Published in final edited form as:

Brain Res. 2009 October 13; 1293: 24–39. doi:10.1016/j.brainres.2009.03.037.

Pharmacotherapy of PTSD: Premises, Principles, and Priorities

Lakshmi N. Ravindran, MD^{1,2} and Murray B. Stein, MD, MPH^{1,2}

¹ University of California San Diego, Department of Psychiatry, La Jolla, CA, USA

² VA San Diego Health Care System, La Jolla, CA, USA

Abstract

Post-traumatic stress disorder (PTSD) is a prevalent anxiety disorder that results in multiple disabling symptoms. Research into the underlying neurobiology has implicated dysregulation in multiple neurotransmitter systems including norepinephrine, serotonin, and glutamate as well as the hypothalamic-pituitary axis. Understanding how these biological systems interact with each other and how they may affect key neural structures, such as the amygdala, hippocampus, and prefrontal cortex, to produce post-traumatic symptoms is critical for the development of effective pharmacological treatments. We briefly discuss the proposed biological dysfunctions underlying PTSD and how agents that target these dysfunctions may be utilized in PTSD. We then provide a review of the different pharmacological agents that have been investigated in PTSD. These drugs include: antidepressants, anti-adrenergic agents, anticonvulsants, benzodiazepines, atypical antipsychotics, and novel agents.

Introduction

Lifetime exposure to traumatic events is common with reported prevalence of up to 90% in some populations (Breslau et al., 2001; Bruce et al., 2001; Frans et al., 2005), yet it is only a fraction of those that develops the problematic cluster of symptoms comprising the syndrome of post-traumatic stress disorder (PTSD). Lifetime prevalence of PTSD has been estimated at 6.8% in the US general population (Kessler et al., 2005a) with a 12-month prevalence of 3.5% (Kessler et al., 2005b), although may be as high as 24% in particular subpopulations, such as military veterans (Milliken et al., 2007). The syndrome of PTSD is characterized by direct or indirect exposure to a traumatic event eliciting an extremely fearful reaction, and subsequently accompanied by more than one month of dysfunction and the presence of symptoms characterized by 3 different symptom clusters: consistent re-experiencing of the trauma, numbing/avoidance behavior, and persistent hyperarousal.

These pathological responses of PTSD have been proposed to result from the failure of the stress response system to appropriately react, adapt and recover from the traumatic event. Although still incompletely understood, the dysregulation of several biological systems have been implicated in the abnormal response underlying the pathophysiology of PTSD. Affected biological pathways may include corticotropin releasing hormone (CRH) and hypothalamic pituitary adrenal (HPA) axis abnormalities, as well as dysfunction in noradrenergic, serotonergic, and glutamatergic systems. By understanding how dysfunction in the different

Corresponding Author: Dr. Murray B. Stein, Department of Psychiatry, University of California San Diego, 8939 Villa La Jolla Drive, Suite 200, La Jolla, CA 92037, USA, Tel: 1-858-534-6400, Fax: 1-858-534-6460, Email: mstein@ucsd.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

neurobiological circuits may contribute to the signs and symptoms of PTSD, we may understand why particular medications are effective for this disorder and what future directions research should take to find other more beneficial therapies. We provide a brief overview of the proposed biological dysregulations seen in PTSD as well as the evidence base for currently available pharmacotherapeutic agents and how they may act to produce symptomatic improvement. For this purpose, we will limit our review of psychopharmacological agents to those with evidence from randomized controlled trials (RCTs). In cases where this is not possible other evidence (e.g., open-label or active-control trials) may be mentioned.

Norepinephrine Dysfunction

Much attention in PTSD research has focused on the two predominant biological systems involved in the stress response: the noradrenergic system and the CRH stress response. Norepinephrine (NE), also known as noradrenaline, is a centrally acting catecholamine, with predominant actions on the sympathetic nervous system. The cell bodies of a large majority of noradrenergic secreting neurons are found in the locus ceruleus (LC) of the brainstem. An important neural structure, the LC has projections into several areas of the brain implicated in emotion, memory, and stress response, such as the amygdala, hippocampus, thalamus and prefrontal cortex (PFC) (Vermetten and Bremner, 2002). Under normal conditions, in the presence of a stressor, the sympathetic nervous system is activated causing NE to be released from the LC. This in turn produces a number of physiological responses, such as vasoconstriction of peripheral blood flow, increased blood flow to the heart, increased respiratory rate, and pupillary dilation – the so-called “fight or flight” response. NE has also been found to have a role in attention, learning, and memory – cognitive functions that are important to a number of psychiatric disorders (Wolf, 2008). However, there is a large body of evidence to suggest that this functioning is altered, and there may in fact be hyperactive noradrenergic function in PTSD.

Early indications for this biological alteration came from clinical observations that patients with PTSD appeared to be in a state of hyperarousal, particularly in the presence of traumatic triggers – displaying hypervigilance, exaggerated startle, and sleeplessness (Sargant and Slater, 1940). Subsequently, evidence from physiologic studies has demonstrated that individuals with PTSD display autonomic hyperactivity at baseline compared to healthy controls. In order to demonstrate that these effects were in fact due to alterations in NE, researchers focused on characterizing measures of peripheral NE (or its metabolite 3-methoxy-4-hydroxyphenylglycol [MHPG]) in PTSD populations. However, measures of basal plasma NE levels failed to demonstrate consistent differences between individuals with PTSD and those without (Jensen et al., 1997; McFall et al., 1992; Murburg et al., 1995; Yehuda et al., 1998).

In contrast, several studies examining 24-hour catecholamine excretion in urine have revealed differences between different populations with PTSD and those without (De Bellis et al., 1994; Kosten et al., 1987; Yehuda et al., 1992). For instance, combat veterans with PTSD have been found to not only have elevated urine NE levels compared to healthy controls but even compared to combat veterans with either major depression or schizophrenia, suggesting this finding is not just due to trauma exposure. In a similar vein, Lemieux (1996) and colleagues compared adult females with a history of sexual abuse both with and without PTSD to a group of non-abused females without PTSD. What they noted was that the group with PTSD and history of abuse had significantly elevated levels of NE compared to the non-abused controls. Interestingly, the group with trauma history but without PTSD had values in between these other two groups, but was not significantly different from either. More recently Delahanty and colleagues (2005) suggested that in boys aged 8-18 years elevated urinary catecholamine and cortisol levels in the period shortly following trauma exposure may be a risk factor for subsequent PTSD development. In contrast, a similar study in adults revealed that only lower

cortisol levels in the aftermath of trauma predicted subsequent post-traumatic symptoms with no reliable relationship found between catecholamine levels and the same (Delahanty et al., 2000).

Few studies have measured CNS NE concentrations. In one of the only studies to examine this, cerebrospinal fluid concentrations of NE were found to be elevated in male combat veterans with chronic PTSD, with levels corresponding to symptom severity as assessed by the Clinician Administered PTSD Scale (CAPS) (Geraciotti et al., 2001).

Although biological measures of NE levels are certainly not entirely consistent across the literature (Pitman et al., 1990; Mellman et al., 1995), results from psychophysiologic studies measuring peripheral and central NE are highly suggestive of increased enhanced noradrenergic activity in PTSD. Additional evidence for noradrenergic alterations in PTSD comes from challenge paradigms used by investigators which have been instrumental in showing that the adrenergic receptors in individuals with chronic PTSD are particularly sensitive to stimulation and prone to hyperactivity. Yohimbine, an α_2 adrenergic antagonist that crosses the blood-brain barrier, has been frequently used as a reliable probe of central noradrenergic function (Peskind et al., 1989). Southwick et al. (1993) found that yohimbine administered in a double-blind fashion to 20 combat veterans with PTSD resulted in panic attacks in 70% and flashbacks in 40% of this population, compared to neither of these events in a healthy control group. A similar challenge using yohimbine vs. placebo was administered to combat veterans with PTSD and a control group of combat veterans without PTSD, while measuring acoustic startle (Morgan et al., 1994). Once again the PTSD group had significantly greater startle responses with yohimbine compared to when placebo was administered and this response was not seen with the healthy group.

Identifying the functional significance of these hyperresponsive noradrenergic systems in the pathophysiology of PTSD is also an issue of importance. Research into the neural circuits involved in PTSD has implicated three brain regions of interest – the amygdala, the hippocampus and the medial prefrontal cortex (mPFC) – which play a key role in responses to emotional events and memories, and in which NE is thought to play an important function.

The amygdala has received particular attention in research into emotional memory. Cahill and colleagues (1996) used positron emission tomography (PET) to demonstrate that enhanced activity in the amygdala during viewing of emotionally arousing films influenced subsequent recall of the arousing material although this was not true of neutral material. Subsequently, research has shown that both the emotional valence of the stimulus and the level of arousal at the time of encoding into memory appear to be important factors in the process of memory consolidation (Zald, 2003). As such, in the presence of an emotionally arousing stimulus, sensory information received by the basolateral nucleus of the amygdala (BLA) is amalgamated along with information from other brain structures to then form an emotional association with the memory of the stimulus. Input from the BLA is then transmitted, via the central nucleus of the amygdala, to other neural structures, including the hypothalamus, to effect motor and autonomic responses. In this way, the amygdala plays a critical role in fear conditioning by creating the association that links a potential threat to a fear response.

The amygdala is also thought to modulate consolidation of these emotional memories in the hippocampus, and this process is significantly influenced by the noradrenergic system. In a pivotal study by Cahill et al. (1994), administration of a central β -adrenergic antagonist (propranolol) prior to viewing a series of emotional slides resulted in selectively impairing effects on recall of emotional material; recall of neutral material was unaffected. Building on this, van Stegeren and colleagues (2005) conducted an fMRI study comparing memory retrieval in a group of healthy controls that received either propranolol or placebo prior to viewing

emotional and neutral pictures. They demonstrated that, following placebo administration, amygdala activation increased in response to emotional pictures, but this response was decreased following propranolol, suggesting that NE is an important modulator of amygdala activation. As such, the enhanced noradrenergic activity seen in patients with PTSD may act to increase amygdala activation and so intensify the fear conditioning process, which in turn may explain in some part why these individuals avoid thoughts, feelings, or physical triggers that remind them of the trauma.

As discussed, another critical brain structure implicated in PTSD is the hippocampus, which has an essential role in the formation and retrieval of episodic and declarative memories. The hippocampus is linked reciprocally to the amygdala and is subject to altered noradrenergic function via NE's actions on the amygdala. A review of evidence from animal studies showed that chronic stress was associated with dendritic atrophy in the CA3 region of the hippocampus and the medial prefrontal cortex (mPFC), as well as decreased neurogenesis (Wolf, 2008). In humans, one commonly cited observation in individuals with PTSD is a finding of decreased hippocampal volumes which was initially postulated to reflect atrophy secondary to chronic stress and glucocorticoid overexposure. More recently, however, research using twins discordant for combat exposure has actually suggested that smaller hippocampal volumes may in fact be a risk factor for subsequent PTSD development rather than a consequence of the illness (Gilbertson et al., 2002).

