Published in final edited form as:

Neurosci Lett. 2017 May 10; 649: 147–155. doi:10.1016/j.neulet.2016.11.064.

Glutamate Dysregulation and Glutamatergic Therapeutics for PTSD: Evidence from Human Studies

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Abstract

Posttraumatic stress disorder (PTSD) is a chronic and debilitating psychiatric disorder afflicting millions of individuals across the world. While the availability of robust pharmacologic interventions is quite lacking, our understanding of the putative neurobiological underpinnings of PTSD has significantly increased over the past two decades. Accumulating evidence demonstrates aberrant glutamatergic function in mood, anxiety, and trauma-related disorders and dysfunction in glutamate neurotransmission is increasingly considered a cardinal feature of stress-related psychiatric disorders including PTSD. As part of a PTSD Special Issue, this mini-review provides a concise discussion of (1) evidence of glutamatergic abnormalities in PTSD, with emphasis on human subjects data; (2) glutamate-modulating agents as potential alternative pharmacologic treatments for PTSD; and (3) selected gaps in the literature and related future directions.

Keywords

posttraumatic stress disorder (PTSD); glutamate; glutamine; GABA; NMDA; neurobiology; neurotransmission; novel therapeutics; treatment; ketamine; d-cycloserine

Introduction

Posttraumatic stress disorder (PTSD) is a chronic and debilitating mental illness with scarce treatment options [1]. Though substantial evidence demonstrates significant structural and functional neural changes in PTSD, the molecular underpinnings of these and other neural alterations remain unclear [2–4]. The neuroendocrine system, notably the hypothalamic-pituitary-adrenal axis (HPA-axis), and the noradrenergic system have been strongly implicated in the pathophysiology of PTSD [5]. Though evidence from human subjects is limited, mounting evidence also relates abnormalities in the glutamatergic system to stress

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All other authors declare no conflicts of interest.

response and PTSD [1, 6]. Perceptions in the field are shifting from a monoamine focused hypothesis of PTSD toward a more complex and integrative neurochemical and neuroplasticity hypothesis, based primarily on the results of preclinical studies, that highlights the role of the glutamatergic system in trauma and stress psychopathology [6]. In this mini-review, we provide a concise report of the evidence of glutamatergic abnormalities in stress and trauma response, with emphasis on human subject data, including the development and perpetuation of PTSD. Next, we briefly discuss selective investigational glutamatergic drugs and their potential as pharmacologic treatments for PTSD. We conclude by presenting some gaps in the literature and related areas for continued investigation.

A Brief Historical Perspective of the Pathophysiology of Chronic Stress

For over half a century, a monoaminergic hypothesis of stress-related psychopathology has dominated the field and directed antidepressant drug development. Currently two antidepressants – paroxetine and sertraline – are considered first-line pharmacotherapy options and are the only drugs FDA approved for PTSD [7]. Unfortunately, even after an adequate trial, response and remission rates are approximately 60% and 30% respectively [7–9].

Converging lines of research across the past fifteen years have demonstrated aberrant glutamatergic function in mood, anxiety, and trauma-related disorders [10–14] and dysfunction in glutamate neurotransmission appears to play a critical role in the pathophysiology of stress-related psychiatric illness [1, 12, 13, 15, 16]. These findings are consistent with the ubiquity of glutamate throughout the brain. In fact, glutamate is the major excitatory neurotransmitter in the central nervous system (CNS) and 80–90% of cortical synapses are glutamatergic. Glutamate, glutamine, and the related gamma-aminobutyric acid (GABA) are critical components in brain metabolism and function [17]. In addition, both emotion and cognition, two phenomena inextricably linked to PTSD, are fundamentally mediated by synaptic glutamate neurotransmission [1, 6, 18].

