further, lower cortisol levels shortly after trauma predict subsequent PTSD severity[72]. This paradoxical finding has been interpreted in terms of cortisol binding to the glucocorticoid receptors in a negative feedback loop that promotes homeostasis of the stress response[73]. This proposal posits that lower cortisol in PTSD may result in elevated ongoing activity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in exaggerated catecholamine response and consequent over-consolidation of trauma memories. This idea has received some support from studies reporting that, in animal models, the administration of hydrocortisone shortly after stressor exposure results in reduced subsequent PTSD-like reactions[74]. There is pilot evidence that this procedure also limits subsequent PTSD symptoms following trauma in humans[75].

A consistent pattern in PTSD research is that females are twice as likely to develop PTSD as males[76]. Females have greater noradrenergic response to aversive stimuli[77,78], display greater context-potentiated startle magnitude[79], and show greater amygdala reactivity after threatening stimuli[80]. The menstrual phase (reflecting cycling levels of progesterone and estradiol) impacts PTSD phenomena, suggesting that sex hormones play an important role in this regard. Females with PTSD (relative to those without PTSD) show impaired extinction learning in the mid-luteal phase (when progesterone and estradiol levels are high)[81]. Indeed, females are more likely to experience flashback memories if they are exposed to traumatic events during the mid-luteal phase[82]. One reason why progesterone may facilitate emotional memories is that it binds to glucocorticoid receptors, thus affecting the release of endogenous glucocorticoids[83].

Supporting fear conditioning models is the robust finding of enhanced psychophysiological reactivity to reminders of the trauma in people with PTSD. Script-driven imagery paradigms direct participants to listen to pre-recorded accounts of their trauma, during which heart rate, skin conductance or facial electromyogram measurements are obtained; this typically results in greater reactivity in PTSD relative to non-PTSD participants[84]. Consistent with fear conditioning models is also the evidence of elevated resting heart rate in the days after trauma in those who subsequently develop PTSD[85], particularly in response to trauma reminders[86]. Further, people with PTSD display impaired extinction learning[87], and deficient capacity for extinction learning is a risk factor for PTSD[88-90].

Genetic factors

The well-documented fact that the vast majority of people who are exposed to trauma do not develop PTSD[40] highlights that there are key individual differences in propensity to manifest this disorder. Much evidence indicates that genetic factors play an important role, accounting for 30-72% of the vulnerability to develop PTSD[91,92].

Many studies have attempted to link PTSD with genetic candidates, and not surprisingly genes associated with PTSD are also linked with other common psychiatric disorders, including major depression, generalized anxiety disorder, panic disorder, and substance use[93]. For example, numerous studies have pointed to the functional polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) across many disorders. The short allele (5-HTTLPR S), which reduces serotonergic expression and uptake by nearly 50%[94], has been linked with impaired extinction learning in both mice and humans[95]. Gene x environment association studies also show that a functional variant in FKBP5, a gene encoding a co-chaperone of the glucocorticoid receptor, increases risk for PTSD following trauma[96].

Over 50 gene variants have been linked with PTSD, involved in the function of HPA axis; noradrenergic, dopaminergic and serotonergic systems; and neurotrophins[97]. However, this field is characterized by poor replication of findings, and accordingly there is convergent agreement that the most promising avenue for understanding the genetic basis of PTSD is via polygenic approaches. The largest genome-wide study to date was conducted by the Psychiatric Genomics Consortium – Posttraumatic Stress Disorder Group, which recently reported an analysis of 20,730 people: no single nucleotide polymorphism was found to be significantly associated with PTSD, but the study did find a polygenic risk profile that overlapped with risk for schizophrenia[98].

The genetic vulnerability to PTSD appears to be moderated by contextual factors. Early life stress is particularly relevant, with evidence that childhood trauma modifies the genetic risk for PTSD[96]. Epigenetic studies in PTSD have typically focused on DNA methylation, with a primary focus on peripheral indicators of candidate genes[99], and epigenetic regulation of the HPA axis in particular[100]. Distinctive methylation in PTSD has been documented in a number of genes, including NR3C1, CRHR1 and FKBP5[97]. However, the evidence has relied to date on peripheral blood assessments, that may not reflect central mechanisms occurring in neural circuits.

Cognitive behavioral models

Although most cognitive behavioral models recognize the role of fear conditioning in the etiology of PTSD, they also place considerable emphasis on memory organization[101]. Cognitive models propose that trauma memories are encoded in a distinctive manner, as a result of the elevated arousal at the time of trauma. They tend to be encoded in predominantly sensory modalities, with a fragmented and disorganized sequencing, thereby reducing the likelihood that the memory is adequately embedded into one's autobiographical memory base[102]. There is some evidence that interfering with the visual memory sys-

tem during the consolidation phase after trauma exposure can limit subsequent PTSD symptoms[103].

