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Posttraumatic Stress Disorder: An Integrated Overview of the Neurobiological Rationale for Pharmacology

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Thirty years of research on the biology of posttraumatic stress disorder now provides a foundation for hypotheses related to the mechanisms underlying the pharmacotherapy of this disorder. Only two medications, sertraline and paroxetine, are approved by the U.S. Food and Drug Administration for the treatment of PTSD. Although these medications are somewhat effective, other treatment mechanisms must be explored to address the unmet need for effective treatment. This article provides a concise summary of advances in our understanding of the neurobiology of PTSD and novel approaches to pharmacotherapy.

Key words: **gamma-amino-butyric acid, glutamate, noradrenergic, pharmacology, posttraumatic stress disorder, serotonin.** ***[Clin Psychol Sci Prac 24: 281–297, 2017]***

Lifetime prevalence of posttraumatic stress disorder (PTSD) in the general population ranges between 6.4% and 7.8% (Pietrzak, Goldstein, Southwick, & Grant, 2011). Rates are much higher among military veterans, with upwards of 20% of combat-exposed veterans meeting criteria for PTSD during their lifetime (Seal et al., 2009). Although there have been significant advances in the understanding of the pathophysiology of PTSD and clinical psychopharmacology, the U.S. Food and Drug Administration (FDA)-approved treatment options are limited. Paroxetine and sertraline, both selective serotonin reuptake inhibitors (SSRIs), are the only FDA-approved pharmacotherapies for PTSD. Unfortunately, there have been no new FDA-approved medications for PTSD for more than 15 years. Although response rates as high as 60% have been reported, only about 30% of PTSD patients achieve clinical remission when administered paroxetine or sertraline monotherapy (Alexander, 2012; Berger et al., 2009). Given the suboptimal response rates of first-line pharmacotherapy for PTSD, research is needed to investigate the basic mechanisms and underlying pathways associated with the pathophysiology of this disorder, and novel drug development is critical. This view is consistent with current clinical practice. In one study of veterans with long-standing antidepressant-resistant symptoms of PTSD, the average patient entering the study was already receiving, on

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average, approximately three psychotropic medications (Krystal et al., 2011).

Although numerous neurobiological mechanisms are implicated in the pathogenesis of PTSD, we do not yet fully understand how these mechanisms interact with individual patients. We hypothesize that these risk mechanisms are present to varying degrees in different patients and that they interact in complex ways to facilitate or reduce PTSD risk and recovery, as well as to influence vulnerability to a variety of comorbid conditions. The current article provides a concise review of the neurobiological factors implicated in PTSD. To highlight factors relevant to pharmacotherapy, which are almost exclusively focused on modulation of neurotransmitter systems, the emphasis is placed on the monoaminergic, glutamatergic, and gamma-aminobutyric acid (GABA)-ergic systems.

BRAIN FUNCTION AND NEUROTRANSMITTER RESPONSE FOLLOWING STRESS

Structural and functional abnormalities have consistently revealed a general imbalance between frontal lobe, amygdala, hippocampus, and anterior cingulate cortex activation in PTSD (Pitman et al., 2012). Imbalances lie within distinct neural systems, namely, systems implicated in the acquisition, expression, and inhibition of fear and anxiety. Specifically, the amygdala, by virtue of being involved in emotional processing and regulation of fear including fear conditioning, generalization, and extinction learning, serves as a connecting hub of the neural circuits implicated in PTSD (Shin, Rauch, & Pitman, 2006). The amygdala activates brainstem monoaminergic inputs to the prefrontal cortex (PFC); thus, it is likely that elevated amygdalar activity leads to increased input to the frontal lobe regions (Mahan & Ressler, 2012). To deal with increased input from the amygdala, an increased feedback inhibition is observed that may explain a decrease in activity in the PFC, which together may be responsible for some of the core behavioral patterns observed in PTSD, such as exaggerated fear response, hypervigilance, and failure to extinguish maladaptive fear response (Shin & Liberzon, 2010; Shin et al., 2006). During mild stress, arousal increases transmission of catecholamines (norepinephrine [NE], serotonin [5-HT], and dopamine [DA]) to the frontal lobe, which enables the PFC to inhibit the amygdala via neuronal glutamatergic outputs that in turn stimulate intra-amygdala GABA-ergic inhibitory interneurons (Pitman et al., 2012). Sensory characteristics of the environment and relevant experiential memories are coded in the hippocampus, which modulates both PFC and amygdala activation (Shin et al., 2006). During high levels of stress or specific threat, monoamine release is increased further to engage noradrenergic (NA) alpha 1, dopaminergic (DA1), and serotonergic (5-HT2A) receptors that interfere with PFC-mediated executive function and inhibition of the amygdala (Robbins & Arnsten, 2009). In addition to modifying PFC function, trauma and stress lead to changes in amygdala circuitry that promote defensive responding. For example, chronic stress and fear conditioning diminish GABA-mediated activity within the amygdala (Mahan & Ressler, 2012). Thus, via this model, with chronicity the PFC loses its regulatory capacity over the amygdala, in turn permitting increased local amygdalar sensitivity to stress. During intense stress, 5-HT2A receptors are also upregulated in the amygdala, as discussed below.