Preclinical Evidence of Glutamatergic Abnormalities in Trauma and Chronic Stress

Based primarily on preclinical data, it is proposed that stress/trauma-activated glutamate circuits lead to glutamate spillover and trigger pro-inflammatory processes and excitotoxicity. There is a relatively narrow window between the brain's adaptive neuroplastic response to stress and the potentially excitotoxic effects of glutamate. When this 'safe' threshold is surpassed, it initiates a cascade of neural incidents altering both structural and functional glutamatergic connectivity [1, 6, 19]. Three primary outcomes are putatively related to this stress-induced glutamate spillover and excitotoxicity: (1) suppressed glutamatergic neural activity due to activation of presynaptic metabotropic glutamate receptors; (2) paradoxical elevation of extra-synaptic glutamate levels secondary to reduced astrocyte function and astrocyte loss; and (3) reductions in synaptic connectivity, as evidenced by dendritic retraction and reduced synaptic density, in corticolimbic circuits (e.g. hippocampus and medial prefrontal cortex; regions known to regulate stress responsivity and emotion) due to HPA dysregulation and overstimulation of the extra-synaptic NR2B-

containing NMDA receptors [1, 20]. Neurotransmission of glutamatergic amino acid plays a critical role in the regulation of the HPA-related stress response including: (1) the inhibition of HPA secretions by GABAergic signaling; (2) activation of corticosterone and adrenocorticotrophic hormone (ACTH) release through central glutamate systems; and (3) potential inhibition of the HPA-axis in the hippocampus through glutamatergic activation of subcortical, paraventricular nucleus of the hypothalamus (PVN)-projecting GABA neurons [21–23]. These trauma-induced alterations contribute both directly and indirectly to negative long-term effects of traumatic stress including a negative feedback loop, perpetuated at least in part, by decreased excitatory/glutamatergic tone in the medial prefrontal cortex [1, 19] and hippocampus [1, 6] (see Figure 1).

Direct Evidence of GABAergic and Glutamatergic Abnormalities from Human Studies

Proton magnetic resonance spectroscopy (MRS), a non-invasive and non-radioactive neuroimaging technique, has been the platform for the majority of empirical evidence of brain GABAergic and glutamatergic abnormalities in PTSD. Most of this work has focused on GABA levels, which is of considerable interest in PTSD given its role in fear conditioning and extinction [12, 24]. Table 1 provides a summary of the direct evidence of GABAergic and glutamatergic abnormalities in PTSD. Most MRS studies have reported altered cortical GABA levels in some, but not all, examined brain regions, though a recent meta-analysis that includes GABA in PTSD reports no significant differences in levels [16]. One of the most consistent findings is the lower cortical GABA in the parieto-occipital region in individuals with PTSD relative to trauma-exposed comparisons (TEC) [25, 26]. Similarly, GABA levels in the anterior insula were reduced in PTSD [27]. In the temporal cortex, one study reported significant reduction in GABA in PTSD [25] while another study failed to show significant differences [26]. In the ACC, the findings were overall negative with three studies reporting no significant alterations in GABA levels [25–27] except for one study, which found increased GABA in PTSD compared to TEC [28]. Single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have reported reduced prefrontal binding of benzodiazepine-GABA receptors in PTSD [29, 30], although not without inconsistency [31]. Peripheral biomarker studies reported lower plasma GABA level in PTSD [32, 33] and elevated serum glutamate in PTSD compared to TEC [34]. In addition, lower plasma GABA at 6 weeks posttrauma predicted higher PTSD 1 year posttrauma [32]. In contrast, a recent prospective study provides data suggesting individuals who developed PTSD, MDD, and other stress-related psychopathology following a combat deployment, show increased GABA levels at six-months post-deployment relative to their pre-deployment baseline [35]. Further, baseline and 1-month post-deployment plasma GABA appeared to have little correlation to the development of psychopathology at either the one- or six-month time point [35].

Correlational analyses have shown that (a) the relationship between PTSD diagnosis and parieto-occipital GABA level may be mediated by the severity of insomnia; (b) heightened insomnia severity is positively associated with increased glutamate as well as reduced GABA in the parieto-occipital and ACC; and (c) ACC glutamate level was negatively

correlated with increased arousal [25]. Patients with comorbid PTSD and alcohol use disorder (AUD) showed reduced glutamate and myo-inositol, a putative marker of glial function, in the ACC relative to those with PTSD only and TEC subjects [26]. In adolescents with PTSD, significantly lower glutamate+glutamine (Glx) levels in the rostral ACC were reported in PTSD relative to HC, as well as in those with remitted symptoms relative to HC [36]. Finally, one candidate gene study explored variation in a glutamate transporter gene (SLC1A1), which codes for the excitatory amino acid transporter 3 (EAAT3) and excitatory amino acid carrier 1 (EAAC1), known to play a key role in regulating extrasynaptic glutamate concentrations [37]. Variation in SLC1A1 is hypothesized to be correlated with heightened risk for developing PTSD and greater symptom severity [37]. They found increased likelihood of PTSD in carriers of allele rs10739062 (a single nucleotide polymorphism or “SNP” of SLC1A1), and though not statistically significant, this allele trended toward a significant association with symptom severity scores [37].

