Glutamate and Anxiety Disorders

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Anxiety disorders are among the most prevalent psychiatric disorders, but they represent a particular challenge for treatment. The standard first-line treatments, including antidepressants, benzodiazepines, and buspirone, result in significant response rates for a majority of patients; however, unfavorable side effect profiles or risk for dependency for particular agents might limit their use by anxious patients, who often have low thresholds for medication discontinuation. Novel pharmacologic agents that modulate particular receptors, ion channels, or transporters relevant to glutamatergic neurotransmission may represent a new approach to the treatment of anxiety disorders, with generally more favorable side effect profiles. Although the role of glutamate in the pathophysiology of anxiety disorders is still being elucidated, the use of these agents in treatment of anxiety disorders and commonly comorbid conditions such as substance abuse and mood disorders will continue to increase.

Introduction

Anxiety disorders are prevalent and disabling, affecting 40 million adults in the United States annually [1]. The most common medication classes used in the treatment of anxiety disorders are antidepressants, benzodiazepines, and the azapirone buspirone [2]. Antidepressants, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, and monoamine oxidase inhibitors, are effective in a majority of patients but may have significant gastrointestinal and sexual side effects, as well as delayed onset of action. Benzodiazepines continue to play a prominent role in current pharmacotherapy options for anxiety disorders but are relatively contraindicated in the elderly, who are more prone to falls or delirium, and in patients with a history of substance abuse [3]. Buspirone has a delayed onset of action and is generally considered to be less effective than antidepressants or benzodiazepines [4]. Thus, despite considerable progress in pharmacologic options for anxiety disorders, there exists an urgent need for novel therapeutic agents.

Glutamate is the most prevalent excitatory neurotransmitter in the mammalian central nervous system (CNS) [5]. Until relatively recently, pharmacologic investigation of the glutamate system had lagged far behind research in monoamine and γ-aminobutyric acid (GABA)/benzodiazepine systems for anxiety and related disorders. Recent insights into the nature of glutamatergic neurotransmission, enabled by the characterization of glutamate receptor subtypes and their functional specificity, as well as recent technical developments in brain imaging have fostered interest in the clinical potential of glutamate-modulating compounds.

This review summarizes the basic pharmacology of glutamate and clinical trials of glutamatergic compounds in patients with *DSM IV* anxiety disorders, including panic disorder, generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), social phobia, and specific phobias. In anticipation of the likely segregation between obsessive-compulsive disorder (OCD) and the other anxiety disorders in *DSM V* [6], we exclude treatment of OCD from our discussion. We also discuss implications of the data for the pathophysiology of anxiety and conclude with directions for future research.

Glutamate, Glutamate Receptors, and Modulators

Glutamate is an anion of the amino acid glutamic acid and serves as a key excitatory neurotransmitter in the CNS and as a precursor to the inhibitory neurotransmitter GABA, in addition to its central roles in protein synthesis and metabolism.

The two principal families of glutamate receptors are ionotropic and metabotropic receptors. Ionotropic receptors are ligand-gated ion channels and include three subtypes of receptors: N-methyl-D-aspartate (NMDA), kainate, and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), whereas metabotropic receptors are G-protein coupled and include eight subtypes named $mGluR_{1-8}$ [7•].

NMDA receptors are ligand gated and voltage dependent and require three conditions in order to open: binding of glutamate, binding by the coagonist glycine, and membrane depolarization. The receptors are heterotetramers comprised of two conserved NR1 glycine-

Table 1. Glutamate psychopharmacology

Drug	FDA indications	Anxiety disorders	Dose range, *mg/d*
Pregabalin	Diabetic neuropathic pain, postherpetic neuralgia, epilepsy	GAD	150–600
Topiramate	Epilepsy, migraine	PTSD, social phobia	25–400
Lamotrigine	Epilepsy, bipolar I disorder	PTSD	50–500
Riluzole	Amyotrophic lateral sclerosis	GAD	100–200
Memantine	Alzheimer's dementia		5–20
Tiagabine	Epilepsy	GAD, PTSD	16–32
Valproic acid	Mania, epilepsy, migraine	Panic disorder, social anxiety disorder	750–2500
Phenytoin	Epilepsy	PTSD	300–1600
Gabapentin	Epilepsy, postherpetic neuralgia	Social phobia	900–3600
Levetiracetam	Epilepsy	Social phobia, panic disorder, PTSD	1000–3000
D-cycloserine	Tuberculosis, urinary tract infection	PTSD, social phobia, acrophobia	50 mg prior to exposure therapy, then 250–500