Animal studies have been able to demonstrate that moderate increases in NE have the ability to enhance cognitive function in the PFC possibly by minimizing attention to irrelevant stimuli. However, in the presence of significantly increased NE levels, activity in the prefrontal cortex is decreased. Under normal conditions, the PFC, including the mPFC, has inhibitory control over the amygdala. However, reduced PFC activity results in control over emotional and fear responses being shifted from higher brain structures to more primitive ones, thus enabling the body for action (Arnsten, 1997). While this might normally be an adaptive response in the face of a threat, for individuals with PTSD (with their consistently elevated NE levels), this chronic readiness for action may explain the hyperarousal (e.g. hypervigilance, exaggerated startle) symptoms that form part of the core clinical picture of this disorder.

In summary, noradrenergic dysfunction appears to play a key role in the pathophysiology of PTSD. Individuals with this disorder appear to display abnormalities in different measures of NE along with hypersensitive adrenergic receptors suggestive of an overall enhanced noradrenergic state. The proposed neural circuitry implicated in PTSD is also influenced by these catecholaminergic alterations. Increased NA may contribute not only to the enhanced fear acquisition and conditioning responses by the amygdala, but also to loss of prefrontal control over the amygdala thus impairing extinction of the fear response.

Serotonin Dysfunction

Compared to the evidence of noradrenergic dysfunction in the pathophysiology of PTSD, a role for alterations in serotonin function is much less clear, and has been driven in large part by empirical evidence of the efficacy of pro-serotonergic agents for this disorder. Many of the symptoms commonly experienced by these patients include: irritability, impulsivity, suicidality, mood and anxiety symptoms, changes in cardiovascular and respiratory activity, and sleep dysregulation – all central nervous system functions affected by serotonin (Evenden, 1999; Monti and Jantos, 2008; Ryding et al., 2008; Villalon and Centurion, 2007). The improvement in many of these symptoms seen following treatment with serotonergic antidepressants (e.g. SSRIs) has been one explanation put forward by investigators to support a role for serotonergic dysfunction in PTSD. The increasing use of functional neuroimaging in psychiatry has provided additional information regarding the possible

mechanism of improvement. Vermetten and colleagues (2003) administered the selective serotonin reuptake inhibitory (SSRI) paroxetine (20-50 mg daily) to individuals with PTSD. They obtained magnetic resonance imaging (MRI) scans both before and following 9-12 months of treatment. Paroxetine was found to be effective for symptomatic treatment of PTSD, but was also associated with an increase in hippocampal volume, supporting evidence from preclinical studies that antidepressants (e.g. SSRIs) may achieve their therapeutic benefit by promoting hippocampal neurogenesis (Duman et al., 2001). Similarly, Seedat et al. (2004) used single photon emission computed tomography (SPECT) to compare brain scans of PTSD patients before and after 8 weeks of open label SSRI (citalopram) treatment. Once again, citalopram was associated with symptomatic improvement as measured by change in scores on the Clinician Administered PTSD scale (CAPS), but more importantly this change in CAPS score correlated significantly with activation in the left mPFC. The authors suggested that SSRIs may achieve their symptomatic benefits in PTSD by normalizing the mPFC inhibition of the amygdala.

Other investigators have argued that the role of serotonin in PTSD is derived mainly from indirect effects, via the modulation of other affected biological systems (Szabo et al., 1999). Serotonergic neurons, derived predominantly from the dorsal and median raphe nuclei of the brainstem, project widely over the brain to key structures involved in fear and anxiety circuits, such as the amygdala and hippocampus. Although the specific effects of serotonin on these brain regions are incompletely understood (Kent et al., 1998), one recent study that may shed light on the issue was published by Arce and colleagues (2008). Using fMRI the investigators demonstrated that subchronic (21 day) administration of the SSRI escitalopram (10 mg daily) to healthy volunteers resulted in attenuated amygdala activation during emotional face processing. Furthermore there are important reciprocal interactions that exist between the serotonin and NE systems. The firing of NE neurons in the LC is under tonic inhibition by projections from the dorsal raphe nucleus. The use of SSRIs which effectively allow increased 5-HT to be released indirectly enhances this inhibitory tone (Szabo and Blier, 2001) which may be a key factor in improving the hyperadrenergic state in PTSD, and the downstream improvement in amygdala activation.

Serotonin has also been found to have modulating effects on the HPA axis. It has been proposed that serotonin may act to inhibit CRH release in the paraventricular nucleus (PVN) either directly or by inhibiting projections from the amygdala to the PVN (Kent et al., 1998). Findings from animal studies suggest that longterm treatment with SSRIs appears to decrease HPA responsiveness at the pituitary level (Jensen et al., 1999) as well as potentially reducing the mRNA expression of CRH in the hypothalamus and the central nucleus of the amygdala in adult rats with early life stress (Nemeroff and Owens, 2005).

HPA Axis Dysfunction

Under normal conditions, the HPA axis serves to regulate the physiological responses to stress. Stress causes release of the 41-amino acid peptide, CRH, from the PVN of the hypothalamus. CRH in turn stimulates secretion of adrenocorticotrophic releasing hormone (ACTH) from the anterior pituitary which then serves to stimulate production of glucocorticoids (e.g., cortisol) from the body's adrenal glands. The subsequent accumulation of cortisol then acts via a negative feedback loop to cease release of ACTH and CRH, effectively terminating the stress response. However, dysfunction of the HPA axis in the stress response has been documented in a number of psychiatric disorders (Lo et al., 2008; Pariante and Lightman, 2008; Sinha, 2008), including PTSD.

Patients suffering from PTSD display several particular neuroendocrinological alterations, although discrepancies between investigations are still found. While normal functioning of the

stress response in response to trauma would suggest that increased CRH levels and subsequently elevated levels of cortisol be seen, as is the case of major depression (Parker et al., 2003), in fact unexpectedly low cortisol levels have been reported not only for urine (Mason et al., 1986; Yehuda et al., 1990; Yehuda et al., 1991a; Yehuda et al., 1992) but also in saliva and plasma (Boscarino, 1996; Ganzel et al., 2007; Goenjian et al., 1996; Oquendo et al., 2003; Wessa et al., 2006; Yehuda et al., 1996). However, these results are by no means consistent across studies and several investigations have since been published offering contradicting results (Bonne et al., 2003; Lindley et al., 2004; Lipschitz et al., 2003; Pitman et al., 1990; Young and Breslau, 2004). A portion of these discrepant results have been attributed to differences in methodological issues (e.g. timing of sampling, cross-sectional vs. 24-hour collection), as well as heterogeneity in patient populations (e.g. time since trauma exposure, type of trauma, and severity of symptoms). In an effort to resolve this issue, a recent meta-analysis noted that lower levels of basal cortisol in plasma and serum were found in patients with PTSD compared to healthy controls with no prior trauma exposure, but not necessarily compared to controls with a history of trauma exposure (Meewisse et al., 2007). The authors suggested that these observed differences in cortisol levels might be attributable to exposure to traumatic events rather than to PTSD itself. Prospective replication of these results with large samples will be necessary to confirm this hypothesis.

Investigators have also been interested in examining the relationship between cortisol levels immediately following trauma and subsequent PTSD development. McFarlane et al. (1997) studied plasma cortisol levels in 40 subjects following a motor-vehicle accident (MVA). At 6 month follow-up the patients who subsequently developed PTSD were found to have had significantly lower cortisol levels at the time of sampling compared to those patients with either no diagnosis or those who developed major depression. Resnick and colleagues (1995) also examined plasma cortisol levels in female rape victims shortly following the assault. They found that women who had a prior history of rape had lower cortisol levels following the more recent event, but an elevated risk of subsequent PTSD development. Trying to characterize this relationship in more detail, Delahanty et al. (2003) assessed a sample of subjects following MVA. Their findings suggest that the relationship between injury severity, prior trauma history, and certain post-traumatic symptoms at one month follow-up is mediated by initial urinary cortisol levels following trauma. However, given the small sample size and lack of objective PTSD assessment, these findings need to be replicated.

One well-replicated neuroendocrinologic finding within the PTSD literature is the enhanced negative feedback sensitivity of the HPA axis (Goenjian et al., 1996; Stein et al., 1997; Yehuda et al., 1991b; Yehuda et al., 2004). Using low-dose dexamethasone suppression tests (0.25 mg and 0.5 mg), Yehuda and colleagues demonstrated that combat veterans with PTSD showed greater cortisol suppression than did combat veterans without PTSD or normal controls (Yehuda et al., 1995) but also that these individuals had greater numbers of lymphocyte glucocorticoid receptors (GR) compared to controls (Yehuda et al., 1991b, Yehuda et al., 1995). Although the numbers of lymphocyte GR were comparable between combat veterans with and without PTSD, dexamethasone induced a greater reduction in number of GR in those with PTSD. Subsequently, enhanced ACTH suppression in response to dexamethasone was also demonstrated, suggesting that there may be enhanced GR sensitivity at the level of the pituitary mediating this response (Yehuda et al., 2004). This finding may also shed light on the previously observed blunted response of ACTH to CRH in PTSD (Smith et al., 1989).

Animal studies suggest that CRH acts principally via 2 G-protein-coupled receptors: CRH1 and CRH2. Although these receptors are distributed widely through the brain, animal studies show the CRH1 receptors to be expressed in greater quantity in certain areas such as the neocortex, BLA, hippocampus, cingulate cortex, and medial and dorsal prefrontal cortices (Charney, 2003; Hauger et al., 2006). In general, CRH has a greater affinity for the CRH1

receptor and when administered exogenously to animals, results in an increase in anxiety-like behaviors (Dunn and File, 1987; Martins et al., 1997; Sutton et al., 1982). The CRH1 receptor in particular has been implicated in CRH mediation of stress-response behaviors with studies of CRH1 knockout rodents demonstrating a reduction in anxiety-related behavior (Hauger et al., 2006; Timpl et al., 1998). Further, administration of CRH1 antagonists prior to stress exposure results in a reduction of anxious behaviors, as measured by reduced freezing and increased exploratory behaviors (Gutman et al., 2003; Hikichi et al., 2000). Based on these findings, the utility of a CRH1 antagonist to treat mood or anxiety disorders with underlying HPA dysfunction has received considerable interest. Although there are no published trials of these agents in PTSD to date, preliminary investigations have explored their use in major depression, albeit with only limited success (Binneman et al., 2008; Zobel et al., 2000); results have been hampered in part by reports of potential hepatotoxicity of some compounds

Although several studies have found evidence of elevated CSF CRH levels in PTSD it remains unclear whether this result represents a pre-existing risk factor or is a consequence of PTSD development (Risbrough and Stein, 2006). As with NE, glucocorticoids (GCs) play a key role in modulating the neural circuits involved in the pathophysiology of PTSD, not only by affecting brain structures themselves but also through their interaction with other neurotransmitters such as NE and serotonin. For instance, studies of GCs and memory have revealed that during acute stress, elevated GC levels work in concert with noradrenergic activation in the BLA to enhance the process of encoding and consolidating emotional memories (Rozendaal et al., 2006). With evidence from functional neuroimaging studies (Dolcos et al., 2004; Kensinger and Corkin, 2004; Kilpatrick and Cahill, 2003; Richardson et al., 2004) suggesting that encoding of emotional episodes involves a functional coupling between the amygdala and hippocampus, it has been suggested that the interaction between elevated levels of GCs and NE could enhance this process. One model that has been put forth hypothesizes that the mPFC which normally has inhibitory control over the noradrenergic neurons of the LC and over the HPA axis, is rendered ineffective at times of acute stress thus permitting enhanced stimulation of the amygdala by GCs and NE, which in turn enhances encoding and consolidation of the traumatic memory (Hurlemann, 2008).

