HHS Public Access

Author manuscript

Biol Psychiatry. Author manuscript; available in PMC 2016 September 01.

Published in final edited form as:

Biol Psychiatry. 2015 September 1; 78(5): E15–E27. doi:10.1016/j.biopsych.2015.06.008.

An overview of translationally informed treatments for PTSD: animal models of Pavlovian fear conditioning to human clinical trials

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Abstract

Posttraumatic stress disorder (PTSD) manifests after exposure to a traumatic event and is characterized by avoidance/numbing, intrusive symptoms and flashbacks, mood and cognitive disruptions, and hyperarousal/reactivity symptoms. These symptoms reflect dysregulation of the fear system likely caused by poor fear inhibition/extinction, increased generalization, and/or enhanced consolidation or acquisition of fear. These phenotypes can be modeled in animal subjects using Pavlovian fear conditioning, allowing investigation of the underlying neurobiology of normative and pathological fear. Pre-clinical studies reveal a number of neurotransmitter systems and circuits critical for aversive learning and memory, which have informed the development of therapies used in human clinical trials. In this review, we discuss the evidence for a number of established and emerging pharmacotherapies and device-based treatments for PTSD that have been developed via a bench to bedside translational model.

Keywords

Exposure; Extinction; Fear; Antidepressant; Morphine; Opioid; D-Cycloserine; Hydrocortisone; Cannabinoid; Glucocorticoid; Propranolol

Introduction

Posttraumatic stress disorder (PTSD) manifests after exposure to a traumatic event and is characterized by four core clusters of symptoms: avoidance/numbing, intrusive symptoms

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Financial disclosures:

Dr. Ressler is a founding member of Extinction Pharmaceuticals/Therapade Technologies to develop D-cycloserine, a generically available compound, for use to augment the effectiveness of psychotherapy. He has received no equity or income from this relationship within the last 5 years. Dr. Bowers reports no biomedical financial interests or potential conflicts of interest.

and flashbacks, mood and cognitive disruptions and hyperarousal/reactivity symptoms (1). An event is considered traumatic if it involves exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence. The estimated lifetime prevalence of PTSD in the United States is between 7–9% (2).

Data suggests that 94% of individuals who experience trauma develop acute PTSD-like symptoms (2, 3). For most, these symptoms will abate over time. Some hypothesize that increased generalization and deficits in extinction underlie symptomatology of PTSD. Enhanced acquisition and consolidation of trauma-related fear may also precipitate the development of PTSD, additionally. Animal studies using Pavlovian fear conditioning and extinction paradigms offer insight on the neurobiology of these fear-related dimensions, allowing identification of functional circuitry and molecular signaling pathways critical for normative and pathological fear, (see Supplementary for Fig S1 and detailed review of *Neurobiological Approaches to Fear*).

Through these pre-clinical studies, researchers have identified the amygdala, interacting critically with the hippocampus and medial prefrontal cortex (mPFC), as the primary anatomical loci of fear learning and extinction (4–6). Furthermore, manipulations of various transmitter systems during different phases of aversive learning point to a number of potential pharmacotherapies and specific treatment windows. Based on pre-clinical indications, pilot and large-scale clinical studies have now been conducted on a number of treatments with a variety of administration protocols, e.g. chronically, administered in the immediate aftermath of trauma, in conjunction with exposure therapy, or during reconsolidation. Additionally, researchers are exploring the efficacy of device-based treatments for PTSD and PTSD-like symptoms in humans and rodents, given the success of deep-brain stimulation (DBS) for the treatment of depression (7).

In this review, we explore established and emerging treatment strategies for PTSD that are supported by pre-clinical and clinical data. Although the number of approved treatments is small, with SSRIs as the only class of drug approved for treatment of PTSD, exciting new evidence points to a number of promising pharmacotherapies and device-based treatments with a variety of treatment protocols.

Pharmacotherapy approaches to Fear- and Anxiety-related disorders

The following sections review pre-clinical and clinical evidence for a variety of established and emerging pharmacotherapies, especially focusing on underlying transmitter and receptor systems, as well targeted brain regions. In discussing the pre-clinical data, we focus on outlining evidence from studies of cued and contextual fear conditioning, but include discussion of evidence from alternative fear and anxiety paradigms where relevant.

