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Post-Traumatic Stress Disorders (T Geracioti and K Chard, Section Editors)

Treatments for Post-traumatic Stress Disorder: Pharmaceutical and Electrophysiologic Considerations

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Opinion statement

Most individuals who experience traumatic events remain asymptomatic or symptoms resolve quickly, but in a minority who develop post-traumatic stress disorder (PTSD), symptoms can persist for decades and can be associated with psychiatric and medical comorbidities and poor social and occupational functioning. Currently, first-line pharmacotherapies are selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) for core symptoms and in individuals with unremitting nightmares, prazosin, is commonly used and often effective. This review appraises these commonly used evidence-based treatments and their conceptual underpinnings. It follows with a discussion of concepts underlying emerging treatment research and development, in particular the use of combined psychotherapeutic-pharmacologic

approaches and electro-physiological technologies that stimulate neural circuits and their potential uses. While the evidence for combined psychotherapy and either pharmacological or physiological treatments is only now emerging, some of these modalities appear promising.

Introduction

Post-traumatic stress disorder (PTSD), as a diagnostic entity, emerged in the early 1980s when the diagnostic criteria were first included in the Diagnostic and Statistical Manual for Mental Disorders, Version III (DSM-III). These criteria have since been revised to the most recent published in DSM-5 [1]. PTSD is atypical among the mental health disorders in that the disease model for symptom emergence is similar to that for infectious diseases in which the precipitation of symptoms follows exposure of a vulnerable host to a pathogenic vector, i.e., an infectious organism in the case of infections and a traumatic event in the case of PTSD. The vector is incorporated into the DSM-5 diagnostic criteria as criterion A defined as exposure to actual or threatened death, serious injury, or sexual violation. The event is either experienced directly, by witnessing it in person as it occurred to others, by learning that it occurred to a family member or close friend, or by experiencing repeated or extreme exposure, such as in the case of first responders [1]. Where rates of exposure have been measured, the lifetime prevalence of the exposure to a traumatic event is high and cumulative over a lifetime, with putative rates ranging from 17 to 89 % [2–5]. There is credible evidence that the risk for PTSD follows a dose–response relationship, increasing with duration and intensity of trauma exposure, and that some types of events are more 'pathogenic' than others, although there is no evidence that the biological mechanism of injury varies by trauma type [6–8, 9•].

The behavioral manifestations that result from exposure to a category A event constitute further the DSM-V diagnostic criteria for PTSD, all associated with the event, including the presence of intrusive symptoms (criteria B); persistent avoidance of stimuli, e.g., avoidance of thoughts/feelings and avoidance of external reminders (criteria C); negative alterations in cognitions/mood, e.g., difficulty remembering, exaggerated negative beliefs/expectations, distorted cognitions, and anhedonia (criteria D); and marked alteration in arousal or reactivity, e.g., irritable behavior, angry outbursts, reckless or self-destructive behavior, hypervigilance, and physiological arousal (criteria E). To qualify for the diagnosis, PTSD symptoms must be present for at least 1 month (criteria F) and must cause either clinically significant distress or functional impairment (criteria G) [1]. The disorder can begin acutely and fail to resolve or emerge over time (from months to years later) [1]. While the common vocabulary provided by DSM diagnostic criteria for PTSD has formed a foundation for advancements in research, inherent in the behaviorally based definition are conceptual constraints that can impede biologically based disease discovery. We discuss current evidence-based PTSD treatment, followed by a discussion of concepts from the neuroscience of fear learning and memory, now actively being researched as they relate to PTSD treatment. These concepts which integrate the new biological (molecular, cellular, and neural connectivity) knowledge offer a translational platform for novel physiologic and pharmacologic approaches to PTSD treatment development.

Pharmacotherapy: evidence base

Pharmacotherapy is a common treatment for PTSD [10•, 11]. The pharmacy records of the US Department of Veterans Affairs in 2004 show that most veterans diagnosed with PTSD received psychotropic medication (80 %); among those, 89 % were prescribed antidepressants, 61 % anxiolytics or sedative hypnotics, and 34 % antipsychotics [10•]. Data from the Market scan database, a database that compiles claims from US private insurers, shows that medication use is common in adult civilians with PTSD, with 60 % receiving

psychotropic medications [12••]. Having a co-occurring diagnosis with PTSD is the most robust predictor of medication use for both the veterans and civilians, and whereas disease-specific use of medications for both PTSD and co-occurring disorders is common, much use is unrelated to the diagnosis, i.e., it appears to target specific symptoms (e.g., insomnia, anxiety, nightmares, and intrusive imagery), rather than the diagnosed illness as a whole [10•, 11, 12••, 13, 14].

