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Targeting memory processes with drugs to prevent or cure PTSD

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Abstract

Introduction—Post-traumatic stress disorder (PTSD) is a chronic debilitating psychiatric disorder resulting from exposure to a severe traumatic stressor and an area of great unmet medical need. Advances in pharmacological treatments beyond the currently approved SSRIs are needed.

Areas covered—Background on PTSD, as well as the neurobiology of stress responding and fear conditioning, is provided. Clinical and preclinical data for investigational agents with diverse pharmacological mechanisms are summarized.

Expert opinion—Advances in the understanding of stress biology and mechanisms of fear conditioning plasticity provide a rationale for treatment approaches that may reduce hyperarousal and dysfunctional aversive memories in PTSD. One challenge is to determine if these components are independent or reflect a common underlying neurobiological alteration. Numerous agents reviewed have potential for reducing PTSD core symptoms or targeted symptoms in chronic PTSD. Promising early data support drug approaches that seek to disrupt dysfunctional aversive memories by interfering with consolidation soon after trauma exposure, or in chronic PTSD, by blocking reconsolidation and/or enhancing extinction. Challenges remain for achieving selectivity when attempting to alter aversive memories. Targeting the underlying traumatic memory with a combination of pharmacological therapies applied with appropriate chronicity, and in combination with psychotherapy, is expected to substantially improve PTSD treatment.

Keywords

amygdala; drugs; fear conditioning; prefrontal cortex; PTSD; stress; therapy

1. Introduction

Most people experience traumatic stress at some point in their lives. Evolution has fashioned robust neurobiological mechanisms that allow organisms to respond adaptively to stressors.

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Declaration of interest

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For most, the intense physiological activation and disrupting impact of aversive memories declines following trauma, allowing life to return to normal.

For some, however, adaptive coping does not occur, as physiological arousal remains and recurring memories of the aversive event persist, strengthen, and disrupt normal functioning. Once post-traumatic stress disorder (PTSD) is diagnosed, treatment may involve psychotherapy, pharmacotherapy, or both. Currently only two drugs are approved in the United States for PTSD, and both are selective serotonin (5-HT) reuptake inhibitor (SSRIs).

Although certain psychosocial interventions and drugs can improve outcomes, there is still considerable unmet need in the treatment of PTSD. We focus primarily on investigational drugs being explored for potential utility in treating PTSD, especially when combined appropriately with therapy. Comprehensive reviews of PTSD psychotherapy are available elsewhere [3,4]. To set the stage for a discussion of investigational drug treatments, Section-2 will provide background on PTSD and explain Diagnostic and Statistical Manual (DSM)-IV criteria. Sections 3 and 4 will then discuss the neurobiology of stress responding and fear conditioning processes, which provide the rationale for psychosocial, pharmacological, and combined approaches.

It is important to acknowledge that many of the principles discussed herein have been derived from data gathered in pre-clinical (animal) studies, and therefore, caution is warranted in extrapolating these results to humans with PTSD. The results from animal studies are intended to help generate hypotheses for human clinical studies which, when tested, could lead to improved treatments.

2. PTSD

In the United States, lifetime prevalence of PTSD is 6.8% [5], and the costs of PTSD to individuals and society are high [6]. Incidence rates and relative costs are even higher in specific populations, such as military, veterans, and first-responders [7,8]. Considerable efforts are underway to improve prevention, diagnosis, and treatment of PTSD in these populations especially, since exposure to severe trauma is common [9].

PTSD (Box 1) is an anxiety disorder that requires exposure to a specific traumatic event. “Exposure” is defined as: experiencing or witnessing an event involving death or serious injury with a resulting feeling of intense fear, helplessness, or horror. Further, a PTSD diagnosis depends on persistent (‡ 1 month) symptoms from three clusters: reexperiencing of the trauma, avoidance/numbing behavior, and hyperarousal. The emphasis on symptom duration is important, as this stems from the recognition that most exposed to severe trauma exhibit PTSD-like symptoms acutely but learn effective coping strategies and recover on their own. Thus, PTSD is at least partly a disorder of recovery [10,11]. Finally, PTSD symptoms must cause severe distress and/or impair normal functioning. Note that criteria for diagnosing and defining PTSD may change for the DSM-V, scheduled for release in 2013.

Currently, both psychotherapy and pharmacotherapy approaches are pursued for the treatment of PTSD. In general, the most effective psychotherapies attempt to treat the pathological memory defining PTSD, whereas drugs are mainly applied to blunt PTSD

symptoms. We will argue that PTSD drugs may be particularly useful when they positively interact with therapy-related learning.

The three symptom clusters may have a common neurobio-logical basis, or they may reflect distinct neurobiological mechanisms requiring multiple pharmacological approaches for their treatment [12]. It is notable that the first two core symptom clusters, reexperiencing and avoidance, must be triggered by memories of a specific traumatic event, whereas the third cluster, hyperarousal, is not restricted to associative responding. Thus, PTSD symptoms may result from dissociable, though interacting, associative, and non-associative processes mediated by separate biological systems (i.e., emotional learning vs. stress-responding).

Vulnerability factors, such as prior traumas (e.g., childhood abuse) or genetic variations may prove important for elucidating heterogeneity in PTSD and devising more appropriate treatment approaches. Further, PTSD is often comorbid with other psychiatric disorders (e.g., depression) and/or substance abuse disorders, which may require additional treatments. Although these topics are beyond the scope of the current manuscript, interested readers may refer to other excellent articles for more information [13-22].

3. Stress response pathways

Organisms have innate, automatic mechanisms for responding to threatening stressors. The acute stress response is a highly activated physiological state that prepares the organism in two major ways: i) energy and resources are diverted from non-essential processes (e.g., digestion) and mobilized to prime sensorimotor processes necessary for defensive behavior, and ii) behavioral responding is restricted to defensive behaviors, often simple, innate, species-specific reactions that evolved because they were adaptive [23]. Adaptive defensive behaviors can vary widely and are usually governed by the perceived proximity of the threat and the behavioral options dictated by the environment. For example, rats freeze in a closed space with a predator nearby, but will attempt escape or fight if cornered by an attacking predator [24]. An adaptive stress response system is hardwired to produce reliable activation, yet flexible enough to produce diverse behavioral actions. It should also be transient, so critical bodily resources return to non-defensive processes, like digestion, when the threat wanes.

The stress response includes multiple physiological components, including endocrine (hypothalamic-pituitary-adrenal, or HPA, axis) and sympathetic responses [25]. Several key neurochemicals are important for the arousal/activational component of the stress response, and excessive or prolonged activation of these pathways likely contributes to hyperarousal symptoms in PTSD (Figure 1). We will focus here on three powerful modulators of defensive brain systems and sympa-thetic responding: i) norepinephrine (NE), ii) corticotropin-releasing factor (CRF), and iii) cortisol (CORT).

NE is a critical mediator of arousal via direct and indirect effects on both central and peripheral processes. Brainstem NE neurons project to all levels of the neuraxis and NE signaling appears hyperresponsive in PTSD [26]. For instance, PTSD is associated with i) greater plasma NE and stress-induced arousal, especially when stressors are trauma-specific,

ii) heightened adrenergic receptor sensitivity, and iii) enhanced yohimbine-facilitated startle (yohimbine increases NE release by blocking autoinhibitory feedback at synapses). NE dysfunction has also been implicated in associative memory, which is discussed in the following section. Norepinephrine's effects are mediated through activation of a_1, a_2, and b-adrenergic receptors, which are widely distributed in the central nervous system and periphery. As reviewed in Section-5, drugs targeting these various receptors have been evaluated for therapeutic utility in PTSD and may have potential to further improve PTSD treatment if used in novel ways.

The neuropeptide CRF also plays a crucial role in stress/arousal processes and has been implicated in PTSD [16]. Central CRF initiates the HPA-axis response to stress, with hypothalamically released CRF binding to receptors in the anterior pituitary, and causing ACTH release into the circulation. ACTH in turn triggers CORT release from the adrenal cortex, which acts on glucocorticoid receptors in the periphery and brain. CRF is also a powerful modulator of defensive brain systems mediating stress, arousal, and memory. CRF signaling may be dysfunctional in PTSD as cerebrospinal fluid CRF levels are elevated and ACTH responding to exogenous CRF is blunted [27]. Beyond these findings, a crucial role for CRF in PTSD is mainly hypothesized based on CRF's HPA-axis role, preclinical research findings [28], and CRF's known association with related conditions like depression [29]. CRF acts on two receptor subtypes, CRF_1 and CRF_2. Small molecule antagonists of the CRF_1 receptor have been developed and administered to humans [28], but to date there are no published clinical data evaluating the effects of CRF_1 receptor antagonists in PTSD.

CORT is a glucocorticoid hormone secreted by the adrenal cortex in response to ACTH or low circulating CORT levels. CORT has a powerful dual role in the coordinated stress response: i) it is a primary mediator of the global stress response, with wide-ranging effects on both peripheral and central processes, and ii) it provides the primary negative feedback signal to halt the stress response by suppressing brain CRF, ACTH and NE release. Thus CORT functions to maintain allostasis and ensure a robust, but transient, response to stressful demands. Not surprisingly, dysfunctions in CORT signaling are associated with PTSD; low circulating CORT and enhanced CORT-mediated negative feedback are usually observed in PTSD patients. This suggests that responses to trauma or distressing reminders may be abnormally prolonged in PTSD [30]. Perhaps most troubling, chronic stress, via a glucocorticoid mechanism, leads to changes in neural and immune functions that weaken the ability to fight off sickness and learn effective coping strategies [31].

Together, it seems clear that dysfunctions throughout the stress-response system contribute to PTSD. NE and CRF systems are hyperresponsive and abnormalities in CORT feedback likely prolong stress-response episodes. This combination could account for hyperarousal symptoms in PTSD, by decreasing thresholds for responding and prolonging the activation of defensive brain and body systems, at the expense of many other bodily functions. This could also indirectly contribute to PTSD by enhancing associative memory symptoms.

4. Fear Conditioning

Dysfunctions in parallel stress-response and defensive-memory systems are evident in PTSD. Many of the defining characteristics of PTSD, such as reliving of trauma, avoidant behavior, and nightmares depend on trauma-related associative learning. Thus, cues present during a traumatic event gain emotional valence and subsequently elicit defensive responses and fear. This learning is normal and even adaptive, however, when dysfunctional, these associative processes disrupt functioning. Although it is useful to consider stress and memory factors in parallel, they are closely related and coordinated systems that surely interact in important ways. For instance, trauma-linked cues can trigger the HPA-axis and circulating stress hormones can have profound effects on associative neural plasticity and thresholds for defensive responding [26,30,31].

