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Pharmacological Treatment of PTSD – Established and New Approaches

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Abstract

A large proportion of humans will experience a traumatic event at least once in their lifetime, with up to 10% then going on to developing post-traumatic stress disorder (PTSD). In this review we will discuss established pharmacological interventions for PTSD as well as highlight novel therapeutic strategies undergoing extensive preclinical research as well as ongoing clinical research. Such strategies include prophylactic treatments and use of pharmacotherapy as adjunctive treatment with established trauma-focused psychological therapies. These potential treatment approaches include modulation of stress effects on memory consolidation after trauma (e.g. glucocorticoid, corticotropin releasing factor and norepinephrine signalling modulators), as well as putative cognitive enhancers that target mechanisms of conditioned fear extinction and reconsolidation (e.g. glucocorticoid receptor modulators and modulators of glutamate signalling such as positive allosteric modulators of glutamate receptors, glycine transporter inhibitors, glycine agonists, autoreceptor antagonists). We will discuss evidence for and against these potential novel treatment strategies and their limitations.

Introduction

Posttraumatic stress disorder (PTSD) results from exposure to a traumatic event which evoked fear, helplessness and horror. It is characterized by three symptom clusters, i.e., (1) hypermnesia for the core traumatic event, with frequent re-experiencing of the traumatic event in form of flashbacks and nightmares – aversive memories that can be triggered by sensorimotor cues, for example, a noise that reminds the patient of the traumatic event – and disturbed memory for peritraumatic events, (2) hyperarousal, characterized by exaggerated startle, hypervigilance and irritability, and (3) avoidance behaviour, such as avoidance of reminders associated with the trauma. Symptoms should persist for a minimum of four weeks before a diagnosis is made. PTSD affects a subpopulation (10–15%) of people exposed to traumatic events, with a lifetime prevalence of 6.8% in the US (Kessler et al., 2005).

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Neural circuits and substrates implicated in PTSD

Conceptually, PTSD can be considered as a maladaptation to a traumatic stressor, with altered fear-related learning (fear conditioning) and extinction, behavioural sensitisation/ kindling, and alterations in brain areas and neurotransmitter systems closely linked to these processes. Here we will review these processes, their interactions and potential treatment strategies to ameliorate them. A large amount of literature now focuses on the corticolimbic circuit in PTSD, with neuroimaging studies reporting abnormalities in the prefrontal cortex (PFC), hippocampus and amygdala in PTSD patients (Milad and Rauch, 2007; Quirk and Mueller, 2008). These neural circuits are implicated in the putative fear learning abnormalities and sensitization reported in PTSD. For example, insufficient top-down control from the PFC to the amygdala has been suggested to play a role in impaired extinction of fear-related memories (Koenigs and Grafman, 2009; Milad et al., 2009) and executive control over fear responses (Aupperle et al 2011, this issue). Poor hippocampal-PFC signalling may also underlie contextual memory deficits in PTSD, resulting in poor contextual control of conditioned fear responses (Acheson et al 2011, this issue). Many of these pathways are involved in different putative phases of PTSD development, either initial fear learning, maintenance of fear memory/responses or extinction. We will discuss the treatment strategies, either prophylactic or therapeutic, targeted at these pathways.

Consideration of these pathways suggests involvement of certain neurotransmitter and -modulator systems: The main projections from the PFC to the amygdala or to dopamine or acetylcholine inputs into the amygdala are glutamatergic in nature (Del Arco and Mora, 2009). Thus, insufficient top-down control from the PFC to the amygdala implies involvement of glutamatergic pathways in PTSD, either directly or indirectly. For example, it is thought that fear extinction requires PFC-activation of intercalated cells in the amygdala, GABAergic interneurons that inhibit local activation and express a unique receptor profile (Likhtik et al. 2008). Hence, at the level of the amygdala, different sub-nuclei can affect each other via glutamatergic or GABAergic interactions (Pitkanen et al., 1997; Amano et al., 2010), bringing the GABAergic system into play as a potential target for PTSD therapeutics. More recently, another functional pathway involved in acute stress responses has been delineated, consisting of an indirect pathway for inhibition of the hypothalamic-pituitary-adrenal (HPA) axis. The PFC inhibits HPA activity via a glutamatergic projection to the bed nucleus of the stria terminalis (BNST), part of the extended amygdala, which activates a GABAergic inhibitory projection from the BNST to the corticotropin-releasing factor (CRF) neurons in the hypothalamic paraventricular nucleus (PVN) (Radley et al., 2009). This pathway may be particularly relevant as PTSD patients exhibit increased cerebrospinal fluid (CSF) levels of CRF (Baker et al., 1999; Bremner et al., 1997) and abnormalities in other HPA axis systems (e.g. pituitary adenylate cyclase-activating polypeptide, PACAP, Ressler et al. 2011) suggests utility of compounds that dampen the CRF system or other HPA axis hormones in the treatment of PTSD (Baker et al., 2009).

Neural circuits and substrates underlying acute stress responding and trauma memory encoding – targets for prevention

A number of interrelated neurochemical systems have been suggested to be involved in the mediation of stress responsivity, formation of traumatic memories and the pathophysiology of PTSD, including glutamate, GABA, CRF and noradrenaline, amongst others. Evidently, there are strong interactions between these systems, giving rise to different therapeutic approaches that could be useful to prevent the development of PTSD. Acute stress exposure, for example, which may mimic the acute traumatic event leading to PTSD, induces increases in glutamate transmission across multiple systems: PFC, amygdala, BNST, hippocampus and noradrenergic locus coeruleus (LC) in rats (Gilad et al., 1990; Moghaddam, 1993;

Reznikov et al., 2007; Walker and Davis, 2008). It has been suggested that insufficient top-down control of these circuits from the PFC could lead to stress hyperreactivity. Poor PFC control of the LC could lead to hyperreactivity of the noradrenergic projection from the LC to the basolateral amygdala (BLA), while poor PFC control of the PVN could lead to increased CRF and downstream glucocorticoid signalling (Hurlemann, 2008; Hurlemann et al., 2007). These systems often act in a reciprocal fashion, with altered glucocorticoid signalling in turn affecting acute glutamatergic neurotransmission in cortico-limbic circuits (Moghaddam et al., 1994). There is also evidence for reciprocal modulation across CRF and NE systems, with increased NE driving increased CRF release and vice versa (Gresack and Risbrough, 2010; Dunn et al. 2004). Thus, there are strong interactions between the different neuroanatomical and chemical systems that have been implicated in PTSD and pharmacological manipulations of the glutamatergic or GABAergic systems, the CRF system, the noradrenergic system, or normalization of HPA axis activity by other means could be of utility in the treatment of PTSD, directly or indirectly affecting the different neurochemical systems involved.

Likewise, the neurochemical systems that mediate acute behavioural and neuroendocrine responses to stress also modulate the neuroplastic events that occur during trauma processing, e.g., increased glutamatergic neurotransmission at the time of exposure to the traumatic event may facilitate encoding of the traumatic memory in PTSD patients. This process may be enhanced by altered glucocorticoid release from the HPA axis as glutamate-induced NMDA receptor activation and stimulation of the glucocorticoid receptor (GR) by glucocorticoids facilitates the activity of common intracellular signalling pathways critical for memory consolidation. Thus, it has been suggested that GR and glutamate signalling may synergistically facilitate activation of the extracellular-signal-regulated kinase (ERK)/ mitogen- and stress-activated kinase (MSK), leading to histone phospho-acetylation and chromatin remodelling, a putative molecular substrate of these memories (Reul and Nutt, 2008). NMDA receptor activation has also been suggested to play a role in some of the kindling-like processes that have been associated with the formation of spontaneous intrusive memories (Grillon et al., 1996; Adamec, 1997) and states of high NMDA receptor activity and high glucocorticoid function may serve as risk factors for developing PTSD as it may increase the likelihood for aversive memory encoding (Reul and Nutt, 2008; Mehta and Binder, in press).

Hyperreactivity of the noradrenergic projection from the LC to the BLA, in conjunction with disinhibited glucocorticoid signalling, and the resultant enhanced signalling from the BLA to the anterior hippocampus via the subiculum, has also been suggested to facilitate encoding of the traumatic event at the time of the trauma, thereby contributing to the development of PTSD (Hurlemann, 2008; Hurlemann et al., 2007). Thus, enhanced glucocorticoid signalling and noradrenergic activation may act synergistically at the level of the BLA, leading to potentiation of noradrenaline-induced activation of the cAMP-dependent protein kinase A (PKA) by GR stimulation (Roozendahl et al., 2002b), which in turn will enhance cAMP response element-binding (CREB) protein phosphorylation and consequently chromatin remodelling as well. At the same time, glucocorticoids interact with noradrenergic mechanisms in interfering temporarily with memory retrieval (De Quervain et al., 2007), which could lead to disturbed recollection of peritraumatic events. Finally, high CRF levels at the time of trauma may also facilitate encoding of trauma memory and enduring anxiety effects via direct action at CRF1 receptors (Hubbard et al. 2007, Roozendaal et al. 2008, Adamec et al. 2010).

Thus, there is strong evidence that many of the systems that mediate stress responses also facilitate encoding of aversive memories, which could form the basis for the development of PTSD and open up avenues for the development of novel prevention strategies.

Neural circuits and substrates underlying chronic stress responding and trauma memory retrieval – targets for symptom reduction

Once PTSD is established, the situation may be different: in established PTSD, lower basal 24h circulating cortisol levels have been reported, which may be due to enhanced negative feedback inhibition of the HPA axis by glucocorticoids at the level of the pituitary gland and/or hyporeactivity of the adrenals or the hypothalamus (Yehuda, 2005). These low cortisol levels have been suggested to play a role in re-experiencing of the traumatic event as they may facilitate retrieval of the aversive memories (De Quervain et al., 2009; but see Baker et al., 2005, reporting elevated CSF cortisol levels in PTSD patients despite normal plasma and urinary cortisol levels, suggesting that plasma cortisol is not representative of central cortisol level). At the same time, it seems that there is a greater reactivity of the HPA axis to stressors, which renders the HPA axis maximally responsive to stress-related cues in PTSD (Yehuda, 2005), potentially facilitating re-consolidation of the aversive memories (Taubenfeld et al. 2009).