In contrast to the enhancing effects on encoding, similarly elevated GC levels may impair delayed memory retrieval, particularly for emotionally arousing material (Buchanan et al., 2006), again in the context of noradrenergic activation within the BLA. An inverted U-shaped curve has thus been proposed to explain how memory retrieval is affected by cortisol concentrations (Wolf, 2008) and this in turn may explain why individuals with PTSD have difficulty subsequently remembering certain aspects of the trauma.

Neuroimaging studies of PTSD patients have fairly consistently noted a finding of smaller hippocampal volumes relative to healthy controls (Bremner et al., 2008). Using evidence from animal studies, this hippocampal atrophy was initially attributed to the effects of neurotoxic effects of excess cortisol associated with chronic stress (Bremner et al., 1995; Bremner, 1999; Sapolsky et al., 1990; Woolley et al., 1990). However, as noted earlier, smaller hippocampal volumes may represent a risk factor for PTSD development rather than being a sequela of the illness (Gilbertson et al., 2002). Further, as noted by Herbert et al. (2006), the hippocampus is rich in GC receptors which may therefore render it more susceptible to GC damage following acute stress. Additional research is needed to elucidate the exact mechanism by which acute stress and GC release interacts with smaller hippocampal volumes to produce the specific cognitive deficits and symptoms of PTSD.

Glutamate Dysfunction

Glutamate is the primary excitatory neurotransmitter in the CNS and has two types of receptors – ionotropic (e.g. N-methyl-D-aspartate (NMDA) receptors) and metabotropic. Glutamate has been proposed to play a role in the pathophysiology of PTSD in part via its actions on the HPA axis where evidence from animal studies support its role in the modulation of CRH release in response to stress (Gabr et al., 1995; Zelena et al., 2005). Further support for this theory is derived from experiments in which pre-treatment with a glutamatergic NMDA-receptor antagonist was seen to decrease stress responsiveness as measured by ACTH release (Jezova et al., 1995; Tokarev and Jezova, 1997). This suggests that changes in glutamate levels play a key role in initiation and maintenance of the HPA response. Further, the production of dissociative-like symptoms (commonly seen in PTSD) observed when ketamine, an NMDA-receptor antagonist that transiently stimulates glutamate release, was administered to humans suggests that a hyperglutamatergic state may be implicated in PTSD (Chambers et al., 1999; Krystal et al., 1994).

Glutamate is also thought to play a fundamental role in memory formation, a key process of PTSD. Specifically, longterm potentiation, the cellular process thought to underlie learning and memory formation, is dependent on glutamate activity. Memories are consolidated as activation of glutamate NMDA receptors permits Ca^{++} influx into cells, thus leading to changes in post-synaptic plasticity. Glutamate, however, also has the potential to be excitotoxic; for example, the greater than normal levels of glutamate released under stressful conditions have been implicated in the structural damage subsequently produced in the hippocampus (Armanini et al., 1990; Lowy et al., 1995; Stein-Behrens et al., 1994). It has thus been suggested that following traumatic events, elevated glutamate levels may serve to encode and consolidate traumatic memories, but also enhance hippocampal damage (Joca et al., 2007).

In contrast, administration of NMDA receptor antagonists has been shown to block acquisition of fear conditioning in the amygdala and hippocampus (Cammara et al., 2004; Joca et al., 2007; Maren, 1999; Miserendino et al., 1990). However, NMDA receptors are also involved in the process of fear extinction – new learning that acts to suppress prior conditioned responses (Bouton and Bolles, 1979). Preclinical studies show that following the acquisition of conditioned fear, rats that then receive intra-amygdalar administration of NMDA antagonists prior to extinction training demonstrate impaired retention of extinction behavior (Baker and Azorlosa, 1996; Falls et al., 1992).

Based on this literature, it would be rational to suppose that use of NMDA receptor antagonists might be useful to impair the fear conditioning and recall of traumatic memories, and limit possible glutamate-induced hippocampal damage seen in PTSD, at least in the acute aftermath of trauma or early in the development of PTSD. Similarly, investigators have proposed a role for agents that augment glutamate transmission during psychotherapeutic processes targeted towards enhancing extinction of conditioned fears and traumatic memories (Davis et al., 2006; Heresco-Levy et al., 2002).

Psychopharmacological Management of PTSD

Initial treatment studies of PTSD largely focused their attention on the efficacy of various antidepressant classes – particularly with the advent of newer more selective agents, such as serotonin reuptake inhibitors, with their improved tolerability and safety profiles. Efficacy studies of these agents formed the bulk of the treatment literature over the last twenty years. However, with the upsurge of research attempting to delineate the underlying biological dysfunctions responsible for post-traumatic symptoms, attention has been redirected towards therapeutic agents that may work by alternate mechanisms to effect improvement and which can be used either in place of or as adjuncts to antidepressants.

A. Selective Serotonin Reuptake Inhibitors (SSRIs)

In part due to the increased focus on PTSD research over the last 20 years as well as the ubiquitous availability of these agents during that time, the largest body of pharmacological treatment literature in PTSD exists for the SSRIs. Given the high degree of comorbidity between PTSD and major depression, and the documented efficacy of SSRIs for depressed populations (as well as for a number of other discrete anxiety disorders), evaluation of these agents does have some basis. At this time there are six SSRIs currently available on the world market: sertraline, paroxetine, fluoxetine, fluvoxamine, citalopram, and escitalopram. Although only the first two listed have FDA approval for PTSD treatment, the others are also commonly used for this purpose.

Van der Kolk et al. (1994) published one of the first reports of SSRI efficacy for both civilian and combat related-PTSD. In their 5-week placebo-controlled trial using fluoxetine, up to 60 mg daily, significant reductions in PTSD symptomatology were seen with the active agent, particularly in the symptom clusters of hyperarousal and numbing. Interestingly, the rates of improvement were markedly different between the civilian and combat-exposed population (40% vs. 15%). Since that time, a number of positive placebo-controlled trials have been published supporting the short-term (≤ 12 weeks) use of sertraline (Brady et al., 2000; Davidson et al., 2001a), paroxetine (Marshall et al., 2001; Tucker et al., 2001), and fluoxetine (Connor et al., 1999; Martenyi et al., 2002). Despite positive results from open trials (English et al., 2006; Seedat et al., 2000; Seedat et al., 2001; Seedat et al., 2002), the only double-blind trial comparing acute treatment (10 weeks) with citalopram to sertraline and placebo (Tucker et al., 2003) for PTSD failed to detect significant differences in overall efficacy between the 3 arms, although all three groups showed symptom improvement. Although double-blind trials do not exist, evidence from open trials suggests that fluvoxamine and escitalopram may also be helpful for PTSD (Davidson et al., 1998; De Boer et al., 1992; Escalona et al., 2002; Marmar et al., 1996; Robert et al., 2006).

Evidence also suggests that extended use of SSRIs, beyond the acute phase, can further improve symptoms and prevent relapse. Two papers have also been published supporting the extended use of sertraline for maintenance of improvement and relapse prevention. In the first study, Lønborg et al. (2001) enrolled 252 patients, who had previously participated in one of two double-blind placebo-controlled trials using sertraline for PTSD, into an open-label continuation phase for a further 24 weeks. They noted that 92% of the original responders maintained their recovery during this period, but also that 54% of non-responders in the original trials converted to responders by the end of the extension phase. Further extending these findings Davidson et al. (2001b) followed a sample of the responders ($N=96$) from this extension phase and re-randomized them to double-blind maintenance treatment with sertraline or placebo for an additional 28 weeks. All measures of relapse and/or discontinuation were seen to significantly favor the group treated with active medication. Martenyi and colleagues (2002) conducted a similar study examining relapse prevention in PTSD using fluoxetine. Following a 12-week double-blind placebo controlled trial, responders to fluoxetine were re-randomized to a further 24 week relapse prevention phase. A significantly greater proportion of those maintained on the fluoxetine completed the extension phase, with the main reason for dropout in placebo-treated individuals being relapse. Further, subjects who were treated with fluoxetine for the entire 36 weeks continued to experience improvement during the continuation phase and had a statistically greater change in PTSD symptom scores from baseline to endpoint compared to subjects who had been switched to placebo (Effect size 0.5).

In contrast, two negative placebo-controlled trials of SSRIs for PTSD have also been published (Hertzberg et al., 2000; Martenyi et al., 2007). These studies, both involving fluoxetine, failed to find benefit for post-traumatic symptoms following 12-weeks of treatment. The chronicity and severity of symptoms of the population used in the first trial, veterans with combat-related

trauma, may have played a role in the lack of response. The authors of the 2nd study theorized that their results may have been affected by their population, predominantly females, and the relatively low dose of fluoxetine (20 or 40 mg) used.

Interestingly, despite the relative abundance of evidence supporting the use of SSRIs for both acute and continuation treatment of PTSD, the Committee on the Treatment of PTSD from the Institute of Medicine (2007) recently published a report concluding that there was insufficient evidence to support this conclusion, based on their view that overall effect sizes seen in these trials were small. Nevertheless, even if one accepts that the efficacy of SSRIs for PTSD could be better, extensive clinical experience with these agents and their efficacy for disorders that are commonly comorbid with PTSD means that their use will likely continue until better treatment options are found.

B. Selective Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

Three SNRIs are currently available in the US, venlafaxine XR, duloxetine and desvenlafaxine, and a fourth, milnacipran, is available in Europe and Japan, and was recently approved in the United States for the treatment of fibromyalgia. To date, only venlafaxine XR has published reports for use in PTSD although trials with duloxetine for this purpose are in progress (NCT00583193, NCT00763178). Venlafaxine works by inhibiting pre-synaptic reuptake of both serotonin and NE, but differentially based on the dose (Thase, 2006). In the first study, Davidson et al (2006a) conducted a randomized, double-blind, parallel group three-arm study comparing venlafaxine, sertraline and placebo in adults with PTSD. Venlafaxine and sertraline resulted in similar significant improvement in post-traumatic symptoms over placebo, particularly in the clusters of avoidance/numbing and hyperarousal. Extending the acute-phase of treatment to 24 weeks, Davidson and colleagues (2006b) found venlafaxine XR once again resulted in significant improvements in PTSD symptoms, particularly for re-experiencing and avoidance/numbing symptom clusters and a trend towards significance for improvement in hyperarousal symptoms.