FDA—US Food and Drug Administration; GAD—generalized anxiety disorder; PTSD—post-traumatic stress disorder.

binding subunits and two regionally specific NR2A or NR2B glutamate-binding subunits [8]. Upon activation, the receptor releases an Mg^{++} ion that blocks the central pore, thus enabling the flow of cations through a central nonselective channel. The cation flow is predominantly Na^{+} and K^{+}, but there is a small Ca^{++} flux as well that is thought to play a role in synaptic plasticity, and therefore learning and memory [9].

AMPA and kainate receptors are also ligand-gated ion channels. AMPA receptors open when at least two of the four glutamate-binding sites are occupied. When open, AMPA receptors are permeable to Na^{+} and K^{+}, as well as Ca^{++} in a subset of the receptors. Kainate receptors are structurally similar to AMPA receptors but are comprised of different functional subunits and open for a much shorter duration than AMPA receptors. Unlike AMPA receptors, which play a major role in synaptic transmission, kainate receptors are thought to function more as pre- and postsynaptic modulators [10].

The metabotropic glutamate receptors $mGluR_{1-8}$ are not ion channels, but rather transmembrane receptors that activate intracellular signaling cascades when activated by an extracellular ligand. Unlike the ion channel glutamate receptors, the metabotropic receptors seem to modulate excitatory signaling rather than propagating it. The subtypes of mGluR are differentially expressed in specific regions of the brain, which may allow for targeted pharmacotherapy. Group I mGluR includes $mGlu_1$ and $mGlu_5$ and are found postsynaptically in the amygdala, hippocampus, and thalamus, and in lesser concentrations in the cortex and ventral striatum. Group II mGluR includes $mGlu_2$, which is found in the cortex and the hippocampal dentate gyrus, and $mGlu_3$, which is found predominantly on glia [11•].

Glutamate Psychopharmacology

The last decade has witnessed exciting advances in the clinical neuropharmacology of glutamate. A number of commonly used medications (for epilepsy, stroke, migraine, alcohol dependence, and neurodegenerative disorders) were found to exert their primary pharmacologic effect by modulating glutamate. More recently, applications of these agents to anxiety disorders have been tested, with reductions in Hamilton Rating Scale for Anxiety (HAM-A) scores serving as the primary outcome measure. We review several commonly used and/or promising glutamatergic agents in anxiety disorders, acknowledging the important caveat that very few randomized, double-blind, placebo-controlled trials (RCTs) of these agents currently exist (Table 1).

Pregabalin

Pregabalin is a drug similar to gabapentin that binds voltage-dependent calcium channels and is thought to reduce glutamatergic tone in the CNS. It is US Food and Drug Administration (FDA) approved for use in treatment of epilepsy and neuropathic pain in the United States, and approved for treatment of GAD in Europe. A number of short-term RCTs have shown pregabalin to be effective in the treatment of GAD, although it is not approved for this indication in the United States.

In a 10-week, four-arm, double-blind trial in GAD comparing pregabalin, 150 mg/d; pregabalin, 600 mg/d; lorazepam, 6 mg/d; and placebo, decreases in HAM-A scores in the low-dose pregabalin group (–9.2) and the high-dose pregabalin group (–10.3) were equivalent to patients receiving lorazepam (–12.0) and significantly

exceeded placebo (–6.8), with no observed withdrawal syndrome after discontinuation [12]. A number of follow-up multicenter RCTs have confirmed these early findings, observing improved tolerability of pregabalin over benzodiazepines measured by higher completion rates [13,14••] and equivalent efficacy of twice-daily and three-times-daily dosing [15].

A recent trial compared 6 weeks of double-blind treatment with pregabalin, 400 mg/d (n = 97); pregabalin, 600 mg/d (n = 110); venlafaxine, 75 mg/d (n = 113); or placebo (n = 101) in patients with GAD. It found that the efficacy of pregabalin at both doses in reducing HAM-A scores was equal to venlafaxine but that pregabalin at both dosage levels demonstrated more rapid onset (1 week vs 2 weeks) and improved tolerability (discontinuation rates 6%–13% vs 20% for venlafaxine). This suggests that this agent may be clinically useful in the treatment of anxiety in patients sensitive to SNRIs [16].