Recent data generated in an animal model of PTSD, i.e., serial application of three different stressors (called the single prolonged stress model), that recapitulates aspects of established PTSD, i.e., enhanced negative feedback of the HPA axis and enhanced startle reactivity (Khan and Liberzon, 2004; Kohda et al., 2007), also suggests that the glutamatergic system may undergo changes over time: contrary to the increase in glutamate release seen following acute stress exposure, it has been reported that single prolonged stress led to attenuated PFC glutamate levels in rats (Knox et al., 2010). This reduction in glutamate levels could model the putative reduced PFC activity in PTSD patients.

The hyperreactivity of the noradrenergic system seems to persist in PTSD patients and has been suggested to mediate the hyperarousal symptoms seen, as well as the sleep disturbances reported in this disorder (Southwick et al., 1999a; Liberzon et al., 2005; Raskind et al. 2003). Increased NE signalling at the amygdala and hippocampus may also facilitate retrieval of aversive memories (Southwick et al., 1999b).

Another monoaminergic system linked to PTSD is the serotonergic (5-HT) system (e.g., Krystal and Neumeister, 2009). Polymorphism of the 5-HT transporter (the 5-HTTLPR genotype), in interaction with adult traumatic events and childhood adversity, has been reported to be a susceptibility factor for PTSD (Lee et al., 2005; Grabe et al., 2009; Xie et al., 2009). Furthermore, stress has been reported to increase 5-HT neurotransmission in several forebrain regions, including frontal cortex, hippocampus and amygdala (Linthorst, 2005). Selective serotonin re-uptake inhibitors (SSRIs) are also efficacious in treating the disorder at least in some individuals, suggestive that 5-HT could play a role in the pathogenesis of the disorder (Bandelow et al., 2008).

Thus, neurotransmitter/neuromodulatory systems that have been or could be targeted by a pharmacological approach to treat PTSD could include serotonergic, noradrenergic, GABAergic and glutamatergic mechanisms, manipulations that affect HPA axis reactivity via, for example, glucocorticoid or CRF receptor manipulations, as well as intracellular signalling cascades associated with these systems and that may represent final common pathways.

It is evident that pharmacological approaches may differ, depending on whether treatment focuses on the development aspects of PTSD (preventive intervention around the time of trauma when processes that could lead to PTSD may be initiated) or whether it aims at treating chronic PTSD (symptom reduction). For instance, one may want to prevent the consolidation of trauma-related memories early on by blockade of glutamatergic activity, while one may wish to facilitate extinction of those memories once they have been

established by enhancing glutamatergic function, i.e., opposite mechanisms of action may be of utility, depending on the stage of the illness one wants to target.

Prevention

The treatment of chronic PTSD encompasses monotherapies or adjunctive therapies to current pharmacological treatments or psychotherapy once symptoms have developed. Preventive treatment starts prior to symptom development. Symptomatic or preventive approaches raise different ethical and socioeconomic concerns: only a subpopulation of those experiencing a traumatic event will also develop PTSD and indiscriminate treatment should be avoided. Therefore, it would be useful for preventive treatment to be effective to distinguish subjects that are at risk to develop PTSD from those that are not. However, although a number of such markers have been proposed, e.g., lower cortisol levels, increased heart rate dynamics shortly after the traumatic event or increased circulating PACAP (Yehuda, 2004; O'Donnell et al. 2007; Ressler et al. 2011) or other vulnerability factors, such as polymorphism of the 5-HT transporter (see above) or of FkBP5, a co-chaperone that modulates the glucocorticoid receptor (GR) (Binder et al. 2008), none qualify so far as a prognostic tool with sufficiently high accuracy. Another complicating factor of preventive pharmacological approaches is the need of such treatment to effectively counteract the development of PTSD symptoms, while leaving normal function undisturbed, i.e., the normal psychological responses to traumatic events, including cognitive and psychomotor function, should remain unimpaired.

There are some at risk populations, e.g. soldiers facing combat, in which preventive pharmacological treatment before the traumatic event may be feasible. This strategy is called prospective or primary prevention. Alternatively, preventive treatment could be given shortly after the traumatic event, but well before symptoms develop. This is called retrospective or secondary prevention and aims at preventing or blocking the induction or consolidation of processes leading to PTSD. In the latter case, only those that really experienced trauma would need intervention, which opens it up to a wider group of people, including those that faced traumatic experiences under circumstances where trauma is less likely to occur, e.g., following a car accident.

Pharmacological approaches for primary prevention

GR ANTAGONISTS, CRF1 ANTAGONISTS and CCK2 ANTAGONISTS—One strategy for preventative treatment would be to enhance stress coping, i.e., to facilitate stress resilience. A number of preclinical studies have investigated molecular mechanisms involved in the stress response: blockade of the glucocorticoid receptor (GR) prior to exposure to a single prolonged stressor prevented the development of enhanced fear responses in rats (Kohda et al., 2007), CRF1 receptor antagonism prevented the initiation of stress effects in a mouse predator stress model of PTSD (Adamec et al., 2010), and similar findings have been reported with CCK2 antagonism (Adamec et al., 1997). These effects may be mediated via inhibition of the HPA axis or via central effects at limbic circuitry. Indeed, CRF1 receptor antagonism directly at the amygdala alone attenuates fear conditioning (Hubbard et al. 2007; Roozendaal et al. 2002a), which may contribute to the effects of these drugs. For drugs affecting HPA axis activity however, these findings would suggest that interventions that prevent an exaggerated stress response may be beneficial prior to the occurrence of the traumatic event. Following this line of reasoning, it would also be conceivable that other classes of compounds that block HPA activity, such as vasopressin antagonists, e.g., V1b antagonists, could be of utility. Interestingly, vasopressin has been shown to affect consolidation processes, either directly or indirectly (e.g., Ettenberg et al., 1982), further strengthening the case.

GR AGONISTS—However, it should also be noted that individuals with lower peri-traumatic cortisol levels have an increased likelihood for developing PTSD (Yehuda, 2004). This finding in turn suggests that the above mentioned approaches to facilitate stress resilience paradoxically may increase the risk of individuals to develop PTSD. This paradoxical effect may be due to loss of feedback inhibition of the HPA axis, in that lower cortisol levels at the time of the traumatic event may prevent termination of the sympathetic stress response and consequently prolonged noradrenergic activity (Pacak et al., 1995; see also below). Based on this hypothesis it was suggested that increased cortisol during the traumatic event may block development of PTSD. Indeed, beneficial effects of posttrauma hydrocortison have been reported in a few small, randomized clinical trials (Schelling et al., 2001, 2004; Weis et al., 2006). Interestingly, high-, but not low-dose corticosterone administered shortly after a predator stress attenuated stress-related behavioural responses in rats, and it has been suggested that high-dose corticosterone disrupts memory consolidation for the traumatic event, while low-dose corticosterone facilitates memory consolidation (Cohen et al., 2008).

Thus, the net effect of direct or indirect GR manipulations seems to be dose-dependent and outcome of such manipulations in PTSD patients may depend on exposure achieved at the GR. It will be difficult to predict this response at the individual level as cortisol efficacy may depend on individual differences in cortisol responses to stress and in expression of genes modulating GR signalling (e.g. FKBP5, see Mehta and Binder, in press, this issue). In sum, there seems to be an inherent risk that interventions that inhibit GR signalling, either directly or indirectly, could actually facilitate the development of PTSD. Clearly more studies are required to delineate the complex role of GR signalling effects during and after trauma to develop appropriate prophylactic treatments targeted at this system.

Pharmacological approaches for secondary prevention

GR ANTAGONISTS, CRF1 ANTAGONISTS and CCK2 ANTAGONISTS—However, the design of the preclinical studies mentioned above do not allow unambiguous conclusions that treatment given prior to stress exposure really mirrors primary prevention. Drug effects may be carried over to post-stress conditions and hence could still have effects on consolidation processes, reflecting secondary prevention. In support of this argument, it has been shown that the protein synthesis inhibitor anisomycin, administered either shortly before or after predator stress, also attenuated anxiety-related behaviour in rats (Cohen et al., 2006). Of note, *de novo* protein synthesis is critical for successful consolidation processes to take place, but not necessarily for stress responsivity. Likewise, it has been shown that CRF1 receptor antagonism or CCK2 receptor blockade also prevented the consolidation of stress effects in rodent stress models of PTSD (Adamec et al., 1997b, 2010; Wang et al., 2010). GR blockade also interferes with aversive memory consolidation at the level of the basolateral amygdala (Roozendaal, 2000). These effects on consolidation support the utility of these compounds in secondary prevention and suggest that their efficacy in models of primary prevention might be confounded with effects on consolidation.

ADRENOCEPTOR AGONISTS and ANTAGONISTS—Other secondary preventive approaches focused on manipulations of the noradrenergic system, for example by prevention of presynaptic noradrenaline release with α2 adrenoceptor agonists or opioids. The α2 adrenoceptor agonist dexmedetomidine indeed blocks fear consolidation (Davies et al., 2004), although this was tested in normal mice not in a PTSD mouse model. However, no preventive clinical PTSD studies using α2 adrenoceptor agonists have been reported. Blocking postsynaptic noradrenaline receptors seems less efficacious as a preventative treatment: the α_1 adrenoceptor antagonist prazosin failed to block increases in stress-related types of behaviour in rats exposed to predator stress (Adamec et al., 1999). Some considered

the β adrenoceptor blocker propranolol as being the most promising candidate drug for intervention after a traumatic event (Pitman and Delahanty, 2005) as it has shown efficacy in preventing some trauma-related physiological reactivity (Pitman et al. 2002). However, a subsequent clinical trial found propranolol to be ineffective when given immediately after trauma (e.g. in the hospital) to prevent the development of PTSD as measured by clinical rating scales (Stein et al., 2007). On a side note, it is worth mentioning that although propranolol may not itself show efficacy, these studies do support the feasibility to examine potential prophylactic treatment approaches with future novel targets.

NMDAR AND GABAERGIC COMPOUNDS—NMDA receptor antagonists also interfered with anxiety-related behaviour in rats if given shortly after exposure to predator stress (Adamec et al., 1999), which may not come as a surprise given the involvement of NMDA receptors in memory consolidation processes. In this respect, it is worth noting that in a preliminary, retrospective study, McGhee et al. (2008) found that in a group of burned service men those treated with the NMDA receptor antagonist ketamine during hospitalization had lower incidence of developing PTSD. These preclinical and clinical findings support the utility of novel pharmacological tools targeting NMDA receptor subunits or function could be of benefit while avoiding some of the side effects inherent to NMDA receptor blockade. Some examples of possible targets are metabotropic glutamate receptor (mGluR) 2 positive allosteric modulators (PAMs), which reduce glutamate release via presynaptic negative feedback, antagonists or negative allosteric modulators (NAMs) of postsynaptic mGluR5 receptors (but see Fendt and Schmid, 2002), or NR2B antagonists.