MONOAMINERGIC SYSTEM

Serotonergic Neurobiology

Studies suggest that the 5-HT system impacts both PTSD risk and symptom severity (Pitman et al., 2012). The cell bodies of the 5-HT system are located in the brainstem's median and dorsal raphe nuclei, which project widely in the brain, including to key fear circuitry loci within the amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC), and primarily targets GABA-ergic inhibitory neurons (Neumeister et al., 2013). Numerous preclinical studies have reported heightened 5-HT release, and increased 5-HT synthesis and turnover in response to acute stress (Krystal & Neumeister, 2009). Some alterations in 5-HT systems have been described in PTSD using positron emission tomography (PET). Sullivan et al. (2013) reported higher density of ligand binding to 5-HT1A receptors in both brainstem and forebrain regions. Since 5-HT1A receptors are somatic autoreceptors for 5-HT neurons, this might suggest that 5-HT neurons see increased feedback inhibition. However, there are signs that 5-HT nerve terminals may have increased efficacy in that both 5-HT1B receptors, terminal autoreceptors,

and 5-HT transporters are downregulated among patients with PTSD (Murrough et al., 2011; Pietrzak et al., 2013). Together, these findings might suggest that enhanced synaptic 5-HT transmission at the level of the nerve terminals might contribute to symptoms of PTSD. This hypothesis was first tested using the 5-HT partial agonist, meta-chlorophenylpiperazine (mCPP), which stimulates 5-HT2C receptors, among other effects on 5-HT signaling. When administered to PTSD patients, this drug evokes anxiety, panic attacks, and PTSD symptoms, including flashbacks (Southwick et al., 1997). The limited efficacy of SSRIs in the treatment of PTSD must be understood in terms of variable individual genetic profile, specific symptom clusters, and other medications typically co-administered with SSRIs and not serve as a clue to abandon our understanding of the 5-HT signaling (see Figure 1 for a more detailed exposition of the role of the 5-HT system in PTSD symptoms).

Serotonergic Pharmacology

Two SSRIs, paroxetine and sertraline, have received FDA approval for the treatment of PTSD. Randomized controlled trials (RCTs) have demonstrated that paroxetine and sertraline improve PTSD symptomatology in contrast to placebo and produce remission in about 30% of study participants (Alexander, 2012), although no statistically significant difference has been established in favor of any single SSRI (Benedek, Friedman, Zatzick, & Ursano, 2009). SSRIs have been shown to have a broad spectrum of action and are effective for managing re-experiencing, avoidance, numbing, and hyperarousal symptoms. Although multiple RCTs have significantly favored SSRIs in comparison with placebo, there have been numerous studies that have failed to show any difference compared to placebo (Brady et al., 2005; Friedman, Marmar, Baker, Sikes, & Farfel, 2007; Shalev et al., 2012; Tucker et al., 2001). A recent systematic review conducted by the Institute of Medicine questioned the use of SSRIs for veterans with a chronic course of combat-related PTSD, reporting that this subgroup responds rather poorly to SSRIs; this refractory group also responds more poorly to psychotherapeutic interventions (Benedek et al., 2009). The heterogeneity of PTSD may also contribute to the inconsistencies across SSRI RCTs. Furthermore, it is possible that a 6–12-week clinical trial does not allot adequate time to separate the magnitude of the benefit. In an open-label study, when the treatment with sertraline was extended from 12 to 36 weeks, the remission rates increased from 30% to 55% (Londborg et al., 2001). This separation of the magnitude of the benefit of pharmacological treatment versus placebo is also demonstrated in double-blind,

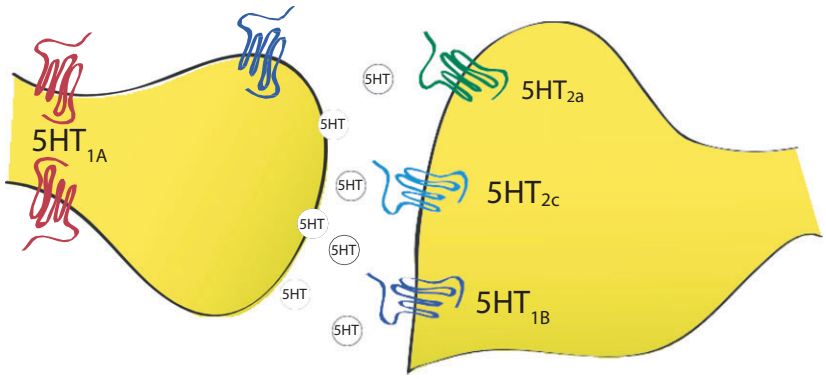

Figure 1. Schematic of serotonin system. Preclinical and clinical studies have implicated stimulation and interaction of 5-HT1A, 5-HT1B, and 5-HT2A or 5-HT2C receptors in antidepressant and/or anxiolytic action in PTSD. Disruption of 5-HT1A expression in the forebrain during development may result in a lifelong anxious phenotype, as 5-HT1A knockout mice demonstrate increased anxiety and fear response. Administration of 5-HT1A receptor antagonist can inhibit stress-induced increases in glucocorticoid receptors. Acute stress can increase synaptic 5-HT levels in the limbic system, an effect that is partially mediated by 5-HT1B receptors, including a diminished capacity to downregulate 5-HT1B receptors in key brain regions implicated in the pathophysiology of PTSD. Preclinical studies have shown an increase in gene expression of 5-HT2C in the amygdala, and administration of an antagonist decreased stress-induced contextual fear-related freezing behavior. Clinical benefits of chronic SSRI use are partly due to 5-HT2C receptor desensitization and downregulation of 5-HT1B receptor 5-HT, 5-hydroxytryptamine.

placebo-controlled trials (Davidson et al., 2001; Davidson, Baldwin, et al., 2006).