Serotonin (5-HT)/selective serotonin reuptake inhibitors (SSRIs)

Use of SSRIs in PTSD stems from the observed efficacy of SSRIs for depression and the high incidence of depression co-morbid with anxiety and PTSD (8). SSRI efficacy in the treatment of depression contributed to the previously accepted biogenic amine hypothesis,

which postulates that disturbances in serotonin, dopamine, and norepinephrine underlie the pathology of depression (9–13).

Similarly, evidence from rodent and human studies implicates brain serotonin systems in the neurobiology of PTSD (14–16). The amygdala, hippocampus, and frontal cortex areas with a demonstrated role in PTSD - receive serotonergic input via projections from the dorsal and median raphe nucleus (17–19). A recent meta-analysis supports an association between the lesser expressing, short allele of 5-HTTLPR (serotonin transporter gene) and PTSD in high-trauma exposed individuals (20). Conclusions from PET analysis are consistent with this model, where individuals with PTSD exhibit reduced amygdala 5-HTT (serotonin transporter protein) binding (14). Additional PET studies observe an association between early trauma exposure and serotonin type 1B receptor binding, as well as higher serotonin 1A binding in PTSD, however these findings have not been uniformly replicated (21–23).

Several studies find increased cued fear acquisition and expression in rodents and humans with acute SSRI administration (24–26). An effect on cued fear acquisition and expression may be mediated by the serotonin 2A receptor, as administration of a serotonin 2A receptor agonist after fear conditioning increases cued fear expression (27), and administration prior to extinction enhances within-session extinction (27). Similarly, serotonin 2A receptor antagonist administration blocks cued fear acquisition (28).

Conversely, chronic SSRI administration impairs fear learning, in particular cued fear acquisition and extinction (29). However, chronic fluoxetine may also prevent return of extinguished fear and facilitate extinction in female rats (30–32). Ultimately, an effect of chronic SSRI administration on extinction, as well as SSRI efficacy for treatment of depression and PTSD, may be driven by a change in glutamatergic transmission, as supported by recent DCS and ketamine findings.

Somewhat consistent with rodent pre-clinical data, several studies indicate that outcomes for individuals treated with SSRIs and CBT outcomes may be worse compared to CBT alone (33–35). Other studies report comparable or modest benefits with combinatorial treatment (36–42). While a 2008 report from the Institute of Medicine (IOM) concludes that SSRIs, among other all other classes of drugs, do not demonstrate efficacy in the treatment of PTSD, a recent meta-analysis supports the efficacy of long-term treatment of PTSD with SSRIs (43). While some suggest that SSRIs are as effective as psychotherapy as a first-line treatment, others recommend SSRIs as a second-line treatment after CBT (41), clearly further investigation of SSRIs is needed (44).

N-methyl-D-aspartic acid (NMDA)/D-cycloserine (DCS)

In combination with cognitive behavioral therapy, D-cycloserine (DCS) - a compound that acts as a partial agonist at the strychnine-insensitive glycine-recognition site of the NMDA receptor has helped the field consider targeted pharmacological augmentation of psychotherapy. In rodents, systemic or intra-amygdala administration of DCS has repeatedly been shown to facilitate extinction of fear-potentiated startle and cued freezing in rats (FPS) (45–48). Furthermore, DCS blocks increases in freezing caused by reinstatement, but has no effect on renewal processes (49, 50). DCS is thought to act on consolidation of emotional

learning, as post-training administration of DCS similarly facilitates extinction (45). Importantly, DCS reverses deficits in fear extinction caused by the single prolonged stress model that is hypothesized to more thoroughly instantiate PTSD-like symptoms and the accompanying underlying pathology (51, 52). Similarly, DCS enhances extinction in 129S1/SvImJ (S1), an alternative genetic mouse model of PTSD that exhibits persistent impairment of fear extinction (53).