Indirect Evidence of Glutamatergic Abnormalities from Human Studies

Though human subjects studies remain inconclusive as to whether grey matter (GM) integrity changes are premorbid risk factors increasing vulnerability to developing PTSD or are acquired post-trauma as signs of psychopathology, substantial data from animal models provide evidence of stress/trauma-induced structural changes, most notably in the hippocampus and medial PFC (for a review see [1, 38]). Alterations in glutamate have been implicated as contributory or indirect factors to these GM changes through three primary means: (a) glutamate’s relationship with brain-derived neurotrophic factor (BDNF), a neurotrophin associated in PTSD [1]; (b) elevations in extrasynaptic glutamate due to glial loss and/or impaired function [1, 6, 19]; and (c) glutamate-induced excitotoxicity leading to reductions in spine density and dendritic remodelling [1, 6, 39].

Reduced astrocyte function and astroglial loss are believed to be responsible for increased extra-synaptic glutamate, as these cells are responsible for glutamate clearance from extra-cellular space and the synaptic cleft as well as converting glutamate to glutamine [1, 38, 40]. Preclinical evidence suggests deficits in glial function precipitate prolonged elevations in extrasynaptic glutamate and related excitotoxicity and this can lead to behavioral pathology and GM abnormalities [1, 38, 41, 42]. Additionally, glial line-derived neurotrophic factor (GDNF) are responsible, in part, for the survival of midbrain neurons [43]. Thus, impairment and loss of glia may also affect neuronal health [38]. Recent investigations in animal models of PTSD showed reduced astrocyte density and altered morphology in the hippocampus [44, 45].

Glutamate-based Pharmacotherapies

The urgent need for innovative drug development for PTSD is underscored by limitations in the clinical effectiveness of standard antidepressant treatments including less than optimal response rates, relatively rare incidents of full remission, the common presence of refractory symptoms, and the high risk for onset or worsening of suicidality ([8, 9]; for a review see [7]). Further, randomized controlled trials RCTs investigating the use of alternative mainstream pharmacological interventions including atypical antipsychotics, anticonvulsants, and

benzodiazepines have shown limited to no benefit, leaving considerable room for improved treatment options for PTSD [7]. Therefore, there is a tremendous need to identify robust pharmacotherapies for PTSD that work through novel neural mechanisms. Drugs associated with glutamatergic system modulation are being examined as a potential outlet for alternative pharmacologic intervention.

Though some novel glutamate modulating compounds are in the early stages of development and clinical trials for depressive disorders, drugs currently being explored for the treatment of PTSD are those being used in an off-label manner (see Table 2 for a summary).

Lamotrigine for example, an anticonvulsant drug that regulates glutamatergic neurotransmission, has been shown to possess antidepressant-like properties in patients with PTSD [7]. A small RCT comparing lamotrigine to placebo in combat Veterans with PTSD reported significant improvement in the active treatment group, with marked reductions in reexperiencing and arousal symptoms [46] and a case report reported significantly reduced aggression associated with PTSD [47]. Riluzole, an FDA approved drug for treatment of Amyotrophic Lateral Sclerosis (ALS), is a modulator of glutamate release, a potent enhancer of glutamate reuptake by glial cells, and putative enhancer of neurotrophic factors [48]. Considering the above proposed model, future studies should investigate the potential utility of riluzole in PTSD treatment, as it has showed promise as an alternative anxiolytic treatment intervention in open-label trials for anxiety disorders including obsessive compulsive [42, 49] and generalized anxiety [50] disorders. Interestingly, riluzole treatment in generalized anxiety disorder (GAD) showed a positive correlation between the improvement in anxiety symptoms and the increase in hippocampal volume following treatment [51], raising the possibility that riluzole may directly address the well-documented hippocampal deficit in PTSD.