In addition to SSRI monotherapy, a few small studies have tested whether combining SSRIs with cognitive-behavioral therapy (CBT) might benefit partial responders. This augmentation strategy is mostly predicated on the idea that each monotherapy is efficacious; therefore, the combination may be superior to either individual therapy. The rationale for utilizing serotonin-modulating agents in augmenting therapy comes from evidence that the serotonin system is implicated in learning processes that are critical to most evidence-based psychotherapies, namely, fear extinction learning (Bauer, 2015). One study randomized patients with PTSD with partial response to prolonged exposure (PE; after eight sessions) to PE continuation with paroxetine augmentation versus placebo and found no benefit to the addition of paroxetine (Simon et al., 2008). On the other hand, two small studies found that the reverse design was effective; PTSD patients who had inadequately responded to sertraline monotherapy showed significant improvement when sertraline treatment was augmented with PE (Otto et al., 2003; Rothbaum et al., 2006). Further research is needed to clarify whether and how SSRIs and CBT should be combined to optimize treatment gains, but the evidence thus far suggests there is no substantial benefit from combining these treatment modalities and combined treatment should not be considered the default option (Otto, Smits, & Reese, 2005).

Other Antidepressants

Besides SSRIs, a number of other antidepressant medications, most of which affect multiple neurotransmitter systems, have been investigated for the treatment of PTSD. Two multicenter RCTs, one 12 weeks (Davidson, Rothbaum, et al., 2006) and the other six months (Davidson, Baldwin, et al., 2006), showed that venlafaxine—a serotonin and NE reuptake inhibitor (SNRI)—is superior to placebo for the treatment of PTSD. Participants who received venlafaxine reported greater overall symptom reduction and greater rates of remission than those who received placebo. In fact, response rates to venlafaxine were about 10% higher than those reported in previous SSRI trials (Davidson, Rothbaum, et al., 2006).

One study has shown that mirtazapine, another antidepressant with a mixed mechanism of action (most potent at blocking histamine 1 [H1] receptor, but also exhibits lower potency blockade of postsynaptic 5-HT2 and 5-HT3 receptors and presynaptic noradrenergic alpha-2A/C receptors), was as effective as sertraline (Chung et al., 2004). However, another RCT found no statistically significant differences between mirtazapine and placebo (Davidson et al., 2003). It is likely that mirtazapine primarily assists with sleep as an antihistamine and is recommended as a second-line agent for PTSD-related sleep disturbance (Forbes et al., 2010). However, a recent review concluded that only prazosin, an adrenergic inhibiting agent (see section below), has had its efficacy established in multiple RCTs and that antidepressants such as sertraline, venlafaxine, and mirtazapine, and benzodiazepines and nonbenzodiazepine hypnotics such as zolpidem appear ineffective in treating PTSD-related sleep disturbance (Lipinska, Baldwin, & Thomas, 2016).

Tricyclic antidepressants, which block presynaptic reuptake of serotonin and NE, such as amitriptyline (Davidson et al., 1990) and imipramine (Kosten, Frank, Dan, McDougle, & Giller, 1991), have demonstrated; superiority to placebo for the treatment of PTSD, although there was also a negative RCT with desipramine (Reist et al., 1989). In another study, paroxetine did not show statistical superiority to desipramine, but desipramine was superior to paroxetine with respect to study retention and alcohol use outcomes (Petrakis et al., 2012). An RCT with a monoamine oxidase inhibitor (MAOI), phenelzine, which blocks the intraneuronal metabolic breakdown of 5-HT, NE, and DA, has been shown to successfully reduce re-experiencing and arousal symptoms (Kosten et al., 1991). Despite some promising results, tricyclics and MAOIs are typically considered after several failed trials of other SRIs due to the potentially serious side effects associated with tricyclics and MAOIs.

An atypical serotonin agent, 3,4-methylenedioxymethamphetamine (MDMA), also identified as the street drug "ecstasy," has been shown to facilitate fear extinction in a preclinical model of PTSD (Young, Andero, Ressler, & Howell, 2015). It induces the release of presynaptic serotonin, activating 5-HT1A, 5-HT1B, and 5-HT2A receptors (Liechti & Vollenweider, 2001).