In humans, DCS shows promise for the treatment of social anxiety, obsessive compulsive disorder (OCD), panic disorder, acrophobia, and nicotine dependence (54–59). Data on efficacy of DCS in the modulation of associative fear learning and treatment of PTSD, however, is mixed. In healthy human volunteers, DCS facilitates consolidation of fear acquisition of previously neutral cues and cued fear extinction (60, 61). Other studies, have also not observe a reduction in conditioned fear with administration of DCS (62–64). For individuals with PTSD, DCS seems particularly effective when administered with virtual reality exposure (VRE) (65, 66). Some studies have not reported increased remission with DCS compared to placebo (when administered in combination with cognitive behavioral therapy) (67, 68). Despite inconsistencies in the literature, meta-analyses suggest that DCS enhances fear extinction/exposure therapy in both animal subjects and humans (69, 70).

The current consensus is that its effects are modulated by a number of factors. DCS yields greater reductions in PTSD-symptoms in subjects with more severe pre-treatment PTSD (71). Furthermore, participants with high conscientiousness and low extraversion exhibit better outcomes with DCS and exposure therapy, compared to placebo (72). DCS also appears to selectively enhance exposure therapy when administered with successful sessions (73). This effect is reflected in rodent models, where subjects who exhibit successful within-session extinction show better long-term extinction with DCS (47, 74). These data suggest that DCS may be an efficacious adjunctive therapy, but only for a subset of the clinical population and with specifically tailored CBT sessions, among other factors (75, 76). Despite its limitations, DCS has been an important molecule in moving the field forward to directly addressing mechanisms of emotional learning from a translational perspective based on a behavioral neuroscience understanding of rodent emotion processing.

Glucocorticoids/Hydrocortisone

Under normative conditions, stress-induced activation of the (HPA)-axis causes an increase in the release of the adrenal hormone cortisol (corticosterone in rodents). Increased cortisol mobilizes biological resources needed to engage the flight or fight response to promote survival. These stress-related increases in cortisol eventually inhibit HPA-axis activity to terminate the stress response. Chronic or extreme stress, however, can contribute to HPA-axis dysregulation and a host of other adverse effects (77, 78).

HPA-axis dysregulation is observed in individuals with PTSD, where low baseline levels of cortisol (although higher levels or no differences have been observed as well (79–82)) and enhanced negative feedback in response to dexamethasone are reported (83–88). Prospective studies suggest that low cortisol in the face of trauma is a predisposing factor for the development of PTSD (87, 89–92). One hypothesis is that reduced cortisol signaling alters normal adaptive responses of the autonomic nervous system, including negative feedback to

the pituitary and hypothalamus to terminate the stress response (93). Specifically, low cortisol could impede cortisol homeostasis, contributing to an inability to contain the stress response and resulting in runaway fear characteristic of PTSD.

A number of investigators have developed animal models that more thoroughly instantiate PTSD-like symptoms and replicate HPA-axis alteration. These approaches suggest that glucocorticoid system manipulations in healthy models, where the corticosterone response is adaptive, might be different from PTSD-like models, where corticosterone responses may be maladaptive. Importantly, these studies report that animals exposed to extreme stress exhibit poor fear extinction, greater acoustic startle, more anxiety-like behavior, and heightened fear expression, as in humans with PTSD (94–102).

For example, Lewis rats, which are more susceptible to PTSD-like behavior, do not exhibit an increase in circulating corticosterone several days after stressor exposure compared to other strains that are less vulnerable (95). Mice and rats exposed to extreme stress exhibit enhanced negative feedback in response to acute stress or cortisol (103–106). In other studies, however, subjects that exhibit PTSD-like behavior in response to extreme stress have increased circulating levels of corticosterone several days after stressor exposure compared to well adapted and non-exposed rats (96, 107, 108). Furthermore, other studies find that baseline corticosterone prior to stressor exposure does not predict subsequent behavioral responses to extreme stress (95, 109). Conflicting HPA-axis activity findings in PTSD-like models may reflect a problem of whether these models recapitulate PTSD and/or depression, similar to the problem seen in clinical studies where PTSD is often comorbid with depression.