Ketamine, an NMDA receptor antagonist, has recently received attention as a possible novel pharmacologic agent for PTSD given the mounting evidence of its rapid antidepressant effects in mood disorders and its robust effect on neuroplasticity (for a review see [20, 52]). To date there is relatively little data published concerning the use of subanesthetic dose of ketamine for PTSD; however, the results, not without inconsistency, are overall promising. A small, naturalistic study of accident victims reported administration of anesthetic (S)-ketamine (faster clearance and a higher affinity for the phencyclidine receptor of the NMDA receptor complex) aggravated both retrospective acute and current posttraumatic symptom severity [53] whereas another group reported perioperative ketamine was associated with comparable [54] or lower [55] PTSD prevalence rates relative to trauma-exposed and burned military service members despite having greater injury severity, larger burns, more necessary medical procedures and longer hospital stays. Of important note, these studies administered anesthetic doses of ketamine as part of surgical procedures; whereas the vast majority of clinical investigations of ketamine's psychotropic effects have been at subanesthetic doses, most commonly 0.5 mg/kg. More recently, the first pilot data from a double-blind crossover study was published in which patients with PTSD were randomized to a single infusion of ketamine (0.5 mg/kg infused over 40-minutes) or midazolam (an active comparator) [56]. Similar to depression studies, dissociative symptoms occurred during infusion, peaked at 40-minutes, were generally well tolerated, and subsided within 80-minutes following ketamine administration. Ketamine showed significant reduction in PTSD symptom severity, relative

to midazolam [56]. A case report of a Veteran with severe treatment-resistant PTSD receiving a single subanesthetic dose of ketamine reported similar symptom improvement and durability of effect [57].

D-cycloserine (DCS), a partial NMDA agonist, has been the target of many clinical and preclinical investigations due to its suspected impact on neuroplasticity and the role it has on fear extinction through its modulation of NMDA receptors in the basolateral amygdala [58]. Early evidence suggests DCS may be helpful as an adjunctive treatment to first-line psychopharmacologic intervention, specifically in alleviating numbing and avoidance symptoms [59]; however, as a monotherapy, DCS failed to show significantly greater improvement in PTSD symptoms than placebo [60]. Results have been variable concerning the use of DCS as an augment to improve the efficacy of exposure therapy with studies reporting improved treatment outcomes [61], detrimental effects [62], or no noticeable effects [63, 64], with the exception of decreased startle response relative to placebo [64].

Gaps in the Literature and Future Directions

Though research focused on the neurobiology of PTSD and potential novel drug development for related psychopathology has made significant strides in the past 50 years, investigators and clinicians continue to look for explanations for the variability in stress response and PTSD symptom presentation including risk and resilience factors. Both preclinical and clinical evidence demonstrates that the glutamatergic system is instrumentally involved in stress responsivity, adaptability, and related psychopathology yet several questions remain unanswered. Specifically, (a) which of these glutamate-based abnormalities and impairments are present prior to exposure to trauma and may predispose an individual to increased maladaptive responses, including the development of psychopathology, (b) what alterations are precipitated by the traumatic exposure and are acquired signs of PTSD [1, 6, 65], and (c) to what extent the normalization of glutamate-related abnormalities is necessary and/or sufficient for recovery in PTSD patients. Relatedly, as exposure to stress appears to invoke plasticity-enhancing effects to a point, as well as toxic effects on a continuum depending on the type, duration, and intensity of the exposure [1, 6], future investigations are required to better characterize these thresholds.

It is possible that inconsistencies in results described above are due, at least in part, to variations in methodology and data acquisition, processing, and analysis methods as well as variability in the brain regions of interest being investigated. Additional research exploring the relationship between specific brain regions, structural and functional alterations, and the role of the glutamatergic system in these as well as the use of imaging as a possible method of predicting treatment response will be valuable. Relatedly, as GABA and glutamate appear relevant to specific dimensions of PTSD symptoms (e.g., [27, 46]), continued work concerning the phenotypes of PTSD will provide the opportunity for tailored psychopharmacologic interventions; as evidence suggests, though PTSD is characterized as a unitary disorder, there is a great deal of heterogeneity across symptoms and symptoms clusters and each may have distinct neurobiological underpinnings [66]. The kynurenine pathway and related metabolites (e.g., kynurenic acid, quinolic acid, tryptophan) have been implicated in schizophrenia [67], bipolar [67, 68] and unipolar depression [69, 70], and

suicidality [70–72]. This, combined with evidence of the role of the kynurenine pathway in both neuroinflammation and glutamate neurotransmission, investigations in this area may provide valuable insights in the pathophysiology of PTSD and inform novel drug development [73].