MDMA also stimulates the release of DA and NE, producing psychostimulant effects, which may increase motivation to engage in psychotherapy (Hysek et al., 2011). A pilot clinical study reported long-lasting improvements in symptoms of PTSD following MDMA-assisted psychotherapy (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011; Mithoefer et al., 2013). Pilot studies suggest it may be possible to safely administer MDMA to patients with PTSD and that MDMA-assisted therapy appears to facilitate the emergence of fearful memories that can then be reprocessed in therapy (Mithoefer et al., 2011). Another MDMA-assisted psychotherapy double-blind active-placebo study (comparing low dose versus high dose of MDMA) found no statistically significant differences in PTSD severity between the two treatment groups at posttreatment, but the severity scores improved further at one-year follow-up (Oehen, Traber, Widmer, & Schnyder, 2013). However, negative mood states, distress reactivity, and substantial abuse liability have been associated with MDMA (Mithoefer et al., 2013). Further research is required to explore both the positive and negative effects of MDMA in the context of PTSD treatment. Given MDMA's effects on extinction learning and its mechanisms (BDNF signaling), investigators should also assess whether this drug can be used to enhance exposure-based CBT for PTSD (Young et al., 2015).

Noradrenergic Neurobiology

The prominence of hyperadrenergic symptoms in PTSD (e.g., hyperarousal, re-experiencing, and anxiety) naturally made the noradrenergic system a compelling point of investigation (Bailey, Cordell, Sobin, & Neumeister, 2013; van der Kolk, Greenberg, Boyd, & Krystal, 1985). Evidence for noradrenergic hyperactivity in PTSD derives from (a) studies showing increased levels of NE and its metabolites in cerebrospinal fluid, blood, and urine at rest or following exposure to trauma reminders (Delahanty, Raimonde, Spoonster, & Cullado, 2003; Strawn, Ekhator, Horn, Baker, & Geracioti, 2004); and (b) increased catecholamine, behavioral, and neural responses to the alpha-2 adrenergic antagonist, yohimbine (Bremner et al., 1997). Early studies found abnormally high levels of catecholamines and their metabolites in the plasma and urine of individuals undergoing severe stress, as well as patients with PTSD, suggesting increased levels of catecholamines may be responsible for some PTSD symptoms (Southwick et al., 1999). Factors that may contribute to noradrenergic hyperactivity in response to traumatic stress or conditioned reminders of stress include decreased expression, affinity, or function of alpha-2 adrenergic autoreceptors (see Figure 2) and genetic or stress-induced decrements in neuropeptide Y (NPY), which inhibits NE release (Rasmusson et al., 2000).

There are increased NE and metabolite levels in blood at rest and after reminder of trauma. By process of increased inhibition, not surprisingly, early studies examining the number of alpha-2 adrenergic receptor sites on blood elements (platelets) have shown that both combat veterans and children diagnosed with PTSD had fewer alpha-2 adrenergic receptor binding sites than healthy controls (Perry, Giller, & Southwick, 1987; Pitman et al., 2012). Reduced alpha-2 receptor function conveys increased response to administration of yohimbine, an alpha-2 adrenergic antagonist that increases synaptic NE by blocking autoinhibitory feedback, associated with symptoms of hyperarousal and re-experiencing in veterans with PTSD and alterations in cortical metabolism (decreased activity in the PFC; Bremner et al., 1997; Southwick et al., 1997). Preclinical studies have shown that yohimbine facilitates not only the formation and recall of aversive memories in rodents, but also extinction of cue and contextual fear (Mueller, Olivera-Figueroa, Pine, & Quirk, 2009). Although clinical trials are currently underway (Wangelin et al., 2013), there is not yet evidence that yohimbine can be used to augment exposure-based therapies for PTSD.

Neuropeptide Y is released in response to intense psychological stress or pain and binds to NPY-Y1 receptors to decreased release of NE (Rasmusson, Southwick, Hauger, & Charney, 1998). NPY is implicated in arousal and the assignment of emotional valences to stimuli and memory (Silva, Xapelli, Grouzmann, & Cavadas, 2005). Not surprisingly, stress-induced reductions in NPY are implicated in overall increased release of NE in PTSD (Neumeister et al., 2013; Perry et al., 1987). Human research suggests NPY-Y1 receptor agonist in the amygdala exerts anxiolytic effects (Pitman et al., 2012) and is also involved in stress resilience (Morgan et al., 2002). Soldiers in the Special Forces who produced higher plasma levels of