Moreover, the benzodiazepine alprazolam exaggerated stress effects when given shortly after predator stress exposure to rats (Matar et al., 2009). In humans, benzodiazepines have also previously been shown to facilitate memory for events that occurred just prior to treatment (Hinrichs et al., 1984), presumably due to blockade of active interference during consolidation. These findings are in line with clinical reports that secondary prevention with benzodiazepines has no effect (Gelpin et al., 1996; Mellman et al., 2002) or could even increase the likelihood of trauma victims to subsequently develop PTSD. This lack of efficacy may be due to the difference in efficacy of benzodiazepines to induce retrograde vs. anterograde amnesia, in other words benzodiazepines predominantly disrupt active associate processes and only affect consolidation when very high doses are used (Cahill et al. 1986; Jensen et al. 1979). Thus drugs that are efficacious in inducing mild retrograde amnesia may be more fruitful than drugs that facilitate anterograde amnesia only (L. Cahill personal communication).

OPIODS—There is some evidence that morphine administration shortly after the traumatic event reduces the likelihood for trauma victims to develop PTSD (Saxe et al., 2001; Bryant et al., 2009; Holbrook et al., 2010). Thus far studies have been purely naturalistic and further random controlled studies are needed to confirm these intriguing findings. The potential mechanism of these effects is unknown, however it is possible that it could be via an indirect reduction in noradrenergic activity after morphine treatment, or a direct action at intercalated cells in the amygdala that are critical for fear extinction processes (Likhtik et al. 2008).

Treatment of Established PTSD – Non-cognitive symptoms

Once the disorder is established, one could consider targeting the emotional response, i.e., the expression of fear or other non-cognitive symptoms associated with PTSD, such as hyperarousal, or the cognitive processes associated with PTSD, such as retrieval of aversive memories or extinction of fear-related memories. Of note, treatments that suppress non-cognitive PTSD symptoms are the only currently approved pharmacotherapeutic strategy.

SSRIs—Selective serotonin re-uptake inhibitors (SSRIs) have shown efficacy in reducing symptom severity and in relapse prevention in PTSD patients (e.g., Van der Kolk et al., 1994; Connor et al., 1999; Brady et al., 2000; Martenyi et al., 2002; McRae et al., 2004; Davidson et al., 2006; Onder et al., 2006), although only approximately 60% of patients respond to the treatment and only about 20 – 30% of patients will achieve full remission (Stein et al., 2002; Zohar et al., 2002). However, a recent report from the Institute of Medicine concluded that current evidence to determine efficacy of SSRIs is at best suggestive (Committee on Treatment of Posttraumatic Stress Disorder, 2008) and more recent guidelines on the treatment of PTSD question the use of SSRIs for veterans with combat-related PTSD relative to their therapeutic benefit in patients with non-combat-related PTSD (Benedek et al., 2009). Thus, while SSRIs can be considered relatively well tolerated and safe, further studies with higher power are needed before conclusions can be drawn. Moreover, SSRIs still suffer a number of shortcomings, including delayed onset of action, partial response with residual symptoms, or non-response, and undesirable side effects (e.g., loss of sexual drive, gastrointestinal effects, changes in body weight) which limits their utility and indicates a major unmet medical need for novel treatment approaches in PTSD.

OTHER ANTIDEPRESSANTS—Besides SSRIs, a number of other pharmacological approaches have been investigated in the clinic for treating PTSD patients, including other antidepressants, adrenoceptor antagonists, anticonvulsants, atypical antipsychotics and benzodiazepines (see Ravindran and Stein, 2010, for a review). Antidepressant drugs include dual serotonin and noradrenaline re-uptake inhibitors, such as venlafaxine (Davidson et al., 2006), tricyclic antidepressants such as amitriptyline (Davidson et al., 1990) and imipramine (Frank et al., 1988), monoamine oxidase inhibitors (MAOIs) like phenelzine (Frank et al., 1988), reversible monoamine oxidase A inhibitors (RIMAs) such as moclobemide (Onder et al., 2006), as well as drugs with other mechanism of action, like the 5-$HT_{2A/2C}$ antagonist/5-HT re-uptake inhibitor nefazodone (McRae et al., 2004), the mixed $\alpha_{2A/2C}$ adrenoceptor antagonist/5-$HT_{2A/2C/3}$ antagonist mirtazapine (Davidson et al., 2003) and 5-HT re-uptake enhancer/glutamate modulator tianeptine (Onder et al., 2006). While these drugs showed therapeutic utility in clinical trials and some of them seem to be equally effective as SSRIs, they have not become first line treatment for PTSD, partly also because they are less well tolerated (Bandelow et al., 2008). Although the primary mechanism of action differs amongst these antidepressant drugs, it is noteworthy that all of them interact with monoaminergic (serotonergic and noradrenergic) systems. In addition, antidepressants of various classes have been shown to normalize HPA axis activity in response to stress and to enhance hippocampal neurogenesis (Reul et al., 1994; Gold et al., 1995; Matheson et al., 1997; Stout et al., 2002; Xu et al., 2006; Kasper and McEwen, 2008; Szymanska et al., 2009; McEwen et al., 2010), which may represent a final common pathway.

ADRENOCEPTOR AGONISTS AND ANTAGONISTS—There have also been attempts to normalize the noradrenergic hyperreactivity suggested to underlay PTSD hyperarousal symptoms. Blockade of the α_1 adrenoceptor with the α_1 adrenoceptor antagonist prazosin has been reported to improve various PTSD symptoms, but in particular sleep and ameliorate nightmares (Peskind et al., 2003; Raskind et al., 2003; 2007; Taylor et al., 2008). A recent comparison study of prazosin and quetiapine for ameliorating night-time sleep disturbance indicates better overall tolerability of prazosin (Byers et al 2010). Ligands acting at the α_2 receptor have been less promising. Mirtazapine has shown positive results in one study of PTSD (Davidson et al., 2003), which suggests that $\alpha_{2A/C}$ adrenoceptor blockade also has beneficial effects, although mirtazapine's effects could of course also be mediated via serotonergic mechanisms (Yamamura et al. 2011). In this respect it is of note that mirtazapine increases NE release in various brain areas via α_{2A} autoreceptor blockade

(Haddjeri et al., 1996), thereby facilitating α_1 activity. Stimulation of presynaptic α_{2A} autoreceptors with the α_{2A} adrenoceptor agonist guanfacine, which should lead to reduced noradrenaline release, on the other hand, failed to reveal therapeutic benefit (Neylan et al., 2006; Davis et al., 2008). However agonist activity at post-synaptic α_{2A} receptors may mask effects of presynaptic blockade of NE release, as guanfacine has potent agonist activity at post-synaptic receptors (Arnsten et al., 1988). Non-selective β adrenoceptor blockade with propranolol was ineffective when given to prevent the development of PTSD in a recent study by Stein et al. (2007), although there is some resurgence of interest in using propranolol in conjunction with therapy (see below). Thus, while there is some evidence that manipulations of noradrenergic activity may have utility specifically for sleep disturbances, efficacy for overall symptom reduction is not supported thus far.

ANTICONVULSANTS—Anticonvulsant drugs have been proposed to be of benefit in treating PTSD due to their anti-kindling effects (Hageman et al., 2001; Berlin, 2007). This is a very heterogeneous group of drugs and often their mechanism of action is poorly understood. However, some anticonvulsants, such as lamotrigine and topiramate, have downstream effects that include inhibition of glutamate neurotransmission (Ahmad et al., 2004; Sitges et al., 2007), which could also be a mechanism through which tianeptine affects PTSD (Reznikov et al., 2007). As will be discussed below, glutamatergic approaches offer potential for the development of novel pharmacological treatments for PTSD. However, while some authors consider treatment with anticonvulsant drugs to be a promising approach for PTSD (e.g., Hageman et al., 2001; Adamou et al., 2007; Berlin, 2007), others conclude that the use of anticonvulsants in PTSD has only very limited support based on recent clinical trials (Berger et al., 2009; Ravindran and Stein, 2010). Likewise, only a limited number of randomized clinical trials have evaluated the effects of benzodiazepines in PTSD, with no or modest beneficial effects in PTSD patients (Braun et al., 1990; Gelpin et al., 1996; Mellman et al., 2002; Cates et al., 2004).

ANTIPSYCHOTICS—Atypical antipsychotic drugs are largely used as adjunctive therapy to e.g. antidepressant drugs in the treatment of PTSD. Only a limited number of randomized, double-blind, placebo-controlled clinical trials have been reported with risperidone and olanzapine, leading to mixed results (e.g., Butterfield et al., 2001; Stein et al., 2002; Hamner et al., 2003; Monnelly et al., 2003; Reich et al., 2004; Padala et al., 2006).

Thus, although there is evidence that pharmacological approaches using psychoactive drugs that are currently in the clinic have some beneficial effects in PTSD, with the most convincing data generated for antidepressant drugs, this evidence must be considered mixed. Almost all of the drug classes examined for efficacy in PTSD suffer from a dearth of adequately powered studies to support definitive conclusions either for or against efficacy. Along these lines, the Committee on Treatment of Posttraumatic Stress Disorder (2008) concluded that for all the drug classes mentioned above, the evidence is inadequate to determine efficacy in the treatment of PTSD. Overall the field clearly requires more efficacious pharmacological approaches to treat this disorder, as well as a more concentrated effort to adequately test potential therapeutics in large randomized clinical trials (Leon and Davis, 2009).

Treatment of Established PTSD – Cognitive symptoms

Once a memory about the traumatic event is formed, a number of processes take place that could still be amenable to pharmacological intervention. Retrieval refers to the activation of an aversive memory trace of the traumatic event that led to PTSD, for example, in flashbacks, nightmares or intrusive recollections of the traumatic event, with an external or

internal stimulus that triggered the recollection. Preventing retrieval of such memories would be one possible strategy to improve PTSD symptoms.