Regarding psychopharmacology, recently published meta-analyses, primarily focused on ketamine in mood disorders, highlight current limitations surrounding a glutamate hypothesis of stress-related psychopathology and related therapeutics relevant to PTSD. Notably, these support the need for careful evaluation of (a) the long-term safety, tolerability, efficacy, and durability of effects of ketamine, including whether there is potential for suicidal ideation/intent/behavior bounce-back or rebound effects [74]; (b) the optimal route(s) of administration, dosing, and treatment schedules; and (c) the potential effects of other glutamatergic agents with fewer significant side effects, decreased abuse potential, and reduced excitotoxic potential [75–77]. Given the considerable psychotomimetic effects of ketamine, issues regarding the lack of an appropriate blind for clinical trials also leaves room for improvement. Further, to date, few investigations have explored the use of glutamatergic drugs for PTSD and those that have included relatively small samples. Though current evidence is promising, future investigations should include larger samples and well-controlled, randomized, double-blind studies that include variable doses and length of treatment period, with careful consideration of the distinct properties, effectiveness, and side-effect profiles of different NMDA receptor antagonists [78].

Ketamine induced dissociative cognitive and perceptual side effects also are important to consider from the perspective of dissociative states in trauma response and PTSD symptomology. Dissociative states are relatively common at the time of exposure to extreme stress and trauma; are a predictor of the development of PTSD, specifically reexperiencing symptoms and future dissociation; and are a highly distressing aspect of the symptom constellation [79, 80]. Studies continuing to explore the mechanism of action of ketamine and other NMDA antagonists may shed light on the relationship between glutamate neurotransmission and dissociation, opening a door to explore potential methods of neuroprotection from glutamate-based neural injury at the time of exposure (e.g., potential drug administration of novel agents that limit glutamatergic activity such as group II/III metabotropic receptor agonists) [81].

With respect to DCS, future studies might consider investigations of dose-dependent response as there is a possibility the inconsistent findings may be due, in part, to limited drug concentration in the brain, rather than simple lack of efficacy of the medication. For example, most clinical investigations of DCS have administered a 50 mg dose, which cannot always be detected in cerebral spinal fluid (CSF) [82]. A study administering a 50 mg dose of DCS on four test days to healthy participants reported detecting only “trace levels” of the drug in the CSF when assessed approximately two hours after dosing [82]. Given much earlier work with DCS that administered a larger dose (250 mg) achieved a peak CSF level [83] and that most bioavailability investigations of DCS were conducted in tuberculosis patients receiving long-term serial administrations at much greater doses [84], it is possible different effects would be seen in clinical trials if the dose was adjusted upward. Other unanswered questions related to DCS include the timing prior to psychotherapy, the

frequency of drug administration, and the nature of performed psychotherapy. While DCS may enhance plasticity and learning, it would be critical for future studies to determine the optimal combined therapy approach to improve PTSD symptoms by facilitating extinction, rather than worsening symptoms by enhancing reconsolidation of trauma memories.

Conclusion

Scientific evidence suggests that the glutamatergic system plays a critical role in stress response and PTSD. Though further investigation is warranted, glutamate-based pharmacotherapeutic agents hold promise as alternative interventions for PTSD, in particular among PTSD patients who have struggled to gain significant clinical benefit or remission from traditional pharmacological agents. Further, glutamate agents could putatively target specific symptoms such as cognitive deficits and suicidal ideation that are often refractory to traditional treatment. Additional research is needed to advance our understanding of the glutamate-based underpinnings of risk and resilience in PTSD as well as the safety, efficacy, and durability of glutamatergic drugs.