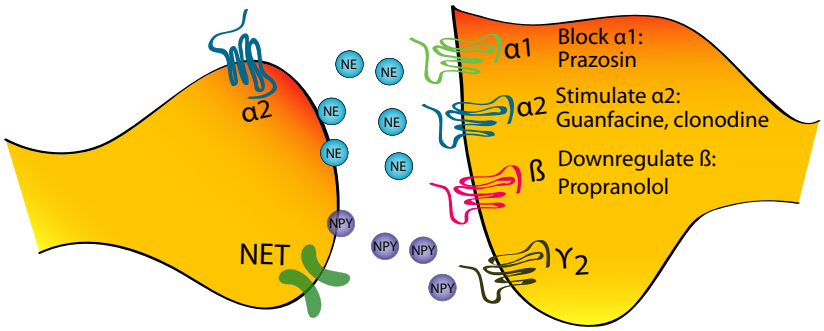

Figure 2. Schematic of noradrenergic system. The hyperactivity of the noradrenergic system seems to persist in patients with PTSD and has been suggested to mediate the hyperarousal symptoms, as well as sleep disturbance. The most compelling clinical evidence suggests that the underlying pathophysiology may involve hyperactive norepinephrine neurotransmission, reduction in alpha-2 receptors, and significantly reduced norepinephrine transporter (NET) in the LC. Surprisingly, the medications acting on alpha-2 receptors such as guanfacine and clonidine, which should lead to reduced norepinephrine release, have been less promising than medications that block alpha-1 receptors such as prazosin. Beta-adrenergic antagonist, propranolol, has shown mixed results both as monotherapy and in animal models of PTSD. However, posttrauma administration of propranolol has shown promising results in preventing fear conditioning. The involvement of NET in the pathophysiology of PTSD has repeatedly been demonstrated in both clinical and preclinical studies, and serotonin–norepinephrine reuptake inhibitors (SNRIs), which act in part through NET, such as venlafaxine, have demonstrated clinical utility in reducing re-experiencing and avoidance/numbing symptoms. And while norepinephrine seems to moderate sympathetic response during stress, NPY seems to attenuate the effects of norepinephrine during a stress response. However, no medications to date have been successful in regulating the reciprocal relationship between NPY and the noradrenergic system. NET, norepinephrine transporter; LC, locus coeruleus; NPY, neuropeptide Y.

NPY levels during highly stressful military training were found to have better performance during training and lower stress-induced dissociation and distress (Morgan et al., 2000). Low baseline plasma NPY levels and blunted NPY response to increased NE levels by administration of yohimbine have been found in male veterans with PTSD (Rasmusson et al., 2000). Pretreatment with intranasal (before exposure to stress paradigm) NPY has been shown to attenuate the development of PTSD-like symptoms in rodent models of PTSD (Sabban, Alaluf, & Serova, 2015). However, efforts to develop pharmacological agents harnessing NPY receptor-mediated effects have thus far been unsuccessful (Pitman et al., 2012).

Reduction in norepinephrine transporter (NET) expression enhances synaptic availability of NE. It is likely that the dysregulation of NET expression may result from ongoing elevated NE levels, as preclinical studies show that endogenous DA and NE stimulate NET expression (Krystal & Neumeister, 2009). NET acts as NE plasma membrane transporter and maintains NE presynaptic storage. Chronic stress leads to a reduction in NET availability in the locus coeruleus (LC), whereas in the PFC, there is an increase in NET expression, suggesting this may represent an attempt to maintain normal availability, and consequently normal function of NE (Bailey et al., 2013). These preclinical findings were recently replicated in a human PET study demonstrating that PTSD is associated with significantly decreased NET availability in the LC, which might, in turn, result in the exaggerated synaptic availability of NE in projection areas, such as the PFC (Pietrzak et al., 2013). Despite these informative preclinical models and clinical evidence, the role of the antidepressants with a high affinity for NETs (e.g., venlafaxine) in the treatment of PTSD is promising, yet remains unclear (Davidson, Baldwin, et al., 2006; Davidson, Rothbaum, et al., 2006).

Noradrenergic Pharmacology

Normalization of hyperadrenergic activity, which is suggested to contribute to hyperarousal symptoms, has been attempted by (a) blocking alpha-1-adrenoreceptor with prazosin (a postsynaptic alpha-1-adrenoreceptor antagonist), (b) stimulating alpha-2-adrenoreceptor with guanfacine and clonidine (both alpha-2-adrenoreceptor agonists with slight differential affinity for different alpha-2 receptors), and (c) blocking beta-adrenergic receptor with propranolol. Two small RCTs have shown prazosin to be more effective than placebo at reducing traumatic nightmares for patients with PTSD (Raskind et al., 2007; Taylor et al., 2006). A recent

RCT with combat-exposed veterans also showed that prazosin effectively reduced overall PTSD symptom severity (Raskind et al., 2013). However, a recent double-blind placebo-controlled study showed that prazosin had no effect in reducing PTSD symptoms or improving sleep in 96 patients with PTSD and comorbid alcohol dependence (Petrakis et al., 2016). Findings thus far suggest that prazosin may be effective at treating sleep disturbances in PTSD; however, results may vary based on comorbid conditions.

Both guanfacine and clonidine have failed to demonstrate efficacy in the treatment of PTSD in open trials (Kolb, Burris, & Griffiths, 1984; Neylan et al., 2006). Preclinical data suggest clonidine may be useful as a reconsolidation blockade. Administration of clonidine blocked reconsolidation of fear memories when administered after fear retrieval (Gamache, Pitman, & Nader, 2012). This effect was dose dependent, with higher doses leading to greater blockage, and longer lasting effects. To our knowledge, no studies have tested the effects of clonidine on fear reconsolidation in humans.

The role of propranolol has been investigated as monotherapy, as prophylactic following the immediate aftermath of trauma, and in conjunction with therapy as an aid to disrupt reconsolidation of traumatic memories in patients with PTSD. Unfortunately, the results have been inconsistent and unpromising (Pitman et al., 2012). Despite the promising results in preventing consolidation of aversive memories in preclinical studies, propranolol has been shown to be ineffective for the prevention of PTSD (Pitman et al., 2012; Stein, Kerridge, Dimsdale, & Hoyt, 2007). Difficulties associated with translating preclinical work into a clinical setting highlight the importance of conducting studies in "real-world" patients with PTSD (Petrakis et al., 2016). Although propranolol may not be effective as monotherapy for treatment of PTSD, there has been a recent resurgence of interest in using it in conjunction with exposure-based therapies and as an aid to reconsolidation interventions (Kindt & van Emmerik, 2016; Soeter & Kindt, 2012).