Pavlovian fear conditioning (FC) is an important paradigm for studying memory processes and brain circuits that make strong contributions to PTSD. FC occurs when neutral conditioned stimuli (CSs) are temporally paired with naturally aversive unconditioned stimuli (USs). Any sensory stimulus can serve as a CS, and USs can be any unpleasant or painful stimulus. CS and US pairings produce plasticity in the fear system, allowing subsequent CSs to control fearful responding. FC is an extremely powerful form of associative learning; if the CS is sufficiently salient and the US sufficiently aversive, even a single brief episode can lead to strong fear memories that last a lifetime [32]. FC studies have greatly enhanced our understanding of the neurobiology of memory and emotional responding (see Box 2). It is also widely believed that studies of FC processes will identify novel behavioral and pharmacological interventions for PTSD in particular, since this disorder is attributable to a distinct traumatic event and is defined largely by pathologic responses to aversive memories.

Although FC does not necessarily produce PTSD, psychological and neural processes mediating FC likely contribute to PTSD if dysfunctional. FC has several important features and phases that may make distinct contributions to PTSD or treatment. Further, learning that depends on FC may also be relevant. These are discussed below and depicted in Figure 2.

4.1 Acquisition

This refers to the initial CS-US learning phase that occurs during a traumatic experience. The prevailing view is that acquisition of FC critically depends on synaptic plasticity within the defensive brain circuitry, especially the amygdala [33]. The strongest evidence comes from studies of the lateral nucleus of the amgydala (LA), where strengthening of synapses between sensory afferents and principle neurons is critical for learning [34]. FC plasticity, especially in LA, has been intensely studied and many transmitters, receptors, intracellular messengers, genes, and gene products have been implicated [35,36]. The core mechanism for acquisition in LA is thought to be temporary enhancement of AMPA receptor function, through an LTP-like process [38,39]. Generally speaking, four processes play critical roles: i) glutamate signaling (via AMPA-, NMDA- and metabotropic receptors); ii) feedforward GABAergic inhibition; iii) intracellular kinase activation (e.g., PKA & CAMKII); and iv) modulatory neurotransmitters/neuropeptides. Although theoretically not necessary for FC plasticity, modulators like NE represent important drug targets because they powerfully

affect all of the other processes. For instance, NE can enhance PKA and glutamate receptor activation, and suppress GABAergic inhibition in LA—all of which favor FC plasticity [36].

4.2 Consolidation/storage

FC produces learning almost instantly and short-term memory (STM) that lasts at least several hours. However, long-term memory (LTM) requires additional cellular processes to stabilize and maintain learning. This consolidation process is usually complete within 6 – 24 h. Consolidation requires intracellular signaling, gene transcription, translation of new proteins, and remodeling/growth of synaptic connections [36]. Interfering with these key steps can block the formation of LTM and essentially erase the FC memory. Although some forms of memory involve an additional "systems-level" consolidation process, where information is transferred to another brain region, FC memories are likely stored in the same region(s) and neurons where initial learning takes place [42]. Interestingly, recent research suggests that a specific kinase, PKMz, is necessary to store FC memories [43] and interference with this molecule can erase memory even without retrieval (but see [44]). However, it is not clear how this mechanism could be exploited to target PTSD memories specifically.

4.3 Retrieval

Sometimes called expression, recall, or performance, retrieval simply refers to conditioned responding (CR) that depends on the associative CS-US relationship during FC. Retrieval is assessed by presenting the CS alone and measuring newly acquired CRs. In addition to probing the state of the FC memory (STM vs. LTM), retrieval tests can provide important information about the strength and specificity of FC memories. Since defensive responding falls along a fear continuum, the CR type, magnitude, and duration indicate the strength of the FC memory [23]. For instance, a rat that initially freezes at 80% and takes 10 min to stop freezing after a CS presentation has a stronger FC memory than one that initially freezes £80% but stops freezing after 2 min. Retrieval tests that include non-conditioned cues can also assess generalization and discrimination (non-specific fear learning and/or lower thresholds for defensive responding). Note that some drugs may affect memory retrieval without having any effect on learning or memory processes. Such drugs would blunt associative PTSD symptoms, but may not help correct the underlying problem.

4.4 Retrieval-induced learning

Recent exciting research has shown that simple FC retrieval events may induce diametrically opposed plasticity processes that can strengthen or weaken CRs. Retrieval returns the memory to a labile state requiring a second reconsolidation process [45-47]. Reconsolidation and consolidation have over-lapping, but distinct, molecular mechanisms [48]. Reconsolidation likely serves an updating function, allowing for incorporation of new information into the LTM trace [49,50]. Although emotionally neutral updating may be possible, retrieval-related learning usually changes CR strength depending on the nature of the new information. For instance, fear extinction occurs when subjects repeatedly experience the CS without the US [51]. These retrieval episodes contradict the predictive validity of the CS and weaken fear. However, brief or less frequent reminders can strengthen fear (incubation) [52,53]. Little is known about the mechanisms of incubation, although NE

makes the clearest contribution [54]. Extinction is better understood. Fear extinction requires prolonged or repeated CS exposure and appears to form a new inhibitory "CS-NoUS" memory that competes for control of emotional behavior [55]. Extinction depends on coordinated activity and plasticity in multiple brain regions including the amygdala [56], periaqueductal gray [57], prefrontal cortex [58], and hippocampus [59]. Extinction also has learning, STM, consolidation, LTM and retrieval phases. Molecularly, extinction depends on some of the same molecules as initial FC (e.g., NMDA receptors and NE) but also distinct molecules (e.g., cannabinoid receptors) [60,61]. And unlike original FC, extinction is highly context-dependent (renewal, reinstatement) and decays with time (spontaneous recovery) [55].

4.5 Other FC-related processes

Additional conditioning processes that depend on FC may have relevance to PTSD, such as conditioned inhibition (CI; safety learning) [62] and instrumental avoidance/escape [63-65]. Dysfunctions in these processes could contribute to the development of PTSD and/or the failure to adequately cope following traumatic experience. However, the exact role for conditioned fear in these processes is unclear, and much less is known about the underlying neurobiology.

4.6 Individual differences and stress-enhanced fear learning (SEFL)

Individual differences in FC behavior may have relevance to understanding and devising better treatments for PTSD. For example, rats that show strong FC, normal retrieval, and extinction, but impaired extinction retrieval [66], may mirror the deficit seen in PTSD. Prior stress can also enhance anxiety and FC [67-69], which could also have relevance to PTSD. Although biomarkers, variability in FC processes and their relation to PTSD vulnerability/resilience are extremely important, this large body of research is beyond the scope of the present discussion and the interested reader is encouraged to consult other excellent reviews [11,14,16-18,70-73].

4.7 Relationship of FC processes to PTSD

Most agree that FC occurs with traumatic experience and contributes to PTSD phenomenology. However, there continue to be debates regarding which FC processes are dysfunctional in PTSD and how to exploit associative learning to enhance treatment. Before proceeding, it is important to note that FC studies, especially those conducted in rodents, relate directly to implicit Pavlovian memories and defensive responses [33]. Thus, one should not assume that findings from FC studies necessarily extend to other types of memory, like explicit/declarative memory, or human emotions and feelings. Strong FC memories likely influence other memory components and emotions, but they are not one in the same. That said, if dysfunctional FC processes are a major contributor to PTSD, addressing this dysfunction should at least dampen PTSD symptoms expressed via other brain systems.

Regarding FC dysfunction as a PTSD cause, two major ideas are prominent: PTSD occurs i) because the FC memory is excessively strong, or ii) because normal fear-coping processes are deficient. Though not mutually exclusive, available data are most consistent with the

latter. As mentioned earlier, PTSD may largely be a disorder of recovery, since most traumatized individuals exhibit symptoms acutely but recover without treatment. Further, when subjected to controlled FC procedures measuring implicit fear responses, PTSD cohorts show reliable impairments of fear extinction recall, compared to trauma-exposed, non-PTSD controls [74]. Fear acquisition effects in those with PTSD are less consistent; some studies show facilitated FC, some do not, and still others report normal FC responding to conditioned cues, but overgeneralization to non-conditioned cues or impaired discrimination/CI [74-77]. Thus, the major deficit appears to involve inhibitory fear learning [78], and especially retrieval of the extinction memory, since PTSD patients learn extinction normally but fail to remember it [74]. This specific memory pattern points to dysfunctions in PFC and hippocampal processes that gate amygdala-dependent fear during extinction retrieval [55,79], and those with PTSD show abnormal PFC, hippocampal, and amygdalar activation with fMRI analyses [74].

Another hypothesis suggests that “overconsolidation” and stronger FC memories are the primary problem in PTSD [80]. Although a recent study [74] failed to detect over-consolidation in PTSD patients, this model also hypothesizes a role for reminder-induced strengthening of the FC memory, to account for the progressive worsening of symptoms in PTSD. This is actually predicted by the impaired-extinction model discussed above; retrieval episodes that fail to induce extinction trigger stress-responses like CRF and NE that enhance reconsolidation, leading to incubation of the FC memory [81]. It remains to be determined whether such a secondary “over-reconsolidation” process contributes to PTSD.

Other FC-related processes could also contribute to PTSD, although the data supporting these mechanisms are much weaker. For instance, “overgeneralization” or impaired safety learning could broaden the ability of innocuous stimuli to trigger fear and increase the frequency of fearful episodes [78,82,83]. Finally, therapy tapping into adaptive active avoidance/coping mechanisms, which can powerfully suppress fear and are more durable than extinction [63,64,84], may offer a viable alternative if the extinction deficit in PTSD patients cannot be treated. More research is needed to understand the neurobiology of these processes and their potential contribution to PTSD and treatment.

5. Investigational drugs and PTSD-related memory processes

Pharmacological and psychotherapeutic approaches have been used in PTSD and certain psychotherapy approaches (e.g., prolonged-exposure therapy or PE) are of particular benefit. As the present review is focused on drug treatments, the reader is referred elsewhere for comprehensive reviews regarding therapy [3,4,85-88]. Nevertheless, certain drugs may be particularly useful if they positively interact with psychotherapy, and this will guide our analysis.

Evaluation of relative drug efficacy is challenging in PTSD for several reasons. First, PTSD is often accompanied by other psychiatric afflictions including depression, addiction, chronic pain, and generalized anxiety [3,4]. Second, patients have varied experiences including differences in the nature and/or frequency of the defining trauma, prior traumatic experience, and prior history with different therapeutic approaches. Third, patients are often

taking additional medications. Fourth, the lack of reliable, standardized, non-subjective measures to diagnose PTSD and evaluate treatment efficacy severely hinder comparisons between studies, both clinical and preclinical. Finally, FC research strongly suggests that drugs should be evaluated in a more sophisticated way. For instance, although benzodiazepines may blunt anxiety symptoms in patients with PTSD, animal studies demonstrate that these drugs clearly impair fear extinction and could potentially counteract therapy-related learning [89]. This example illustrates that some drugs could be both beneficial and detrimental to PTSD treatment, depending on when they are applied.