PTSD-like models have also allowed researchers to test the hypothesis that glucocorticoid administration in the face of extreme stress might contain the stress response and prevent the development of PTSD-like effects. Indeed, acute pharmacological intervention with corticosterone after stress is able to rescue PTSD-like behavioral effects (95, 102, 110, 111). This is now being tested in humans. As in rodent models, administration of hydrocortisone during a critical window after trauma has been shown to reduce the risk of PTSD development (112–114). In humans, administration of hydrocortisone in combination with traumatic memory reactivation reduces PTSD symptoms (115); and greater patient retention was observed in the treatment group with hydrocortisone administered in combination with prolonged exposure therapy (116). Glucocorticoid modulation may also enhance extinction for other fear-related disorders besides PTSD, as seen in successful reduction of fear in combination with exposure therapy for social phobia, spider phobia, and phobia of heights (117, 118). These studies suggest that glucocorticoid modulation enhances extinction memory, in line with pre-clinical evidence implicating the glucocorticoids in memory consolidation (119, 120). It may also acutely reduce fear (118), as seen with daily hydrocortisone reducing re-experiencing and avoidance symptoms of PTSD (121).

Though promising, there remain some inconsistences in the HPA modulation field, consistent with the human literature, where the development of an extreme behavioral response to “trauma” is associated with an increase or decrease in circulating levels of

glucocorticoids. Prospective studies evaluating glucocorticoid levels at baseline and in response to a stressor before and after trauma across species would be the most informative.

Opioids/Morphine

Along with marijuana and alcohol, opiates are one of the most commonly abused substances among individuals with PTSD, indicating that aberrant endogenous opioid signaling may underlie PTSD (122). In rodents, administration of opioid antagonists increase conditioned fear by enhancing fear acquisition or blocking fear extinction (123–125). Conversely, morphine (opioid receptor agonist) administration blocks conditioned fear acquisition in normal and prior-stress models (126, 127). Opioid signaling in ventrolateral periaqueductal gray matter (vlPAG) regulates conditioned fear extinction, potentially via activation of mPFC and the BLA (128, 129).

Research addressing specificity of opioid regulation of conditioned fear implicates the mu (μ) and kappa (κ) opioid and nociceptin (NOP)/orphanin FQ receptors. Antagonism of the μ opioid receptor facilitates contextual fear conditioning (130) and blocks extinction of cued fear (131). Similarly, antagonism of the κ opioid receptor blocks conditioned fear on a fear-potentiated startle paradigm (132, 133). In PTSD-like rodent models, differential levels of CSF nociceptin (NOP)/orphanin FQ and nociceptin (NOP)/orphanin FQ receptor mRNA are observed (134, 135). Furthermore, nociceptin (NOP)/orphanin FQ receptor agonist administration blocks contextual and cued fear consolidation in normal and PTSD-like rodent models (135–137).

In humans, genetic analysis revealed a significant interaction between the *OPRL1* (opioid receptor-like 1) gene and childhood trauma that is associated with PTSD and neural correlates of PTSD (135). Similarly, other studies suggest that a polymorphism in the *OPRM1* gene (opioid receptor μ–1) is associated with less severe PTSD symptoms (138). Regarding specific PTSD-related symptoms, κ opioid receptor availability in the amygdala-anterior cingulate cortex-ventral striatal circuit mediates the expression of dysphoria where lower κ opioid receptor is associated with greater severity of trauma-related loss symptoms (139).

Interestingly, some evidence suggests that morphine may be effective for secondary prevention of PTSD. Children administered morphine after acute burns exhibit decreased PTSD symptoms months to years after treatment in a dose-dependent fashion (140–142). Studies of traumatized adults administered morphine mirror results found in pediatric data sets (143). Prospective studies find that patients who meet criteria for PTSD at 3 months post-trauma received significantly less morphine acutely after injury (144). Data from healthy volunteers, where opioid agonists inhibit and antagonists promote fear acquisition, support the hypothesis that morphine administration in the immediate aftermath of trauma may prevent the development of PTSD by inhibiting the acquisition of fear in response to trauma (145, 146), consistent with above data in rodents (126, 127).

A critical alternative explanation may be that a reduction in pain caused by morphine administration is able to mitigate the development of PTSD. This hypothesis is supported by several reports that pain after trauma is significantly associated with later development of

PTSD (144, 147, 148). Nonetheless, previous and ongoing studies suggest that the effects on PTSD buffering may be independent of pain. Further prospective studies are needed to more safely establish morphine's efficacy as a secondary preventative therapy. Concomitant pain monitoring, or comparison with non-opioid analgesics, will help determine the mechanism by which morphine may prevent the development of PTSD.