Much emphasis is also placed on the extent to which people appraise the traumatic event, their responses to it, and their future likelihood of harm. It is postulated that excessively negative appraisals tend to exaggerate the individual's sense of threat, thereby maintaining PTSD[104,105]. As noted above, there is abundant evidence of the predictive role of catastrophic appraisals in the development and maintenance of PTSD, as well as of their decline after successful therapy[106]. These appraisals tend to result in strong avoidance of potential threats, which impairs emotional processing of trauma memories and extinction learning[107].

Implicit in most cognitive (and biological) models of PTSD is the attentional bias towards threat, as reflected in the inclusion of hypervigilance in the DSM-5/ICD-11 descriptions of PTSD. Using a range of experimental paradigms, PTSD has been found to be characterized by a strong bias towards potentially threatening stimuli[108-110]. Relatedly, PTSD patients have problems with disengagement from threat, response inhibition, and orienting[62]. The resulting intrusions and arousal can contribute to the well-documented deficits in neuropsychological functions such as concentration, sustained attention, executive control, and working memory[111].

PREVENTION

Defence organizations have sometimes tried to prepare their personnel for deployment to combat by targeting key mechanisms known to increase the risk for PTSD.

One example comes from an Israeli initiative that built on evidence regarding the attentional biases in PTSD. The disorder is characterized by both a bias towards threat[109,112] and a bias towards avoidance of the threat[113,114], resulting in greater attentional variability[115]. A computerized prevention program tested in Israeli soldiers involved training them to control their attentional biases by using a modified dot-probe task administered prior to deployment. The study found that soldiers receiving the program had fewer subsequent PTSD symptoms than those in a control condition, and this result was mediated by a reduction in attentional variability[116]. This program appears to be a promising preventive strategy, at least in military personnel, and has been found to reduce PTSD symptoms in treatment seeking combat veterans[117].

PSYCHOLOGICAL TREATMENTS

The treatment of choice for PTSD is trauma-focused cognitive behavior therapy (TF-CBT), as suggested by most treatment guidelines[118,119].

There are numerous variants of TF-CBT, including prolonged exposure, eye movement desensitization and reprocessing, cognitive therapy, cognitive processing therapy, and imagery rescripting therapy. Although these treatments are presented as distinctive, they all essentially comprise emotional processing of the traumatic memory and integration of new corrective information. This form of therapy has been shown to be effective in many populations, including victims of traumatic injury and assault, sexual assault, combat, terrorist attacks, displacement, and childhood sexual abuse[120-125].

The core component of this treatment typically involves exposure, i.e. the patient is directed to engage with the trauma memory for a prolonged period. This strategy is commonly conceptualized as a form of extinction learning, insofar as the person learns that the trauma reminder is no longer a signal of threat. Although this exposure was traditionally implemented for 40-60 min, later trials have shown that it can be effective with repeated sessions lasting 20 or even 10 min[126,127].

The introduction of the diagnosis of acute stress disorder triggered a series of early intervention studies targeting people who were regarded as being at high risk for PTSD development. These programs evaluated abridged versions of TF-CBT (usually 5-6 sessions), and typically found that they were more efficacious than control conditions[128-132]. Meta-analytic studies have supported the utility of early targeted intervention to limit later PTSD[133,134]. However, one large study found that, whereas early provision of TF-CBT facilitated recovery, all patients typically adapted in the long-term regardless of the type of intervention[135].

Although TF-CBT has been shown to be effective in PTSD, it is important to note that only two-thirds of patients respond adequately to this intervention[136]. This has led to attempts to augment treatment, mostly based on pharmacological or psychological strategies to increase extinction learning, building on animal neuroscience work[137,138]. These approaches have targeted the mechanisms of extinction by combining exposure therapy with device-based, pharmacological or behavioral techniques that promote neural processes to enhance associative learning.

Device-based techniques include repetitive transcranial magnetic stimulation (rTMS) focusing on the ventromedial and dorsolateral prefrontal cortex, areas that are relevant to extinction learning. Several studies suggest that rTMS is superior to sham in augmenting exposure therapy[139,140].

One of the earlier pharmacological attempts used D-cycloserine, an antibiotic that acts as an agonist of N-methyl-D-aspartate (NMDA) receptors and promotes extinction learning in animals. A series of trials tested this drug to augment exposure therapy for PTSD. One study found evidence of a faster rate of symptom reduction[141], while another reported a detrimental effect[142], and three further trials found no effect[143-145]. The conclusion was that this adjunctive treatment is not useful[146].