Topiramate

Topiramate is a novel agent that is FDA approved for the treatment of epilepsy and migraine prophylaxis, with multiple pharmacologic mechanisms, including voltage-dependent sodium and calcium channel modulation, GABA-A potentiation, and AMPA/kainate antagonism [17]. Several open-label studies have suggested efficacy of topiramate as monotherapy and adjunctive therapy in civilian PTSD, although a recent 12-week RCT of topiramate (n = 19, mean dose = 150 mg/d) versus placebo (n = 19) failed to demonstrate significant drug-placebo differences on the primary outcome measure, the Clinician-Administered PTSD Scale (CAPS), likely due to underpowering of the study [18].

In an open-label, flexible-duration (mean = 33 weeks), flexible-dosage (mean = 42 mg/d, median = 25 mg/d) trial of topiramate in civilian patients with chronic PTSD, 79% of patients reported decreased nightmares and 86% had decreased flashbacks, with 95% response rates at dosages up to 75 mg/d [19]. A follow-up confirmatory study in a similar population of patients with similar dosages of topiramate showed a 77% response rate at 4 weeks of treatment, with a 49% reduction in symptoms [20].

Topiramate also may be effective in treating symptoms of social phobia. In a small (n = 23) 16-week open trial of topiramate, titrated from 25 mg/d to a maximum of 400 mg/d, 75% of patients completing the study (n = 12) responded to topiramate, with a mean reduction of 45% in Leibowitz Social Anxiety Scale (LSAS) scores [21].

Lamotrigine

Lamotrigine, FDA approved for treatment of epilepsy and as maintenance therapy for bipolar disorder, blocks voltage-dependent sodium channels and subsequently inhibits glutamate release. In a 12-week, double-blind, placebo-controlled trial, 50% of patients with PTSD receiving lamotrigine, up to 500 mg/d, responded by Duke Global Rating for PTSD scores, compared with a response rate of 25% in patients receiving placebo [22]. Although promising, the trial was limited by a small sample size (n = 10 in treatment group, n = 4 in placebo group) and has yet to be replicated.

Riluzole

Riluzole, which blocks sodium and calcium channels and inhibits presynaptic glutamate release, is a novel agent approved for the treatment of amyotrophic lateral sclerosis. In an 8-week, open-label, fixed-dose pilot study of riluzole, 100 mg/d, in patients with GAD, 53% of patients completing the trial met remission criteria of HAM-A scores less than or equal to 7, and 80% of patients completing the trial met response criteria of 50% or greater reductions in HAM-A scores [23•]. Improvements in anxiety symptoms also were noted in patients with treatment-resistant major depression, who were administered open-label riluzole flexibly dosed up to 200 mg/d for 6 weeks [24].

Memantine

Memantine, a drug approved for use in Alzheimer's dementia, is a noncompetitive antagonist at several receptors, including NMDA, 5-HT_3, and the nicotinic acetylcholine receptor [25]. A small RCT of memantine in major depressive disorder did not demonstrate efficacy over placebo [26]. Several ongoing studies are evaluating the role of memantine as augmentation therapy in treatment-resistant anxiety disorders.

Tiagabine

Tiagabine is a selective GABA reuptake inhibitor currently approved for the treatment of epilepsy. Non-benzodiazepine drugs acting on the GABA system reduce glutamatergic tone and may have fewer side effects than benzodiazepines, making them potential long-term pharmacotherapy options. Although there are promising reports of tiagabine in several anxiety disorders (described subsequently), the widespread use of this agent has been significantly limited by an FDA warning against off-label use after the report of 31 cases of new-onset seizures following 3 to 4 months of treatment [27].