Cannabinoids/Nabilone/Delta-9-tetrahydrocannabinoil

Overwhelming evidence from rodent models suggest that the endocannabinoids are critically involved in stress, fear, and anxiety (149, 150). Knockout or antagonism of Cnr1 increases anxiety-like behavior on a number of different paradigms across a variety of species (149, 151, 152). Increased synthesis of the endocannabinoids and subsequent activation of Cnr1 in the amygdala is thought to mediate fear extinction in mice and rats, potentially via inhibition of the anxiogenic neuropeptide cholecystokinin (CCK) and/or modulation of the GABAergic system (151, 153, 154). Additionally, Cnr1 is critical for acquisition, retrieval, and extinction of both cue and context fear, as well as reconsolidation of cued fear memory (153, 155–157). Cnr1 involvement in cued fear is thought to be mediated primarily by the amygdala and mPFC (154, 156, 157). Furthermore, the endocannabinoid system is implicated in stress and stress-sensitization of fear behavior, where Cnr1 is thought to modulate glutamatergic and GABAergic signaling primarily in the bed nucleus of the stria terminalis, the basolateral amygdala, and the central amygdala (158–164). Administration of a Cnr1 agonist acutely after shock prevents PTSD-like symptoms in rats, suggesting that cannabinoid drugs might be administered acutely after trauma to prevent development of PTSD (163).

Evidence implicating Cnr1 involvement in stress, fear, and anxiety in rodent models has stimulated investigation of Cnr1 involvement in PTSD and fear processes in humans. Studies suggest delta-9-tetrahydrocannabinoil (Δ9-THC) facilitates extinction of conditioned fear in healthy human volunteers (64, 165). As mentioned, PTSD diagnosis is significantly associated with greater marijuana use, indicating that Δ9-THC is used as a form of self-medication to compensate for cannabinoid system dysregulation (166). In fact, several genetic association studies reveal specific *Cnr1* and *FAAH* (fatty acid amide hydrolase, an anandamide degradative enzyme) allelic risk factors for threat processing, anxiety, extinction, stress-coping, and PTSD (167–170). Furthermore, PET studies suggest that individuals with PTSD have increased brain Cnr1 availability, possibly due to changes in peripheral levels of the endocannabinoids (171–173). Although the data is preliminary, several studies show that cannabinoid receptor agonists, including nabilone and Δ9-THC, improve insomnia, subjective chronic pain, nightmares, and other symptoms related to PTSD (174–177). While these studies suggest that chronic administration of Cnr1 agonists can improve general mood and symptoms related to PTSD, more studies are needed to address the role of the cannabinoid system in memory processes, as they relate to PTSD and traumatic memory consolidation. As the cannabinoids have been implicated in primary consolidation, extinction, and reconsolidation across rodents and humans, it is of great interest to determine an effect, if any, of drugs targeting the cannabinoid system on PTSD development and treatment when administered during trauma consolidation, in combination with exposure therapy, and/or traumatic memory reactivation.

Norepinephrine/Propranolol/Yohimbine

Researchers and clinicians hypothesize that hyper-consolidation of trauma and/or poor extinction might contribute to development of PTSD. Given the vast amount of data implicating the noradrenergic/norepinephrine (NE) system in memory consolidation, some suggest that noradrenergic dysfunction might underlie pathology of PTSD, in particular, deficits in fear acquisition and extinction, as well as symptoms of hyperarousal (119, 178–180). Indeed, multiple studies find evidence of abnormal noradrenergic function in PTSD (181–185).

In rodents, stress-induced release of norepinephrine (NE) into the amygdala, specifically the BLA, is critical for emotional memory consolidation (186). Although numerous studies implicate NE, via β-adrenergic receptors, in consolidation of aversive memory (inhibitory avoidance learning, in particular), the role of NE in associative fear learning is less clear (179, 187). Studies find evidence of noradrenergic activity in consolidation of associative fear learning and extinction (188–194). Others, however, report that treatment with NE or propranolol, a β-adrenergic receptor antagonist, has no effect on consolidation of auditory fear learning. Furthermore, propranolol administration significantly impairs auditory fear acquisition (whereas, treatment with an α1-adrenergic receptor antagonist facilitates fear acquisition) (195–197).