C. Tricyclic Antidepressants (TCAs) and Monoamine Oxidase Inhibitors (MAOIs)

Although the TCAs are less selective in their actions on specific neurotransmitters, their primary mechanism of action involves varying degrees of serotonin and NE reuptake inhibition. MAOIs, on the other hand, work by irreversibly inhibiting the enzyme, monoamine oxidase, normally involved in metabolism of serotonin and NE. Both of these medication classes are generally consigned to second or third-line treatment for anxiety and depressive disorders, mainly due to their adverse event profile and need for dietary restriction (in the case of MAOIs). Nonetheless a few controlled trials of these agents in PTSD although the results are less than compelling. Desipramine, for instance, was found to be helpful for depressive but not for anxiety symptoms in an 8-week placebo controlled cross-over trial (Reist et al., 1989). However, limitations in this trial include the brief duration of active treatment (4 weeks) and the lack of a discrete structured objective measure of post-traumatic symptoms. That desipramine acts primarily by NE reuptake blockade may also have affected treatment outcomes. Similarly, results from an 8-week placebo-controlled trial of amitriptyline showed that active treatment resulted in a degree of improvement in depressive and anxious symptoms, but 64% of the amitriptyline-treated subjects continued to meet criteria for PTSD at the end of the trial (Davidson et al., 1990). Two PTSD-related trials that involve MAOIs also involve TCAs. Two 8-week randomized controlled trials comparing phenelzine, imipramine and placebo in veterans with PTSD have been conducted. As opposed to the results of the earlier TCA trials, both studies in this case concluded that imipramine and phenelzine were effective agents in reducing post-traumatic symptoms compared to placebo, with the latter study finding a more pronounced advantage for the phenelzine-treated group (Frank et al., 1988; Kosten et al., 1991). However, an earlier single double-blind cross-over study of phenelzine and placebo

reported no differences between treatments (Shestatzky et al., 1988). In this case, however, the number of patients was quite small (N=10) and the active treatment period was limited to only 5 weeks which could have impacted the outcome.

D. Other Antidepressant Agents

Bupropion SR is a novel antidepressant agent thought to work primarily by selective NE and dopamine reuptake inhibition. Only one published controlled trial investigating PTSD symptom improvement as a primary outcome exists (Becker et al., 2007). In this case no statistically significant differences were noted in outcomes between the bupropion SR- and the placebo-treated groups. Mirtazapine is an antidepressant agent that enhances both serotonergic and noradrenergic transmission via a dual mechanism of action: blockade of both presynaptic α_2 auto- and α_2 heteroreceptors, as well as antagonism of post-synaptic 5-HT₂ and 5-HT₃ receptors (Gorman et al., 1999). Evidence from a randomized open trial comparing mirtazapine and sertraline suggested mirtazapine has similar efficacy to SSRIs in treating PTSD (Kim et al., 2005). One placebo-controlled trial (N=29) supports this conclusion (Davidson et al., 2003) but these results have not been confirmed using larger samples. Nefazodone, an older antidepressant that is thought to work through post-synaptic 5-HT_{2A} receptor antagonism, inhibition of presynaptic serotonin and NE reuptake, and as α_1 receptor blockade, is now rarely used due to concerns of hepatotoxicity in some patients. However, both open trials and a placebo-controlled trial supported its use for PTSD (Davis et al., 2000; Davis et al., 2004). Similarly, double-blind comparison of nefazodone to sertraline resulted in significant post-traumatic symptom improvement over time with no-between group differences detected (McRae et al., 2004). Theorizing that patients with PTSD displayed hypersensitivity to noradrenergic activation (via presynaptic α_2 autoreceptor blockade), Spivak and colleagues (2006) theorized that reboxetine, a selective noradrenergic reuptake inhibitor, might work to stabilize NE-mediated signaling. In an 8-week double blind randomized controlled trial, they conducted a head-to-head comparison of reboxetine and the SSRI fluvoxamine in 40 individuals with PTSD following an MVA. Both medications had comparable efficacy in significantly reducing post-traumatic symptoms across the three symptom clusters, although more subjects taking reboxetine dropped out early because of side-effects. These results have not been replicated.

E. Anti-Adrenergic Agents

Based on the putative noradrenergic alterations seen in PTSD, several pharmacological agents have been proposed as possible treatments. Clonidine, commonly used as an antihypertensive agent, is a centrally acting α_2 adrenergic agonist that works to decrease sympathetic tone. As such, it was theorized to have potential effects on the hyperarousal symptoms seen in PTSD. However, there is only one published report of clonidine for PTSD, in which it is used as an adjunct to imipramine in the treatment of traumatized Cambodian refugees (Kinzie and Leung, 1989). Although it was suggested to have a role in reduction of nightmares for this population, no controlled trials have been published to substantiate this. Guanfacine, another α_2 adrenergic agonist with a similar mechanism of action, has also been investigated. There are now two negative published double-blind placebo-controlled trials for its use (either as monotherapy or adjunct to existing pharmacological treatment) in combat veterans with chronic PTSD (Davis et al., 2008a; Neylan et al., 2006). In the more recent of these, an additional two month open-extension period followed the 8-week double-blind period and still no benefit was seen.

In contrast, use of the centrally acting selective α_1 antagonist, prazosin, has been more successful. Arguing that α_1 receptor stimulation is linked to sleep disruption, stress-induced disruptions in PFC cognitive processing, and increased release of CRH – all phenomena commonly seen in PTSD (Raskind et al., 2007), investigators theorized that the use of prazosin might result in improvement in the sleep disruptions (e.g. difficulty falling or staying asleep,

trauma-related nightmares) commonly seen in PTSD as well as other post-traumatic symptoms. Three controlled trials have now been published that support the use of prazosin for sleep related disturbances in chronic PTSD (Raskind et al., 2003; Raskind et al., 2007; Taylor et al., 2008) particularly in combat veterans. The principal findings of note from these trials were a shift in dream content from trauma-related nightmares to more “normal”, less distressing content and a considerable increase in total sleep time (>90 minutes).

The use of β -adrenergic antagonists has also been investigated in PTSD, but primarily for a role in the secondary prevention of this disorder. The rationale for these agents is based in part on animal research that found low dose NE injected into the amygdala of rats produced enhanced memory retention; however, this effect was blocked when propranolol was simultaneously administered (Liang et al., 1986). Subsequently, Cahill et al. (1994) demonstrated that a single dose of propranolol administered to healthy humans impaired subsequent recall of an emotionally arousing story but not for an emotionally neutral one, thus lending to support for the theory that memory for emotional experiences involved the β -adrenergic system. These findings were subsequently extended by Reist and colleagues (2001) who conducted a similar experiment in both healthy controls and a sample of patients with PTSD. Once again single-dose propranolol blocked delayed retrieval of the emotionally arousing narrative in both the healthy and PTSD samples. Based on these findings, PTSD researchers theorized that administration of a β -adrenergic antagonist in the peritraumatic period might have a beneficial effect in blocking consolidation of the traumatic memory and thus prevent development of PTSD.

However, results from controlled trials using this agent are conflicted. In the first trial, Pitman and colleagues (2002) provided propranolol or placebo in a double-blind fashion to 41 subjects visiting the emergency room following a traumatic event. Within 6 hours of the traumatic events, subjects received the first dose of study medication – either propranolol (40 mg QID) or placebo for 10 days followed by a 9 day taper period. At one month follow up, there was no significant difference in rates of PTSD between the placebo (6/20) and propranolol group, even if one excluded the notably outlying results of a patient in the latter group (1/10; $p=0.19$, one tailed). However, the results were in part hindered by the notable attrition in the propranolol group during this period. In a subsequent study, Vaiva et al. (2003) compared PTSD development in 11 emergency room patients who agreed to an open 7-day course of propranolol (40 mg TID followed by an 8-12 day taper period) following a traumatic event to 8 similar patients who refused treatment with propranolol, but agreed to participate in the study. At 2 month follow-up, both the rate of PTSD (9% vs. 37.5%, $p=0.012$) and symptom severity were significantly lower in the propranolol-treated group.

In contrast to these results, Stein et al. (2007) conducted a randomized, double-blind, 3-arm parallel-group trial of propranolol, gabapentin, or placebo administered to physically injured trauma patients ($N=48$) within 48 hours of injury. Although the study was somewhat underpowered, the investigators did not see differences in rates of acute stress disorder at one month between groups, nor were there significant differences between groups in rates of PTSD development (propranolol 25%, gabapentin 20%, placebo 25%) at 4-month follow-up. The authors concluded that further research aimed at pharmacoprevention of PTSD was definitely warranted and feasible, though enthusiasm for including these particular pharmacological agents in such trials was limited, based on their findings

Despite the inconsistent evidence, the use of β -adrenergic agents may still hold promise in PTSD. Hopefully, larger controlled trials will resolve its role in secondary prevention and even explore its use either as monotherapy or adjunct therapy to psychological treatments.

F. Anticonvulsants in PTSD

In one of the earlier animal models, behavioural sensitization and kindling was proposed as a mechanism of PTSD. Based on the phenomenon seen in PTSD patients that initially cue-triggered memory flashbacks replay over time and eventually occur spontaneously without a precipitant, Post and colleagues theorized that a kindling model might be at play (Post et al., 1997). They suggested that recurrent biological or psychological stresses could result in cumulative bioelectric changes, particularly in the amygdala, leading to changes in normal neuronal and limbic sensitization (seen in Lipper et al., 1986). As such, anticonvulsant medications, with their putative anti-kindling effects, have been investigated for PTSD. Although the bulk of the evidence for use of these agents (which include carbamazepine, valproic acid, lamotrigine, gabapentin, oxcarbazepine, vigabatrin, tiagabine, pregabalin, and levetiracetam) stems from case series and open trials (Berlant and van Kammen, 2002; Berlant, 2004; Clark et al., 1999; Fesler, 1991; Kinrys et al., 2006; Otte et al., 2004), a limited number of controlled trials have also been conducted.

Lamotrigine is an anticonvulsant medication with antidepressant effects that is thought to limit glutamate release by inhibition of calcium channels and voltage-dependent sodium channels (Garakani et al., 2006). In the first RCT of an anticonvulsant for PTSD, 15 subjects were randomized to 12 weeks of double-blind treatment with lamotrigine or placebo (Hertzberg et al., 1999). Particular improvements were noted in re-experiencing and the avoidance/numbing clusters of symptoms although these results have yet to be replicated in a larger trial. Tiagabine, an anticonvulsant presumed to work by inhibition of presynaptic GABA reuptake, has been investigated in two controlled trials. The first (Connor et al., 2006) study was a relapse prevention trial which involved open label treatment with tiagabine for 12 weeks, at which time responders were randomized to double-blind continuation treatment or placebo for a further 12 weeks. Although most patients maintained their symptom improvement, and no statistical differences were detected in relapse rates between the two groups at endpoint, there was a greater trend toward remission in the tiagabine group ($p < 0.08$). However, a significantly larger double-blind RCT trial (Davidson et al., 2007) failed to find any differences between tiagabine and placebo following 12 weeks of treatment. A more recent trial comparing 8 weeks of double-blind divalproex treatment similarly failed to find differences between active medication and placebo in this group of combat veterans with chronic PTSD (Davis et al., 2008b). Topiramate is the other agent that been investigated in PTSD. A recent trial of double-blind topiramate augmentation therapy did not show significant benefits over placebo after 7 weeks of treatment (Lindley et al., 2007). On the other hand, Tucker et al. (2007) did find evidence of benefit for topiramate monotherapy in improving re-experiencing type symptom in a civilian population with PTSD. However, overall improvement in PTSD symptoms was not significantly different between subjects receiving active treatment and those receiving placebo. What is striking about the results of trials using anticonvulsants in PTSD is the lack of consistent results. Factors that may contribute to this include the relative lack of controlled investigations for these agents as well as, with the exception of one of the tiagabine trials (Davidson et al., 2007), the limited sample sizes that preclude definitive conclusions of the efficacy or lack thereof for anticonvulsants in PTSD.