Overall, the clinical use of pharmaceutical treatments for PTSD has changed little in the past decade, and adequately powered and well-designed PTSD medication trials are relatively few [12••, 15, 16]. In fact, the Institute of Medicine and the National Institute of England have argued that there is insufficient evidence to show proven efficacy of any drug or drug class, although the strongest evidence (i.e., largest number of subjects studied) has been with selective serotonin reuptake inhibitors (SSRIs), considered the treatment first-line pharmaceutical treatment for PTSD and the only class of drugs approved by the Federal Drug Administration [see 12••, 15 for review]. There is evidence for the efficacy of serotonin-norepinephrine reuptake inhibitors (SNRIs) for PTSD as well, but the evidence base is smaller than that for SSRIs, and SNRIs are not FDA approved [17, 18].

An example of a medication being used to target specific PTSD symptoms is prazosin, an α1-adrenergic blocker that has been increasingly accepted as a treatment for PTSD-related nightmares. Its use is supported by an accumulating number of clinical trials, most of them positive [14, 19•]. Until the past few years, the approach to pharmaceutical development for PTSD has relied on goals of either mitigation of global PTSD symptoms, predicated on normalizing putative underlying pathological processes, or upon mitigation of targeted symptoms, e.g., nightmares, by modifying biological processes driving those symptoms [12••]. Increasingly, however, new discoveries of the underlying genetics, gene expression, molecular biology, and cell signaling of neurotransmitter systems responsive to stress offer tantalizing new pharmaceutical targets. However, since the specific mechanism(s) of injury in PTSD are unknown, the choice of which targets will effectively reduce overall symptoms has remained elusive, and few large-scale trials have been implemented, although some compounds, e.g., nepicastat (dopamine beta-hydroxylase antagonist), ganaxolone (synthetic analogs of allopregnenolone, a neurosteriod), mifepristone (glucocorticoid antagonist), and neuropeptide-Y, are undergoing small clinical trials in humans [20, 21].

In testing of genetic overlap for PTSD with bipolar disorder, major depressive disorder (MDD), and schizophrenia (SCZ) cohorts from the Psychiatric Genomics Consortium, PTSD diagnosis was observed to be associated with risk of bipolar disorder, but not MDD or SCZ; however, a recent study using the Positive and Negative Syndrome Scale (PANSS) showed some overlap in symptom structure between PTSD and SCZ, except that PTSD patients were less symptomatic on psychosis-related factors and more symptomatic on depression [22, 23]. Despite symptom structure similarities, however, a large, randomized double-blind placebo-controlled multicenter trial that tested the efficacy of 6-month treatment with risperidone in veterans with SSRI-resistant PTSD failed to show a significant reduction in PTSD symptoms when compared with placebo [24].

While some treatment trials targeting general PTSD symptoms are ongoing, recent pharmaceutical development has focused on strategies to modulate transmitter systems involved in learning and memory, with the key

conceptual underpinnings of this research being to elucidate and modify the neurobiology of fear acquisition, extinction, and memory reconsolidation [25]. Likewise, neural networks involved in fear memory acquisition and maintenance are key targets of inquiry for the development of physiological interventions [26–28]. This targeted approach holds promise but may have limits in its ability to address the full range of post-trauma pathology [29••].

Underlying concepts and biology

Memory acquisition and consolidation in organisms as complex as humans involve multiple layers of neural activity from the macro- to micro-level, i.e., 1) system-level communication (neural networks), 2) cell-to-cell communication (neurotransmitter systems), and 3) intracellular changes (epigenetic and protein) [30–32]. The core pathology of PTSD, fear memories, are long lasting and intensely emotion laden, but recent research shows memory longevity and strength to be a dynamic process that is dependent on contextual and biological influences [33, 34]. At the core of fear memory research design are concepts of fear extinction and reconsolidation, which are also the conceptual basis for cognitive-based verbal treatments for PTSD.

Most simply, extinction learning can be defined as learning in which conditioned responding to a stimulus decreases when the reinforcer is omitted. Extinction learning is thought to be new learning that overrides prior aversive memory. Thus, in this paradigm, extinction does not alter the threat memory itself but, instead, regulates its expression through an inhibitory (cognitive) influence of the pre-frontal cortex (PFC) over the amygdala (emotions). Like other forms of learning, extinction occurs in three phases: acquisition, consolidation, and retrieval, each of which depends on specific structures (amygdala, pre-frontal cortex, and hippocampus in particular) and molecular mechanisms (receptors and signaling pathways) [35, 36]. A number of pharmacological reviews have been published on novel compounds that facilitate consolidation and retrieval of extinction; some of these compounds are under study for use in PTSD treatment, and others are being proposed based on recent pre-clinical research [12••, 20, 37••].