Interestingly, noradrenergic signaling is critical for reconsolidation of fear learning across multiple paradigms (197–199). Reconsolidation involves transiently rendering memories labile through memory reactivation (200). Through this reactivation (and as in the primary consolidation phase), memories undergo a stabilization process that is sensitive to protein-synthesis inhibitors. Propranolol administered systemically or intra-amygdala blocks reconsolidation of cue and context fear conditioning (197, 198). Intra-LA infusion of isoproterenol, a β-adrenergic receptor agonist, enhances reconsolidation, blocking extinction of cued fear (201). Similarly, yohimbine, an α2-adrenoceptor antagonist that increases release of norepinephrine from the locus coeruleus, enhances reconsolidation, whereas clonidine, an α2-adrenoceptor agonist, blocks reconsolidation of conditioned fear (194, 202, 203).

Studies in healthy human subjects support a role for norepinephrine in memory consolidation, additionally. Propranolol attenuates responses to aversively conditioned stimuli and memory for emotionally arousing stories when administered during the consolidation window (204–206). Memory retrieval, however, is not impaired by propranolol (207, 208).

As the noradrenergic system is implicated in PTSD and, more generally, in memory consolidation processes, drugs that target the noradrenergic system are being tested for their efficacy in blocking primary consolidation or reconsolidation of traumatic memory, or alternatively, strengthening extinction of traumatic memory, in individuals with PTSD and other anxiety disorders. Studies show that propranolol administration in the immediate aftermath of trauma might be effective at secondary prevention of PTSD, as rates and symptoms of PTSD are lower over a period of weeks to months post-trauma in individuals who receive propranolol (209–211). However, a recent double-blind pilot study in children

finds weak evidence for a decrease in PTSD symptoms in boys acutely administered propranolol, but an increase in symptoms in similarly-treated girls (212).

Increasingly, research is examining the effect of propranolol on reconsolidation to weaken the strength of emotional salience of traumatic memory. Propranolol administration with trauma reactivation decreases physiological responses, such as heart rate and skin conductance, during subsequent mental imagery of the event (213). In separate studies, propranolol administered in combination with six brief trauma reactivation sessions significantly improves PTSD symptoms compared to placebo (214). Several other studies report improvement of PTSD symptoms with propranolol treatment, however, dosage and administration is either unknown or not reported (215, 216). Notably, there are a number of negative trials across rodents and humans examining an effect of propranolol on reconsolidation (198, 208, 217). While a meta-analysis suggests that propranolol blocks primary consolidation and reconsolidation of long-term emotional memory in healthy humans, inconsistencies in the propranolol literature will benefit from a similar analysis examining individuals with PTSD (218).

New evidence indicates that modulation of the noradrenergic system may be able to facilitate exposure therapy, additionally. Individuals with Social Anxiety Disorder and claustrophobia exhibit better outcomes when administered yohimbine in conjunction with exposure sessions, compared to outcomes in individuals administered placebo plus exposure (219, 220). An additional study, however, finds no effect of yohimbine on extinction of fear of flying using virtual reality (221). Further study, specifically examining an effect on extinction in individuals with PTSD, is needed to more confidently assess therapeutic efficacy of yohimbine.

Device-based treatments

Increasingly, researchers are investigating device-based treatments to alter pathological brain activity and connectivity in psychiatric disease. A number of different stimulation tools - including deep-brain stimulation (DBS), vagus nerve stimulation (VNS), transcranial direct current stimulation (tDCS), and transcranial magnetic stimulation (TMS) - are under investigation and each are at various stages of development and testing at the pre-clinical and clinical level (222, 223). Similar to traditional pharmaceutical drugs, device-based treatments are being tested in combination with Pavlovian fear conditioning to determine efficacy in the treatment of PTSD.

Relative to other device-based treatments, DBS is the most extensively studied therapy with a comparatively large amount of evidence accumulated supporting efficacy in the treatment of psychiatric disorders. DBS is demonstrably efficacious for the treatment of Parkinson’s Disease, its original indication, and is now being investigated for the treatment of and depression, obsessive compulsive disorder (OCD), and PTSD (7, 222, 224–226). At the pre-clinical level, several studies find enhanced cued fear extinction with DBS of the ventral striatum that may be mediated by enhanced BDNF expression (53, 227, 228). Others find decreased PTSD-like symptoms and cued fear expression in rats with DBS of the amygdala (229–231). Based on these studies, participants are now being recruited to evaluate the

efficacy of DBS targeting the amygdala for the treatment of PTSD (224). Because the mechanism of action is still relatively unclear (i.e. whether DBS activates or inhibits targeted brain regions), future pre-clinical studies are important for the interpretation, and thus refinement, of DBS and DBS treatment protocols.