G. Benzodiazepines

Benzodiazepines, as a class, work on the CNS via their effects on the GABA_A receptors. Activation at the special benzodiazepine receptor site on the GABA_A receptor promotes enhanced activity of the inhibitory neurotransmitter γ -aminobutyric acid (GABA), thus resulting in various effects including: anxiolysis, sedation, muscle relaxation, cognitive effects, and anticonvulsant actions. These functions, particularly the first two would seem to have particular benefits for PTSD, yet there are surprisingly few controlled trials of BZDs for this population. In one of the earlier trials, Braun et al. (1990) used a double-blind cross-over design

comparing 5 weeks each of alprazolam compared to placebo treatment. Modest improvement in anxiety symptoms was seen during treatment with alprazolam but core PTSD symptoms remained much unchanged. Similarly, Cates and colleagues (2004) were unable to find any benefits for clonazepam following a single-blind cross-over study comparing clonazepam and placebo for sleep related disturbances. Following positive results using temazepam in a case series of 7 patients with PTSD (Mellman et al., 1998), a placebo-controlled study by Mellman et al. (2002) was unable to find benefit for early intervention with temazepam for patients identified with early post-traumatic stress symptoms and sleep disturbance. Of note, the treatment period was quite brief (7 days). The results of these trials notwithstanding, BZDs have been commonly used in clinical practice as adjunctive medications for individuals with PTSD. Their role in this case has been largely directed towards symptomatic treatment of residual sleep disturbance, irritability, and other hyperarousal symptoms (Mohamed and Rosenheck, 2008). Large, adequately powered clinical trials confirming their utility as adjunctive agents are needed.

H. Atypical Antipsychotics

The use of atypical antipsychotics, particularly as adjunctive medication, for treatment of mood and anxiety disorders is increasingly common in clinical practice. These drugs differ from the more typical antipsychotics due to their actions on various neurotransmitter systems apart from dopamine. Specific actions common to these medications include antagonism of D₂, 5-HT₂, and α_1 adrenergic receptors as well as antihistaminic activity, with partial 5-HT_{1A} effects seen in particular atypicals (Hamner and Robert, 2005). Dopaminergic dysfunction has been implicated in the presence of psychotic symptoms that are sometimes seen in PTSD, but has also been proposed to play a role in hyperarousal symptoms such as irritability, hypervigilance and exaggerated startle (Weiss, 2007). On the basis of the multiple neurotransmitters affected in PTSD and the presumed actions of atypicals, a theoretical rationale exists to support their efficacy in treatment of this disorder.

However, only a small number of controlled trials have investigated the adjunctive use of these drugs (which include olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole) in PTSD, and even fewer have explored their utility as monotherapy. Stein et al. (2002) found some benefit for adjunctive olanzapine in combat-related PTSD resistant to SSRI treatment. In trials of augmentation with risperidone, one trial found evidence of modest improvement in psychotic symptoms associated with PTSD as well as a trend towards significant improvement in re-experiencing type symptoms (Hamner et al., 2003), whereas a later trial noted significant improvements in PTSD symptoms overall and in the hyperarousal symptom cluster but not in re-experiencing or avoidance/numbing symptoms (Bartzokis et al., 2005). Only two published RCTS have reported results on atypical antipsychotics as monotherapy for PTSD. Butterfield et al. (2001) failed to find benefits in their group of PTSD patients randomized to olanzapine or placebo for 10 weeks, but a later pilot study (Padala et al., 2006) did find support for risperidone monotherapy in women with PTSD related to sexual assault and domestic abuse. Validation of these results is needed with larger trials given the small sample sizes used in both trials above.

I. Other agents

One model for the development of PTSD symptoms over time suggests that a positive feedback loop emerges in which traumatic memories are constantly retrieved (following exposure to traumatic triggers), replayed and thus reconsolidated (Pitman, 1989). If indeed exposure to elevated levels of GCs impairs delayed memory retrieval, it is possible that administration of exogenous GCs may interrupt this positive feedback loop of replayed traumatic memories allowing individuals to encode and consolidate more recent, non-traumatic memories, resulting in gradual fear extinction. Much of the current psychopharmacological research investigating

GC use in PTSD has focused on administering GCs in the peri-traumatic period to prevent the development of subsequent post-traumatic pathology; however, only a single placebo-controlled trial of cortisol exists as a treatment for PTSD (Aerni et al., 2004). In this 3 month study with a randomized, double-blind, placebo-controlled, cross-over design, three individuals with chronic PTSD were treated with 1 month of oral cortisol (10 mg daily) and two months of placebo. Although the authors noted low-dose cortisol was associated with a degree of improvement in re-experiencing and avoidance-type symptoms, two of the patients were on concurrent sleep medications and one continued to receive psychotherapy throughout the trial. These limitations and the small sample size restrict further conclusions.

D-cycloserine (DCS), a partial agonist at the NMDA receptor has also been investigated as a potential treatment for PTSD. Arguing that the presence of flashbacks and intrusive memories in PTSD may be a function of extinction failure, and that learning and memory are both glutamate-dependent processes, Heresco-Levy and colleagues (2002) argued that enhancing glutamate transmission could facilitate the learning of new memories to replace the traumatic ones. To that end, they conducted a randomized controlled trial of DCS with a crossover design in 11 patients with chronic PTSD. During the active treatment period (4 weeks each), DCS was associated with significant improvement of numbing/avoidance symptoms and certain neurocognitive measures, however, similar improvements were also seen during treatment with placebo. Furthermore, 6 of the original 11 participants were on concomitant antidepressant treatment at baseline. Thus larger parallel group studies in future may be useful to clarify the utility of DCS as either a monotherapy or antidepressant adjunct.

Discussion

Literature contributing to a better understanding of the neurobiological dysregulations that occur in PTSD is appearing at a rapid rate. Evidence from translational research studies is providing greater insight into the underlying neural circuitry and neurotransmitters implicated in the pathophysiology of this illness. From these studies, evidence of dysfunction in NE, serotonin, glutamate and HPA axis systems predominates, with particular emphasis placed on specific neural structures, such as the amygdala, hippocampus and mPFC. Altered neurotransmitter levels themselves may serve to produce certain post-traumatic symptoms including hypervigilance, exaggerated startle, sleep disturbance and irritability. In parallel, traumatic stress may serve to disengage the regular inhibitory tone of the mPFC, thus amplifying the fear conditioning process mediated by the amygdala in the context of elevated catecholamine and GC levels and enhancing consolidation of traumatic memories in the hippocampus. These effects, in the presence of increased arousal, may serve to initiate a positive feedback loop in which the triggers associated with the event precipitate intrusive memories which are in turn reconsolidated further, thereby strengthening aversive associations and leading to both re-experiencing symptoms and accompanying avoidance and numbing behaviors, along with further arousal.

Developing rational pharmacotherapeutic strategies that use agents targeting not only the clinical symptoms but also the causal mechanisms underlying these symptoms should be a goal of future research. Although the various medication classes described above provide an initial foundation for this, the presence of residual symptoms following treatment with these drugs is a common clinical occurrence and so highlights the need to develop novel agents with greater efficacy. Several investigators have conducted promising pilot studies involving innovative agents (e.g. DCS, cortisol) that have yet to be replicated using larger samples and more stringent methodology. Other agents that show promise from a theoretical perspective but have yet to be investigated in a PTSD population include CRH antagonists, NMDA modulators, neurokinin-1 antagonists and neuropeptide Y enhancers (Vermetten and Bremner, 2002). Future clinical trials may also incorporate translational research methodologies, such as

genetics or neuroimaging, to further personalize medication options for particular individuals. In one intriguing study, Lawford and colleagues (2003) reported that combat veterans with PTSD who were in possession of the DRD2 A1 allele were more likely to show improvement in social functioning following treatment with paroxetine. Investigations of possible genetic markers mediating treatment response to different psychotropic medications will be helpful in rapid, focused symptom relief. In a similar vein, the idea of neuroimaging as a future clinical tool to predict treatment response in psychiatric illness is gaining increasing credence (Evans et al., 2006) with a small body of research already available for predictors of response in patients with depression or OCD (Brody et al., 1998; Little et al., 1996; Mayberg et al., 1997; Saxena et al., 1999) that could, possibly, be extended to those with PTSD.

In summary, the pathophysiology of PTSD implicates many different neurotransmitter systems as well as different neuroanatomical circuits. While delineation of these chemical, structural, and circuitry abnormalities is of critical importance, these will take time to fully elucidate. In the interim, it is crucially important to pursue parallel lines of research focusing on clinical treatment which will include rigorous investigation of existing classes of psychotropics with a theoretical basis for efficacy in PTSD treatment. Use of sophisticated scientific techniques, including genetic analyses and neuroimaging, will hopefully enhance these investigations and also lead to the development of additional pharmacologic options.

Reference List

- 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 Psychiatry* 2004;161:1488–1490. [PubMed: 15285979]
- Arce E, Simmons AN, Lovero KL, Stein MB, Paulus MP. Escitalopram effects on insula and amygdala BOLD activation during emotional processing. *Psychopharmacology (Berl)* 2008;196:661–672. [PubMed: 18058090]
- Armanini MP, Hutchins C, Stein BA, Sapolsky RM. Glucocorticoid endangerment of hippocampal neurons is NMDA-receptor dependent. *Brain Res* 1990;532:7–12. [PubMed: 2149301]
- Arnsten AF. Catecholamine regulation of the prefrontal cortex. *J Psychopharmacol* 1997;11:151–162. [PubMed: 9208378]
- Baker JD, Azorlosa JL. The NMDA antagonist MK-801 blocks the extinction of Pavlovian fear conditioning. *Behav Neurosci* 1996;110:618–620. [PubMed: 8889007]
- Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. *Biol Psychiatry* 2005;57:474–479. [PubMed: 15737661]
- Becker ME, Hertzberg MA, Moore SD, Dennis MF, Bukenya DS, Beckham JC. A placebo-controlled trial of bupropion SR in the treatment of chronic posttraumatic stress disorder. *J Clin Psychopharmacol* 2007;27:193–197. [PubMed: 17414245]
- Berlant J, van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. *J Clin Psychiatry* 2002;63:15–20. [PubMed: 11838620]
- Berlant JL. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. *BMC Psychiatry* 2004;4:24. [PubMed: 15315714]
- Binneman B, Feltner D, Kolluri S, Shi Y, Qiu R, Stiger T. A 6-week randomized, placebo-controlled trial of CP-316,311 (a selective CRH1 antagonist) in the treatment of major depression. *Am J Psychiatry* 2008;165:617–620. [PubMed: 18413705]
- Bonne O, Brandes D, Segman R, Pitman RK, Yehuda R, Shalev AY. Prospective evaluation of plasma cortisol in recent trauma survivors with posttraumatic stress disorder. *Psychiatry Res* 2003;119:171–175. [PubMed: 12860372]
- Boscarino JA. Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: findings and clinical implications. *J Consult Clin Psychol* 1996;64:191–201. [PubMed: 8907099]