Whereas extinction is thought to create a new, competing memory trace that decreases fear expression, reconsolidation is hypothesized to be process involving protein synthesis by which memories, when reactivated, enter a transient, labile state that is followed by a re-stabilization, labeled reconsolidation. Reconsolidation mediates memory maintenance and updating, including strengthening or diminishment; memory diminishment can be accomplished by use of a protein inhibitor, e.g., anisomycin, but most protein inhibitors are too toxic for human use. Consequently, pre-clinical research on memory reconsolidation is proceeding rapidly, but most human reconsolidation research have been limited to propranolol, which interferes with the noradrenergic signaling thought to be necessary to strengthen and encode the emotional components of memory [38, 39]. During the reconsolidation process, memory persistence can be influenced by various means (behavioral, physiological, and pharmaceutical) that lead to the potential memory updating (reviewed in detail by Agren) [40••].

Cognitive behavioral approaches: state of the art

Two cognitive behavioral (CBT) treatments, prolonged exposure (PE) and cognitive processing therapy (CPT), have a strong evidence base [15, 41, 42]. Typically, PE is conducted in 8 to 15 sessions, lasting 60 to 90 min each and involves imaginal exposure in an office setting as well as in vivo exposure, i.e., systematically approaching safe situations that are perceived to be dangerous or are avoided because they are reminders of the trauma. Treatment procedures (i.e., exposure to trauma-related cues) are posited to assist in the development of new associations that compete with (or inhibit) pathological fear memories in PTSD, i.e., extinction learning. CPT is based on a social cognitive theory of PTSD which holds that maladaptive construal of the trauma leads to pathological emotional responses and behaviors, and that changing maladaptive beliefs associated with the trauma are posited to result in recovery. While the treatment protocol in its original form includes a specific exposure component involving writing a detailed narrative of the trauma and reading it aloud in session, a version of the protocol omitting exposure to the trauma narrative has also been developed and has been demonstrated to be equally effective [43]. The underlying biological mechanisms, extinction, and reconsolidation remain under investigation at the pre-clinical and clinical levels as they apply to these treatment modalities [36, 44–46]. While there is solid evidence for effectiveness of these CBT treatments for PTSD, they are not universally beneficial. In fact, non-response to CBT in individuals with PTSD can be as high as 50 %, leaving considerable room for improvement from new approaches, such as augmentation with either pharmaceuticals or behavioral technologies [12••, 47].

Pharmacologic and combined pharmacologic/behavioral approaches

Any salutatory effect of pharmaceutical augmentation with CBT could be hypothesized to be simply additive, conceived of as a facilitator of extinction learning, reconsolidation, or both. Sertraline has effects on fear conditioning and on pre-frontal-amygdala connectivity [48, 49]. In a series of studies, SSRIs (sertraline and paroxetine) were add-ons to CBT studies, or visa versa, with mixed results [see [50, 51• for review]. In a small study, in which subjects were randomized to SSRI (paroxetine) with CBT augmentation or CBT alone, the paroxetine augmentation initially appeared to be more effective, but the advantage disappeared by follow-up [50]. The authors speculated that the initial enhanced efficacy of the combined treatment reflected additive mechanisms but based on serotonin effects on fear learning, other mechanisms may be at play [48–50].

In contrast to use of adjunct SSRI-CBT treatment, recently studied CBT augmentation is predicated upon the enhancement of fear extinction by the pharmaceutical agent; thus, the drug is given intermittently, proceeding psychotherapy, rather than continuously as has been the case with SSRI augmentation. While there are many putative fear extinction enhancers identified in pre-clinical studies, few have yet been studied in humans, the first being *d*-

cycloserine (DCS), an *N*-methyl-*d*-aspartate (NMDA) glutamate receptor partial agonist [52]. The treatment trials have recently been reviewed; results are mixed [51•, 53]. In the study by Litz et al., DCS augmentation, combined with imaginal exposure (six sessions), did significantly worse than placebo [54]. Likewise, De Kleine et al. found no overall effect of DCS on augmentation of PE (12 sessions), but did report higher symptom reduction between therapy sessions in a subgroup with severe PTSD symptoms [55]. Both of these studies used 50 mg DCS an hour prior to the exposure treatments. The other two trials that used virtual reality exposure (VRE) in conjunction with DCS were more positive. In a randomized, double-blind, placebo-controlled trial in which the subjects were given 100 mg of DCS or placebo, Difede et al. showed earlier and greater improvement in the VRE-DCS group than the VRE-placebo group, as well as significantly greater (46 vs 8 % at post-treatment; 69 vs 17 % at 6 months) remission rates [56]. The study by Rothbaum et al. of 167 subjects was not as positive. A primary analysis of the outcome showed no advantage of DCS augmentation, but based on a secondary analysis, alprazolam augmentation impaired recovery whereas DCS enhanced virtual reality outcome in patients who demonstrated within-session learning [57].