Additionally, transcranial magnetic stimulation shows promise for the treatment of psychiatric disorders, where non-invasive electrical current is delivered via magnetic coil placed on the scalp (232). In combination with a brief trauma re-exposure with script driven imagery, and in combination with exposure therapy, TMS of mPFC ameliorates PTSD symptoms when administered repetitively over two weeks (233–235). These studies, along with evidence that transcranial direct current stimulation (tDCS) of dorsolateral prefrontal cortex modulates consolidation of cued fear, underline the importance of mPFC in fear learning, which has been extensively studied in rodents (6, 236, 237).

While the efficacy of device-based treatments for PTSD is still being evaluated in pre-clinical and clinical studies, largely in combination with classical Pavlovian fear extinction/exposure therapy, DBS, VNS, tDCS, and TMS may be viable treatment options, particularly for individuals with treatment-resistant PTSD.

Discussion

We have examined the evidence regarding efficacy of some specific treatment strategies for PTSD informed by rodent pre-clinical studies. We have focused on Pavlovian fear conditioning and extinction experiments in animals, which allow researchers to model aversive learning processes that may underlie development of PTSD in response to trauma, as well as extinction of pathological fear via exposure therapy. Even in prior stress models, which are thought to more thoroughly model PTSD, fear acquisition and extinction using fear conditioning is often assessed to determine the extent to which prior stress instantiates a PTSD-like phenotype. In this way, fear conditioning and extinction have initiated the discovery of promising therapies for the treatment of PTSD.

PTSD can be conceptualized as involving a number of transitional steps, from pre-existing vulnerability prior to trauma to expression of pathological fear after traumatic memory consolidation. Each of these steps can be targeted by various drugs or device-based therapies (Fig. 1). Individuals who experience trauma may be rendered more vulnerable to the development of PTSD by pre-existing sensitivities, including genetic makeup and prior environmental context (e.g. abuse during childhood). Fear memory is consolidated in the hours and days following traumatic experience, and those with PTSD are thought to over-consolidate traumatic fear memory. Morphine has been shown to block fear acquisition in animals and is now being evaluated for secondary prevention of PTSD (126, 127, 143, 144). Hydrocortisone has also been shown to ameliorate PTSD symptoms when administered after extreme stress; however a mechanism is still being determined (113). According to one hypothesis, hydrocortisone normalizes low cortisol, thought to be a risk factor for PTSD, in order to contain the stress response and maintain homeostasis (93). In line with evidence from pre-clinical models, hydrocortisone, D-cycloserine, yohimbine, and deep brain stimulation, in combination with exposure therapy, appear to enhance extinction (53, 69, 70,

115–118, 219, 220, 227, 228). Alternatively, traumatic fear memory may be rendered labile through brief reactivation via reconsolidation. Propranolol shows some promise in improving PTSD symptoms by blocking reconsolidation processes (218), although these studies require replication.

In surveying the literature, we make several tentative conclusions about the current status and future of treatment strategies for PTSD. First, the time surrounding exposure therapy may be the best target window for administering treatment, for several reasons. However, not all people who experience trauma will develop PTSD, there is the question of whether resilient individuals should receive treatment. Clinical trials investigating the efficacy of secondary preventatives, such as opiates or hydrocortisone in the aftermath of trauma, may benefit from a better understanding of pre-trauma risk factors that predispose individuals to PTSD. At this stage, the use of secondary preventatives might be best for administration after trauma in known high risk populations.

Additionally, the window surrounding exposure therapy may be the best time for administering adjunctive therapies, as exposure therapy is the gold standard treatment for PTSD. Drug or device-based treatment in combination with exposure therapy may allow real-time assessment of its success. This is critical, as short exposure therapy sessions or sessions where individuals insufficiently inhibit fear can limit the effectiveness of adjunctive treatment, or, worse, strengthen traumatic fear memory (73). Thus a better approach may focus on therapies administered *after* individual exposure therapy sessions, allowing clinicians to assess the potential success of the therapy session before administering the adjunctive treatment.