- Bouton ME, Bolles RC. Role of conditioned contextual stimuli in reinstatement of extinguished fear. *J Exp Psychol Anim Behav Process* 1979;5:368–378. [PubMed: 528893]
- Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, Farfel GM. Efficacy and safety of sertraline 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 Psychiatry* 1990;51:236–238. [PubMed: 2189869]
- Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 1995;152:973–981. [PubMed: 7793467]
- Bremner JD. Does stress damage the brain? *Biol Psychiatry* 1999;45:797–805. [PubMed: 10202566]
- 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]
- Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P. Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. *Arch Gen Psychiatry* 1998;55:626–632. [PubMed: 9672053]
- Brody AL, Saxena S, Schwartz JM, Stoessel PW, Maidment K, Phelps ME, Baxter LR Jr. FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. *Psychiatry Res* 1998;84:1–6. [PubMed: 9870412]
- Bruce SE, Weisberg RB, Dolan RT, Machan JT, Kessler RC, Manchester G, Culpepper L, Keller MB. Trauma and Posttraumatic Stress Disorder in Primary Care Patients Prim Care Companion. *J Clin Psychiatry* 2001;3:211–217.
- Buchanan TW, Tranel D, Adolphs R. Impaired memory retrieval correlates with individual differences in cortisol response but not autonomic response. *Learn Mem* 2006;13:382–387. [PubMed: 16741288]
- 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]
- Cahill L, Prins B, Weber M, McGaugh JL. Beta-adrenergic activation and memory for emotional events. *Nature* 1994;371:702–704. [PubMed: 7935815]
- Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, Wu J, McGaugh JL. Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci U S A* 1996;93:8016–8021. [PubMed: 8755595]
- Cammarota M, Bevilacqua LR, Bonini JS, Rossatto JI, Medina JH, Izquierdo N. Hippocampal glutamate receptors in fear memory consolidation. *Neurotox Res* 2004;6:205–212. [PubMed: 15325959]
- Cates ME, Bishop MH, Davis LL, Lowe JS, Woolley TW. Clonazepam for treatment of sleep disturbances associated with combat-related posttraumatic stress disorder. *Ann Pharmacother* 2004;38:1395–1399. [PubMed: 15252193]
- Chambers RA, Bremner JD, Moghaddam B, Southwick SM, Charney DS, Krystal JH. Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. *Semin Clin Neuropsychiatry* 1999;4:274–281. [PubMed: 10553033]
- Charney DS. Neuroanatomical circuits modulating fear and anxiety behaviors. *Acta Psychiatr Scand Suppl* 2003;38–50. [PubMed: 12950435]
- Clark RD, Canive JM, Calais LA, Qualls CR, Tuason VB. Divalproex in posttraumatic stress disorder: an open-label clinical trial. *J Trauma Stress* 1999;12:395–401. [PubMed: 10378177]
- Committee on the treatment of posttraumatic stress disorder. National Academies Press; Washington DC: 2007. Treatment of PTSD: An assessment of the evidence Institute of Medicine. For full text of report please see <http://www.nap.edu>
- Connor KM, Sutherland SM, Tupler LA, Malik ML, Davidson JR. Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. *Br J Psychiatry* 1999;175:17–22. [PubMed: 10621763]
- Connor KM, Davidson JR, Weisler RH, Zhang W, Abraham K. Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. *Psychopharmacology (Berl)* 2006;184:21–25. [PubMed: 16341846]

- Davidson J, Kudler H, Smith R, Mahorney SL, Lipper S, Hammett E, Saunders WB, Cavenar JO Jr. Treatment of posttraumatic stress disorder with amitriptyline and placebo. *Arch Gen Psychiatry* 1990;47:259–266. [PubMed: 2407208]
- Davidson JR, Weisler RH, Malik M, Tupler LA. Fluvoxamine in civilians with posttraumatic stress disorder. *J Clin Psychopharmacol* 1998;18:93–95. [PubMed: 9472854]
- Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry* 2001a;58:485–492. [PubMed: 11343529]
- Davidson J, Pearlstein T, Lonnberg P, Brady KT, Rothbaum B, Bell J, Maddock R, Hegel MT, Farfel G. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. *Am J Psychiatry* 2001b;158:1974–1981. [PubMed: 11729012]
- 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 sertraline- and placebo-controlled study. *J Clin Psychopharmacol* 2006a;26:259–267. [PubMed: 16702890]
- Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, Ahmed S, Pedersen R, Musgnung J. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 2006b;63:1158–1165. [PubMed: 17015818]
- Davidson JR, Brady K, Mellman TA, Stein MB, Pollack MH. The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. *J Clin Psychopharmacol* 2007;27:85–88. [PubMed: 17224720]
- Davis LL, Nugent AL, Murray J, Kramer GL, Petty F. Nefazodone treatment for chronic posttraumatic stress disorder: an open trial. *J Clin Psychopharmacol* 2000;20:159–164. [PubMed: 10770453]
- Davis LL, Jewell ME, Ambrose S, Farley J, English B, Bartolucci A, Petty F. A placebo-controlled study of nefazodone for the treatment of chronic posttraumatic stress disorder: a preliminary study. *J Clin Psychopharmacol* 2004;24:291–297. [PubMed: 15118483]
- Davis LL, Ward C, Rasmussen A, Newell JM, Frazier E, Southwick SM. A placebo-controlled trial of guanfacine for the treatment of posttraumatic stress disorder in veterans. *Psychopharmacol Bull* 2008a;41:8–18. [PubMed: 18362867]
- Davis LL, Davidson JR, Ward LC, Bartolucci A, Bowden CL, Petty F. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. *J Clin Psychopharmacol* 2008b;28:84–88. [PubMed: 18204347]
- Davis M, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry* 2006;60:369–375. [PubMed: 16919524]
- De Bellis MD, Lefter L, Trickett PK, Putnam FW Jr. Urinary catecholamine excretion in sexually abused girls. *J Am Acad Child Adolesc Psychiatry* 1994;33:320–327. [PubMed: 8169176]
- De Boer M, Op d V, Falger PJ, Hovens JE, De Groen JH, Van Duijn H. Fluvoxamine treatment for chronic PTSD: a pilot study. *Psychother Psychosom* 1992;57:158–163. [PubMed: 1410191]
- Delahanty DL, Raimonde AJ, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. *Biol Psychiatry* 2000;48:940–947. [PubMed: 11074232]
- Delahanty DL, Raimonde AJ, Spoonster E, Cullado M. Injury severity, prior trauma history, urinary cortisol levels, and acute PTSD in motor vehicle accident victims. *J Anxiety Disord* 2003;17:149–164. [PubMed: 12614659]
- Delahanty DL, Nugent NR, Christopher NC, Walsh M. Initial urinary epinephrine and cortisol levels predict acute PTSD symptoms in child trauma victims. *Psychoneuroendocrinology* 2005;30:121–128. [PubMed: 15471610]
- Dolcos F, LaBar KS, Cabeza R. Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* 2004;42:855–863. [PubMed: 15182723]
- Duman RS, Nakagawa S, Malberg J. Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology* 2001;25:836–844. [PubMed: 11750177]

- Dunn AJ, File SE. Corticotropin-releasing factor has an anxiogenic action in the social interaction test. *Horm Behav* 1987;21:193–202. [PubMed: 2886414]
- English BA, Jewell M, Jewell G, Ambrose S, Davis LL. Treatment of chronic posttraumatic stress disorder in combat veterans with citalopram: an open trial. *J Clin Psychopharmacol* 2006;26:84–88. [PubMed: 16415713]
- Escalona R, Canive JM, Calais LA, Davidson JR. Fluvoxamine treatment in veterans with combat-related post-traumatic stress disorder. *Depress Anxiety* 2002;15:29–33. [PubMed: 11816050]
- Evans KC, Dougherty DD, Pollack MH, Rauch SL. Using neuroimaging to predict treatment response in mood and anxiety disorders. *Ann Clin Psychiatry* 2006;18:33–42. [PubMed: 16517451]
- Evenden J. Impulsivity: a discussion of clinical and experimental findings. *J Psychopharmacol* 1999;13:180–192. [PubMed: 10475725]
- 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]
- Fesler FA. Valproate in combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1991;52:361–364. [PubMed: 1894587]
- 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]
- Frans O, Rimmo PA, Aberg L, Fredrikson M. Trauma exposure and post-traumatic stress disorder in the general population. *Acta Psychiatr Scand* 2005;111:291–299. [PubMed: 15740465]
- Gabr RW, Birkle DL, Azzaro AJ. Stimulation of the amygdala by glutamate facilitates corticotropin-releasing factor release from the median eminence and activation of the hypothalamic-pituitary-adrenal axis in stressed rats. *Neuroendocrinology* 1995;62:333–339. [PubMed: 8544946]
- Ganzel BL, Eckenrode JJ, Kim P, Wethington E, Horowitz E, Temple E. Salivary cortisol levels and mood vary by lifetime trauma exposure in a sample of healthy women. *J Trauma Stress* 2007;20:689–699. [PubMed: 17955533]
- Garakani A, Mathew SJ, Charney DS. Neurobiology of anxiety disorders and implications for treatment. *Mt Sinai J Med* 2006;73:941–949. [PubMed: 17195879]
- Geraciotti TD Jr, Baker DG, Ekhtator NN, West SA, Hill KK, Bruce AB, Schmidt D, Rounds-Kugler B, Yehuda R, Keck PE Jr, Kasckow JW. CSF norepinephrine concentrations in posttraumatic stress disorder. *Am J Psychiatry* 2001;158:1227–1230. [PubMed: 11481155]
- Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci* 2002;5:1242–1247. [PubMed: 12379862]
- Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, Najarian LM, Fairbanks LA. Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. *Am J Psychiatry* 1996;153:929–934. [PubMed: 8659616]
- Gorman JM. Mirtazapine: clinical overview. *J Clin Psychiatry* 1999;60:9–13. [PubMed: 10446735]
- Gutman DA, Owens MJ, Skelton KH, Thrivikraman KV, Nemeroff CB. The corticotropin-releasing factor1 receptor antagonist R121919 attenuates the behavioral and endocrine responses to stress. *J Pharmacol Exp Ther* 2003;304:874–880. [PubMed: 12538845]
- 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]
- Hamner MB, Robert S. Emerging roles for atypical antipsychotics in chronic post-traumatic stress disorder. *Expert Rev Neurother* 2005;5:267–275. [PubMed: 15853496]
- Hauger RL, Risbrough V, Brauns O, Dautzenberg FM. Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: new molecular targets. *CNS Neurol Disord Drug Targets* 2006;5:453–479. [PubMed: 16918397]
- Herbert J, Goodyer IM, Grossman AB, Hastings MH, de Kloet ER, Lightman SL, Lupien SJ, Roozendaal B, Seckl JR. Do corticosteroids damage the brain? *J Neuroendocrinol* 2006;18:393–411. [PubMed: 16684130]
- Heresco-Levy U, Kremer I, Javitt DC, Goichman R, Reshef A, Blararu M, Cohen T. Pilot-controlled trial of D-cycloserine for the treatment of post-traumatic stress disorder. *Int J Neuropsychopharmacol* 2002;5:301–307. [PubMed: 12466030]