Continued research into PTSD biomarkers, PTSD risk/resilience, as well as basic studies of the neurobiology of PTSD-relevant processes may be critical to improving drug, psychosocial, and combination therapies [90]. Nevertheless, recent research suggests that new drugs have great potential to improve PTSD outcomes. This will be discussed below and compared to approved or common drug regimens. Previous reviews have provided overviews of investigational drugs in PTSD with regard to general effects on PTSD symptoms as well as specific symptoms such as anxiety, insomnia, and nightmares [91]. These drugs affect diverse targets, including monoamines (norepinephrine, dopamine, serotonin), amino acids (GABA, glutamate), neurosteroids, neuropeptides (substance P, CRF) and opiates. Although we summarize general results for many of these agents in Table 1 (drugs with monoamine-based mechanisms) and Table 2 (non-monoamine mechanisms), our discussion will emphasize drugs that have potential to significantly alter dysfunctional aversive memories and results from randomized clinical trials (RCTs) [85,92]. Particularly exciting preclinical findings with relevance to PTSD treatment are also included. Finally, Table 3 (monoamine-mechanisms) and Table 4 (non-monoamine mechanisms) summarize ongoing clinical trials with investigational drugs in PTSD.

5.1 FDA-approved drugs for PTSD: SSRIs

Currently, the SSRIs sertraline and paroxetine are the only FDA-approved drugs for treating PTSD (for reviews of clinical trials, see [85,93,94]). While able to reduce symptoms from all three PTSD clusters, SSRIs alone are not the solution for a large percentage of patients. Effect sizes can be small and anywhere from 70 – 80% of patients fail to achieve complete remission [95-98].

Both preclinical and clinical data indicate that combining SSRIs with psychotherapy may improve outcomes. In mice, extinction + fluoxetine produces “conditioned fear erasure” [99], perhaps by returning the adult fear circuitry to a developmental state where extinction reverses original learning, rather than producing normal context-specific inhibitory learning. Consistent with this, paroxetine combined with PE was more effective than therapy or drug alone in treating PTSD [100]. Chronic post-FC paroxetine also prevents the spontaneous fear incubation seen in rodents subjected to a SEFL procedure [101]. Together these data suggest that, although not always effective in reducing PTSD symptoms, SSRIs may prevent worsening of symptoms and could significantly facilitate the effects of exposure therapy. Further, SSRIs may be superior to other drugs because they are unlikely to exacerbate FC processes [102] or impair natural recovery-related learning occurring outside of therapy.

Venlafaxine, which blocks 5-HT and NE reuptake, demonstrated efficacy in the treatment of PTSD [103,104]. In rodents, acute pre-extinction venlafaxine facilitates extinction retrieval and chronic post-extinction treatment prevents reinstatement, suggesting that combining this drug with extinction may produce FC erasure even when administered post-training in adults [105]. Venlafaxine may selectively improve extinction consolidation, since fear retrieval and extinction learning were unaffected. This profile is consistent with a medial prefrontal cortex (mPFC) mechanism, but this has yet to be tested. Although not FDA-approved for PTSD, venlafaxine is a recommended treatment and is considered to be as efficacious as SSRIs [106]. It is notable that venlafaxine specifically improves extinction consolidation/retrieval in rodents, providing further support for the notion that this FC process is especially relevant to PTSD treatment.

5.2 Other 5-HT drugs

5.2.1 Buspirone—5-HT_{1A}-receptor knockout mice demonstrate excessive generalization (as is suggested to occur in PTSD) [76,107], suggesting that 5-HT_{1A} receptor agonism may be of therapeutic utility in PTSD. Buspirone, an anxiolytic 5-HT_{1A} receptor partial agonist, reduced PTSD symptoms in case studies or small trials [108-110]. Buspirone also potentiates SSRI responses in PTSD [111] though larger trials are needed to confirm these findings. Vilazodone, which has both 5-HT reuptake inhibition and 5-HT_{1A} receptor partial agonism, was active prophylactically in a rat model of hypervigilance following severe stress [112] and would be of potential interest to explore clinically in PTSD.

5.2.2 5-HT_2 receptor antagonists—5-HT_{2A} receptor antagonists may have utility in PTSD, based on animal studies [113], though clinical studies are lacking. Nefazodone, a 5-HT reuptake inhibitor/5-HT_{2A} antagonist, showed promising results in a small PTSD pilot study [114], although this drug has fallen out of favor because of liver toxicity issues. Positive findings were also reported for mirtazapine, an antidepressant with antagonist actions at multiple 5-HT_2 receptor subtypes as well as at a_2-adrenergic receptors [115]. In preclinical FC tests, mirtazapine suppressed FC retrieval [116,117].

5.2.3 3,4-methylenedioxymethamphetamine (MDMA)—MDMA (“Ecstacy”) is a substituted amphetamine that increases 5-HT release from presynaptic terminals and a drug that has been explored previously as an adjunct to psychotherapy [118]. MDMA decreased PTSD symptoms in subjects who were non-responsive to pharmacological or psychotherapeutic interventions [119], with 83% responding to drug versus 25% for placebo. The authors reported that there were no apparent long-term side effects noted in this study but the ongoing discussion of the potential for neurotoxicity in humans following chronic MDMA use (e.g., [120]) necessitates that caution be exercised in evaluating this drug.

5.3 Norepinephrine (NE)

NE contributes to hyperarousal and FC processes, providing the rationale for evaluating compounds affecting a_1-, a_2-, and b-adrenergic receptors in PTSD.

5.3.1 Prazosin—Hyperarousal is linked to sleep disturbances which are difficult to treat with SSRIs. Prazosin, an a_1-adrenergic receptor antagonist, decreased sleep-related disturbances in PTSD, as measured by latency to sleep and trauma-related nightmares [121-127]. These effects may result from decreased arousal, though it is possible that prazosin is affecting FC memory processes (e.g., disrupting reconsolidation or incubation of trauma memories causing nightmares), a hypothesis requiring formal testing. Notably, a_1 blockers increase fear learning and impair fear extinction in animals [128,129] suggesting that further clinical research is needed to evaluate whether a_1 blockers given before exposure therapy sessions are detrimental.

5.3.2 Propranolol—Blocking b-adrenergic receptors with propranolol may improve PTSD, though RCT findings are mixed. Propranolol attenuated retrieval of an emotionally arousing narrative in both normal volunteers and those with PTSD [130], suggesting utility when administered after exposure to trauma. In a small emergency room study, propranolol administered within 6 h of trauma, and daily thereafter for 10 days [131], showed a non-significant trend for PTSD reduction at 1 month. A similar study where propranolol was given for 7 days (3x/day, beginning 2 – 20 h post-trauma) reduced PTSD development at 1 month [132]. In contrast, a third study reported no effect of propranolol administered up to 48 h post-trauma on the development of PTSD symptoms [92]. In this latter study, the small sample size, dosing, and long delay between trauma and treatment may account for the different outcome. Another study in juveniles found that a moderate/low dose of propranolol given within 12 h of admission increased PTSD symptoms in girls but non-significantly decreased the same measures in boys [133]. A recent study found that propranolol given within 12 h of trauma and continued for 19 days failed to improve clinical outcomes but did have a modest effect on script-driven physiological arousal [134]. Thus, propranolol does not appear to strongly block the consolidation of traumatic memories to prevent PTSD, although it is important to note that subjects in these studies received the drug as the consolidation window was closing, or in many cases, after FC consolidation was likely complete.

Recent preclinical (rodent) work may help explain the mixed results for propranolol in PTSD. Although it clearly disrupts consolidation of hippocampal-dependent memories when given immediately post-training [135], consolidation of Pavlovian FC is not hippocampal-dependent and propranolol fails to disrupt fear when given post-conditioning [136]. However, propranolol does impair the acquisition, retrieval and reconsolidation of FC [137], and thus may be useful for PTSD if given i) before a trauma (limited potential except for military and first responders, perhaps), ii) between therapy sessions (to block reminder-induced reconsolidation/incubation) or, iii) during therapy designed to reactivate, but not extinguish, FC (to intentionally block reconsolidation). Two recent studies in humans support the notion that propranolol given after traumatic-memory retrieval (PTSD patients; [138]), or before FC reactivation (normals; [139]), weakens reconsolidation and blunts subsequent memory-induced arousal and fear behavior. However, null results have also been reported and methodological issues temper enthusiasm for these early results [140], so further work is needed to determine whether propranolol can blunt fear by blocking reconsolidation. Finally, propranolol administered to the PFC in rats impairs fear extinction

[141], thus, mixed effects could relate to propranolol having both positive and negative effects on PTSD-relevant FC processes.

5.3.3 Yohimbine—a_2-Adrenergic antagonists like yohimbine can exacerbate PTSD symptoms, presumably by blocking autoinhibitory feedback and increasing synaptic NE. Indeed, pre-training yohimbine induces stronger LTM and more generalization [142], and pre-test yohimbine enhances FC retrieval. However, yohimbine facilitates fear extinction in both rodents [143,144] and humans [145] and thus may be a useful adjunct to exposure-based psychotherapies. This idea is supported by a recent study using a mouse strain with a poor-extinction phenotype: pre-training yohimbine treatment led to significant LTM for extinction whereas vehicle- and d-cycloserine-treatment did not [146]. Yohimbine is currently being evaluated in an open clinical trial as an adjunct to exposure therapy (Table 3).

5.4 GABA

Benzodiazepines (which facilitate $GABA_A$ receptors and are used as anxiolytics) have well-documented amnestic effects on anterograde memory. Benzodiazepines administered in the post-trauma period did not prevent, and possibly even enhanced, the subsequent development of PTSD (Table 2). Time after trauma may be an important factor here, as drugs were generally administered 2 or more days post-trauma, well beyond the FC consolidation window. An ongoing clinical study (Table 4) is administering diazepam in the emergency room within hours after trauma (and before the first night's sleep) in an effort to prevent fear memory consolidation and development of PTSD.

5.5 Opiates

Clinical studies (Table 2) have indicated that administration of opiates for pain relief at the time of acute physical trauma may reduce the subsequent incidence of PTSD, possibly from impairment of memory consolidation, though controlled studies are needed to confirm this finding. One preclinical study of FC suggests that morphine can block consolidation if given soon after conditioning [147].

5.6 Glutamate

Drugs clinically tested for efficacy in treating PTSD symptoms interact with the NMDA receptor complex as ion channel blockers (ketamine), partial (d-cycloserine) or full (d-serine) agonists.

5.6.1 D-cycloserine—D-cycloserine, first shown to facilitate fear extinction in rodents [148], has demonstrated utility for facilitating the beneficial effects of psychotherapy in treating phobia as well as other anxiety disorders. Though two pilot studies suggested efficacy as a monotherapy in PTSD [149] and for decreasing negative symptoms as an adjunctive therapy to neuroleptics [150], recent trials presented in abstract form suggest no benefit when combined with cognitive behavior therapy (see Table 2 references). A recent preclinical study found that d-cycloserine can enhance reconsolidation and strengthen fear, though the clinical implications of these findings for combining this drug with exposure

therapy need to be assessed [49]. Numerous clinical trials evaluating d-cycloserine are underway (Table 4).