The other pharmacological adjunct that has received considerable recent attention is methylenedioxy-methamphetamine (MDMA). This drug enhances activity in the ventromedial prefrontal cortex, which is key for extinction. Furthermore, it increases cortisol release, which can promote emotional engagement and enhance extinction[147]. Several small trials suggest that MDMA-assisted psychotherapy does have a superior effect[148,149], and large multi-site studies are now underway[150].

Further attempts to augment PTSD treatment have combined

exposure with acute bouts of exercise, because this can promote extinction retention (possibly via increased release of brain-derived neurotrophic factor)[151]. One small pilot study did show that acute bouts of exercise after exposure can boost the effect of therapy[152].

Although some attempts to augment psychotherapy for PTSD appear to offer promise, we are not at the point of recommending any of them. Larger trials, more targeted augmentation strategies, and replication of findings are needed before we are in a position to integrate these approaches into clinical practice.

PHARMACOLOGICAL INTERVENTIONS

There is much less compelling evidence for pharmacological treatment of PTSD. In fact, psychotherapeutic approaches yield more robust effect sizes than pharmacological agents, and the potential for adverse side effects and relapse after discontinuation of medications supports the idea, endorsed by treatment guidelines, that psychotherapy should be the first line of treatment.

At present, two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, are the only medications approved by the US Food and Drug Administration for treatment of PTSD, although their effect size in this disorder is small (0.23; 95% CI: 0.12-0.33)[153]. There is also some evidence for efficacy of the selective noradrenaline reuptake inhibitor (SNRI) venlafaxine. One common reason why these drugs are prescribed is that they are efficacious in treating major depressive disorder, which is highly comorbid with PTSD.

Other pharmacological agents have been used for specific PTSD symptoms: as noted above, multiple studies have found prazosin (an alpha1-adrenergic antagonist) to be effective in reducing nightmares and hyperarousal[154]. Benzodiazepines have often been prescribed in the context of PTSD, but they are generally contraindicated, because of limited efficacy and risk of abuse.

Over the past 20 years, there have been attempts to limit PTSD development by the early administration of agents that target key neurobiological processes occurring in the initial days after trauma exposure.

The proposition that PTSD is largely driven by a surge of noradrenergic release in the acute post-trauma period has led to attempts to reduce noradrenergic activity. These attempts have focused on administering propranolol (a beta-adrenergic antagonist) in the hours or days after trauma exposure, because of preclinical evidence that this drug blocks fear memory reconsolidation[155]. As noted above, the initial trial of propranolol found that it resulted in reduced subsequent reactivity to trauma reminders, even though it did not reduce the severity of PTSD[68]. Subsequent trials were negative, and one meta-analysis concluded that there was no evidence for the utility of propranolol in limiting PTSD development[156].

It is also worth noting that there is indirect evidence of a potentially protective role for morphine in the acute phase after trauma. The locus coeruleus, which produces noradrenaline, is inhibited by morphine, and animal work indicates that morphine injections into the amygdala impair memory for fear conditioning in rats[157]. It has been suggested that the administration of morphine in the initial days after trauma exposure may be associated with reduced PTSD at follow-up[158,159], but no randomized controlled trials are available.

The evidence that low levels of cortisol after trauma are predictive of subsequent PTSD[72,160] has led to attempts to limit later PTSD severity by increasing cortisol levels in the period shortly after trauma exposure. As noted above, animal studies reported that administering hydrocortisone to rats after exposure to a stressor results in less fear behavior compared to placebo[74]. Similarly, administering cortisol to humans immediately after exposure to a stressful event results in fewer memories of the event[161,162]. Indeed, a preliminary study found that the administration of cortisol within hours of trauma exposure is more efficacious that placebo in limiting subsequent PTSD[75].

MAJOR CHALLENGES FOR THE PTSD FIELD

The diagnostic conundrum

One of the main challenges in the PTSD field is the fact that we have two official definitions of the disorder that are somewhat different. As noted above, whereas the DSM-5 definition intentionally encompasses a broad range of trauma-related presentations, the ICD-11 adopts a much narrower approach focused on fear circuitry.

This situation is problematic, because multiple studies indicate that PTSD is diagnosed at higher rates using the DSM-5 criteria compared to the ICD-11 guidelines[163-165], although there are also some reports that rates are comparable[166]. Further concern comes from the evidence that the two diagnostic systems tend to identify different individuals, with one study showing that only 42% of trauma survivors were diagnosed as having PTSD using both definitions[163].