In an 8-week RCT of tiagabine, up to 16 mg/d (mean dose = 10.2 mg/d), in 266 patients with GAD, observed case and mixed-model repeated measures analyses demonstrated significant reduction in HAM-A scores versus placebo, although the primary analysis, using the more conservative last observation carried forward, failed to differentiate tiagabine from placebo [28]. In an 8-week, open-label study of 18 patients with any *DSM IV*, non-OCD anxiety disorder who had failed at least one 4-week course of antianxiety medication, augmentation of baseline pharmacotherapy with tiagabine, titrated up to a maximum of 20 mg/d, reduced HAM-A scores by 10 for the sample, with 76% of patients classified as treatment responders (≥ 50% decrease in HAM-A scores) and 59%

of patients remitting (HAM-A ≤ 7), with the most common side effect reported being cognitive slowing in 44% of patients [29].

In a 12-week, open-label and a 12-week, double-blind discontinuation trial of tiagabine, titrated up to 16 mg/d (mean dose = 12.5 mg/d), in treatment of PTSD (n = 19), symptoms measured by the Short PTSD Rating Interview decreased by 50% within 4 weeks of initiation of treatment, an effect that lasted through week 12 [30]. Patients who did not meet remission criteria by week 12 but were randomized to tiagabine in the double-blind phase were more likely to remit than those switched to placebo.

Valproic acid

Valproic acid is an anticonvulsant approved for the treatment of epilepsy, migraine headache prophylaxis, and acute bipolar mania. A number of trials have shown efficacy for valproic acid in the treatment of panic disorder [31,32]. More recently, valproic acid was studied as a treatment for social anxiety disorder. In a 12-week, open-label, flexible-dose trial of valproic acid (range = 500–2500 mg/d, mean dose = 1985 mg/d) in 15 patients with generalized social anxiety disorder, 46.6% responded by achieving a Clinical Global Impression (CGI) score of 2 or less, with statistically significant decreases in LSAS scores [33].

Phenytoin

Phenytoin is a sodium channel blocker used in the treatment of epilepsy. In a 3-month, open-label trial of phenytoin (300–400 mg/d, dosed by blood levels) in nine patients with PTSD, phenytoin treatment resulted in statistically significant decreases in CAPS scores, including the intrusion, avoidance, and hyperarousal symptom clusters [34]. Symptoms improved within the first 4 weeks of treatment and continued to improve for the remainder of treatment.

Gabapentin

Gabapentin is an anticonvulsant with an unknown mechanism of action approved for treatment of epilepsy. In a 14-week RCT of flexibly dosed gabapentin (range = 900–3600 mg/d) in 69 patients with social anxiety disorder, patients receiving gabapentin showed early and sustained reduction improvements in LSAS scores, with twice as many (n = 11) patients on active medication reaching response criteria as those on placebo [35]. A similarly designed RCT in panic disorder showed less promising results. In this 8-week RCT of flexibly dosed gabapentin (again, 600–3600 mg/d) in 103 patients with panic disorder, no overall drug-placebo difference was observed in scores on the Panic and Agoraphobia Scale [36].

Levetiracetam

Levetiracetam is an anticonvulsant that modulates voltage-gated calcium channels and is approved for the treatment of epilepsy. The first published trial of levetiracetam in anxiety disorders was an 8-week, open-label trial in 20 patients with social anxiety disorder treated flexibly with 500 to 3000 mg/d (mean dose = 2013 mg/d) [37]. The drug was well tolerated, with the most common side effect being mild sedation reported by six subjects. A statistically significant improvement in LSAS scores (mean decrease = 20.5) was evident by week 2 and persisted through the trial.

In a small follow-up RCT, patients with social phobia were randomized to receive levetiracetam, 500 to 3000 mg/d (n = 9, mean dose = 1500 mg/d), or placebo (n = 7) for 7 weeks [38]. The study showed a trend toward efficacy, with the active group showing a 44% response rate by Brief Social Phobia Scale score reductions versus 14% in the placebo group. However, the study was underpowered to show a statistically significant superiority.

A retrospective, naturalistic study examining levetiracetam (mean dose = 1967 mg/d) for an average of 10 weeks in 23 patients with treatment-resistant PTSD showed a 56% response rate and a 26% remission rate by PTSD Checklist-Civilian Version and CGI-Severity of Illness scale scores [39].