5.7 Glucocorticoids

There are a number of agents which can work at various levels of the HPA axis to affect its functioning, but of these, only hydrocortisone (CORT), an agonist at glucocorticoid receptors, has been evaluated in PTSD. In chronic PTSD, low-dose hydrocortisone reduced traumatic memories and reexperiencing symptoms [151]. Hydrocortisone decreased fear responses as measured with fear-potentiated startle (a FC paradigm) in civilian and combat-related PTSD patients as well as non-PTSD controls [152,153].

Other studies assessed hydrocortisone given near the time of trauma for its ability to prevent the development of PTSD. Hydrocortisone administered during cardiac surgery decreased chronic stress symptoms [154,155] and decreased the development PTSD when administered to patients with septic shock [156].

Hydrocortisone was evaluated for activity in augmenting memory extinction and reducing clinical symptoms in veterans with combat-related PTSD [157]. Subjects dosed with hydrocortisone after a memory reactivation task showed a reduction of PTSD symptoms 1 week later, though this effect was attenuated at 1 month. The authors explained this as glucocorticoid-mediated enhancement of extinction, though a reduction in memory reconsolidation is possible.

5.8 Neuropeptides

5.8.1 GSK561679—CRF, a key stress-response mediator, may be hyperactive in PTSD. CRF_1 receptor antagonists are proposed to be useful in treating PTSD, and, while there are no clinical data available, a trial is currently underway evaluating GSK561679 in women with chronic PTSD (Table 4). As reviewed elsewhere [158], animal FC studies indicate that CRF_1 receptor blockade may impact both consolidation and expression of conditioned fear. Furthermore, recent analyses indicate that CRF_1 receptor antagonism may facilitate extinction (Figure 3; [159]), suggesting that clinically, these agents should be evaluated in combination with psychotherapy for their effects on moderating fear memories in PTSD.

5.9 Drug combinations

Although there are no clinical data available, drug combination studies may be worth pursuing. For example, preclinical work has shown that combination of dexamethasone and d-cycloserine facilitate extinction better than either treatment alone [160].

6. Conclusions

Mechanistically diverse agents have been evaluated in a large number of studies for their potential efficacy in treating PTSD. However, a relatively small number of studies have specifically evaluated the ability of drugs, either alone or in combination with psychotherapy, to affect specific memory processes and thereby attempt to “correct” the core underlying problem in PTSD. These agents have primarily targeted adrenergic and

glutamatergic pathways. Ongoing trials demonstrate a greater focus on evaluating drug effects on learning processes.

7. Expert opinion

PTSD is a large problem, especially given the upswing of terrorism in the last decade and the nature of modern warfare, where soldiers operate under chronically stressful conditions with uncertain enemies using novel tactics like improvised explosive devices (IEDs). Advances in modern medicine and protective equipment also raise the PTSD incidence rate as more survive traumatic experiences and are subjected to multiple deployments. PTSD is also a major concern for civilians, and especially those with dangerous careers (e.g., first-responders).

PTSD treatment usually involves psychotherapy, pharmacotherapy, or, more likely, some combination of the two, even if not by design. However, even the most successful monotherapies (e.g., PE or SSRIs) leave many with significant symptoms. In our opinion, the cure for PTSD has remained elusive because pharmacotherapies and psychotherapies have largely developed in parallel without a full understanding of how they may interact. Even combined therapies guided by knowledge of the stress response and FC neurobiology often underutilize basic findings that could improve efficacy. Below we highlight recommendations based on clinical, preclinical and neurobiological findings that could speed the development of a PTSD cure. Since many of these ideas are inspired by studies of memory and neurobiology in rodents, these points should not be taken as recommendations for immediate changes in clinical practice, but rather, recommendations for new research to evaluate novel PTSD treatment strategies at the preclinical and clinical levels.

7.1 Blunt original consolidation

Weakening consolidation in the hours post-trauma may be the most efficacious strategy for preventing PTSD altogether, regardless of whether PTSD is caused by excessive conditioning or impaired recovery learning. This is not novel, however, enthusiasm for this strategy has waned since the disappointing results of propranolol treatment post-trauma. Propranolol was predicted to block consolidation based on studies of emotional learning, however, recent work shows that consolidation of Pavlovian FC is not sensitive to propranolol. Thus, agents with potential to block FC consolidation, such as morphine and others (Tables 1, 2, 3, 4; [48]), should be explored and applied immediately (£6 h) post-trauma to prevent PTSD. Encouraging results from victims with physical injuries support this strategy.

7.2 Target the dysfunctional memory

At its core, PTSD is an associative memory disorder. It is defined by specific experience and the major symptoms relate to specific traumatic memories. Normal living is disrupted by intense, recurring memories and avoidance of trauma-related cues. Although hyperarousal is also a defining feature, this may be largely secondary to the memory problem as traumatic memories activate the stress response. Even if hyperarousal is independent of memory dysfunction, treating hyperarousal alone will likely not correct the memory dysfunction and

significant symptoms will therefore remain. However, if the pathological PTSD memory is corrected, the core problem is removed and even hyperarousal symptoms should wane.

7.3 Combined therapies may be necessary to cure PTSD

If one accepts that specific traumatic memories must be targeted for correction to cure PTSD, then monotherapies may never be adequate. First, although drugs can alleviate PTSD symptoms temporarily, it is difficult to envision a way that drugs alone could dampen a traumatic memory. Available neurobiology findings suggest that memory retrieval is necessary for targeted disruption. Second, although psychotherapy can target a specific memory for correction, PTSD patients show clear impairments in learning processes known to effectively suppress conditioned fear (e.g., extinction). Combining drug treatment with memory-specific psychotherapy may offer the best route to permanent recovery—by returning the pathological memory to a state amenable to change, inducing new learning to correct the dysfunction, and facilitating the underlying neuroplasticity processes with drugs targeting key molecules.

7.4 Target neurobiological systems known to be dysfunctional

A great deal is known about the psychological and neurobiological systems that are awry in PTSD. For instance, the stress-response system depends critically on NE, CRF, ACTH and CORT and FC depends on glutamate receptors, intracellular kinases, transcription and translation, growth factors, and neuromodulators. Yet the currently approved/recommended drugs are antidepressants that largely affect 5-HT signaling. 5-HT clearly modulates stress responding and conditioning, however, the core stress-response and FC mechanisms do not require 5-HT. It appears that these drugs were evaluated based on their demonstrated safety and efficacy in treating depression and anxiety [86] rather than their ability to alter learning processes which might improve memory-related core PTSD symptoms. Recent findings indicate that SSRIs have a positive interaction with extinction-based therapy, though this extinction facilitation was only discovered after they were approved for treating PTSD. Advances in drug treatment strategies are likely to come quicker if limited clinical-trial resources are first devoted to mechanisms that are awry in PTSD and/or known to contribute to therapy-related learning processes. We predict that dual-role drugs, those that counteract stress-response abnormalities and make a positive contribution to therapy-related learning, will be especially effective for PTSD. One promising but untested drug type is CRF_1 receptor antagonists. These drugs may weaken HPA-axis activation and facilitate fear extinction learning (see Figure 3).

7.5 Apply drugs more selectively

If deciding which drugs to use is important, deciding when to use them is equally important. For instance, a recent survey found that approximately 30 – 40% of U.S. veterans with PTSD are taking benzodiazepines for comorbid conditions like anxiety [161]. FC research suggests that benzodiazepines may have beneficial and detrimental effects, depending on when they are taken. Benzodiazepines are anxiolytic and amnestic, and if taken post-trauma, could blunt consolidation, reconsolidation and/or retrieval of FC to prevent or ameliorate PTSD symptoms. However, if taken before therapy they could impair therapy-related learning. Indeed, it has been known for >20 years that benzodiazepine treatment impairs fear

extinction. Propranolol is another example. Although propranolol has little effect on FC consolidation, it does interfere with acquisition, incubation and reconsolidation of FC. Thus, propranolol is unlikely to have a profound effect when given post-trauma, but could be useful if given pre-trauma or post-retrieval, to blunt or erase the FC memory. At minimum, drugs given chronically should be evaluated to ensure that they do not impair learning processes necessary for normal or therapy-assisted recovery.

7.6 PFC processes may be particularly important

Although many components of the stress-response and fear circuitry show abnormalities in PTSD, it can be a challenge to determine which component(s) represent the primary dysfunction and which are secondary. Targeting the primary problem is the clearest path to developing a real cure. Data suggest that PFC dysfunction may be particularly important. PTSD is at least partly a disorder of recovery and the PFC is particularly important for extinction and other forms of emotion regulation (e.g., active coping) [162]. PTSD patients can acquire, consolidate, retrieve and extinguish fear normally, but have significantly impaired extinction retrieval. Ventral PFC is critical for extinction retrieval and PTSD patients show PFC hypoactivity. Finally, the best currently available drugs for PTSD treatment are SSRIs and the mixed 5-HT/NE reuptake blocker venlafaxine and these agents have been shown to enhance fear extinction. Although the SSRIs may enhance extinction learning, venlafaxine has no effect on extinction learning but strongly facilitates extinction retrieval when given only after extinction training. This pattern is most consistent with an extinction consolidation enhancement, most likely PFC-mediated. Thus, it is likely that drug/therapy combinations that effectively normalize PFC function will contribute to the PTSD cure. Most of the other PTSD symptoms could also result from PFC impairments since PFC suppresses amygdala-dependent fear responding including HPA-axis activation.

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Article highlights

- Although robust neurobiological mechanisms mediate adaptive responding to traumatic stressors, some individuals fail to adequately adapt, leading to the severe disruption of normal functioning characteristic of PTSD.

- PTSD is a unique anxiety disorder that is induced by specific traumatic experience(s) and characterized by dysfunctional fear memories, although hyperarousal also makes a strong contribution.

- Studies of fear conditioning provide insights into the mechanisms underlying the formation and maintenance of aversive memories. Potential therapeutic approaches for modulating such memories include altering processes of fear memory consolidation, reconsolidation and/or extinction.

- Selective serotonin reuptake inhibitors (SSRIs) are currently the only FDA-approved pharmacological treatment for PTSD, however, there is a considerable amount of clinical data for investigational drugs that target diverse neurotransmitter systems, including monoamines (norepinephrine, dopamine, serotonin), amino acids (GABA, glutamate), and peptides. Tables of investigational drugs are provided to summarize findings from completed clinical trials, highlight ongoing clinical trials, and facilitate comparisons between preclinical and clinical studies.

- Approaches that combine pharmacological agents with psychotherapy to modulate the core aversive fear memories in PTSD have considerable potential for improving treatment outcomes.

- Conversely, preclinical findings suggest that some drugs commonly prescribed for comorbid conditions may actually impair psychotherapy-related learning processes. More clinical research is needed to determine whether drugs can facilitate or impair psychotherapies for PTSD.

This box summarizes key points contained in the article.