Acknowledgments

This work was supported by the Department of Veterans Affairs (NCPTSD; IK2CX000772), NIMH (K23MH101498), and the Yale Center for Clinical Investigation (UL1RR024139). The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or other sponsoring institutions. Dr. Krystal has served as a scientific consultant to the following companies (the Individual Consultant Agreements listed are <\$10,000 per year): Aisling Capital, Astellas Pharma Global Development, AstraZeneca Pharmaceuticals, Biocortech, Brintnall & Nicolini, Easton Associates, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck Research USA, Medivation, Merz Pharmaceuticals, MK Medical Communications, Hoffmann–La Roche, SK Holdings, Sunovion Pharmaceuticals, Takeda Industries, and Teva Pharmaceutical Industries. He is on the Scientific Advisory Board for the following companies: Abbott Laboratories, Bristol-Myers-Squibb, Eisai, Eli Lilly, Forest Laboratories, Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Naurex, Pfizer Pharmaceuticals, and Shire Pharmaceuticals. He holds <\$150 in exercisable warrant options with Tetragenex Pharmaceuticals. He is on the Board of Directors of the Coalition for Translational Research in Alcohol and Substance Use Disorders. He was the principal investigator of a multicenter study in which Janssen Research Foundation provided drug and some support to the Department of Veterans Affairs. He is Editor of *Biological Psychiatry*. He has a patent on dopamine and noradrenergic reuptake inhibitors in treatment of schizophrenia (patent number 5447948) and is a coinventor on a filed patent application by Yale University related to targeting the glutamatergic system for the treatment of neuropsychiatric disorders (PCTWO06108055A1). He has a patent pending on intranasal administration of ketamine to treat depression. Dr. Abdallah has served on advisory boards for Genentech.

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Figure 1. The vicious cycle of trauma and stress

This provides a schematic representation of the synaptic model of PTSD. This model is based on the hypothesis that severe trauma, combined with predisposing vulnerabilities (e.g., early life stress, genetic factors, sex differences, etc.), converge to trigger inflammatory and excitotoxicity processes leading to synaptic dysconnectivity in brain areas critical to emotional regulation, fear conditioning, and stress response. This trauma-altered circuitry underlies components of PTSD symptomatology, which in turn constitute a major chronic stressor that perpetuate the stress-induced synaptic deficits

Table 1
Studies examining direct evidence of GABAergic and glutamatergic abnormalities

Study	Method	Target	N	ROIs	Additional Findings
<i>Blood Serum and Plasma Analysis</i>					
Nishi et al. (2015) [34]	BSA	Glu, Gln	97 cTEC 8 cPTSD±	Serum	Elevated serum Glu in cPTSD±; Glu positively correlated with cPTSD severity; Glu/Glu ratio inversely correlated with PTSD severity.
Vaiva et al. (2006) [32]	BPA	GABA	6wks (1yr): 44(22) cPTSD± 34(7) cTEC	Plasma	Lower plasma GABA in PTSD± at 6 weeks and at 1 year posttrauma; Lower GABA at 6 weeks predicted higher cPTSD± at 1 year.
Vaiva et al. (2004) [33]	BPA	GABA	57 cPTSD 51 cTEC 69 HC	Plasma	Lower plasma GABA in cPTSD compared to cTEC or HC.
Schur et al. (2016) [16]	BPA	GABA	731 TE/CD	Plasma	Increased GABA levels 6-months postdeployment positively correlated with onset of PTSD and other psychopathology
<i>DNA / Candidate Gene Studies</i>					
Zhang et al. (2014) [37]	DNA	SLC1A1	264 mPTSD 154 mTEC	—	RS10739062 was associated with mPTSD diagnosis and severity.
<i>¹H-MRS</i>					
Meyerothoff et al. (2014) [25]	¹ H-MRS	GABA, Glu	27 mPTSD 18 mTEC	POC TEMP ACC	Lower GABA in POC and TEMP in mPTSD; reduced POC GABA & elevated POC Glu correlated with increasing insomnia severity; reduced ACC Glu correlated with increased arousal scores.
Michels et al. (2014) [28]	¹ H-MRS	GABA	12 cPTSD 17 cTEC	ACC DLPFC	Elevated GABA in ACC & DLPFC in cPTSD.
Pennington et al. (2014) [26]	¹ H-MRS	GABA, Glu, ml	10 xPAUD 28 xPTSD 20 xTEC	POC TC ACC	Lower POC GABA & higher TC Glu in xPTSD compared to xTEC; Lower ACC Glu and ml in xPAUD compared to xPTSD and xTEC; increased GABA and Glu correlated with improved neurocognition in xPAUD.
Rosso et al. (2014) [27]	¹ H-MRS	GABA	13 cPTSD 13 HC	Insula dACC	Lower insular GABA in cPTSD; reduced insular GABA associated with increased state and trait anxiety in the whole cohort.
Yang et al. (2015) [36]	¹ H-MRS	Glx	10 cPTSD-c 23 cPTSD-r 21 HC	rACC	ACC Glx: cPTSD-c < cPTSD-r < HC.
<i>PET</i>					
Gueze et al. (2008) [30]	PET	GABA(A) BZD receptor	9 mPTSD 7 mTEC	Voxel-wise	Lower receptor binding in the cortex, HPC, and THAL in mPTSD.
<i>SPECT</i>					
Bremner et al. (2000) [29]	SPECT	BZD receptor	13 mPTSD 13 HC	Voxel-wise	Lower PFC receptor binding in mPTSD