Memory retrieval, consolidation and re-consolidation

GR AGONISTS—Memory retrieval in animals (De Quervain et al., 1998) and humans (Newcomer et al., 1999) has been shown to be impaired by the administration of glucocorticoids (but see Tollenaar et al., 2009, for negative results measuring physiological responses to aversive emotional memories in healthy volunteers following cortisol administration). Preliminary data from a case-control study with three PTSD patients seem to support the idea that low-dose cortisol treatment reduced the ratings of the severity of traumatic memories (Aerni et al., 2004). These preliminary findings need to be substantiated in an appropriately powered vehicle controlled, randomized, double-blind clinical trial before any conclusions can be drawn. However, the data would suggest that cortisol treatment may be beneficial both as secondary prevention and to interfere with the retrieval of aversive memories once PTSD is established.

Another therapeutic option that has been more widely investigated would be to modify reconsolidation processes. Reconsolidation refers to the fact that a memory is "re-consolidated" after reactivation/retrieval. In PTSD, flashbacks or intrusive memories about the traumatic event represent a retrieval of that aversive memory trace, that will subsequently be reconsolidated (Charney 2004). Prevention of reconsolidation, which over time should lead to a weakening of the aversive memory trace, may represent another window of opportunity for pharmacological intervention. Not surprisingly, some of the same pharmacological mechanisms that have been suggested to play a role in the consolidation of traumatic memories have also been suggested to be of relevance for reconsolidation processes, including GR receptors (Tronel and Alberini, 2007; Taubenfeld et al., 2009). For example, a recent double-blind placebo controlled study found that glucocorticoid administration after imagery-driven reactivation of trauma memories had a temporary (<1 mo) effect on PTSD symptom severity (Suris et al. 2010).

NMDAR AND GABAERGIC COMPOUNDS—NMDA receptors also play an important role in reconsolidation processes (Suzuki et al., 2004; Lee et al., 2006) and it can be suggested that manipulations that (indirectly) attenuate NMDA receptor function (such as treatment with mGluR2 PAMs or mGluR5 NAMs) may also be of benefit. Conversely, facilitation of GABAergic function by the benzodiazepine midazolam disrupted reconsolidation processes of fear memory (Bustos et al., 2006; Zhang and Canney, 2008), suggesting that this class of drugs may have utility in the treatment of PTSD, although possibly not for preventive treatment. The question is how these effect on reconsolidation can be readily translated to clinical research, at what times does reconsolidation normally occur post-trauma, either naturalistically or how can it be induced during clinical intervention.

It has also been reported that inhibition of the mammalian target of rapamycin (mTOR) inhibits reconsolidation of fear memory (Blundell et al., 2008). This finding is interesting for two reasons: First, it could open another new avenue of treatment for PTSD using mTOR kinase inhibitors, although it is of note that those compounds also modulate the immune response, which may prevent their use for the indication of PTSD. Second, it has recently been reported that mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists (Li et al., 2010), and it is tempting to speculate that the same signalling cascades may also play a role in the potential therapeutic effects of NMDAR blockade in PTSD.

CANNABINOIDS—Another interesting pharmacological approach could be the manipulation of the cannabinoid system, as it was shown that bilateral infusion of CB1 receptor agonists into the amygdala after memory reactivation blocked reconsolidation of fear memory (Lin et al., 2006), while bilateral hippocampal CB1 blockade facilitated reconsolidation of fear memory (De Oliveira Alvares et al., 2008). Clearly, treating PTSD patients with CB1 agonists would be problematic, not at least because of the abuse risk of such compounds. However, one could consider indirect manipulation of the endocannabinoid system, for example, by fatty acid amide hydrolase (FAAH) inhibition, which prevents degradation of endogenous endocannabinoids such anandamide. Interestingly, anandamide administration into the hippocampus blocked reconsolidation of fear conditioning (De Oliveira Alvares et al., 2008), suggesting increasing endogenous levels may be a useful strategy to attenuate reconsolidation processes in PTSD.

ADRENOCEPTOR ANTAGONISTS—The effects of the β-adrenoceptor antagonist propranolol were studied by Debiec and LeDoux (2004), reporting that propranolol injected into the amygdala blocked reconsolidation, but not consolidation. These findings suggest that propranolol may be of utility in PTSD patients during reconsolidation, while being less efficacious for secondary prevention. However, other studies suggest that the efficacy of systemically administered propranolol to affect reconsolidation is limited and depends on the specific preclinical test used - inhibitory avoidance versus fear conditioning in that particular study (Muravieva and Alberini, 2010). In humans, there is preliminary evidence from a recent small, placebo-controlled, randomized double-blind clinical trial by Brunet et al. (2008) suggesting that propranolol may be beneficial when given to patients with chronic PTSD after they had to retrieve the traumatic memory, i.e., during reconsolidation. While encouraging, this finding must be confirmed in a larger trial.

Limitations to the strategy of disrupting consolidation or re-consolidation are that the treatment must not disrupt other critical processes such as fear extinction learning, and must not disrupt normal, non-trauma related cognitive processes. One practical way to get around this issue is to treat the patient only in the clinic during specific re-consolidation based therapy (e.g. Brunet et al. 2008). For chronic use pre-clinical studies of such target compounds will need to be conducted to evaluate the potential side effects of these drugs on other cognitive domains. Legal/ethical concerns have also been voiced for drugs that alter memory of traumatic events that result in legal actions (e.g. rape). For a consideration of the legal aspects of therapeutic strategies that interfere with memory consolidation see a recent review by Fletcher et al. (2010).

Fear extinction

Patients suffering from PTSD are also impaired in extinction of learned fear (Guthrie and Bryanth, 2006; Blechert et al., 2007), with impairment predicting symptom severity (Norrholm et al 2011). Extinction is a process whereby a learned fear response is reduced via repeated presentation of the conditioned stimulus (CS, i.e., a trauma-related cue, for example, a noise of a horn previously associated with a car crash or a tone previously associated with foot shock in a rodent fear conditioning experiment) in the absence of the unconditioned stimulus (US; in our examples, the traumatic event of a car crash or the foot shock). It is considered to be a process whereby new memories are formed, i.e., the patient learns that the CS is not necessarily associated with the US. As such, extinction memory is encoded, consolidated and expressed as are other types of memory.

NMDAR COMPOUNDS—Extinction of learned fear has been shown to be susceptible to NMDA receptor blockade in the amygdala (Falls et al., 1992), while enhancement of NMDA receptor function (e.g., indirectly by the glycine receptor partial agonist d-

cycloserine either systemically administered or infused into the amygdala) facilitates extinction learning (e.g., Walker et al., 2002; Ledgerwood et al., 2003; see also Myers et al., 2011, for a recent review on glutamatergic mechanisms involved in extinction processes). Likewise, d-cycloserine attenuates impaired fear extinction induced by single prolonged stress (Yamamoto et al., 2008), providing evidence from a preclinical PTSD model that d-cycloserine in support of potential beneficial effects on extinction in PTSD patients. Clinically, beneficial effects of d-cycloserine in combination with exposure therapy have been reported in agoraphobia (Ressler et al., 2004), social anxiety disorder (Guastella et al., 2008) and panic disorder (Otto et al., 2010), although controlled clinical trials looking specifically at the potentially beneficial effects of d-cycloserine on extinction processes in PTSD are outstanding. Interestingly extinction of learned “fear” produced in the laboratory using shock stimuli in healthy controls does not seem to be affected by d-cycloserine treatment (Guastella et al 2007). This somewhat surprising finding may be due to differing neural substrates underlying trauma-related clinical symptoms versus fear conditioning in the laboratory (Grillon 2009). Along similar lines to dcycloserine as a putative adjunctive treatment to exposure-based therapy, it can be argued that other drugs that facilitate NMDA receptor function, such as glycine transporter inhibitors, mGluR2 NAMs or mGluR5 PAMs, or that enhance other aspects of glutamatergic neurotransmission, such as AMPA PAMs, should also enhance extinction of fear responses to trauma memories. In rats, the AMPA receptor potentiator PEPA and glycine transporter inhibitor NFPS facilitated extinction learning for contextual and cued fear respectively (Zushida et al., 2007, Mao et al. 2009). PAMs of mGluR5 have been shown to facilitate extinction of cocaine contextual memory (Gass and Olive, 2009), although no data showing similar effects of mGluR5 modulation on fear conditioning or investigation of these mechanisms in PTSD models have been published yet.

Histone deacetylase (HDAC) inhibition, which prevent the deacetylation of histones, thereby affecting the same intracellular signalling cascade that is also susceptible to NMDA receptor modulation (Reul and Nutt, 2008), has also shown promise in facilitating extinction in preclinical models (Lattal et al., 2007). A limitation to this target however is that HDAC inhibitors, especially non-subtype selective ones, may be associated with a safety profile that again would prevent their use in this indication (Menegola et al., 2005).

CANNABINOIDS—Facilitation of extinction of fear conditioning was also seen following administration of a CB1 receptor agonist (Pamplona et al., 2006; but see Lin et al., 2008, showing that chronic CB1 agonism impaired fear conditioning extinction) or inhibitor of endocannabinoid breakdown and reuptake (Chhatwal et al. 2005). However, the abuse potential associated with CB1 agonism is likely to make this approach for treating PTSD patients undesirable due to an increased risk/benefit ratio.

ADRENOCEPTOR ANTAGONISTS—Activation of norepinephrine has also shown promise in preclinical models of fear extinction as well as treatment with the non-specific alpha2 adrenoceptor antagonist yohimbine (Cain et al., 2004; Morris and Bouton, 2007; Holmes and Quirk, 2010, but see Mueller et al., 2009). However, yohimbine itself can cause panic attacks in PTSD patients (Southwick et al. 1997; 1999b).

A complicating factor is that many of the potential therapeutic approaches that facilitate extinction also enhance other forms of learning and memory, at least preclinically. For example, NMDA receptor blockade not only interferes with extinction of aversive memories, but also with reinstatement of conditioned fear, i.e., also prevents the reinstatement of aversive memories, which occurs when the US is presented alone following extinction of the CS (Johnson et al., 2000). Thus facilitation of NMDA receptor function might not only enhance extinction or habituation, but also reinstatement of conditioned fear,

depending on which process predominated at the time of adjunctive treatment to exposure therapy, thereby worsening rather than improving the clinical condition. However, this potential issue has not yet been sufficiently investigated clinically to allow firm conclusions.