These findings highlight the complexity of memory modulation, suggesting that similar to findings observed in animal models, extinction or enhancement of fear memories depends on contextual and biological factors that may vary across studies [36, 37••, 58••, 59]. Despite these complexities, pharmaceutical extinction learning enhancers are an extremely active area of pre-clinical inquiry, with many putative new pharmaceutical enhancers being proposed for future clinical trials in humans, especially those targeting glutamate signaling, but completed human trials are few [20]. One trial of rapamycin, an inhibitor of mTOR kinase (a critical regulator of mRNA translation known to be involved in various long-lasting forms of synaptic and behavioral plasticity), is currently underway as a single-dose challenge in men with combat-related PTSD for its potential in reducing the emotional strength of the PTSD-related traumatic memory (Clinical trials.gov).

Electro-physiological approaches

Considerable progress has been made in identifying neural circuits underlying fear learning, with prominent brain areas being the amygdala, hippocampus, ventromedial pre-frontal cortex (vmPFC), dorsal anterior cingulate cortex (dACC), and the insular cortex [60–65]. Newer imaging techniques show evidence of dysregulation of these neural circuits in PTSD [66, 67]. Specifically, functional imaging studies demonstrate that individuals with PTSD exhibit hyper-responsive amygdala activity to trauma or fear-related stimuli as well as during the resting state [26, 67–70]. The impaired ability for extinction has been linked to decreased activity in the vmPFC and hippocampus, with hyperactivity demonstrated in the amygdala and dACC, all potential targets of neuromodulation by various means, including neural stimulation techniques used either alone or as augmentation to CBT [71, 72]. While these methods are applied across neural networks, they likely involve reconsolidation at the cellular level, thus have been suggested as possible superior treatments for individuals with PTSD co-occurring with mild traumatic brain injury, in

contrast to verbal treatments such as PE, since reconsolidation presupposes that the memory trace is persistently altered, not inhibited, and therefore is not dependent upon an intact vmPFC for modulation of amygdalar activity [73•].

Repetitive transcranial magnetic stimulation

In repetitive transcranial magnetic stimulation (rTMS), a magnetic coil is placed on the scalp, applying a powerful and variable magnetic field to the underlying neural tissues. In vitro and in vivo studies suggest that is allows fields of neurons to be depolarized or hyperpolarized depending on the frequency of stimulation (see Fitzgerald et al. for review) [74]. Current technology limits the penetration of the magnetic field in rTMS to just a few centimeters; thus, at this time, deep structures (e.g., the amygdala) are not viable targets for rTMS. Protocols that use rTMS to treat PTSD have thus largely been similar to existing FDA-approved protocols for MDD, which target the dorsolateral pre-frontal cortex (dlPFC), reported to be abnormal in PTSD [26]. To date, there have been eight published studies (132 total subjects); five of these studies were randomized, controlled trials, all recently reviewed by Karsen et al. [75••]. All targeted pre-frontal areas and most used a figure 8 coil, although other types of coils were used including angular, circular, and H-coil. The main variables studied were effectiveness of treatment based on laterality (right vs left) and stimulation frequency (0.3, 1, 5, 10, and 20 Hz). In a double-blind placebo-controlled trial (30 subjects), Boggio et al. used high-frequency (20 Hz) transcranial magnetic stimulation (TMS) over ten sessions to compare the effectiveness of right versus left pre-frontal cortex stimulation for PTSD [76]. Both right- and left-sided treatment were effective in reducing PTSD symptoms compared to sham, with right-sided treatment (48.6 %) showing superior improvement over left-sided treatment (22.8 %) at post-treatment follow-up [76]. Treatment effects remained over months. Three of the randomized trials used rTMS alone. Two others tested TMS in combination with imaginal exposure. Osuch et al. used low-frequency (1 hz) inhibition over the right pre-frontal cortex and did not show benefit of TMS augmentation over exposure, whereas a trial by Isserles et al. which used high-frequency (20 Hz) stimulation of the medial pre-frontal cortex in combination with imaginal exposure showed benefit of this protocol over either TMS or exposure alone [77, 78]. Treatment was generally well tolerated with reports of mild adverse effects of headaches and dizziness, and no major adverse effects reported [75••].