Dopaminergic Neurobiology

Less is known about the involvement of the dopaminergic system in PTSD because unlike 5-HT and NE, peripheral measures of dopamine function do not correlate well with the central measures (Rasmusson, Riddle, Leckman, Anderson, & Cohen, 1990). Yet the dopaminergic system is implicated in the pathophysiology of this disorder by virtue of being one of the most important neurotransmitters in reward signal processing, a process that appears to be downregulated in PTSD (Elman et al., 2009). Further evidence for the involvement of the dopaminergic system in PTSD comes from rodent studies showing that DA release in the amygdala promotes modulation of unconditional and conditional stress responding.

Dopaminergic Pharmacology

Atypical antipsychotics that primarily affect the dopaminergic system have largely been considered as adjunctive medications for partial responders to antidepressants. A series of small RCTs involving olanzapine and risperidone suggests that they might be useful as SSRI adjunctive medications for PTSD (Pitman et al., 2012). However, these findings are limited by small-to-moderate sample sizes. A recent large multisite RCT investigated adjunctive risperidone in 247 veterans who were partial responders to antidepressants and found that risperidone augmentation was no better than placebo (Krystal et al., 2011). To date, the evidence for the use of atypical antipsychotics is insufficient to determine efficacy in the treatment of PTSD.

GLUTAMATERGIC SYSTEM

Neurobiology

The main projections from the PFC to the amygdala and hippocampus are glutamatergic in nature; more specifically, the PFC can modulate the activity of these areas either directly or indirectly by acting on DA and acetylcholine neurons (Del Arco & Mora, 2009). The deficient top-down control from the PFC to the amygdala, as described above, implies that the glutamatergic pathways are potentially involved in the pathophysiology of PTSD. Furthermore, glutamatergic projections from the PFC, specifically vmPFC, hippocampus, and amygdala are crucial in the modulation of fear learning, extinction learning, and contextual fear conditioning (Morrison & Ressler, 2014), a firmly established finding in the literature.

Glutamate, the most common and main excitatory neurotransmitter in the central nervous system, binds to a variety of receptors most generally classified into two categories: (a) ionotropic (ion-bearing channel) glutamatergic receptors consist of *N*-methyl-D-aspartate receptor (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainite; and (b) metabotropic glutamatergic receptors (mGluRs), which can be eight different types ($mGluR_1$–$mGluR_8$), operate pre- and postsynaptically to increase or decrease ionotropic activity. Ionotropic receptors are crucial for synaptic plasticity and, as such, most forms of learning and memory. Aberrant glutamatergic transmission is implicated in the pathophysiology of PTSD via the essential role NMDA receptors play in fear conditioning and extinction (Bailey et al., 2013). This makes ionotropic receptors critically important for the development and treatment of PTSD. Although metabotropic glutamate receptors have also been implicated in stress-related pathology, much of the work is isolated to preclinical models of anxiety, and more conclusive work remains to be done in human studies.

NMDA receptor activation plays an essential role in fear learning, whereas blockade of NMDA receptors with an antagonist blocks the memory consolidation processes (Morrison & Ressler, 2014). Paradoxically, anesthetic doses of ketamine, an NMDA receptor antagonist, administered to burn victims receiving surgery has been shown to reduce posttraumatic stress symptoms (McGhee, Maani, Garza, Gaylord, & Black, 2008). Conversely, peritraumatic administration of anesthetic ketamine before surgery was associated with a worsening of acute posttraumatic stress symptoms among accident victims (Schonenberg, Reichwald, Domes, Badke, & Hautzinger, 2005, 2008). Furthermore, dissociative symptoms, including emotional numbing, reduction in awareness of one's environment, depersonalization, and memory impairment, frequently seen in acute trauma have all been observed in ketamine intoxication (Krystal et al., 1994). Individuals who dissociate following a trauma are more likely to develop PTSD than those who do not (Chambers et al., 1999). Ketamine administration in the hours following trauma may make the development of PTSD more likely (Schonenberg et al., 2005, 2008), suggesting an important role of intact NMDA receptors for healthy trauma response and providing further evidence that NMDA receptor dysfunction contributes to PTSD symptomatology.

Pharmacological Interventions

The abovementioned studies suggest that anesthetic doses of ketamine might potentiate memory if administered shortly following a traumatic event and may reduce symptomatology if administered well after the traumatic event. A recent case report suggested that a single intravenous subanesthetic dose of ketamine may temporarily reduce posttraumatic stress symptoms (D'Andrea & Sewell, 2013). A more recent study administered ketamine and midazolam to 41 patients with a primary diagnosis of PTSD in a randomized, double-blind, crossover trial and found that single ketamine infusion provided a temporary reduction in symptoms (Feder et al., 2014). Both drugs were associated with rapid reductions in posttraumatic stress symptoms, but ketamine outperformed midazolam; however, no inactive placebo was used in this study.