Summary

Because PTSD involves a precipitating traumatic event that often leads to medical evaluation there is a significant potential window for prophylactic treatment that should not be ignored. Preclinical models of PTSD and some early clinical trials suggest that prophylactic treatment approaches are feasible. Clearly such treatments, as with most preventive treatments (e.g. aspirin for heart attack prevention or statin drugs for cholesterol reduction), must be extremely safe for use across patients with varied degrees of physical injury. This risk/benefit ratio will be a high bar for drug development to clear. The impact of an effective prophylactic treatment would be vast however, especially in socially critical and high risk personnel such as police, fire fighters and the military. We have also reviewed a number of potential targets from preclinical models that could modulate conditioned fear processes after PTSD has developed. In the clinic, the efficacy of such putative adjunctive treatments with trauma-focused therapies will greatly depend not only on the efficacy of the compound itself, but also the protocol of the psychological therapy (e.g. being focused on extinction learning or being targeted towards reconsolidation). Nonetheless, pharmacological treatments that aid specific therapies in mental health, such as learning new skills (e.g. oxytocin to facilitate social interaction training in autism, Hollander et al. 2007) and remodulating memories or behaviours (e.g. exposure therapy in PTSD) is an exciting avenue of research that could represent a paradigm shift in pharmacological treatment of PTSD. Such therapeutic approaches may also circumvent some safety issues as they will be taken only under therapy supervision, given over limited periods of time, thus reducing issues of tolerance, abuse potential, and side effects linked to chronic administration.

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References

Adamec R. Transmitter systems involved in neural plasticity underlying increased anxiety and defense - implications for understanding anxiety following anxiety following traumatic stress. Neurosci Biobehav Rev. 1997; 21:755–765. [PubMed: 9415900]

Adamec RE, Shallow T, Budgell J. Blockade of CCK(B) but not CCK(A) receptors before and after the stress of predator exposure prevents lasting increases in anxiety-like behavior: implications for anxiety associated with posttraumatic stress disorder. Behav Neurosci. 1997; 111:435–449. [PubMed: 9106682]

Adamec RE, Burton P, Shallow T, Budgell J. NMDA receptors mediate lasting increases in anxiety-like behaviour produced by the stress of predator exposure – implications for anxiety associated with posttraumatic stress disorder. Physiol Behav. 1999; 65:723–737. [PubMed: 10073474]

Adamec R, Fougere D, Risbrough V. CRF receptor blockade prevents initiation and consolidation of stress effects on affect in the predator stress model of PTSD. Int J Neuropsychopharm. 2010; 13:747–757.

Adamou M, Puchalska S, Plummer W, Hale AS. Valproate in the treatment of PTSD: systematic review and meta analysis. Curr Med Res Opin. 2007; 23:1285–1291. [PubMed: 17559727]

Aerni A, Traber R, Hock C, Roozendaal B, Schelling G, Papassotiropoulos A, Nitsch RM, Schnyder U, de Quervain DJ. Low-dose cortisol for symptoms of posttraumatic stress disorder. Am J Psychiat. 2004; 161:1488–1490. [PubMed: 15285979]

Ahearn EP, Mussey M, Johnson C, Krohn A, Krahn D. Quetiapine as an adjunctive treatment for post-traumatic stress disorder: an 8-week open-label study. J Clin Psychopharmacol. 2006; 21:29–33.

Ahmad S, Fowler L, Whitton PS. Effects of acute and chronic lamotrigine treatment on basal and stimulated extracellular amino acids in the hippocampus of freely moving rats. Brain Res. 2004; 1029:41–47. [PubMed: 15533314]

Amano T, Unal CT, Pare D. Synaptic correlates of fear extinction in the amygdala. Nature Neurosci. 2010; 13:489–495. [PubMed: 20208529]

Arnsten A, Cai J, Goldman-Rakic P. The alpha-2 adrenergic agonist guanfacine improves memory in aged monkeys without sedative or hypotensive side effects: evidence for alpha-2 receptor subtypes. J Neurosci. 1988; 8(11):4287–4298. [PubMed: 2903226]

Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr . Serial CSF corticotrophin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 1999; 156:585–588. [PubMed: 10200738]

Baker DG, Ekhator NN, Kasckow JW, Dashevsky B, Horn PS, Bednarik L, Geracioti TD Jr. Higher levels of basal serial CSF cortisol in combat veterans with posttraumatic stress disorder. Am J Psychiatry. 2005; 162:992–994. [PubMed: 15863803]

Baker DG, Nievergelt CM, Risbrough VB. Post-traumatic stress disorder: emerging concepts of pharmacotherapy. Expert Opin Emerg Drugs. 2009; 14(2):251–272. [PubMed: 19453285]

Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Zohar J, Hollander E, Kasper S, Moller HJ, Bandelow B, Allgulander C, Ayuso-Gutierrez J, Baldwin DS, Buenvicius R, Cassano G, Fineberg N, Gabriels L, Hindmarch I, Kaiya H, Klein DF, Lader M, Lecrubier Y, Lepine JP, Liebowitz MR, Lopez-Ibor JJ, Marazziti D, Miguel EC, Oh KS, Preter M, Rupprecht R, Sato M, Starcevic V, Stein DJ, van Ameringen M, Vega J. WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disoders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry. 2008; 9:248–312. [PubMed: 18949648]

Benedek DM, Fiedman MJ, Zatzick D, Ursano RJ. Guideline watch (March 2009): Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. J Lifelong Learning. 2009; 7:204–213.

Berger W, Mendlowicz MV, Marques-Portella C, Kinrys G, Fontenelle LF, Marmar CR, Figueira I. Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: a systematic review. Prog Neuropsychopharmacol Biol Psychiat. 2009; 33:169–180.

Berlin HA. Antiepileptic drugs for the treatment of post-traumatic stress disorder. Curr Psychiat Reports. 2007; 9:291–300.

Binder EB, Bradley RG, Liu W, Epstein MP, Deveau TC, Mercer KB, Tang Y, Gillespie CF, Heim CM, Nemeroff CB, Schwartz AC, Cubells JF, Ressler KJ. Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA. 2008; 299:1291– 1305. [PubMed: 18349090]

Blechert J, Michael T, Vriends N, Markgraf J, Wilhelm FH. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experimental, and behavioural responses. Behav Res Ther. 2007; 45:2019–2033. [PubMed: 17442266]

Blundell J, Kouser M, Powell CM. Systemic inhibition of mammalian target of rapamycin inhibits fear memory reconsolidation. Neurobiol Learn Mem. 2008; 90:28–35. [PubMed: 18316213]

Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, Farfel GM. Efficacy and safety of sertaline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA. 2000; 283:1837–1844. [PubMed: 10770145]

Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiat. 1990; 51:236–238.

Bremner JD, Licinio J, Darnell A, Krystall JH, Owens MJ, Soutwick SM, Nemeroff CB, Charney DS. Elevated CSF corticotrophin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry. 1997; 154:624–629. [PubMed: 9137116]

Bremner JD, Elzinga B, Schmahl C, Vermetten E. Structural and functional plasticity of the human brain in posttraumatic stress disorder. Prog Brain res. 2008; 167:171–186. [PubMed: 18037014]

Brunet A, Orr SP, Tremblay J, Robertson K, Nader K, Pitman RK. Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. J Psychiat Res. 2008; 42:503–506. [PubMed: 17588604]

Bryant RA, Cremer M, O'Donnell M, Silove D, McFarlane AC. A study of the protective function of acute morphine administration on subsequent posttraumatic stress disorder. Biol Psychiat. 2009; 65:438–440. [PubMed: 19058787]

Bustos SG, Maldonado H, Molina VA. Midazolam disrupts fear memory reconsolidation. Neuroscience. 2006; 139:831–842. [PubMed: 16542779]

Butterfield MI, Becker ME, Connor KM, Sutherland S, Churchill LE, Davidson JR. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. Int Clin Psychopharmacol. 2001; 16:197–203. [PubMed: 11459333]

Byers MG, Allison KM, Wendel CS, Lee JK. Prazosin versus quetiapine for nighttime posttraumatic stress disorder symptoms in veterans: an assessment of long-term comparative effectiveness and safety. J Clin Psychopharmacol. 2010; 30(3):225–229. [PubMed: 20473055]

Cahill L, Brioni J, Izquierdo I. Retrograde memory enhancement by diazepam: its relation to anterograde amnesia, and some clinical implications. Psychopharmacology. 1986; 90:554–6. [PubMed: 3101111]

Cain CK, Blouin AM, Barad M. Adrenergic transmission facilitates extinction of conditional fear in mice. Learn Mem. 2004; 11:179–187. [PubMed: 15054133]

Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. Annals Pharmacother. 2004; 38:1395–1399.

Charney DS. Psychological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiat. 2004; 161:195–216. [PubMed: 14754765]

Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. Neuropsychopharmacology. 2005; 30:516–524. [PubMed: 15637635]

Cohen H, Kaplan Z, Matar MA, Loewenthal U, Kozlovsky N, Zohar J. Anisomycin, a protein synthesis inhibitor, disrupts traumatic memory consolidation and attenuates posttraumatic stress responses in rats. Biol Psychiat. 2006; 60:767–776. [PubMed: 16735032]

Cohen H, Matar MA, Buskila D, Kaplan Z, Zohar J. Early post-stressor intervention with high-dose corticosterone attenuates posttraumatic stress responses in an animal model of posttraumatic stress disorder. Biol Psychiat. 2008; 64:708–717. [PubMed: 18635156]

Committee on Treatment of Posttraumatic Stress Disorder. Treatment of Posttraumatic Stress Disorder: An Assessment of the Evidence. National Academies Press; Washington DC, USA: 2008.