Study	Method	Target	N	ROIs	Additional Findings
Fujita et al. (2004) [31]	SPECT	BZD receptor	19 mPTSD 19 HC	Voxel-wise	No difference between groups; Receptor binding negatively correlated with childhood trauma in right STG.

Abbreviations (methods): BPA = blood plasma analysis; BSA = blood serum analysis; DNA = candidate gene study/DNA isolation and genotyping; 1H-MRS = proton magnetic resonance spectroscopy; PET = positron emission tomography; SPECT = single-photon emission computed tomography. **Abbreviations (metabolites/receptors):** BZD = benzodiazepine; GABA = gamma-aminobutyric acid; Glu = glutamate; Glx = glutamate + glutamine; mI = Myo-inositol; SLC1A1 = glutamate transporter gene thought to be associated with PTSD; **Abbreviations (population):** cPTSD = civilian PTSD; cTEC = civilian trauma-exposed control; mPTSD = military PTSD; mTEC = military trauma-exposed control; PTSD = posttraumatic stress disorder; PTSD-c = PTSD current; HC = healthy control; xPAUD = mixed civilian and military PTSD with comorbid alcohol use disorder; PTSD± = full or subthreshold; PTSD-r = PTSD remission; TEC = trauma exposed control; TE/CD = trauma exposed/combat deployment; xPTSD = mixed military and civilian PTSD population; xTEC = mixed military and civilian trauma-exposed control population; **Abbreviations (ROIs):** ACC = anterior cingulate cortex; dACC = dorsal ACC; DLPFC = dorsolateral prefrontal cortex; HPC = hippocampus; POC = parietooccipital cortex; rACC = rostral ACC; STG = superior temporal gyrus; TEMP = temporal cortex/cortices; THAL = thalamus; **Abbreviations (other):** CAPS = clinician administered PTSD scale.