Box 1. DSM-IV-TR Diagnostic Criteria for PTSD

A1. The person experience, witnessed, or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others

A2. The person's response involved intense fear, helplessness or horror

B. Re-experiencing Symptoms (1 or more)	C. Avoidant/Numbing Symptoms (3 or more)	D. Hyperarousal Symptoms (2 or more)
B1. Intrusive recollections	C1. Avoidance of thoughts, feelings or conversations associated with the stressor	D1. Sleep problems
B2. Distressing nightmares	C2. Avoidance of activities, places or people associated with the stressor	D2. Irritability
B3. Acting/feeling as though event were recurring (flashbacks)	C3. Inability to recall important aspects of traumatic aspects of traumatic event	D3. Concentration problems
B4. Psychological distress when expose to traumatic reminders	C4. Diminished interest in significant activities	D4. Hypervigilance
B5. Physiological reactivity when exposed to traumatic reminders	C5. Detachment from others	D5. Exaggerated startle response
	C6. Restricted range of affect	
	C7. Sense of foreshortened future	

E. Duration of the disturbance is at least 1 month

"Acute": duration of symptoms is less than 3 months; "Chronic": symptoms last 3 months or longer; "With Delayed Onset": at least 6 months have elapsed between the traumatic event and onset of symptoms

F. Requires significant distress or functional impairment

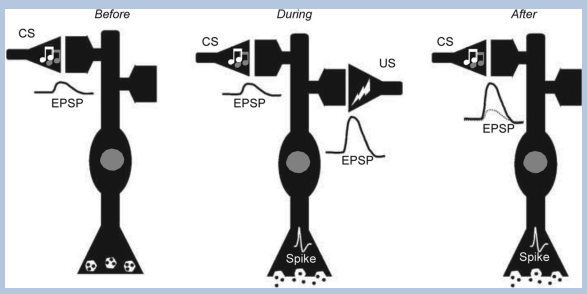
Key Changes Recommended for DSM-5 (see [1,2])

- Define a "Trauma and Stressor-Related Disorders" section (move PTSD out of Anxiety Disorder into this new section which recognizes trauma as etiological factor)

- Modify PTSD Criteria, including switch from a 3-factor model to a 4-factor model (Intrusion Symptoms; Persistent Avoidance; Alterations in Cognitions and Mood; Hyperarousal and Reactivity Symptoms)

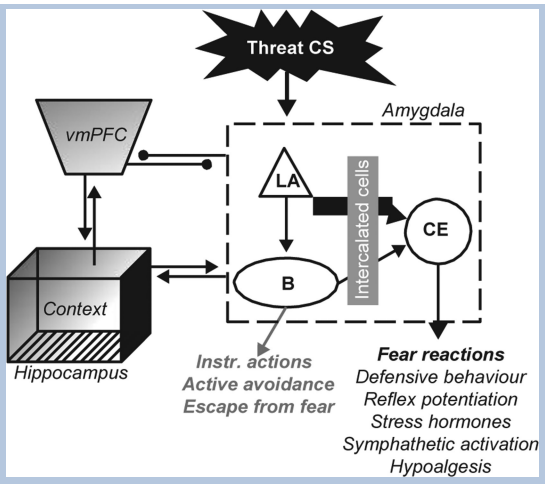
Box 2. Neurobiology of Pavlovian FC and Extinction.

LA is necessary for all aspects of FC[1]. LA neurons (below) receive CS (e.g.tones) and US (e.g. shocks) information. Before conditioning, CS afferents excite LA neurons weakly and fail to elicit fear. During conditioning, US inputs strongly depolarize LA neurons, trigger action potentials and drive defensive responses. Coincident CS-US activity opens calcium channels at CS synapses triggering plasticity mechanisms necessary for STM and LTM. After conditioning, CS-synapses are potentiated and CS-alone presentations now excite LA neurons enough to spike and drive fear responding. Although plasticity occurs throughout the network with FC, LA plasticity is essential for learning and most extra-amygdala plasticity. Unlike some other memory systems, FC memories are believed to be stored in the same neurons responsible for acquisition. Thus, FC permanently links CSs with the defensive brain system. In this view, retrieval is simply the consequence of CS-processing changes in the fear circuit, an automatic readout of FC plasticity, not a process requiring conscious thought or decision making.



LA lies at the center of a broader defensive network that can control fear responding. CS information reaches LA via thalamus and cortex. LA then projects to CE, both directly and indirectly through the basal nucleus (B) and intercalated (IC) cell masses. CE coordinates fear responding via its projections to downstream effector regions that mediate specific responses. For instance, projections to hypothalamus and LC allow the CS to activate NE and HPA-axis hormones. CE plasticity is also necessary for consolidation and linking the CS-US memory to appropriate responses. B has a complex role in FC, extinction and avoidance, via connections to CE, hippocampus, striatum and PFC.

[1]This explanation is based on prominent ‘serial processing’ (e.g., [37]) and ‘synaptic plasticity’ (e.g., [38]) models of amygdala-based Pavlovian fear conditioning. For an alternative ‘parallel processing’ view, see [40].



Several regions and processes are critical for extinction[2]. In LA, strengthening of GABAergic inhibition is associated with extinction learning. PAG may provide the error signal that drives learning. B neurons allow for switching from high to low fear states. PFC plays a crucial role in extinction consolidation/retrieval, which may be a core deficiency in PTSD. PFC may suppress amygdala fear outputs by exciting inhibitory IC cells that lie between LA and CE. Finally, hippocampus provides key contextual information that gates extinction memory retrieval.

[2]See [41] for a detailed review of fear extinction neural mechanisms.

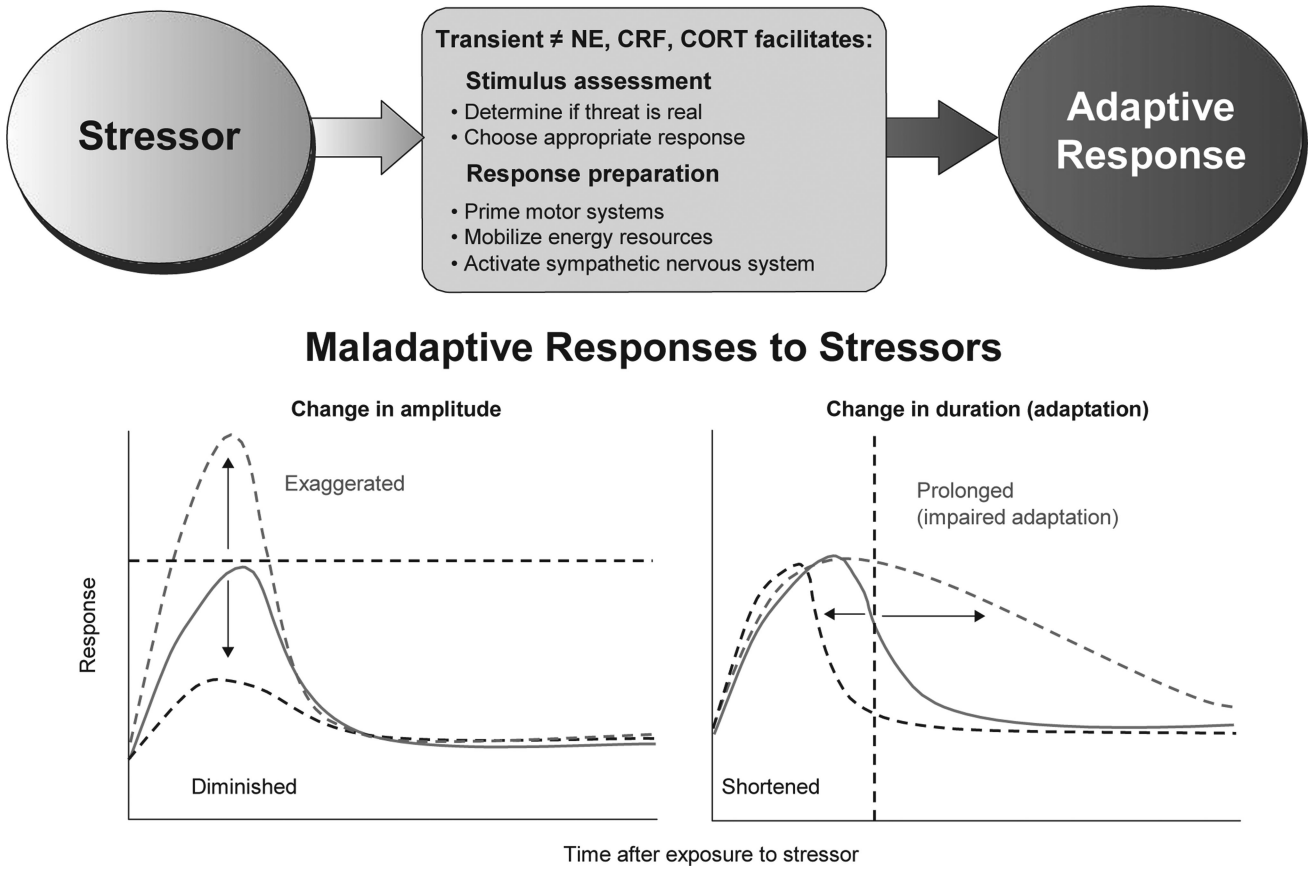


Figure 1.

The Stress Response System (SRS). TOP: The SRS is composed of behavioral, endocrine, and autonomic components which act in concert to generate an appropriate, adaptive response to a stressor. Three key mediators in the SRS are norepinephrine (NE), corticotropin releasing factor (CRF) and cortisol (CORT). Stressor-induced release of NE, CRF and CORT facilitates physiological processes which allow the organism to evaluate the stressor and choose an adaptive response, while in parallel activating effector systems. Execution of a successful response will minimize the impact of the stressor and in parallel, feedback inhibitory systems will ensure that the stress response system will return to normal, pre-stress levels. BOTTOM: Abnormal activation of NE, CRF and CORT pathways can result in a dysfunctional SRS in which normal alarm reactions may be maladaptive. A complex interplay of genetic risk factors, vulnerability factors (prior history), stressor factors (intensity, duration, chronicity), may be expressed neuronally as imbalances in different neurochemical pathways and functionally, as different alterations in the alarm reaction. Thus, the CRF and NE hyperactivation, and perhaps CORT hypoactivation, seen in different disorders may be manifested as alarm reactions with exaggerated or diminished amplitude and/or prolonged or shortened duration. Hypothetical curves represent a normal physiological response to a stressor that, after reaching a maximum, declines to baseline level. Examples are stress hormone responses or levels of physiological arousal. Return to baseline could result from successful removal of the activating threatening stimulus and/or from feedback inhibition processes (e.g. CORT inhibition of pituitary mediated ACTH

release). Exposure to traumatic stimuli, possibly in conjunction with vulnerability attributable to genetic and/or environmental (e.g. prior history of stress) factors, has the potential to produce sustained maladaptive responses (dashed lines).
Adapted from [217], printed with permission from Bentham Publishers.