Connor KM, Sutherland SM, Tupler LA, Malik MK, Davidson JR. Fluoxetine in posttraumatic stress disorder. Randomised, double-blind study. Br J Psychiatry. 1999; 175:17–22. [PubMed: 10621763]

Davidson J, Kudler H, Smith R, Mahorney SL, Lipper S, Hammett E, Saunders WB, Cavenar JO Jr. Treatment of posttraumatic stress disorder with amitryptiline and placebo. Arch gen Psychiat. 1990; 58:485–492. [PubMed: 11343529]

Davidson JR, Weisler RH, Butterfield MI, Casat CD, Connor KM, Barnett S, Van Meter S. Mirtazapine vs. placebo in posttraumatic stress disorder: a pilot trial. Biol Psychiatry. 2003; 53:188–191. [PubMed: 12547477]

Davidson J, Rothbaum BO, Tucker P, Asnis G, Benattia I, Musgnung JJ. Venlafaxine extended release in posttraumatic stress disorder: a sertaline and placebo-controlled study. J Clin Psychopharmacol. 2006; 26:259–267. [PubMed: 16702890]

Davies MF, Tsui J, Flannery JA, Li X, DeLorey TM, Hoffman BB. Activation of alpha2 adrenergic receptors suppresses fear conditioning: expression of c-Fos and phosphorylated CREB in mouse amygdala. Neuropsychopharmacology. 2004; 29:229–239. [PubMed: 14583739]

Davis LL, Ward C, Rasmusson A, Newell JM, Frazier E, Southwick SM. A placebo-controlled trial of guanfacine for the treatment of posttraumatic stress disorder in veterans. Psychopharmacol Bull. 2008; 41:8–18. [PubMed: 18362867]

Debiec J, Ledoux JE. Disruption of reconsolidation but not consolidation of auditory fear conditioning by noradrenergic blockade in the amygdala. Neuroscience. 2004; 129(2):267–272. [PubMed: 15501585]

Del Arco A, Mora F. Neurotransmitters and prefrontal cortex–limbic system interactions: implications for plasticity and psychiatric disorders. J Neural Transm. 2009; 116:941–952. [PubMed: 19475335]

De Oliveira Alvares L, Pasqualini Genro B, Diehl F, Molina VA, Quillfeldt JA. Oposite action of hippocampal CB1 receptors in memory reconsolidation and extinction. Neuroscience. 2008; 154:1648–1655. [PubMed: 18554811]

De Quervain DJ, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature. 1998; 394:787–790. [PubMed: 9723618]

De Quervain DJ, Aerni A, Roozendaal B. Preventive effect of β-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. Am J Psychiatry. 2007; 164:967–969. [PubMed: 17541058]

De Quervain DJ, Aerni A, Schelling G, Roozendaal B. Glucocorticoids and the regulation of memory in health and disease. Front Neuroendocrinol. 2009; 30:358–370. [PubMed: 19341764]

Dunn AJ, Swiergiel AH, Palamarchouk V. Brain Circuits Involved in Corticotropin-Releasing Factor-Norepinephrine Interactions during Stress. Ann NY Acad Sci. 2004; 1018(1):25–34. [PubMed: 15240349]

Ettenberg A, Le Moal M, Koob GF, Bloom FE. Vasopressin potentiation in the performance of a learned appetitive task: reversal by a pressor antagonist analog of vasopressin. Pharmacol Biochem Behav. 1982; 18:645–647. [PubMed: 6867069]

Falls WA, Miserendino MJ, Davis M. Extinction of fear-potentiated startle: blockade by infusion of an NMDA antagonist into the amygdala. J Neurosci. 1992; 12:854–863. [PubMed: 1347562]

Fendt M, Schmid S. Metabotropic glutamate receptors are involved in amygdaloid plasticity. Eur J Neurosci. 2002; 15:1535–1541. [PubMed: 12028364]

Frank JB, Kosten TR, Giller EL Jr, Dan E. A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. Am J Psychiatry. 1988; 145:1289–1291. [PubMed: 3048121]

Fletcher S, Creamer M, Forbes D. Preventing post traumatic stress disorder: are drugs the answer? Aust N Z J Psychiatry. 2010; 44(12):1064–1071. [PubMed: 21070102]

Gass JT, Olive MF. Positive allosteric modulation of mGluR5 receptors facilitates extinction of a cocaine contextual memory. Biol Psychiat. 2009; 65:717–720. [PubMed: 19100966]

Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiat. 1996; 57:390–394.

Gilad GM, Gilad VH, Wyatt RJ, Tizabi Y. Region-selective stress-induced increase of glutamate uptake and release in rat forebrain. Brain Res. 1990; 525:335–338. [PubMed: 1979236]

Gold PW, Licinio J, Wong ML, Chrousos GP. Corticotropin releasing hormone in the pathophysiology of melancholic and atypical depression and in the mechanism of action of antidepressant drugs. Ann NY Acad Sci USA. 1995; 771:716–729.

Grabe HJ, Spitzer C, Schwahn C, Marcinek A, Frahnow A, Barnow S, Lucht M, Freyberger HJ, John U, Wallaschofski H, Völzke H, Rosskopf D. Serotonin transporter gene (SLC6A4) promoter polymorphisms and the susceptibility to posttraumatic stress disorder in the general population. Am J Psychiatry. 2009; 166:926–933. [PubMed: 19487392]

Gresack JE, Risbrough VB. Corticotropin-releasing factor and noradrenergic signaling exert reciprocal control over startle reactivity. The International Journal of Neuropsychopharmacology. 2010:1–16. Epub of preprint.

Grillon C, Southwick SM, Charney DS. The psychobiological basis of posttraumatic stress disorder. Mol Psychiat. 1996; 1m:278–297.

Grillon C. D-Cycloserine Facilitation of Fear Extinction and Exposure-Based Therapy Might Rely on Lower-Level, Automatic Mechanisms. Biological Psychiatry. 2009; 66(7):636–641. [PubMed: 19520359]

Guastella AJ, Richardson R, Lovibond PF, Rapee RM, Gaston JE, Mitchell P, Dadds MR. A randomized controlled trial of D-cycloserine enhancement of exposure therapy for social anxiety disorder. Biol Psychiat. 2008; 63:544–549. [PubMed: 18179785]

Guastella AJ, Lovibond PF, Dadds MR, Mitchell P, Richardson R. A randomized controlled trial of the effect of D-cycloserine on extinction and fear conditioning in humans. Behav Res Ther. 2007; 45(4):663–672. [PubMed: 16962066]

Guthrie RM, Bryant RA. Extinction learning before trauma and subsequent posttraumatic stress. Psychosom Med. 2006; 68:307–311. [PubMed: 16554398]

Haddjeri N, Blier P, De Montigny C. Effect of the α2-adrenoceptor antagonist mirtazapine on the 5-hydroxytryptamine system in the rat brain. J Pharmacol Exp Ther. 1996; 277:861–871. [PubMed: 8627568]

Hageman I, Andersen HS, Jørgensen MB. Post-traumatic stress disorder: a review of psychobiology and pharmacotherapy. Acta Psych Scand. 2001; 104:411–422.

Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol. 2003; 18:1–8. [PubMed: 12490768]

Hollander E, Bartz J, Chaplin W, Phillips A, Sumner J, Soorya L, et al. Oxytocin Increases Retention of Social Cognition in Autism. Biological Psychiatry. 2007; 61(4):498–503. [PubMed: 16904652]

Holmes A, Quirk GJ. Pharmacological facilitation of fear extinction and the search for adjunct treatments for anxiety disorders--the case of yohimbine. Trends Pharmacol Sci. 2010; 31:2–7. [PubMed: 20036429]

Hubbard DT, Nakashima BR, Lee I, Takahashi LK. Activation of basolateral amygdala corticotropin-releasing factor 1 receptors modulates the consolidation of contextual fear. Neuroscience. 2007; 150(4):818. [PubMed: 17988803]

Hurlemann R. Noradrenergic-glucocorticoid mechanisms in emotion-induced amnesia: from adaptation to disease. Psychopharmacology. 2008; 197:13–23. [PubMed: 18038126]

Hurlemann R, Matusch A, Klingmuller D, Hawellek B, Kolsch H, Maier W, Dolan RJ. Emotion-induced retrograde amnesia varies as a function of noradrenergic-glucocorticoid activity. Psychopharmacology. 2007; 194:261–269. [PubMed: 17588225]

Jensen RA, Martinez JL Jr, Vasquez BJ, McGaugh JL. Benzodiazepines alter acquisition and retention of an inhibitory avoidance response in mice. Psychopharmacology (Berl). 1979; 64(1):125–126. [PubMed: 39313]

Johnson DM, Baker JD, Azorlosa JL. Acquisition, extinction, and reinstatement of Pavlovian fear conditioning: the roles of the NMDA receptor and nitric oxide. Brain Res. 2000; 857:66–70. [PubMed: 10700553]

Kasper S, McEwen BS. Neurobiological and clinical effects of the antidepressant tianeptine. CNS Drugs. 2008; 22:15–26. [PubMed: 18072812]

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005; 62:593–602. [PubMed: 15939837]

Khan S, Liberzon I. Topiramate attenuates exaggerated acoustic startle in an animal model of PTSD. Psychopharmacology. 2004; 172:225–229. [PubMed: 14586539]

Koenigs M, Grafman J. Posttraumatic stress disorder: the role of medial prefrontal cortex and amygdala. Neuroscientist. 2009; 15:540–548. [PubMed: 19359671]

Kohda K, Harada K, Kato K, Hoshino A, Motohashi J, Yamaji T, Morinobu S, Matsuoka N, Kato N. Glucocorticoid receptor activation is involved in producing abnormal phenotypes of single-prolonged stress rats: a putative post-traumatic stress disorder model. Neuroscience. 2007; 148:22–33. [PubMed: 17644267]

Kozaric-Kovacic D, Pivac N. Quetiapine treatment in an open trial in combat-related posttraumatic stress disorder with psychotic features. Int J Neuropsychopharmacol. 2007; 10:253–261. [PubMed: 16945162]

Knox D, Perrine SA, George SA, Galloway MP, Liberzon I. Single prolonged stress decreases glutamate, glutamine, and creatine concentrations in the rat medial prefrontal cortex. Neurosci Letters. 2010; 480:16–20.

Krystal JH, Neumeister A. Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience. Brain Res. 2009; 1293:13–23. [PubMed: 19332037]

Lattal KM, Barrett RM, Wood MA. Systemic or intrahippocampal delivery of histone deacetylase inhibitors facilitates fear extinction. Behav Neurosci. 2007; 121:1125–1131. [PubMed: 17907845]

Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behav Neurosci. 2003; 117:341–349. [PubMed: 12708530]

Lee HJ, Lee MS, Kang RH, Kim H, Kim SD, Kee BS, Kim YH, Kim YK, Kim JB, Yeon BK, Oh KS, Oh BH, Yoon JS, Lee C, Jung HY, Chee IS, Paik IH. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. Depr Anx. 2005; 21:135–139.