- Hertzberg MA, Butterfield MI, Feldman ME, Beckham JC, Sutherland SM, Connor KM, Davidson JR. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry* 1999;45:1226–1229. [PubMed: 10331117]
- Hertzberg MA, Feldman ME, Beckham JC, Kudler HS, Davidson JR. Lack of efficacy for fluoxetine in PTSD: a placebo controlled trial in combat veterans. *Ann Clin Psychiatry* 2000;12:101–105. [PubMed: 10907802]
- Hikichi T, Akiyoshi J, Yamamoto Y, Tsutsumi T, Isogawa K, Nagayama H. Suppression of conditioned fear by administration of CRF receptor antagonist CP-154,526. *Pharmacopsychiatry* 2000;33:189–193. [PubMed: 11071021]
- Hurlemann R. Noradrenergic-glucocorticoid mechanisms in emotion-induced amnesia: from adaptation to disease. *Psychopharmacology (Berl)* 2008;197:13–23. [PubMed: 18038126]
- Jensen CF, Keller TW, Peskind ER, McFall ME, Veith RC, Martin D, Wilkinson CW, Raskind MA. Behavioral and neuroendocrine responses to sodium lactate infusion in subjects with posttraumatic stress disorder. *Am J Psychiatry* 1997;154:266–268. [PubMed: 9016280]
- Jensen JB, Jessop DS, Harbuz MS, Mork A, Sanchez C, Mikkelsen JD. Acute and long-term treatments with the selective serotonin reuptake inhibitor citalopram modulate the HPA axis activity at different levels in male rats. *J Neuroendocrinol* 1999;11:465–471. [PubMed: 10336728]
- Jezova D, Tokarev D, Rusnak M. Endogenous excitatory amino acids are involved in stress-induced adrenocorticotropin and catecholamine release. *Neuroendocrinology* 1995;62:326–332. [PubMed: 8544945]
- Joca SR, Ferreira FR, Guimaraes FS. Modulation of stress consequences by hippocampal monoaminergic, glutamatergic and nitroergic neurotransmitter systems. *Stress* 2007;10:227–249. [PubMed: 17613938]
- Kensinger EA, Corkin S. Two routes to emotional memory: distinct neural processes for valence and arousal. *Proc Natl Acad Sci U S A* 2004;101:3310–3315. [PubMed: 14981255]
- Kent JM, Coplan JD, Gorman JM. Clinical utility of the selective serotonin reuptake inhibitors in the spectrum of anxiety. *Biol Psychiatry* 1998;44:812–824. [PubMed: 9807637]
- 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* 2005a;62:593–602. [PubMed: 15939837]
- Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005b;62:617–627. [PubMed: 15939839]
- Kilpatrick L, Cahill L. Amygdala modulation of parahippocampal and frontal regions during emotionally influenced memory storage. *Neuroimage* 2003;20:2091–2099. [PubMed: 14683713]
- Kim W, Pae CU, Chae JH, Jun TY, Bahk WM. The effectiveness of mirtazapine in the treatment of post-traumatic stress disorder: a 24-week continuation therapy. *Psychiatry Clin Neurosci* 2005;59:743–747. [PubMed: 16401254]
- Kinrys G, Wygant LE, Pardo TB, Melo M. Levetiracetam for treatment-refractory posttraumatic stress disorder. *J Clin Psychiatry* 2006;67:211–214. [PubMed: 16566615]
- Kinzie JD, Leung P. Clonidine in Cambodian patients with posttraumatic stress disorder. *J Nerv Ment Dis* 1989;177:546–550. [PubMed: 2769247]
- Kosten TR, Mason JW, Giller EL, Ostroff RB, Harkness L. Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. *Psychoneuroendocrinology* 1987;12:13–20. [PubMed: 3588809]
- Kosten TR, Frank JB, Dan E, McDougall CJ, Giller EL Jr. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. *J Nerv Ment Dis* 1991;179:366–370. [PubMed: 2051152]
- Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry* 1994;51:199–214. [PubMed: 8122957]
- Lawford BR, McD YR, Noble EP, Kann B, Arnold L, Rowell J, Ritchie TL. D2 dopamine receptor gene polymorphism: paroxetine and social functioning in posttraumatic stress disorder. *Eur Neuropsychopharmacol* 2003;13:313–320. [PubMed: 12957328]

- Lemieux AM, Coe CL. Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. *Psychosom Med* 1995;57:105–115. [PubMed: 7792368]
- Liang KC, Juler RG, McGaugh JL. Modulating effects of posttraining epinephrine on memory: involvement of the amygdala noradrenergic system. *Brain Res* 1986;368:125–133. [PubMed: 3955350]
- Lindley SE, Carlson EB, Benoit M. Basal and dexamethasone suppressed salivary cortisol concentrations in a community sample of patients with posttraumatic stress disorder. *Biol Psychiatry* 2004;55:940–945. [PubMed: 15110738]
- Lindley SE, Carlson EB, Hill K. A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. *J Clin Psychopharmacol* 2007;27:677–681. [PubMed: 18004136]
- Lipper S, Davidson JR, Grady TA, Edinger JD, Hammett EB, Mahorney SL, Cavenar JO Jr. Preliminary study of carbamazepine in post-traumatic stress disorder. *Psychosomatics* 1986;27:849–854. [PubMed: 3543990]
- Lipschitz DS, Rasmusson AM, Yehuda R, Wang S, Anyan W, Gueogueieva R, Grilo CM, Fehon DC, Southwick SM. Salivary cortisol responses to dexamethasone in adolescents with posttraumatic stress disorder. *J Am Acad Child Adolesc Psychiatry* 2003;42:1310–1317. [PubMed: 14566168]
- Little JT, Ketter TA, Kimbrell TA, Danielson A, Benson B, Willis MW, Post RM. Venlafaxine or bupropion responders but not nonresponders show baseline prefrontal and paralimbic hypometabolism compared with controls. *Psychopharmacol Bull* 1996;32:629–635. [PubMed: 8993084]
- Lo SC, Ravaldi C, Cabras PL, Faravelli C, Ricca V. Stress, hypothalamic-pituitary-adrenal axis and eating disorders. *Neuropsychobiology* 2008;57:95–115. [PubMed: 18552511]
- Londborg PD, Hegel MT, Goldstein S, Goldstein D, Himmelhoch JM, Maddock R, Patterson WM, Rausch J, Farfel GM. Sertraline treatment of posttraumatic stress disorder: results of 24 weeks of open-label continuation treatment. *J Clin Psychiatry* 2001;62:325–331. [PubMed: 11411812]
- Lowy MT, Wittenberg L, Yamamoto BK. Effect of acute stress on hippocampal glutamate levels and spectrin proteolysis in young and aged rats. *J Neurochem* 1995;65:268–274. [PubMed: 7790870]
- Maren S. Long-term potentiation in the amygdala: a mechanism for emotional learning and memory. *Trends Neurosci* 1999;22:561–567. [PubMed: 10542437]
- Marmar CR, Schoenfeld F, Weiss DS, Metzler T, Zatzick D, Wu R, Smiga S, Tecott L, Neylan T. Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. *J Clin Psychiatry* 1996;57:66–70. [PubMed: 8698684]
- Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 2001;158:1982–1988. [PubMed: 11729013]
- Martenyi F, Brown EB, Zhang H, Prakash A, Koke SC. Fluoxetine versus placebo in posttraumatic stress disorder. *J Clin Psychiatry* 2002;63:199–206. [PubMed: 11926718]
- 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]
- Martenyi F, Brown EB, Caldwell CD. Failed efficacy of fluoxetine in the treatment of posttraumatic stress disorder: results of a fixed-dose, placebo-controlled study. *J Clin Psychopharmacol* 2007;27:166–170. [PubMed: 17414240]
- Martins AP, Marras RA, Guimaraes FS. Anxiogenic effect of corticotropin-releasing hormone in the dorsal periaqueductal grey. *Neuroreport* 1997;8:3601–3604. [PubMed: 9427334]
- Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L. Urinary free-cortisol levels in posttraumatic stress disorder patients. *J Nerv Ment Dis* 1986;174:145–149. [PubMed: 3950596]
- Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT. Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 1997;8:1057–1061. [PubMed: 9141092]
- McEwen BS. Possible mechanisms for atrophy of the human hippocampus. *Mol Psychiatry* 1997;2:255–262. [PubMed: 9152991]
- McFall ME, Veith RC, Murburg MM. Basal sympathoadrenal function in posttraumatic distress disorder. *Biol Psychiatry* 1992;31:1050–1056. [PubMed: 1511075]

- McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. *Ann N Y Acad Sci* 1997;821:437–441. [PubMed: 9238224]
- McRae AL, Brady KT, Mellman TA, Sonne SC, Killeen TK, Timmerman MA, Bayles-Dazet W. Comparison of nefazodone and sertraline for the treatment of posttraumatic stress disorder. *Depress Anxiety* 2004;19:190–196. [PubMed: 15129422]
- Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *Br J Psychiatry* 2007;191:387–392. [PubMed: 17978317]
- Mellman TA, Kumar A, Kulick-Bell R, Kumar M, Nolan B. Nocturnal/daytime urine noradrenergic measures and sleep in combat-related PTSD. *Biol Psychiatry* 1995;38:174–179. [PubMed: 7578660]
- Mellman TA, Byers PM, Augenstein JS. Pilot evaluation of hypnotic medication during acute traumatic stress response. *J Trauma Stress* 1998;11:563–569. [PubMed: 9690193]
- Mellman TA, Bustamante V, David D, Fins AI. Hypnotic medication in the aftermath of trauma. *J Clin Psychiatry* 2002;63:1183–1184. [PubMed: 12530420]
- Milliken CS, Auchterlonie JL, Hoge CW. Longitudinal assessment of mental health problems among active and reserve component soldiers returning from the Iraq war. *JAMA* 2007;298:2141–2148. [PubMed: 18000197]
- Miserendino MJ, Sananes CB, Melia KR, Davis M. Blocking of acquisition but not expression of conditioned fear-potentiated startle by NMDA antagonists in the amygdala. *Nature* 1990;345:716–718. [PubMed: 1972778]
- Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. *J Clin Psychiatry* 2008;69:959–965. [PubMed: 18588361]
- Monti JM, Jantos H. The roles of dopamine and serotonin, and of their receptors, in regulating sleep and waking. *Prog Brain Res* 2008;172:625–646. [PubMed: 18772053]
- Morgan CA III, Southwick SM, Grillon C, Davis M, Krystal JH, Charney DS. Yohimbine-facilitated acoustic startle reflex in humans. *Psychopharmacology (Berl)* 1993;110:342–346. [PubMed: 7831429]
- Murburg MM, McFall ME, Lewis N, Veith RC. Plasma norepinephrine kinetics in patients with posttraumatic stress disorder. *Biol Psychiatry* 1995;38:819–825. [PubMed: 8750041]
- Nemeroff CB, Owens MJ. Pharmacologic differences among the SSRIs: focus on monoamine transporters and the HPA axis. *CNS Spectr* 2004;9:23–31. [PubMed: 15181382]
- 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]
- Oquendo MA, Echavarría G, Galfalvy HC, Grunebaum MF, Burke A, Barrera A, Cooper TB, Malone KM, John MJ. Lower cortisol levels in depressed patients with comorbid post-traumatic stress disorder. *Neuropsychopharmacology* 2003;28:591–598. [PubMed: 12629542]
- Otte C, Wiedemann K, Yassouridis A, Kellner M. Valproate monotherapy in the treatment of civilian patients with non-combat-related posttraumatic stress disorder: an open-label study. *J Clin Psychopharmacol* 2004;24:106–108. [PubMed: 14709964]
- 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]
- Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends Neurosci* 2008;31:464–468. [PubMed: 18675469]
- Parker KJ, Schatzberg AF, Lyons DM. Neuroendocrine aspects of hypercortisolism in major depression. *Horm Behav* 2003;43:60–66. [PubMed: 12614635]
- Peskind ER, Veith RC, Dorsa DM, Gumbrecht G, Raskind MA. Yohimbine increases cerebrospinal fluid and plasma norepinephrine but not arginine vasopressin in humans. *Neuroendocrinology* 1989;50:286–291. [PubMed: 2552342]
- Pitman RK. Post-traumatic stress disorder, hormones, and memory. *Biol Psychiatry* 1989;26:221–223. [PubMed: 2545287]