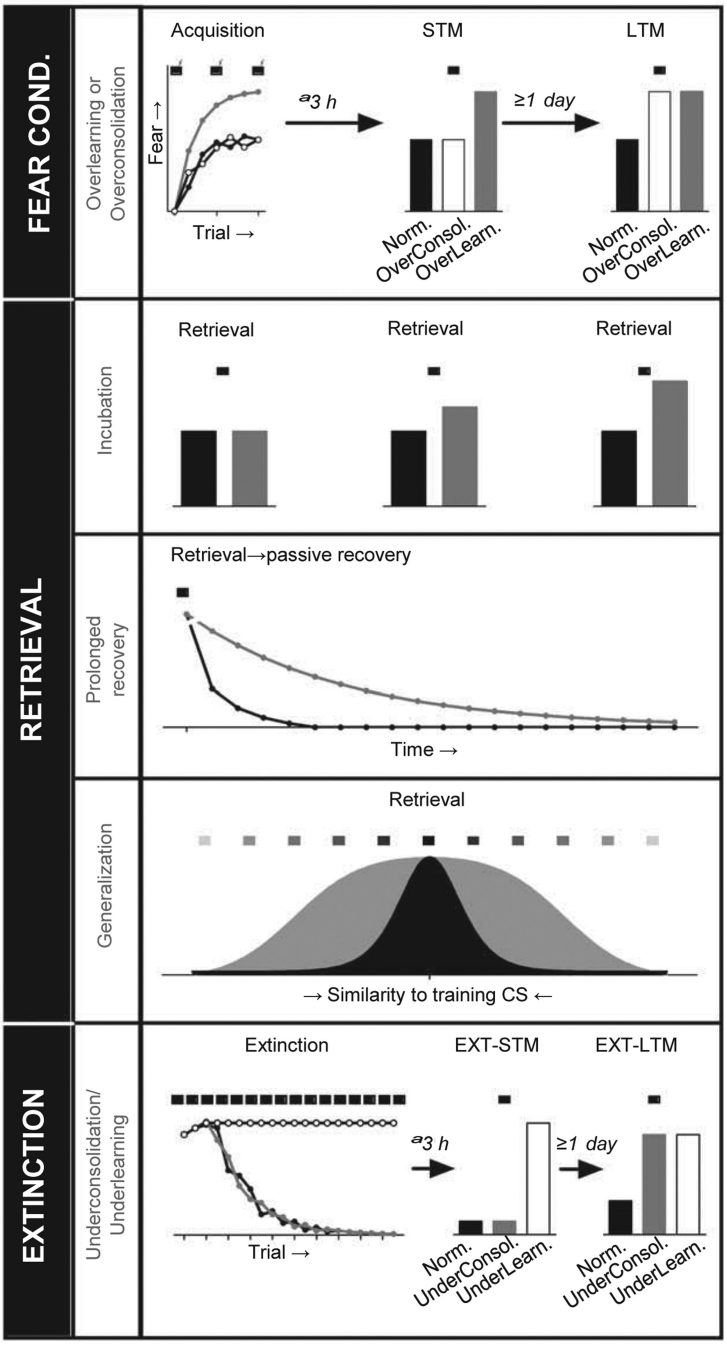


Figure 2.

FC Processes Could Contribute to PTSD. Prior experience(s) and/or biological factors may interact with stress-responding and associative memory to produce PTSD. Precise analyses of memory processes may continue to refine our understanding of the core memory deficits in PTSD. Identification of specific impairments should help identify brain regions and cellular/molecular mechanisms important for PTSD and its treatment. For instance, recent studies suggest that extinction consolidation/retrieval and generalization/discrimination are impaired in PTSD, highlighting the importance of inhibitory learning and PFC function.

Note that this list is not exhaustive and important learning processes like latent inhibition, conditioned inhibition and avoidance learning have been omitted. Black bars/lines represent normal FC and gray or white bars/lines represent potential abnormalities in PTSD.

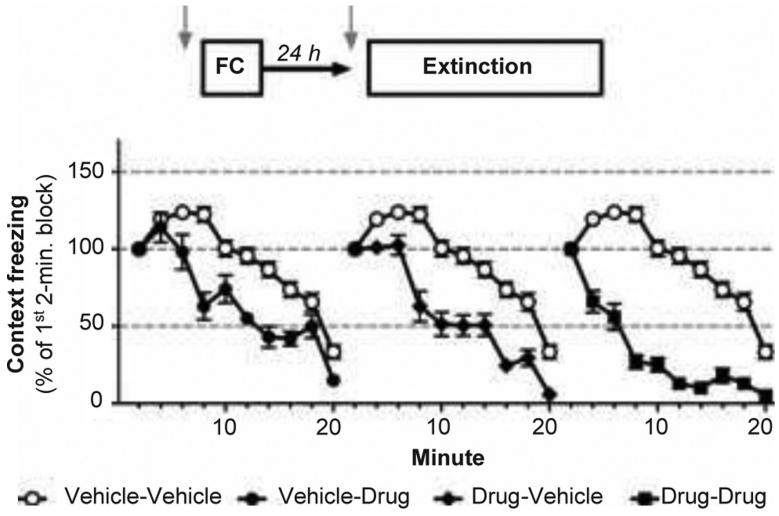


Figure 3.

The CRF_1 receptor antagonist antalarmin weakens FC and accelerates fear extinction in rats. CRF powerfully modulates memory and stress-responding through activation of CRF_1 receptors. However, no data exists on the potential utility of these drugs for treating PTSD. We reanalyzed data from a 1999 study by Deak et al published in Endocrinology (experiment 1) examining the effect of antalarmin on context FC and retrieval [159]. Since this experiment used 20-min LTM tests that produced significant extinction, we hypothesized that antalarmin reduced retrieval primarily by facilitating fear extinction. Original data were generously provided by Terrence Deak for the new analysis. Since antalarmin did slightly weaken initial fear retrieval as assessed by freezing behavior, we normalized responding to freezing in the first 2-min of the test to evaluate extinction. Rats were injected with Drug or Vehicle prior to context FC on Day 1. On Day 2, half of each group received the same treatment and half received the opposite treatment. (Left) Antalarmin accelerated extinction learning in rats that were conditioned drug-free. (Middle) Rats conditioned after antalarmin injections showed faster extinction when tested drug-free on Day 2. (Right) These effects were additive, as rats injected with antalarmin pre-conditioning and pre-extinction extinguished faster than any other group. These data support the notion that CRF_1 receptors antagonists may be particularly useful drugs for PTSD since they can blunt fear learning and facilitate fear suppression when combined with CS exposure. However, since the experiment wasn't designed to assess extinction processes it remains unclear whether the facilitation by antalarmin acutely translates to LTM for extinction in the drug-free state.

Table 1

Survey of non-SSRIs evaluated for clinical efficacy in treating PTSD: Monoamine mechanisms.

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
Venlafaxine	SNRI	” Extinction	Chronic PTSD	DBPC/538	#[104]	12 weeks treatment. Similar efficacy vs. sertraline
			Chronic PTSD	DBPC/329	#[103]	24 weeks treatment
Duloxetine	SNRI	untested	Chronic PTSD, military-related, co-morbid MDD	OL/21	#[163]	8 weeks treatment
			Chronic PTSD, military-related	OL/20	#[164]	12 weeks treatment
Propanolol	NE: b receptor antagonist	# Acquisition $ Consolidation # Retrieval # Incubation # Reconsolidation $ Extinction	Post-trauma, pediatric	DBPC/29	$[133]	Trends: #PTSD symptoms in boys, ”PTSD symptoms in girls
			Post-trauma	DBPC/48	$[92]	Gabapentin also failed to provide significant benefit
			Chronic PTSD	DBPC/19	#[138]	In combination with post-reactivation therapy. Reduced subsequent physiologic responses to recall
			Post-trauma	OL/19	#[132]	Reduced emergence of PTSD
			Post-trauma	DBPC/41	#[131]	Pilot study results suggest preventative effect on PTSD
			Chronic PTSD	DBPC/38	#[130]	Reduced emotional enhancement of memory in PTSD and normal subjects
Prazosin	NE: a_1 receptor antagonist	” Acquisition $ Consolidation # Extinction	Chronic PTSD, military-related	Historical 237	$[125]	Prazosin is better tolerated than quetiapine for nighttime PTSD symptoms but both failed to provide significant therapeutic effect (p = 0.54)
			Chronic PTSD	RPCC/13	#[121]	Improved sleep parameters and decreased nightmares
			Chronic PTSD	Historical/23	#[127]	Decreased nightmares and overall PTSD symptoms

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
			Chronic PTSD, military-related	DBPC/34	#[123]	Decreased nightmares and overall PTSD symptoms; improved sleep parameters
			Chronic PTSD	DBPC/10	#[126]	Daytime administration reduced PTSD-related psychological distress
			Chronic PTSD, elderly men	OL/9	#[124]	Reduced nightmares and overall PTSD severity
			Chronic PTSD, military-related	DBPC/10	#[165]	Decreased nightmares and overall PTSD symptoms; improved sleep parameters
			Chronic PTSD, military-related	Historical/59	#[122]	Reduced nightmares and overall PTSD severity
Clonidine	NE: a_2 receptor agonist	# Acquisition	Chronic PTSD	Historical/68	#[168]	Combination with imipramine for PTSD and depression
		# Retrieval				
Guanfacine	NE: a_2 receptor agonist	# Retrieval	Chronic PTSD, military-related	DBPC	$[166]	Taking no other psychiatric medication or stable dose of antidepressant
			Chronic PTSD, military-related	DPBC/63	$[167]	Taking no other psychiatric medication or stable dose of antidepressant
MDMA	5HT: releaser, reuptake inhibitor (DA, NE)	untested	Chronic, treatment-resistant PTSD	DPBC/20	#[119]	MDMA assisted psychotherapy
Bupropion	DA/NE reuptake inhibitor	$ FC	Chronic PTSD	DBPC/30	$[169]	
		# Retrieval				
Nefazodone	SSRI/5-HT2A Antagonist	# Retrieval	Chronic PTSD, military related	DBPC/41	#[114]	12-Week trial
Buspirone	5HT: 5HT1A partial agonist	# FC	Chronic PTSD	OL/8	#[108]	
		# Consolidation				
		# Retrieval				
		$ Extinction				
Risperidone	DA: D2 (and 5HT2A) antagonist	# Retrieval	Chronic PTSD, military-related	DBPC/247	$[170]	Serotonin reuptake-inhibiting antidepressant resistant PTSD
			SSRI resistant civilian PTSD	DBPC/45	$[171]	Post-hoc analysis suggested risperidone augmentation may be helpful in sertraline non-responders
			PTSD in women survivors of domestic abuse and rape trauma	DBPC/20	#[172]	Risperidone monotherapy
			Psychotic combat-related PTSD	OL /26	#[173]	Risperidone monotherapy