Although it is clear that rodent models inform clinical studies, the traditional bench to bedside translational paradigm has shifted. Pharmacotherapies currently being tested in humans, stemming from rodent studies using Pavlovian fear conditioning paradigms, are being further developed in their original model systems to safely refine 1) dosages, 2) targeted molecular epitopes, and 3) treatment windows. In the case of SSRIs or DBS, for instance, rodent models are now being developed based on indications from human studies. In another shift away from the traditional pre-clinical to clinical translation model, more studies are now focusing on the effects of specific treatments on intermediate phenotypes - such as amygdala activation using fMRI or fear inhibition - rather than overall symptoms of PTSD. These types of studies will increase with the establishment of Research Domain Critieria (RDoc) by NIMH, a move that emphasizes the classification of psychiatric disorders based on behavioral dimensions and neurobiological measures.

While the number of approved treatments for PTSD is minimal, and research appears to be moving away from the traditional translational model, fear conditioning and extinction may still offer hope for the development of new therapies, as this model is among the best-validated in psychiatric research. Through these models, researchers and clinicians have established efficacious treatment strategies and are beginning to develop a number of promising pharmacotherapies and device-based treatments for PTSD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support was provided by NIH (T32-GM08605, 1F31MH097397, and R01MH096764), the Burroughs Wellcome Fund, and by an NIH/NCRR base grant (P51RR000165) to Yerkes National Primate Research Center.

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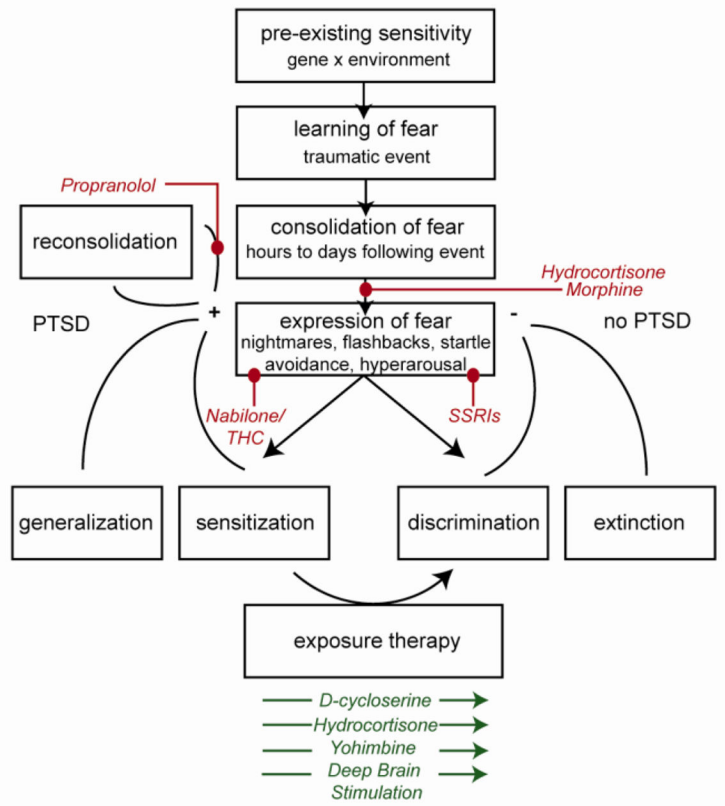

Figure 1. Overview of translationally informed treatments for PTSD and mechanism of action

The development of PTSD can be organized into a framework of pre- and post-trauma risk factors and pathological learning, each of which can be uniquely targeted by therapeutics. Hydrocortisone and morphine have been shown to interrupt primary consolidation of conditioned fear and trauma across species. While evidence is inconsistent, propranolol has been suggested to block reconsolidation, a process which renders previously consolidated memories labile, and thus vulnerable to interference. Exposure therapy, the recommended first line treatment for PTSD, is facilitated by D-cycloserine, yohimbine, hydrocortisone, and deep brain stimulation. Furthermore, nabilone and THC (Cnr1 agonists) and SSRIs have been shown to reduce expression of fear with chronic administration. The color red indicates that a specific drug blocks the indicated process, while green indicates a facilitating effect.