- Pitman RK, Orr SP. Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. *Biol Psychiatry* 1990;27:245–247. [PubMed: 2294983]
- 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 Psychiatry* 2002;51:189–192. [PubMed: 11822998]
- Post RM, Weiss SR, Smith M, Li H, McCann U. Kindling versus quenching. Implications for the evolution and treatment of posttraumatic stress disorder. *Ann N Y Acad Sci* 1997;821:285–295. [PubMed: 9238212]
- 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 Psychiatry* 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]
- Reist C, Kauffmann CD, Haier RJ, Sangdahl C, DeMet EM, Chicz-DeMet A, Nelson JN. A controlled trial of desipramine in 18 men with posttraumatic stress disorder. *Am J Psychiatry* 1989;146:513–516. [PubMed: 2648867]
- Reist C, Kauffmann CD, Chicz-Demet A, Chen CC, Demet EM. REM latency, dexamethasone suppression test, and thyroid releasing hormone stimulation test in posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 1995;19:433–443. [PubMed: 7624494]
- Reist C, Duffy JG, Fujimoto K, Cahill L. beta-Adrenergic blockade and emotional memory in PTSD. *Int J Neuropsychopharmacol* 2001;4:377–383. [PubMed: 11806863]
- Resnick HS, Yehuda R, Pitman RK, Foy DW. Effect of previous trauma on acute plasma cortisol level following rape. *Am J Psychiatry* 1995;152:1675–1677. [PubMed: 7485635]
- Richardson MP, Strange BA, Dolan RJ. Encoding of emotional memories depends on amygdala and hippocampus and their interactions. *Nat Neurosci* 2004;7:278–285. [PubMed: 14758364]
- Risbrough VB, Stein MB. Role of corticotropin releasing factor in anxiety disorders: a translational research perspective. *Horm Behav* 2006;50:550–561. [PubMed: 16870185]
- Robert S, Hamner MB, Ulmer HG, Lorberbaum JP, Durkalski VL. Open-label trial of escitalopram in the treatment of posttraumatic stress disorder. *J Clin Psychiatry* 2006;67:1522–1526. [PubMed: 17107242]
- Roozendaal B, Okuda S, Van der Zee EA, McGaugh JL. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc Natl Acad Sci U S A* 2006;103:6741–6746. [PubMed: 16611726]
- Ryding E, Lindstrom M, Traskman-Bendz L. The role of dopamine and serotonin in suicidal behaviour and aggression. *Prog Brain Res* 2008;172:307–315. [PubMed: 18772039]
- Sapolsky RM, Uno H, Rebert CS, Finch CE. Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *J Neurosci* 1990;10:2897–2902. [PubMed: 2398367]
- Sargant W, Slater E. Acute War Neuroses. *The Lancet* 1940;236:1–2.
- Saxena S, Brody AL, Maidment KM, Dunkin JJ, Colgan M, Alborzian S, Phelps ME, Baxter LR Jr. Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology* 1999;21:683–693. [PubMed: 10633474]
- Seedat S, Stein DJ, Emsley RA. Open trial of citalopram in adults with post-traumatic stress disorder. *Int J Neuropsychopharmacol* 2000;3:135–140. [PubMed: 11343590]
- Seedat S, Lockhat R, Kaminer D, Zungu-Dirwayi N, Stein DJ. An open trial of citalopram in adolescents with post-traumatic stress disorder. *Int Clin Psychopharmacol* 2001;16:21–25. [PubMed: 11195256]
- Seedat S, Stein DJ, Ziervogel C, Middleton T, Kaminer D, Emsley RA, Rossouw W. Comparison of response to a selective serotonin reuptake inhibitor in children, adolescents, and adults with posttraumatic stress disorder. *J Child Adolesc Psychopharmacol* 2002;12:37–46. [PubMed: 12014594]

- Seedat S, Warwick J, van Heerden B, Hugo C, Zungu-Dirwayi N, Van Kradenburg J, Stein DJ. Single photon emission computed tomography in posttraumatic stress disorder before and after treatment with a selective serotonin reuptake inhibitor. *J Affect Disord* 2004;80:45–53. [PubMed: 15094257]
- Shestatzky M, Greenberg D, Lerer B. A controlled trial of phenelzine in posttraumatic stress disorder. *Psychiatry Res* 1988;24:149–155. [PubMed: 3406235]
- Sinha R. Chronic stress, drug use, and vulnerability to addiction. *Ann N Y Acad Sci* 2008;1141:105–130. [PubMed: 18991954]
- Smith MA, Davidson J, Ritchie JC, Kudler H, Lipper S, Chappell P, Nemeroff CB. The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. *Biol Psychiatry* 1989;26:349–355. [PubMed: 2548631]
- Southwick SM, Krystal JH, Morgan CA, Johnson D, Nagy LM, Nicolaou A, Heninger GR, Charney DS. Abnormal noradrenergic function in posttraumatic stress disorder. *Arch Gen Psychiatry* 1993;50:266–274. [PubMed: 8466387]
- Spivak B, Strous RD, Shaked G, Shabash E, Kotler M, Weizman A. Reboxetine versus fluvoxamine in the treatment of motor vehicle accident-related posttraumatic stress disorder: a double-blind, fixed-dosage, controlled trial. *J Clin Psychopharmacol* 2006;26:152–156. [PubMed: 16633143]
- Stein-Behrens BA, Lin WJ, Sapolsky RM. Physiological elevations of glucocorticoids potentiate glutamate accumulation in the hippocampus. *J Neurochem* 1994;63:596–602. [PubMed: 7913489]
- Stein MB, Yehuda R, Koverola C, Hanna C. Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. *Biol Psychiatry* 1997;42:680–686. [PubMed: 9325561]
- Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry* 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-concept trial in physically injured patients. *J Trauma Stress* 2007;20:923–932. [PubMed: 18157888]
- Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W. Corticotropin releasing factor produces behavioural activation in rats. *Nature* 1982;297:331–333. [PubMed: 6978997]
- Szabo ST, de Montigny C, Blier P. Modulation of noradrenergic neuronal firing by selective serotonin reuptake blockers. *Br J Pharmacol* 1999;126:568–571. [PubMed: 10188964]
- Szabo ST, Blier P. Serotonin (1A) receptor ligands act on norepinephrine neuron firing through excitatory amino acid and GABA(A) receptors: a microiontophoretic study in the rat locus coeruleus. *Synapse* 2001;42:203–212. [PubMed: 11746719]
- 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]
- Thase ME. Treatment of anxiety disorders with venlafaxine XR. *Expert Rev Neurother* 2006;6:269–282. [PubMed: 16533131]
- Timpl P, Spanagel R, Sillaber I, Kresse A, Reul JM, Stalla GK, Blanquet V, Steckler T, Holsboer F, Wurst W. Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. *Nat Genet* 1998;19:162–166. [PubMed: 9620773]
- Tokarev D, Jezova D. Effect of central administration of the non-NMDA receptor antagonist DNQX on ACTH and corticosterone release before and during immobilization stress. *Methods Find Exp Clin Pharmacol* 1997;19:323–328. [PubMed: 9379780]
- Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001;62:860–868. [PubMed: 11775045]
- Tucker P, Trautman RP, Wyatt DB, Thompson J, Wu SC, Capece JA, Rosenthal NR. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68:201–206. [PubMed: 17335317]
- Vaiva G, Ducrocq F, Jezequel K, Averland B, Lestavel P, Brunet A, Marmar CR. Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biol Psychiatry* 2003;54:947–949. [PubMed: 14573324]

- 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]
- van Stegeren AH, Goekoop R, Everaerd W, Scheltens P, Barkhof F, Kuijer JP, Rombouts SA. Noradrenaline mediates amygdala activation in men and women during encoding of emotional material. *Neuroimage* 2005;24:898–909. [PubMed: 15652324]
- Vermetten E, Bremner JD. Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. *Depress Anxiety* 2002;16:14–38. [PubMed: 12203669]
- 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]
- Villalon CM, Centurion D. Cardiovascular responses produced by 5-hydroxytryptamine: a pharmacological update on the receptors/mechanisms involved and therapeutic implications. *Naunyn Schmiedeberg Arch Pharmacol* 2007;376:45–63. [PubMed: 17703282]
- Weiss SJ. Neurobiological alterations associated with traumatic stress. *Perspect Psychiatr Care* 2007;43:114–122. [PubMed: 17576304]
- Wessa M, Rohleder N, Kirschbaum C, Flor H. Altered cortisol awakening response in posttraumatic stress disorder. *Psychoneuroendocrinology* 2006;31:209–215. [PubMed: 16154709]
- Wolf OT. The influence of stress hormones on emotional memory: relevance for psychopathology. *Acta Psychol (Amst)* 2008;127:513–531. [PubMed: 17900515]
- Woolley CS, Gould E, McEwen BS. Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Res* 1990;531:225–231. [PubMed: 1705153]
- Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL Jr, Mason JW. Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis* 1990;178:366–369. [PubMed: 2348190]
- Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW. Hypothalamic-pituitary-adrenal dysfunction in posttraumatic stress disorder. *Biol Psychiatry* 1991a;30:1031–1048. [PubMed: 1661614]
- Yehuda R, Lowy MT, Southwick SM, Shaffer D, Giller EL Jr. Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. *Am J Psychiatry* 1991b;148:499–504. [PubMed: 2006697]
- Yehuda R, Southwick S, Giller EL, Ma X, Mason JW. Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. *J Nerv Ment Dis* 1992;180:321–325. [PubMed: 1583475]
- Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr. Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. *Arch Gen Psychiatry* 1995;52:583–593. [PubMed: 7598635]
- Yehuda R, Teicher MH, Trestman RL, Levengood RA, Siever LJ. Cortisol regulation in posttraumatic stress disorder and major depression: a chronobiological analysis. *Biol Psychiatry* 1996;40:79–88. [PubMed: 8793040]
- Yehuda R, Siever LJ, Teicher MH, Levengood RA, Gerber DK, Schmeidler J, Yang RK. Plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol concentrations and severity of depression in combat posttraumatic stress disorder and major depressive disorder. *Biol Psychiatry* 1998;44:56–63. [PubMed: 9646884]
- Yehuda R, Golier JA, Halligan SL, Meaney M, Bierer LM. The ACTH response to dexamethasone in PTSD. *Am J Psychiatry* 2004;161:1397–1403. [PubMed: 15285965]
- Young EA, Breslau N. Saliva cortisol in posttraumatic stress disorder: a community epidemiologic study. *Biol Psychiatry* 2004;56:205–209. [PubMed: 15271590]
- Zald DH. The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Brain Res Rev* 2003;41:88–123. [PubMed: 12505650]
- Zelena D, Mergl Z, Makara GB. Glutamate agonists activate the hypothalamic-pituitary-adrenal axis through hypothalamic paraventricular nucleus but not through vasopressinergic neurons. *Brain Res* 2005;1031:185–193. [PubMed: 15649443]
- Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. *J Psychiatr Res* 2000;34:171–181. [PubMed: 10867111]