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
			Chronic PTSD, military-related	DBPC /73	#[174]	
			PTSD related to childhood abuse in women	DBPC /21	#[175]	
			PTSD, military-related	OL /17	#[176]	
			Chronic PTSD, military-related	DBPC /15	#[177]	Reduced irritability and intrusive thoughts in combat-related PTSD
Quetiapine	Mixed DA, 5HT, NE antagonist and H1 antagonist	untested	Chronic PTSD, military-related	Historical /237	$[125]	Prazosin is better tolerated than quetiapine for nighttime PTSD symptoms but both failed to provide significant therapeutic effect (p = 0.54)
			Chronic PTSD, military-related	OL /53	#[178]	Quetiapine monotherapy
			Chronic PTSD	OL /15	#[179]	Adjunctive therapy to SSRI
			Chronic PTSD, military-related	OL /19	#[180]	Reduced sleep disturbances
			Chronic PTSD, military related	OL /20	#[181]	Adjunctive treatment
Mirtazipine	5HT, a-adrenergic, H1 antagonist	# Retrieval	Chronic PTSD	DBPC /29	#[115]	
Amitriptyline	TCA with SNRI activity	# Retrieval	Chronic PTSD, military related	DBPC /46	#[182]	Improved some symptom measures including HAMA-A and HAM-D but not structured interview on PTSD symptoms
Imipramine	TCA	#FC #Retrieval	Chronic PTSD, military related	DBPC /34	#[183]	The MAO inhibitor phenelzine was also effective in this trial
			Chronic PTSD, military related	60	#[184]	The MAO inhibitor phenelzine appeared more effective in this trial
Olanzapine	Mixed DA, 5HT, NE antagonist and H1 antagonist	# FC	Chronic psychotic PTSD, military related	OL /55	#[185]	Olanzapine monotherapy was better than fluphenazine in reducing most of the psychotic and PTSD symptoms, and was better tolerated in psychotic PTSD patients
			Chronic PTSD, military-related	DBPC /19	#[186]	Adjunctive therapy in SSRI resistant patients. Reduced some PTSD symptom measures and improved sleep. No significant effect on clinician-rated global response
			Chronic PTSD, military-related	OL /48	#[187]	30 patients completed the study
			Chronic PTSD	DBPC /15	$[188]	
Aripiprazole	DA: D2, partial agonist, 5HT: 5HT1A partial agonist, 5HT2A antagonist	# Retrieval	PTSD, military-related	OL /17	#[189]	Augmentation of existing pharmacotherapy

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
			Chronic PTSD	OL /32	#[190]	Aripiprazole monotherapy. Nine patients discontinued treatment
			Chronic PTSD	OL /22	#[191]	Aripiprazole monotherapy. Eight patients discontinued treatment

zEffects of drugs on Symptoms: $ No significant effect; # improved symptoms; ” worsened symptoms.

DBPC: Double Blind Placebo-Controlled; FC: Fear conditioning; Historical: Retrospective chart review; OL: Open Label; RPCC: Randomized Placebo-Controlled Crossover; SNRI: Serotonin–norepinephrine reuptake inhibitor; TCA: Tricyclic antidepressant.

*Effects of drugs on Pavlovian FC processes: ” = enhanced, # = impaired, $ mixed results. No entry means either the drug has not been tested for that process or available tests show null effects. Both preclinical and clinical studies were considered, but only if drugs were evaluated on explicit FC paradigms. Acquisition: refers to a clear learning effect (either within-session or STM effect, or effect with pre-training but not post- training administration); Consolidation: refers to a clear consolidation effect (drug given post-training but washed out before fear retrieval test). FC is used when data aren't available to distinguish between acquisition and consolidation effects (Note: Pavlovian FC Processes column excludes findings from instrumental avoidance studies).

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Table 2

Survey of non-SSRIs evaluated for clinical efficacy in treating PTSD: Non-monoamine mechanisms.

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
Morphine	Opiate: μ agonist	# FC $ Consolidation # Retrieval # Extinction	Acute trauma, military-related	Historical /696	#[192]	Reduced risk of developing PTSD following traumatic injury
			Acute trauma, civilian	Historical /155	#[193]	Lower morphine dose associated with increased risk of PTSD
			Acute trauma, children	Historical /70	#[194]	Higher doses of morphine reduced subsequent PTSD symptoms
			Acute trauma, children	Historical /24	#[195]	Higher doses of morphine reduced subsequent PTSD symptoms
Nalmefene	Opiate antagonist	Untested	Chronic PTSD	OL /18	#[196]	Thought to block endogenous opiate effect thereby reducing emotional avoidance
Naltrexone	Opiate antagonist	” FC $ Consolidation $ Extinction	Chronic PTSD	OL /8	#[197]	Reduction in hyperarousal symptoms but at doses producing side-effects
D-Cycloserine	NMDA partial agonist (developed as broad spectrum antibiotic)	” Consolidation $ Retrieval ”Reconsolidation ” Extinction	Chronic PTSD	DBPC	$[198,199]	No benefit vs. placebo when combined With CBT. Several other clinical trials in PTSD are ongoing.
Ketamine	GLU: NMDAR antagonist	# Acquisition # Retrieval	Acute stress disorder following trauma	Historical /50	”[200]	Ketamine increased symptoms of dissociation, reexperiencing, hyperarousal and avoidance

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
			Acute trauma, military-related	Historical /147	#[201]	Patients who received ketamine had lower rates of PTSD than those who did not
Hydrocortisone	Glucocorticoid Receptor: agonist	” Acquisition	Trauma-exposed, with and without PTSD	OL	#[152]	Decreased fear-potentiated startle in PTSD patients
		” Generalization		100		
		# Cond. Inhib.				
		# Retrieval				
		” Extinction				
			Veterans, with and without PTSD	DBPC /63	#[153]	Decreased fear-potentiated startle in both PTSD and non-PTSD participants
			Chronic PTSD, military-related	DBPC /20	#[157]	Used in combination with memory reactivation; effect is significant at 1 week but diminished after 1 month
			Cardiac surgery patients	DBPC /28	#[154]	Hydrocortisone given at time of surgery decreased chronic stress symptoms
			Chronic PTSD	OL /3	#[151]	Reduced recall of traumatic memories
			Cardiac surgery patients	Randomized 48	#[155]	Hydrocortisone given at time of surgery decreased chronic stress symptoms
			Septic shock patients	DBPC /20	#[156]	Decreased development of PTSD
Topiramate	Anticonvulsant; Multiple effects	untested	Chronic PTSD	DBPC /38	#[202]	Monotherapy significantly reduced reexperiencing symptoms and Treatment Outcome PTSD scale.
			Chronic PTSD, military-related	DBPC /40	$[203]	Augmentation to standard pharmacotherapy and psychotherapy. Higher dropout rate in topiramate group due to

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
						CNS adverse events prevented definitive asses
						CNS adverse events prevented definitive asses
						CNS adverse events prevented definitive asses
			Chronic PTSD	OL /35	#[204]	Monotherapy and augmentation. Decreased nightmares and other PTSD symptoms.
Lamotrigine	Anticonvulsant; Na^+ channel inhibitor	# FC	Chronic PTSD	DBPC /14	#[205]	Reduced reexperiencing and avoidance/numbing symptoms
Tiagabine	Anticonvulsant; GABA uptake blocker	Untested	Chronic PTSD	DBPC /232	$[206]	
			Chronic PTSD	OL/DBPC /18	#[207]	Responders identified in OL trial had greater incidence of relapse when switched to placebo (p = 0.08)
Divalproex	Anticonvulsant; GABA enhancer	” FC	Chronic PTSD, military- related	DBPC /85	$[208]	
		” Generalization				
		” Reconsolidation				
		” Extinction				
Gabapentin	Anticonvulsant: calcium channel a2d subunit	Untested	PTSD	Historical /30	#[209]	Adjunctive therapy with gabapentin improved sleep and decreased nightmares
Levetiracetam	Anticonvulsant; unknown mechanism	Untested	Chronic PTSD	Historical /23	#[210]	Adjunctive therapy in PTSD patients with partial or no response to antidepressant therapy
Eszopiclone	GABA: $GABA_A$ PAM (BZD site)	Untested	Chronic PTSD	DBPC /24	#[211]	3 weeks treatment improved sleep and overall PTSD symptoms
Alprazolam	GABA: $GABA_A$ PAM (BZD site)	# Retrieval	PTSD in recent trauma survivors	OL /26	$[212]	Clonazepam (n = 10)
						Alprazolam (n = 3)
			Chronic PTSD	DBPC /10	$[213]	Cross-over design. Modest reduction in anxiety with alprazolam.
Clonazepam	GABA: $GABA_A$ PAM (BZD site)	Untested	Chronic PTSD, military-related	Randomized 6	$[214]	
Temazepam	GABA: $GABA_A$ PAM (BZD site)	Untested	Acute trauma, civilian	Randomized 21	$[215]	Treatment for 1 week following trauma; follow-up at 6 weeks

Drug	Primary mechanism	Pavlovian FC Process*	Population	Trial Type/#Enrolled	Effect on symptoms‡	Comment
GR205171	NK1 Receptor Antagonist	# Retrieval	Chronic PTSD	DBPC /39	$[216]	

[z]Effects of drugs on Symptoms: $ No significant effect; # improved symptoms; ” worsened symptoms.

DBPC: Double Blind Placebo-Controlled; FC: Fear conditioning; OL: Open Label; Historical: Retrospective chart review.

*Effects of drugs on Pavlovian FC processes: ” enhanced, #impaired, $mixed results. No entry means either the drug has not been tested for that process or available tests show null effects. Both preclinical and clinical studies were considered, but only if drugs were evaluated on explicit FC paradigms. Acquisition: refers to a clear learning effect (either within-session or STM effect, or effect with pre-training but not post-training administration); Consolidation: refers to a clear consolidation effect (drug given post-training but washed out before fear retrieval test). FC is used when data aren't available to distinguish between acquisition and consolidation effects (Note: Pavlovian FC Processes column excludes findings from instrumental avoidance studies).

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Table 3

Open trials evaluating the effects of investigational drugs on the treatment of PTSD: Monoamine mechanisms.