D-Cycloserine (DCS) is a partial NMDA receptor agonist that has been tested as a monotherapy and treatment augmentation agent for PTSD. The DCS clinical studies have mostly failed to demonstrate efficacy in the treatment of PTSD. There is minimal evidence that DCS is efficacious as monotherapy (Heresco-Levy et al., 2002) or as an add-on for standard pharmacological treatments for PTSD (Attari, Rajabi, & Maracy, 2014). Despite strong evidence showing that DCS can improve extinction learning (Norberg, Krystal, & Tolin, 2008), there is weak evidence that DCS can enhance the efficacy of exposure therapy for PTSD. Only one RCT has found that PTSD patients who receive DCS and exposure therapy fare better than their counterparts who receive exposure therapy with a placebo pill (Difede et al., 2014); two other RCTs failed to show therapeutic exposure enhancing effects of DCS (de Kleine, Hendriks, Kusters, Broekman, & van Minnen, 2012; Rothbaum et al., 2014). One study reported that DCS was detrimental to therapeutic learning (Litz et al., 2012). The only study to report positive effects of DCS used a larger dose (100 mg) than the studies that reported negative findings (50 mg; Difede et al., 2014), raising the possibility that larger doses are required in PTSD to significantly enhance exposure therapy.

GABA

Neurobiology

The deficits in GABA signaling demonstrated in PTSD may contribute more broadly to risk for PTSD symptoms (Goddard et al., 2001; Pollack, Jensen, Simon, Kaufman, & Renshaw, 2008; Rosso et al., 2014). For example, deficits in GABA-ergic inhibition may explain why the administration of mCPP exacerbates PTSD symptoms in patients but not in healthy controls, but mCPP can produce panic attacks and dissociative symptoms in healthy controls when pretreated with iomazenil, an inverse GABA agonist (D'Souza et al., 2006). GABA-ergic inhibitory control seems to be critically involved in fine-tuning regulation of expression, consolidation, and extinction of fear conditioning (Bustos, Maldonado, & Molina, 2006; Mahan & Ressler, 2012). Not surprisingly, studies have shown significantly lower GABA levels among individuals exposed to trauma who developed PTSD as compared to those who did not (Meyerhoff, Mon, Metzler, & Neylan, 2014; Rosso et al., 2014), and reduced GABA levels are strongly correlated with severity of insomnia symptoms among patients with PTSD (Meyerhoff et al., 2014). Decreased GABA levels in PTSD are consistent with previous findings of low cortical and subcortical benzodiazepine receptor binding in patients with PTSD and panic disorder (Bremner, Southwick, Darnell, & Charney, 1996; Charney, 2004) and suggest that the GABA-ergic system may be a potential therapeutic target.

Pharmacological Interventions

Treatment of PTSD-related symptoms has long included benzodiazepines, GABA receptor agonists. However, the results from RCTs indicate that this class of medications has not been helpful in the treatment of PTSD, despite their widespread use in the treatment for PTSD. Though recently their use has been in decline (Lund, Bernardy, Alexander, & Friedman, 2012) due to low risk/benefit ratio because of addictive potential, sedation in older adults, and the possibility that they might interfere with psychological processes needed to benefit from CBT. Therefore, the 2010 VA/DoD Clinical Practice Guideline discouraged the use of benzodiazepines for the treatment of both acute stress disorder and PTSD (Forbes et al., 2010). Eszopiclone—a high-affinity GABA-A receptor agonist—has been shown to significantly improve sleep disturbance associated with PTSD (Pollack et al., 2008). GABA-ergic anticonvulsants are also often prescribed for PTSD-related symptoms, but results have not been uniform. One large placebo-controlled study of tiagabine found no significant effect of the drug on PTSD, depression, or functional impairment (Davidson, Brady, Mellman, Stein, & Pollack, 2007). Divalproex was similarly shown to have no significant effect on PTSD symptoms (Hamner et al., 2009). In a small international trial, topiramate was reported to significantly reduce PTSD symptoms (Yeh et al., 2011), but these results have yet to be replicated. In summary, GABA-ergic drugs are widely prescribed but incompletely understood, and clinical trials have thus far yielded underwhelming results. Each comes with potential side effects, tolerance issues, and addictive potential, as well as possible effects on neurocognitive functioning.

FUTURE DIRECTIONS

Pharmacological trials for PTSD, so far, have utilized agents with established efficacy for other psychiatric disorders. The only two medications (sertraline and paroxetine) that have FDA approval as indicated treatments for PTSD have remission rates of about 30%, after a 12-week clinical trial. The lack of capacity of these medications in achieving more favorable treatment response rates is probably related, in part, to the relative lack of specificity of these medications; SSRIs indiscriminately modulate and potentiate action at all of the many different kinds of serotonin receptor sites in the brain. Another weakness of the current clinical research is the lack of focus on how treatments help different PTSD symptom clusters; although the effects of treatments on specific symptoms of PTSD have been investigated in controlled clinical trials (such as GABA-ergic mechanism, glutamatergic, and anticonvulsants), they have produced inconclusive results. Perhaps what is needed are treatments designed to target specific known psychological and neurobiological abnormalities associated with PTSD. Thus, to identify effective treatments for PTSD, research could focus on identifying which disruptions in neural circuitry and neurotransmitter systems relate to specific symptom clusters. The development of more specific treatment modalities

would have to identify predictors beyond those that have been traditionally investigated, and potentially examine subtypes of PTSD. This approach should reveal important findings about the key ingredients of efficacious treatments and ultimately lead to developing medications designed to address various dimensions of PTSD symptomatology.