Lee JL, Milton AL, Everitt BJ. Reconsolidation and extinction of conditioned fear: inhibition and potentiation. J Neurosci. 2006; 26:10051–10056. [PubMed: 17005868]

Leon AC, Davis LL. Enhancing clinical trial design of interventions for posttraumatic stress disorder. Journal of Traumatic Stress. 2009; 22(6):603–611. [PubMed: 19902462]

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science. 2010; 329:959 – 964. [PubMed: 20724638]

Liberzon, I.; Khan, S.; Young, EA. Animal models of posttraumatic stress disorder. In: Steckler, T.; Kalin, NH.; Reul, JMHM., editors. Handbook of Stress and the Brain. Vol. part 2. Elsevier; Amsterdam: 2005. p. 231-250.

Likhtik E, Popa D, Apergis-Schoute J, Fidacaro GA, Pare D. Amygdala intercalated neurons are required for expression of fear extinction. Nature. 2008; 454:642–5. [PubMed: 18615014]

Lin HC, Mao SC, Gean PW. Effects of intra-amygdala infusion of CB1 receptor agonists on the reconsolidation of fear-potentiated startle. Learn Mem. 2006; 13:316–321. [PubMed: 16705137]

Lin HC, Mao SC, Chen PS, Gean PW. Chronic cannabinoid administration in vivo compromises extinction of fear memory. Learn Mem. 2008; 15:876–884. [PubMed: 19050159]

Linthorst, ACE. Stress, corticotrophin-releasing factor and serotonergic neurotransmission. In: Steckler, T.; Kalin, NH.; Reul, JMHM., editors. Handbook of Stress and the Brain. Vol. part 1. Elsevier; Amsterdam: 2005. p. 503-524.

Mao SC, Lin HC, Gean PW. Augmentation of fear extinction by infusion of glycine transporter blockers into the amygdala. Mol Pharmacol. 2009; 76(2):369–378. [PubMed: 19411609]

Martenyi F, Brown EB, Zhang H, Koke SC, Prakash A. Fluoxetine v. placebo in prevention of relapse in post-traumatic stress disorder. Br J Psychiatry. 2002; 181:315–320. [PubMed: 12356658]

Matar MA, Zohar J, Kaplan Z, Cohen H. Alprazolam treatment immediately after stress exposure interferes with the normal HPA-stress response and increases vulnerability to subsequent stress in an animal model of PTSD. Eur Neuropsychopharm. 2009; 19:283–295.

Matheson GK, Knowles A, Guthrie D, Gage D, Weinzapfel D, Blackbourne J. Actions of serotonergic agents on hypothalamic-pituitary-adrenal axis activity in the rat. Gen Pharmacol. 1997; 29:823–828. [PubMed: 9347333]

McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. J Trauma Injur Inf Crit Care. 2008; 64(2 Suppl):S195–S198.

McEwen BS, Chattarji S, Diamond DM, Jay TM, Reagan LP, Svenningsson P, Fuchs E. The neurobiological properties of tianeptine (Stablon): from monoamine hypothesis to glutamatergic modulation. Mol Psychiat. 2010; 15:237–249.

McRae AL, Brady KT, Mellman TA, Sonne SC, Killeen TK, Timmerman MA, Bayles-Dazet W. Comparison of nefazodone and sertaline for the treatment of posttraumatic stress disorder. Depr Anxiety. 2004; 19:190–196.

Mellman TA, Bustamante V, David D, Fins AI. Hypnotic medication in the aftermath of trauma. J Clin Psychiat. 2002; 63:1183–1184.

Menegola E, Di Renzo F, Broccia ML, Prudenziati M, Minucci S, Massa V, Giavini E. Inhibition of histone deacetylase activity on specific embryonic tissues as a new mechanism for teratogenicity. Birth Defects Res (Part B). 2005; 74:392–398.

Mehta D, Binder EB. Gene × Environment vulnerability factors for PTSD: the HPA axis. Neuropharmacology. (in press). in press.

Milad MR, Pitman RK, Ellis CB, Gold AL, Shin LM, Lasko NB, Zeidan MA, Handwerger K, Orr SP, Rauch SL. Neurobiological basis of failure to recall extinction memory in posttraumatic stress disorder. Biol Psychiat. 2009; 66:1075–1082. [PubMed: 19748076]

Milad MR, Rauch SL. The role of the orbitofrontal cortex in anxiety disorders. Ann NY Acad Sci. 2007; 1121:546–561. [PubMed: 17698998]

Moghaddam B. Stress preferentially increases extraneuronal levels of amino acids in the prefrontal cortex: comparison to hippocampus and basal ganglia. J Neurochem. 1993; 60:1650–1657. [PubMed: 8097232]

Moghaddam B, Bolinao ML, Stein-Behrens B, Sapolsky R. Glucocorticoids mediate the stress-induced extracellular accumulation of glutamate. Brain Res. 1994; 655:251–254. [PubMed: 7812782]

Monnelly EP, Ciraulo DA, Knapp C, Keane T. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol. 2003; 23:193–196. [PubMed: 12640221]

Morris RW, Bouton ME. The effect of yohimbine on the extinction of conditioned fear: a role for context. Behav Neurosci. 2007; 121:501–514. [PubMed: 17592941]

Mueller D, Olivera-Figueroa LA, Pine DS, Quirk GJ. The effects of yohimbine and amphetamine on fear expression and extinction in rats. Psychopharmacology. 2009; 204:599–606. [PubMed: 19242678]

Muravieva EV, Alberini CM. Limited efficacy of propranolol on the reconsolidation of fear memories. Learn Mem. 2010; 17:306–313. [PubMed: 20516209]

Myers KM, Carlezon WA Jr, Davis M. Glutamate receptors in extinction and extinction-based therapies for psychiatric illness. Neuropsychopharmacol Rev. 2011; 36:274–293.

Newcomer JW, Selke G, Melson AK, Hershey T, Craft S, Richards K, Alderson AL. Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Arch Gen Psychiat. 1999; 56:527–533. [PubMed: 10359467]

Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, Lindley SE, Otte C, Schoenfeld FB, Yesavage JA, Marmar CR. No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. Am J Psychiatry. 2006; 163:2186–2188. [PubMed: 17151174]

Norrholm SD, Jovanovic T, Olin IW, Sands LA, Karapanou I, Bradley B, et al. Fear Extinction in Traumatized Civilians with Posttraumatic Stress Disorder: Relation to Symptom Severity. Biological Psychiatry. (in press). In Press, Corrected Proof.

O'Donnell ML, Creamer M, Elliott P, Bryant R. Tonic and Phasic Heart Rate as Predictors of Posttraumatic Stress Disorder. Psychosom Med. 2007; 69(3):256–261. [PubMed: 17420442]

Onder E, Tural U, Aker T. A comparative study of fluoxetine, moclobemide, and tianeptine in the treatment of posttraumatic stress disorder following an earthquake. Eur Psychiat. 2006; 21:174–179.

Otto MW, Tolin DF, Simon NM, Pearlson GD, Basden S, Meunier SA, Hofmann SG, Eisenmenger K, Krystal JH, Pollack MH. Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. Biol Psychiat. 2010; 67:365–370. [PubMed: 19811776]

Pacak K, Palkovits M, Kopin IJ, Goldstein DS. Stress-induced norepinephrine release in the hypothalamic paraventricular nucleus and pituitary-adrenocortical and sympatho-adrenal activity: in vivo microdialysis studies. Front Neuroendocrinol. 1995; 16:89–150. [PubMed: 7621982]

Padala PR, Madison J, Monnahan M, Marcil W, Price P, Ramaswamy S, Din AU, Wilson DR, Petty F. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol. 2006; 21:275–280. [PubMed: 16877898]

Pamplona FA, Prediger RD, Pandolfo P, Takahashi RN. The cannabinoid receptor agonist WIN 55,212-2 facilitates the extinction of contextual fear memory and spatial memory in rats. Psychopharmacology. 2006; 188:641–649. [PubMed: 16947018]

Peskind ER, Bonner LT, Hoff DJ, Raskind MA. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. J Geriat Psychiat Neurol. 2003; 16:165–171.

Pitkänen A, Savander V, LeDoux JE. Organization of intra-amygdaloid circuitries in the rat: an emerging framework for understanding functions of the amygdala. Trends Neurosci. 1997; 20:517–523. [PubMed: 9364666]

Pitman RK, Delahanty DL. Conceptually driven pharmacologic approaches to acute trauma. CNS Spectrums. 2005; 10:99–106. [PubMed: 15685120]

Pitman RK, Sanders KM, Zusman RM, Healy AR, Cheema F, Lasko NB, Cahill L, Orr SP. Pilot study of secondary prevention of posttraumatic stress disorder with propranolol. Biol Psychiat. 2002; 51:189–192. [PubMed: 11822998]

Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology. 2008; 33:56–72. [PubMed: 17882236]

Radley JJ, Gosselink KL, Sawchenko PE. A discrete GABAergic relay mediates medial prefrontal cortical inhibition of the neuroendocrine stress response. J Neurosci. 2009; 29:7330–7340. [PubMed: 19494154]

Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, Dobie DJ, Hoff D, Rein RJ, Straits-Troster K, Thomas RG, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiat. 2003; 160:371–373. [PubMed: 12562588]

Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J, O'Connell J, Taylor F, Gross C, Rohde K, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. Biol Psychiatry. 2007; 61:928–934. [PubMed: 17069768]

Ravindran, LN.; Stein, MB. Pharmacotherapy of post-traumatic stress disorder. In: Stein, MB.; Steckler, T., editors. Behavioral Neurobiology of Anxiety and Its Treatment. Springer; Heidelberg: 2010. p. 505-525.

Reich DB, Winternitz S, Hennen J, Watts T, Stanculescu C. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. J Clin Psychopharmacol. 2004; 65:1601–1606.