Drug	Primary Mechanism	Pavlovian FC Process*	Population/Primary Outcome	Trial Type/# Enroll	Start Date/Estimated Completion	Comment
Propanolol	NE: b receptor antagonist	# Acquisition $ Consolidation # Retrieval # Incubation # Reconsolidation $ Extinction	Chronic PTSD CAPS	DBPC/50	Feb 2010 Jun 2012	Single dose with memory reactivation each week for six weeks. Evaluation at baseline and after 8 weeks
			PTSD and non-PTSD with distress CAPS, IES, TMDM	DBPC/66	Feb 2010 Sep 2011	Single treatment with memory reactivation. Assessments at baseline and after 4 weeks
			Chronic PTSD, military-related Psychophysiologic Responses	DBPC/60	Sep 2007 Oct 2012	Single treatment with memory reactivation. Measurements pre and post-treatment
			Chronic PTSD with Alcohol Depend. Subjective Distress	DBPC/50	Jan 2010 Aug 2012	Propranolol coupled with the elicitation/retrieval of trauma-related memories. Single treatment with 2 week follow-up
Prazosin	NE: a_1 receptor antagonist	” Acquisition $ Consolidation # Extinction	Chronic PTSD, military-related Nightmares, sleep quality and quantity, and global clinical status	DBPC/326	Jan 2010 Mar 2013	Titrated to stable daily dose to be maintained throughout study. Evaluate changes versus baseline at 6, 10, 14, 18, 22 and 26 weeks
			Chronic PTSD, military-related CAPS, PSQI, CGIC	DBPC/300	Sep 2009 Jun 2014	Treatment for 15 weeks to test augmentation of previous psychotropic medications and/or psychotherapy
Yohimbine	NE: a_2 receptor antagonist	” Acquisition $ Retrieval ” Extinction	Chronic PTSD, military-related CAPS	DBPC/60	Dec 2010 May 2015	Yohimbine given one hour before first imaginal exposure in PE. Evaluation at baseline, 15 weeks and 27 weeks
Sertraline	5-HT: SSRI	# Retrieval	Chronic PTSD, military-related CAPS	DBPC/441	Nov 2011 Dec 2015	Treatment with up to 13 sessions of PE therapy +24

Drug	Primary Mechanism	Pavlovian FC Process*	Population/Primary Outcome	Trial Type/# Enroll	Start Date/Estimated Completion	Comment
						weeks of daily sertraline compared to placebo +PI
						weeks of daily sertraline compared to placebo +PI
Venlafaxine	5-HT, NE: SNRI	” Extinction	CAPS PTSD HTQ	OL/150	Dec 2015 Apr 2012 Apr 2014	Six months of daily treatment with venlafaxine combined with CBT compared to sertraline + CBT
Mirtazapine Sertraline	TCA, SSRI	# Retrieval	Chronic PTSD CAPS and time to discont	DBAC 60	Jun 2010 Jun 2013	Daily doses for 12 weeks. Patients that respond will continue treatment another 12 weeks
MDMA	5HT: releaser, reuptake inhibitor (DA, NE)	untested	Chronic PTSD, military-related CAPS	DBPC 24	Sep 2010 Dec 2013	Introductory 90 min psychotherapy followed by two 8 h sessions 3 – 5 weeks apart and combined with MDMA. Evaluations at baseline; at 1 month following session 2; at 2 months following session 3 and at 12 months
Methylene Blue	MAO: Inhibitor	” Extinction	Chronic PTSD PTSD symptom severity	DBPC 42	Sep 2009 Apr 2013	Daily psychotherapy followed by a dose of methylene blue. Assessment at pre- and post-treatment, 1 and 3 months
PRX-03140	5HT: 5HT4 partial agonist	untested	Chronic PTSD Change in adverse events	OL/12	Apr 2012 Dec 2012	PRX-03140 given daily for 10 weeks with dose escalation

Source: ClinicalTrials.gov.

CAPS: Clinician-Administered PTSD Scale; CGIC: Clinical Global Impression of Change Scale; DBAC: Double Blind Active Control; FC: Fear Conditioning; HTQ: Harvard Trauma Questionnaire; IES: Impact of Event; POMS: Profile of Mood States; PSQI: Pittsburgh Sleep Quality Index; TMDM: Traumatic Memory Description Measure.

*Effects of drugs on Pavlovian FC processes: ” = enhanced, # = impaired, $mixed results. No entry means either the drug has not been tested for that process or available tests show null effects. Both preclinical and clinical studies were considered, but only if drugs were evaluated on explicit FC paradigms. Acquisition: refers to a clear learning effect (either within-session or STM effect, or effect with pre-training but not post-training administration); Consolidation: refers to a clear consolidation effect (drug given post-training but washed out before fear retrieval test). FC is used when data aren't available to distinguish between acquisition and consolidation effects (Note: Pavlovian FC Processes column excludes findings from instrumental avoidance studies).

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Table 4

Open trials evaluating the effects of investigational drugs on the treatment of PTSD: Non-monoamine mechanisms.

Drug	Primary mechanism	Pavlovian FC Process	Population/Primary Outcome	Trial Type/# Enroll	Start Date/Estimated Completion	Comment
D-Cycloserine	NMDA partial agonist (developed as broad spectrum antibiotic)	” Consolidation $ Retrieval ” Reconsolidation ” Extinction	Chronic PTSD CAPS, PCL	DBPC/124	May 2008 May 2013	D-Cycloserine prior to cognitive behavioral treatment with exposure therapy (~9 out of 12 – 14 weekly CBT treatments). Assessments at baseline and after sessions 3, 6 and 10 and 6 months after treatment
			Chronic PTSD CAPS, PCL	DBPC/40	Jan 2005 Dec 2012	D-Cycloserine prior to virtual reality exposure therapy (10 – 12 weekly treatments). Assessments at baseline and after sessions 3, 6 and 10 and 6 months after treatment
			Chronic PTSD Number of PTSD symptoms	DBPC/56	Jun 2010 Jun 2012	D-Cycloserine prior to sessions 5 – 12 of the 12-session CBT protocol. Assessments at baseline, after sessions and 3 months after treatment
			PTSD in youth	DBPC/56	Jun 2010	D-Cycloserine prior to sessions 5 – 12 of the 12-session CBT protocol. Assessments at baseline, after sessions and 3 months after treatment

Drug	Primary mechanism	Pavlovian FC Process	Population/Primary Outcome	Trial Type/# Enroll	Start Date/Estimated Completion	Comment
			Number of PTSD symptoms		Jun 2012	
Mifepristone D-Cycloserine	Progesterone receptor antagonist/partial agonist; NMDA partial agonist		Chronic PTSD Psychophys. measures	DBPC/135	Mar 2009 Jul 2013	D-Cycloserine prior to script-driven traumatic imagery with Mifepristone also given on treatment days
Mifepristone	Competitive progesterone receptor antagonist/partial agonist	# Consolidation # Retrieval # Reconsolidation # Extinction	Chronic PTSD, military-related CAPS-2, dichotomously defined clinical responder status	DBPC/80	May 2008 Oct 2011	Daily doses for 1 week. Evaluations at baseline, 1 week and 4 weeks
Hydrocortisone	Glucocorticoid Receptor: agonist	” Acquisition ” Generalization # Cond. Inhib. # Retrieval ” Extinction	Chronic PTSD, military-related CAPS	DBPC/50	Feb 2010 Nov 2013	Hydrocortisone given prior to each of 10 weekly PE sessions. Assessments at 0, 10 and 16 weeks
			Chronic PTSD, military-related CAPS	DBPC/60	Apr 2011 Sep 2015	Hydrocortisone given prior to each of 11 weekly PE sessions. Assessments at 0, 12 and 23 weeks
			Acute trauma victims with anxiety PTSD diagnosis at the end of the trial	DBPC/120	Apr 2009 Aug 2014	Single IV injection of hydrocortisone given within 6 h of trauma. Assessments at 0.5, 1, 3, 8 and 13 months
			Females with PTSD IES-R	DBPC/25	Oct 2008 Sep 2012	Comparison of 1 week treatment with

Drug	Primary mechanism	Pavlovian FC Process	Population/Primary Outcome	Trial Type/# Enroll	Start Date/Estimated Completion	Comment
						hydrocortisone vs. placebo with asses
						hydrocortisone vs. placebo with asses
						hydrocortisone vs. placebo with asses
						hydrocortisone vs. placebo with asses
			IES-R		Sep 2012	
Dexamethasone	Glucocorticoid Receptor: agonist	” FC	Chronic PTSD vs. non-PTSD	DBPC/150	Nov 2011	Baseline and FPS response at 1 h and 10 h following dexamethasone administration
		” Generalization	Psychophys. measures		Jun 2013	
		# Retrieval				
		” Extinction				
			Chronic PTSD, military-related	DBPC/102	Apr 2010	Dexamethasone given following traumatic memory reactivation every 7 days for 4 weeks. Evaluation at baseline and at 1, 3 and 6 months after final treatment
			Psychophys. measures		Oct 2012	
GSK561679	CRF: CRF1 antagonist	untested	Women with Chronic PTSD, CAPS	DBPC/150	Dec 2009	Daily treatment for 6 weeks. Assessments at baseline and 6 weeks
					Dec 2013	
Oxytocin	Oxytocin: Receptor agonist	# Retrieval	Chronic PTSD	DBPC/40	Oct 2011	Impact of a single intranasal administration on impact on fear renewal and reinstatement at 1 day after treatment
		# Extinction	Psychophys. measures		Mar 2013	
Ketamine	GLU: NMDAR antagonist	# Acquisition	Chronic PTSD	DBAC/40	Jan 2009	Single ketamine IV infusion vs. single IV infusion of midazolam
		# Retrieval	IES-R		Jan 2013	
Diazepam	GABA: BZ site PAM	# Acquisition	Acute Trauma	OL/60	Oct 2011	Single dose of diazepam given within hours of trauma and before a night of sleep to
		# Retrieval	CAPS		May 2013	
		# Extinction				

Drug	Primary mechanism	Pavlovian FC Process	Population/Primary Outcome	Trial Type/# Enroll	Start Date/Estimated Completion	Comment
						reduce PTSD development
						reduce PTSD development
		# Retrieval	CAPS		May 2013	
		# Extinction				
Ganaxolone	GABA: steroid site PAM	Untested	Chronic PTSD	DBPC/120	Apr 2011	Twelve weeks of daily treatment with assessment of CAPS at week 6
			CAPS		Nov 2012	
NPY	NPY; NPY receptor agonist	# FC	Chronic PTSD	DBPC/20	Jan 2012	Single intranasal administration. Evaluation within 3 h
		# Retrieval	POMS, BDI-II, BAI, Appetite Scale		Dec 2012	
		” Extinction				
Omega-3 Fatty Acids	Neurogenesis	# Retrieval	Chronic PTSD, military-related	DBPC	Sep 2008	Daily dosing with evaluations at baseline and after 10 weeks
			CAPS, BAC-A	40	Dec 2011	
			Chronic PTSD/CAPS	DBPC/140	Dec 2008	Dosing for 12 weeks. Evaluations at baseline, 4 and 12 weeks
					Dec 2013	
NPY	NPY; NPY receptor agonist	# FC	Chronic PTSD	DBPC/20	Jan 2012	Single intranasal administration. Evaluation within 3 h
		# Retrieval	POMS, BDI-II, BAI, Appetite Scale		Dec 2012	
		” Extinction				

Source: ClinicalTrials.gov.

*Effects of drugs on Pavlovian FC processes: ” = enhanced, # = impaired, $mixed results. No entry means either the drug has not been tested for that process or available tests show null effects. Both preclinical and clinical studies were considered, but only if drugs were evaluated on explicit FC paradigms. Acquisition: refers to a clear learning effect (either within-session or STM effect, or effect with pre-training but not post-training administration); Consolidation: refers to a clear consolidation effect (drug given post-training but washed out before fear retrieval test). FC is used when data aren't available to distinguish between acquisition and consolidation effects (Note: Pavlovian FC Processes column excludes findings from instrumental avoidance studies).

BAC-A: Brief Assessment of Cognition in Affective Disorders; BAI: Beck Anxiety Inventory; BDI-II: Beck Depression Inventory (Second Edition); CAPS: Clinician-Administered PTSD Scale; DBAC: Double Blind Active Control; IES-R: Impact of Event Scale – Revised; PAM: Positive Allosteric Modulator; PCL: PTSD Checklist; POMS: Profile of Mood States.