Table 2

Investigational Glutamate-based Pharmacotherapies

Study	Subjects	(N) - Treatment	Duration	Study Design	Treatment Response and Findings
<i>Lamotrigine (LM)</i>					
Hertzberg et al. (1999) [46]	xPTSD	(10) LM, 25mg/day; titrated to max of 500mg/day if tolerated. (4) Placebo	12 weeks	Randomized 2:1, double-blind, placebo-controlled	50% improvement in LM compared to 25% in placebo; marked improvement in reexperiencing, avoidance, numbing in LM
Kozanic-Kovacic & Eterovic (2013) [47]	cTRPTSD	(1) LM, 125mg/day	12 weeks	Case Report	Reduced PTSD symptoms including aggressive behaviors, improved interpersonal relations
<i>Ketamine (Ket)</i>					
Schonenberg et al. (2005) [53]	cPTSD	(17) R-Ket* (12) S-Ket* (27) OPI *+Mdz	Single or fractionated peritraumatically administered dose.	Retrospective analysis of acute & current PTSD 1 year posttrauma	PTSD symptoms: S-Ket > R-Ket = OPI;
McGhee et al. (2008) [54]	mPTSD	(119) Ket (28) No Ket	Intraoperative dose.	Retrospective chart review	PTSD prevalence was lower in Ket group (27% vs. 46%); Ket group had more severe trauma/burns.
McGhee et al. (2014) [55]	mPTSD	(189) Ket (100) No Ket	Intraoperative dose.	Retrospective analysis 30+ days posttrauma	PTSD prevalence did not differ between Ket and no Ket (24% vs. 27%); Ket group had more severe trauma/burns/surgeries.
Feder et al. (2014) [56]	cPTSD	(22) Ket, 0.5mg/kg. (19) Mdz, 0.045mg/kg [First-period of crossover]	Single IV dose of each administered over 40 minutes, separated by 2 weeks.	Randomized, double-blind, crossover, active placebo controlled trial.	PTSD improvement in Ket compared to Mdz @ 24 hours with no evidence of period or crossover effects; PTSD improvement remained significant after controlling for BL & 24-hour depression; Durability of benefit was ~15 days
<i>D-cycloserine (DCS)</i>					
Altari et al. (2014) [59]	mPTSD	(38) DCS, 50mg/day. (38) Placebo. [First-period of crossover]	11 weeks total; 4 week 1 st period - 2-week washout - 4 week 2 nd period.	Randomized, double-blind, placebo-controlled crossover trial.	Decreased intensity of avoidance and numbing symptoms in DCS compared to placebo.
Heresco-Levy et al. (2002) [60]	cPTSD	(6) DCS, 50mg/day. (5) Placebo [First-period of crossover]	12 weeks; 2 week washout - 4 week 1 st period - 2-week washout - 4 week 2 nd period.	Randomized, double-blind, placebo-controlled crossover trial.	Study failed to show difference between DCS & placebo.
Difede et al. (2014) [61]	cPTSD	(13) DCS+VRE 100mg (12) Placebo + VRE	12 weeks total; Dosed 1x/week 90 minutes prior to VRE session for 10 sessions.	Randomized, double-blind, placebo-controlled trial.	Greater PTSD remission for DCS+VRE compared to placebo+VRE (46% vs 8% posttreatment; 69% vs 17% at 6 months FU; secondary analysis suggest earlier & greater improvement in PTSD as well as depression, anger expression, & sleep in DCS compared to placebo.
Litz et al. (2012) [62]	mPTSD	(13) DCS+IE 50mg (13) Placebo + IE	6 weeks total; Dosed 1x/week 30 minutes prior to IE sessions for 4 sessions.	Randomized, double-blind, placebo-controlled trial.	DCS showed no beneficial effect; 70% of placebo+IE showed improvement compared to

Study	Subjects	(N) - Treatment	Duration	Study Design	Treatment Response and Findings
de Kleine et al. (2012) [63]	cPTSD	(33) DCS+PE 50mg (34) Placebo+PE	~10 weeks total; Dosed 1x/week 60 minutes prior to ~8–10 PE sessions.	Randomized, double-blind, placebo-controlled trial.	30% in DCS+IE; 3 DCS+IE patients reported significant worsening of symptoms. Study failed to show difference between DCS +PE and placebo+PE on primary outcome; secondary analysis suggest greater response rate in DCS+PE (64%) compared to placebo+PE (38%).
Rothbaum et al. (2014) [64]	mPTSD	(53) DCS+VRE 50mg (50) APZ+VRE 0.25mg (53) Placebo+VRE	6 weeks; Dosed 1x/week 30 minutes prior to VRE session for 5 sessions.	Randomized, double-blind, active-placebo controlled trial.	Study failed to show difference between DCS +VRE and placebo+VRE on primary outcome; secondary analysis suggest DCS+VRE had lower startle during VRE sessions relative to APZ +VRE or placebo+VRE.

Abbreviations: APZ = alprazolam; BL = baseline; cPTSD = civilian posttraumatic stress disorder; DCS = D-cycloserine; dx = diagnostic; FU = follow-up; IE = imaginal exposure (psychotherapy); Ket = ketamine; LM = lamotrigine; Mdz = midazolam; mPTSD = military posttraumatic stress disorder; OPI = opioid; PE = prolonged exposure (psychotherapy); PTSD = posttraumatic stress disorder; R-Ket = racemic ketamine; SI = seriously injured; S-Ket = (S)-ketamine; TRPTSD = treatment-resistant posttraumatic stress disorder; VRE = virtual reality exposure (psychotherapy); xPTSD = mixed military and civilian PTSD population