Ressler KJ, Rothbaum BO, Tannenbaum L, Anderson P, Graap K, Zimand E, Hodges L, Davis M. Cognitive enhancers as adjuncts to psychotherapy: use of D-cycloserine in phobic individuals to facilitate extinction of fear. Arch Gen Psychiat. 2004; 61:1136–1144. [PubMed: 15520361]

Ressler KJ, Mercer KB, Bradley B, Jovanovic T, Mahan A, Kerley K, Norrholm SD, Kilaru V, Smith AK, Myers AJ, Ramirez M, Engel A, Hammack SE, Toufexis D, Braas KM, Binder EB, May V. Posttraumatic stress disorder is associated with PACAP and the PAC1 receptor. Nature. 2011; 470:492–7. [PubMed: 21350482]

Reul JM, Nutt DJ. Glutamate and cortisol – a critical confluence in PTSD? J Psychopharmacol. 2008; 22:469–472. [PubMed: 18701640]

Reul JM, Labeur MS, Grigoriadis DE, De Souza EB, Holsboer F. Hypothalamic-pituitary-adrenocortical axis changes in the rat after long-term treatment with the reversible monoamine oxidase-A inhibitor moclobemide. Neuroendocrinology. 1994; 60:509–519. [PubMed: 7845541]

Reznikov LR, Grillo CA, Piroli GG, Pasumarthi RK, Reagan LP, Fadel J. Acute stress-mediated increases in extracellular glutamate levels in the rat amygdala: differential effects of antidepressant treatment. Eur J Neurosci. 2007; 25:3109–3114. [PubMed: 17561824]

Roozendaal B. 1999 Curt P. Richter award: glucocorticoids and the regulation of memory consolidation. Psychoneuroendocrinology. 2000; 25:213–238. [PubMed: 10737694]

Roozendaal B, Brunson KL, Holloway BL, McGaugh JL, Baram TZ. Involvement of stress-released corticotropin-releasing hormone in the basolateral amygdala in regulating memory consolidation. Proc Natl Acad Sci U S A. 2002a; 99(21):13908–13913. [PubMed: 12361983]

Roozendahl B, Quirarte GL, McGaugh JL. Glucocorticoids interact with the basolateral amygdala beta-adrenoceptor-cAMP/PKA system in influencing memory consolidation. Eur J Neurosci. 2002b; 15:553–560.

Roozendaal B, Schelling G, McGaugh JL. Corticotropin-Releasing Factor in the Basolateral Amygdala Enhances Memory Consolidation via an Interaction with the {beta}-Adrenoceptor-cAMP Pathway: Dependence on Glucocorticoid Receptor Activation. J Neurosci. 2008; 28:6642–51. [PubMed: 18579737]

Rowe DL. Off-label prescription of quetiapine in psychiatric disorders. Exp Opin Neurother. 2007; 7:841–852.

Saxe G, Stoddard F, Courtney D, Cunningham K, Chawla N, Sheridan R, King D, King L. Relationship between acute morphine and the course of PTSD in children with burns. J Am Acad Child Adolesc Psychiat. 2001; 40:915–921.

Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhausler HB, Kapfhammer HP. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder survivors. Biol Psychiat. 2001; 50:978–985. [PubMed: 11750894]

Schelling G, Kilger E, Roozendaal B, de Quervain DJ, Briegel J, Dagge A, Rothenhausler HB, Krauseneck T, Nollert G, Kapfhammer HP. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: a randomized study. Biol Psychiat. 2004; 55:627–633. [PubMed: 15013832]

Sitges M, Guarneros A, Nekrassov V. Effects of carbamazepine, phenytoin, valproic acid, oxcarbazepine, lamotrigine, topiramate and vinpocetine on the presynaptic Ca2+ channel-mediated release of [3H]glutamate: comparison with the Na+ channel-mediated release. Neuropharmacology. 2007; 53:854–862. [PubMed: 17904592]

Southwick SM, Krystal JH, Bremner JD, Morgan CA III, Nicolaou AL, Nagy LM, Johnson DR, Heninger GR, Charney DS. Noradrenergic and serotonergic function in posttraumatic stress disorder. Arch Gen Psychiatry. 1997; 54:749–758. [PubMed: 9283511]

Southwick SM, Bremner JD, Rasmusson A, Morgan CA 3rd, Arnsten A, Charney DS. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biol Psychiat. 1999a; 46:1192–1204. [PubMed: 10560025]

Southwick SM, Morgan CA III, Charney DS, High JR. Yohimbine use in a natural setting: effects on posttraumatic stress disorder. Biol Psychiatry. 1999b; 46:442–444. [PubMed: 10435213]

Stein MB, Klein NA, Matloff JL. Adjunctive olanzapine for SRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiat. 2002; 159:1777–1779. [PubMed: 12359687]

Stein MB, Kerridge C, Dimsdale JE, Hoyt DB. Pharmacotherapy to prevent PTSD: results from a randomized controlled proof-of-consept trial in physically injured patients. J Trauma Stress. 2007; 20:923– 932. [PubMed: 18157888]

Storsve AB, McNally GP, Richardson R. US habituation, like CS extinction, produces a decrement in conditioned fear responding that is NMDA dependent and subject to renewal and reinstatement. Neurobiol Lear Mem. 2010; 93:463–471.

Stout SC, Owens MJ, Nemeroff CB. Regulation of corticotropin-releasing factor neuronal systems and hypothalamic-pituitary-adrenal axis activity by stress and chronic antidepressant treatment. J Pharmacol Exp Ther. 2002; 300:1085–1092. [PubMed: 11861819]

Suris A, North C, Adinoff B, Powell CM, Greene R. Effects of exogenous glucocorticoid on combat-related PTSD symptoms. Ann Clin Psychiatry. 2010; 22(4):274–279. [PubMed: 21180658]

Suzuki A, Josselyn SA, Frankland PW, Masushige S, Silva AJ, Kida S. memory reconsolidation and extinction have distinct temporal biochemical signatures. J Neurosci. 2004; 24:4787–4795. [PubMed: 15152039]

Szymanska M, Budziszewska B, Jaworska-Feil L, Basta-Kaim A, Kubera M, Leśkiewicz M, Regulska M, Lason W. The effect of antidepressant drugs on the HPA axis activity, glucocorticoid receptor level and FKBP51 concentration in prenatally stressed rats. Psychoneuroendocrinol. 2009; 34:822–832.

Taubenfeld SM, Riceberg JS, New AS, Alberini CM. Preclinical assessment for selectively disrupting a traumatic memory via postretrieval inhibition of glucocorticoid receptors. Biol Psychiat. 2009; 65:249–257. [PubMed: 18708183]

Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, Peskind ER, Raskind MA. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry. 2008; 63:629–632. [PubMed: 17868655]

Tollenaar MS, Elzinga BM, Spinhoven P, Everaerd W. Psychophysiological responding to emotional memories in healthy young men after cortisol and propranolol administration. Psychopharmacology. 2009; 203:793–803. [PubMed: 19139852]

Tronel S, Alberini CM. Persistent disruption of a traumatic memory by postretrieval inactivation of glucocorticoid receptors in the amygdala. Biol Psychiat. 2007; 62:33–39. [PubMed: 17207472]

Van der Kolk BA, Dreyfuss D, Michaels M, Shera D, Berkowitz R, Fisler R, Saxe G. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry. 1994; 55:517–522. [PubMed: 7814344]

Vermetten E, Vythilingam M, Southwick SM, Charney DS, Bremner JD. Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. Biol Psychiatry. 2003; 54:693–702. [PubMed: 14512209]

Vermetten E, Vythilingam M, Schmahl C, De Kloet C, Southwick SM, Charney DS, Bremner JD. Alterations in stress reactivity after long-term treatment with paroxetine in women with posttraumatic stress disorder. Ann NY Acad Sci USA. 2006; 1071:184–202.

Walker DL, Davis M. Role of the extended amygdala in short-duration versus sustained fear: a tribute to Dr. Lennart Heimer. Brain Struct Funct. 2008; 213:29–42. [PubMed: 18528706]

Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci. 2002; 22:2343–2351. [PubMed: 11896173]

Wang HN, Peng Y, Tan QR, Chen YC, Zhang RG, Qiao YT, Wang HH, Liu L, Kuang F, Wang BR, Zhang ZJ. Quetiapine ameliorates anxiety-like behavior and cognitive impairments in stressed rats: implications for the treatment of posttraumatic stress disorder. Physiol Res. 2010; 59:263–271. [PubMed: 19537923]

Weis F, Kilger E, Roozendaal B, de Quervain DJ, Lamm P, Schmidt M, Schmolz M, Briegel J, Schelling G. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: a randomized study. J Thorac Cardiovasc Surg. 2006; 131:277–282. [PubMed: 16434254]

Xie P, Kranzler HR, Poling J, Stein MB, Anton RF, Brady K, Weiss RD, Farrer L, Gelernter J. Interactive effect of stressful life events and the serotonin transporter 5-HTTLPR genotype on posttraumatic stress disorder diagnosis in 2 independent populations. Arch gen Psychiatry. 2009; 66:1201– 1209. [PubMed: 19884608]

Xu H, Chen Z, He J, Haimanot S, Li X, Dyck L, Li XM. Synergetic effects of quetiapine and venlafaxine in preventing the chronic restraint stress-induced decrease in cell proliferation and BDNF expression in rat hippocampus. Hippocampus. 2006; 16:551–559. [PubMed: 16652337]

Yamamoto S, Morinobu S, Fuchikami M, Kurata A, Kozuru T, Yamawaki S. Effects of single prolonged stress and D-cycloserine on contextual fear extinction and hippocampal NMDA receptor expression in a rat model of PTSD. Neuropsychopharmacology. 2008; 33:2108–2116. [PubMed: 17957211]

Yamamura S, Abe M, Nakagawa M, Ochi S, Ueno S-i, Okada M. Different actions for acute and chronic administration of mirtazapine on serotonergic transmission associated with raphe nuclei and their innervation cortical regions. Neuropharmacology. 2011; 60(4):550–560. [PubMed: 21195096]

Yehuda R. Risk and resilience in posttraumatic stress disorder. J Clin Psychiat. 2004; 65:29–36.

Yehuda, R. Neuroendocrine aspects of PTSD. In: Steckler, T.; Kalin, NH.; Reul, JMHM., editors. Handbook of Stress and the Brain. Vol. part 2. Elsevier; Amsterdam: 2005. p. 251-272.

Zhang S, Cranney J. The role of GABA and anxiety in the reconsolidation of conditioned fear. Behav Neurosci. 2008; 122:1295–1305. [PubMed: 19045949]

Zohar J, Amital D, Miodownik C, Kotler M, Bleich A, Lane RM, Austin C. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. J Clin Psychopharm. 2002; 22:190–195.

Zushida K, Sakurai M, Wada K, Sekiguchi M. Facilitation of extinction learning for contextual fear memory by PEPA: a potentiator of AMPA receptors. J Neurosci. 2007; 27:158–166. [PubMed: 17202483]

- PTSD currently has few proven pharmacotherapeutics
- In this review we will discuss novel treatment targets and approaches
- Novel approaches can be prophylactic or adjunctive
- Pharmacological modulation of extinction or reconsolidation may hold promise