D-cycloserine (DCS)

DCS is an antituberculous antibiotic and also a partial agonist of the NMDA receptor at the glycine site that was found to improve cognitive function in schizophrenia [40]. Based on these findings and the supposition that cognitive enhancement may be a useful adjunct therapy in the treatment of PTSD [41], a pilot RCT of 4 weeks of DCS, 50 mg/d, in 11 patients with chronic PTSD showed a clinically significant reduction in numbing and avoidance symptoms and a statistically significant reduction in mean CAPS scores, although the outcomes did not reach statistical segregation from placebo [42]. The study was limited by a small sample size, fixed dosing, lack of standardized psychotherapy, and a crossover design in which participants served in both active drug and placebo groups, and it did not examine the effects of acute versus chronic administration of DCS.

To test the hypothesis that DCS enhances extinction learning in conjunction with exposure psychotherapy for phobic disorders, a clinical trial of DCS, 50 or 500 mg, versus placebo, administered in conjunction with virtual reality exposure therapy (VRE), was performed in 28 patients with acrophobia [43••]. Patients receiving DCS immediately prior to VRE therapy had a faster improvement of physiologic and self-reported psychological measures of fear following VRE therapy that persisted at 3-month follow-up. Although it was still a pilot trial limited by a small sample size and very narrow inclusion criteria, this study offers intriguing and promising insights into one role for glutamatergic NMDA partial agonists in the facilitation of extinction in phobias.

Further evidence of the efficacy of DCS as augmentation to exposure therapy was recently described in patients with social phobia. A small sample of patients (n = 27)

were randomized to DCS, 50 mg, or placebo administered 1 hour prior to individual or group exposure therapy challenging patients with public speech situations and videotaped feedback [44••]. Patients receiving DCS had significant reductions in Social Phobia and Anxiety Inventory scores as compared with placebo, which persisted at 1-month follow-up.

Multiple larger trials with more clinically heterogeneous samples are underway and may offer insights into the clinical utility of DCS in augmenting psychotherapies to extinguish fear responses in anxiety disorders.

Metabotropic Glutamate Receptor Agents

LY354740

LY354740 is a glutamate analogue with high specificity for mGlu2/3. Activation of presynaptic mGlu2/3 downregulates glutamate release [45]. In preclinical and early clinical trials, LY354740 was shown to have robust anxiolytic properties [46]. However, when tested in a phase II, placebo-controlled, double-blind, randomized study in panic disorder, the drug did not differ from placebo and was less effective than paroxetine [47].

Other agents in development

Other agents in development for anxiety and various neuropsychiatric conditions, including stroke, epilepsy, pain, depression, and alcohol dependence, include group 1 mGluR antagonists, selective glycine$_B$ receptor antagonists, NMDA subtype selective antagonists (NR2A, NR2B), and glutamate glial transporter blockers.

Conclusions

Pharmacologic agents that modulate the glutamate system may offer a promising avenue for further investigation for the treatment of anxiety disorders. Many of the drugs discussed in this review have been used extensively in mood disorders and varied neuropsychiatric disorders that are highly comorbid with anxiety. Several potential advantages of glutamate-modulating agents, relative to existing anxiolytics, include the following: 1) low incidence of sexual side effects and generally limited weight gain; 2) compared with SSRIs and SNRIs, there might be a more rapid onset of action (adequately designed comparative studies to test this hypothesis are needed); and 3) given the mood-stabilizing quality of several of these agents, antiglutamatergics also may provide a lower risk of inducing hypomania and mood cycling in those patients in whom an underlying bipolar disorder has not been ruled out. Finally, whereas benzodiazepines are generally effective for the acute treatment of anxiety, glutamatergic agents may have broader clinical applications given their limited abuse liability and their lack of pharmacologic tolerance or potentiation of the effects of alcohol.

Currently, there is no well-parsed algorithmic approach for the use of glutamate modulators in the treatment of anxiety disorders. An important challenge to a rational pharmacology is the broad phenotype represented in clinical trials of anxiety disorders, with high degree of comorbidity among the *DSM IV* anxiety disorders and with affective disorders. Another confounding factor is the high incidence of substance abuse among patients with anxiety disorders, who often self-medicate with recreational or prescription medications. Finally, although a significant literature on the neuroanatomic, genetic, and epidemiologic correlates of anxiety disorders exists, the etiology of these disorders remains unclear, posing a clear challenge to drug discovery.

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