Specific systems implicated in the pathophysiology of PTSD to be considered for future research include, but are not limited to, NPY enhancers, more specific serotonergic agents such as MDMA, endocannabinoid, oxytocin system modulators, glutamatergic agents that promote neurogenesis, or cortical releasing factor (CRF) antagonists (for a more detailed review of the role of the glucocorticoid system in PTSD, see Yehuda, 2009). However, as these neurobiological systems are further explored and developed, systematic exploration of adjunctive enhancers of psychotherapeutic treatments such as extinction-based therapies and CBT should be given top priority.

The combination of CBT with pharmacotherapy, usually SRIs, is quite common in clinical practice. In general, CBT alone appears to be as effective as CBT administered with an SRI; however, there is some evidence that the addition of CBT is warranted when response to paroxetine is inadequate. This suggests that the default treatment should not necessarily be SRIs plus CBT, but that it may be beneficial to recommend CBT in addition to SRIs to patients who chose to try SRIs first, but fail to respond adequately.

One promising approach to improving the treatment for PTSD is to combine pharmacological agents with behavioral interventions that specifically target fear processing and learning. Neuroimaging studies over the past two decades have repeatedly revealed neural abnormalities in fear circuitry in patients with PTSD. Similarly, decades of research have progressively clarified the neurobiological mechanisms of fear extinction learning, and not surprisingly, neural abnormalities associated with PTSD often lie within the putative fear extinction network or are associated with the molecular mechanisms of extinction learning. This robust neural signal has guided attempts to develop improved exposure-based therapies for PTSD; therapeutic exposure can be improved by targeting the mechanisms of fear extinction learning (Morrison & Ressler, 2014; Singewald, Schmuckermair, Whittle, Holmes, & Ressler, 2015).

D-Cycloserine is perhaps the most well-known pharmacological agent to be tested in conjunction with therapeutic exposure for PTSD and other forms of anxious psychopathology. The goal of administering DCS prior to or shortly after exposure is to enhance therapeutic extinction learning and its consolidation into long-term memory. As reviewed in the previous section, this work has been by and large disappointing. On the whole, studies have failed to demonstrate that the combination of DCS and exposure-based CBT is superior to CBT alone. One potential reason for these failures is the fact that DCS+CBT is often compared to full-scale CBT. This makes it difficult to detect an effect of DCS; posttreatment effects of CBT alone are often so large that there is little room for improvement. Moving forward, investigators should focus on the alternative outcomes, such as speed of treatment, dropout rates, or treatment acceptability (Tuerk, 2014).

Preliminary evidence indicates that MDMA may be effective for assisting psychotherapeutic interventions for PTSD. In this context, the administration of MDMA is hypothesized to not only improve therapeutic extinction learning, but may also reduce the fear response to the emotional threat, allowing patients to revisit traumatic memories in a therapeutic setting with less overwhelming emotions (Mithoefer et al., 2011). Like DCS, MDMA has been shown to facilitate fear extinction in a preclinical model of PTSD. However, studies have yet to demonstrate its ability to augment exposure-based CBT.

Along these same lines of research, agents targeting the cannabinoid system have shown preliminary support for management of anxious and dysphoric symptoms and sleep disturbances in PTSD (Berardi, Schelling, & Campolongo, 2016; Neumeister, Seidel, Ragen, & Pietrzak, 2015), and recent research suggests activation of the cannabinoid system, via administration of oral dronabinol, can improve recall of fear extinction learning (Rabinak et al., 2013). Studies have yet to test the effects of dronabinol or similar drugs on exposure-based CBT for PTSD.

Fearful memories are unstable and pliable following their retrieval and reconsolidation. These memories can

be modulated during the reconsolidation window with behavioral or pharmacological interventions. Although propranolol and clonidine have, at best, demonstrated mixed results as monotherapies for PTSD, there has been a resurgence of interest in developing methods for using noradrenergic drugs to block reconsolidation of fear memories. Preliminary research suggests that administration of propranolol or clonidine during the reconsolidation window can interfere with restabilization of the memory, thus diminishing its ability to provoke fearful responding upon future retrieval. This is an exciting area of research that warrants further investigation.

CONCLUSION

Currently, FDA-approved treatments have demonstrated mild-to-moderate success. The research reviewed in this article reveals that, although much knowledge has been generated toward the underlying pathophysiology of PTSD and many putative pharmacological treatments have emerged, very few studies have resulted in treatments that are novel, effective, and specific to PTSD symptoms. Most novel treatments have insufficient evidence to draw meaningful conclusions about their efficacy. One promising possible treatment approach for this complex disorder may be the use of multiple drugs simultaneously. The development of treatment algorithms to guide such combinatorial treatments will be a necessary next step. Another promising direction in the field is the use of brain plasticity inducers as monotherapies or in conjunction with learning-based psychotherapies, such as extinction-based CBT or even reconsolidation interventions.

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