There has been considerable discussion about the relative merits of the two diagnostic definitions. On the one hand, it has been emphasized that the DSM-5 definition is applicable to a larger number of trauma survivors[164]. On the other, it has been argued that moving beyond the traditional focus on fear symptoms undermines much of the evidence base of exposure-based treatments for PTSD and may increase the rate of psychiatric comorbidities[167]. Actually, some studies suggest that the ICD-11 definition of PTSD is associated with less psychiatric comorbidity[166,168], while others indicate that there is not a marked difference in this respect between the DSM-5 and ICD-11 definitions[163,164]. A further argument is that, when using the DSM-5 definition of PTSD, there are 636,120 permutations of how the disorder may present[169], which may impair the identification of meaningful biomarkers.

Delayed-onset PTSD

Delayed-onset PTSD, traditionally defined as PTSD that develops at least 6 months after exposure to trauma, has been

described for many years, with cases of PTSD reportedly commencing decades after the trauma occurrence[170]. Systematic reviews indicate that, of those people who develop PTSD, approximately 25% may be delayed-onset cases[171,172].

Longitudinal studies suggest that most of these cases actually experience sub-syndromal levels of PTSD in the acute phase, and this reaction subsequently compounds to a more severe disorder, so that the diagnostic threshold for PTSD is surpassed[173-176]. Systematic reviews recognize, however, that some people do apparently have an initial period of minimal symptoms and subsequently develop PTSD[172]. This latter scenario has been particularly noted in military cohorts, where delayed-onset PTSD is markedly more common than in civilian trauma survivors[177]. It appears that many troops return from deployment with little indication of stress response, while on follow-up they display full PTSD symptoms.

Different theories have been put forward for delayed-onset PTSD. It is possible that, in the initial phase, denial and numbing inhibit PTSD responses and that, as time progresses and numbing abates, PTSD symptoms emerge[178] – however, no strong evidence supporting this hypothesis is available. A second possibility is that, immediately after the traumatic event, people are more preoccupied with immediate needs (such as pain, legal proceedings, post-deployment activities, or dislocation) that distract their attention from their stress reactions[179] – again, there is a paucity of evidence in favor of this explanation. The observation that many delayed PTSD cases experience significant acute stress responses that subsequently worsen has prompted the proposal that delayed PTSD may be caused by additional stressors in the post-trauma phase, compounded with diminished resources to deal with these demands[180] – indeed, there is evidence that delayed-onset PTSD is predicted by the severity of post-trauma stressors[135,173,181,182]. One further possibility is that relief from the immediate threat of danger may provide people with a temporary sense of safety, that subsequently gives way to ongoing perceptions of threat, leading to PTSD – this interpretation may be especially applicable to military cohorts, who may be relieved by abandoning the combat zone, but may then have difficulties to readjust to ordinary life[177].

PTSD in poorly resourced countries

The majority of people with PTSD do not access care. This situation is particularly stark in low- and middle-income countries, which are disproportionately affected by wars, natural disasters, and humanitarian crises that can facilitate the emergence of mental disorders such as PTSD[183]. A major challenge for the management of PTSD worldwide is the dissemination of evidence-based interventions that can be scaled up affordably in settings lacking adequate numbers of mental health specialists.

It is well documented that evidence-based programs can be implemented effectively in low- and middle-income countries[184,185]. However, they are rarely applied in ordinary conditions, because they typically involve many therapy sessions, require mental health specialists, and are predicated on a skilled diagnosis of PTSD. In response to this situation, there has been a concerted effort in recent years to engage in "task-shifting", which involves training non-specialists to deliver evidence-based programs to address a range of common mental disorders[186]. This approach has been used successfully in treating PTSD[187,188].

While some programs have been successful in addressing PTSD in low- and middle-income countries by adopting a transdiagnostic approach, that does not require sophisticated diagnostic skills but relies on targeting common problems that underpin anxiety and depression[189], others have used a modular approach that tailors key strategies to the primary problems that a person is experiencing[190,191]. Despite these promising developments, massive challenges remain in disseminating affordable evidence-based programs in low- and middle-income countries, because most of them lack the resources to implement and sustain mental health initiatives.

CONCLUSIONS

Since the introduction of the PTSD diagnosis 40 years ago, our understanding of traumatic stress conditions has grown significantly. However, despite this burgeoning knowledge, our capacity to facilitate recovery from PTSD appears to have stalled over recent decades. Although our treatments are reasonably efficacious, too many patients fail to respond optimally, and many more are not able to access them.

These problems remain a major challenge for the field. Considering the millions of people directly affected by trauma, the limited success in providing the majority of them with efficacious treatments is resulting in a major public health burden. Identifying novel mechanisms that can be translated into optimizing treatment outcomes, and overcoming the major barriers facing most health systems in delivering evidence-based treatments, should remain the top priorities for the field of traumatic stress in the years to come.

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