Problematic for the theory underlying the use of high vs low frequency simulation is that both high (presumably stimulatory) and low (presumably inhibitory) frequency stimulation have both been shown to have benefits for PTSD symptoms. At this point, it is not clear if one protocol will become dominant as a method for using rTMS to treat PTSD or if several different protocols will be advanced. As technology improves, it is also possible that entirely different anatomical targets will be advanced.

Vagus nerve stimulation

Surgically implanted vagus nerve stimulation (sVNS) devices have been shown to be effective (now FDA approved) in the treatment of epilepsy and refractory depression [79, 80]. The surgically implanted electrode is placed around the vagus nerve at the level of the neck, and does not require any craniotomy or

direct access to the brain. The vagus nerve at the level of the neck carries efferent parasympathetic fibers (thought to comprise 20 % of total vagus nerve fibers) as well as afferent sensory fibers (thought to comprise 80 % of total vagus nerve fibers). With vagus nerve stimulation, there is activation of the nucleus solitary tract (NTS), then relaying of information to other targets that include the amygdala and hypothalamus [81]. Pre-clinical data demonstrate that amygdalar activation potentiates hippocampal activity, substantially enhancing memory consolidation. Clinical studies demonstrate enhanced neurocognitive performance with sVNS, perhaps a result of sVNS activation of polysynaptic norepinephrine projections to hippocampus, locus coeruleus and amygdala, as suggested by pre-clinical data [82, 83]. Adding to this growing literature are recent pre-clinical findings that sVNS-potentiated fear extinction learning is correlated with facilitated long-term potentiation in the hippocampus [84, 85]. Thus, taken together, pre-clinical and emerging clinical evidences support the use of vagus nerve stimulation as a potential treatment for PTSD, either alone or as a combined physiological-psychotherapy augmentation approach. Currently, surgically implanted vagus nerve stimulation (VNS) is the only treatment available for PTSD; however, non-invasive VNS technology is being developed. There are no published treatment trials for PTSD as yet using these non-invasive devices.

Deep brain stimulation

Deep brain stimulation (DBS) is a surgically implantable technique in which an implanted electrode repeatedly administers electrical stimulation [86]. Electrode placement may vary, but the current targets remain subcortical structures [87•]. Initially, DBS had been used to effectively treat movement disorders including Parkinson's disease or other dystonias [88]. Currently, it is being investigated for the treatment of major depression disorder (MDD) and obsessive compulsive disorder (OCD). DBS for MDD treatment targets a number of brain areas: the subgenual cortex, ventral capsule/ventral striatum, and the nucleus accumbens, and is reported to be a success in 40–60 % of recipients at 6 months to 1 year [89–92]. In addition to MDD, OCD has been successfully treated with DBS [93, 94]. Similar success has been noted in pre-clinical DBS studies of the basolateral nucleus of the amygdala (a key node in the fear learning network) that resulted in a decrease in fear-related behavior [95, 96]. A single clinical trial is currently ongoing of DBS to the basolateral nucleus of the amygdala to treat PTSD [97].

Other physiological technologies

Other potential technologies are 1) direct current stimulation (tDCS), a non-invasive neuromodulation technique using low current electrodes placed on the surface of the scalp that deliver current though the skull to modify cortical excitability; 2) cranial electrical stimulation (CES), a low-level alternating electrical current; 3) transcranial alternating current stimulation (tACS) which is similar to CES in that it uses a low-intensity alternating current applied to the head; and 4) electroconvulsive therapy (ECT) which is established as an effective therapy for treatment-resistant depression. While some of these methods show effects on memory and fear learning, none, as yet, has been studied for efficacy in treating PTSD except for ECT. In a single prospective study, six

bilateral ECT treatments were carried out twice weekly in 20 patients with medication refractory PTSD, resulting in 40 % decrease in the Clinician-Administered Post-traumatic Stress Disorder Scale scores with a total response rate of 82 % [98]. This treatment gain was sustained up to 4 years later.

Conclusion

Overall, clinical care recommendations over the past decade have continued to rely on SSRI, prazosin, as first-line treatment for nightmares. During this time, however, there have been significant advancements in understanding the neurobiology of fear learning and extinction, and the role of specific neural circuits in this learning. These concepts are now at the center of a renaissance in PTSD treatment research and development.

Compliance with Ethics Guidelines

Conflict of Interest
Dewleen G Baker declares that she has no conflict of interest, Immanuel Lerman declares that he has no conflict of interest, Emmanuel P. Espejo declares that he has no conflict of interest, and Robert McLay declare declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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