

# Glutamatergic agents for OCD and related disorders

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Published online: 3 July 2015

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This article is part of the Topical Collection on *Anxiety, Obsessive Compulsive and Related Disorders*

**Keywords** Obsessive-compulsive disorder · Glutamate · NMDA receptor · Memantine · Riluzole · Ketamine · D-Cycloserine

## Opinion statement

Pharmacotherapy remains inadequate for many patients with obsessive-compulsive disorder (OCD); there is an urgent need for alternative pharmacological strategies. Convergent evidence suggests imbalance in glutamate, the brain's primary excitatory neurotransmitter, in some patients. This has motivated interest in glutamate modulators in patients who are unresponsive to standard pharmacotherapeutic approaches. While no glutamate modulator can be considered proven as an efficacious treatment of OCD, promising suggestions of benefit have been reported for memantine and riluzole. The evidence is thinner for *N*-acetylcysteine, but this agent's low cost and benign side effect profile make it a reasonable consideration in certain patients. Intriguing research on *D*-cycloserine and ketamine suggest potential benefit as well. It is notable that these agents all work by different, and in some cases opposite, mechanisms; this suggests that we have much to learn about the role of glutamate dysregulation in the etiology of OCD and of glutamate modulators in its treatment.

## Introduction

Approximately 30 % of the population experiences troubling obsessions or compulsions [1]. In one person in 40, these produce a degree of impairment or distress sufficient to merit a diagnosis of obsessive-compulsive disorder, or OCD, at some point in their lives [2]. Similar phenomenology is seen in a range of other diagnoses, some of which have been categorized as "obsessive-compulsive-related disorders" in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders

[3]. The associated morbidity is substantial [4, 5], as is the cost to society [6].

Obsessions are intrusive, stereotyped, unwanted thoughts that cause anxiety or distress; there is typically some effort to control or neutralize them. Common obsessions include concerns about contamination, fears of imminent harm, and preoccupations with order or symmetry. Compulsions are repetitive, stereotyped behaviors that are typically undertaken in an effort to

neutralize the discomfort associated with obsessions; common examples include washing, checking, and ordering or arranging [3, 7]. Comorbidity is common in OCD, occurring in up to 90 % of patients; the most common comorbidities include depression, panic disorder, social phobia and other phobias, and alcohol use [1].

Established treatments can be of substantial benefit to many [7]. In particular, specialized cognitive-behavioral therapy and pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) are both first-line treatments, and approximately two in three patients will benefit significantly from these interventions [7, 8]. Evidence-based options after these first-line treatments are exhausted are, however, limited [7, 9, 10]. This leaves approximately one in three patients without meaningful benefit even after optimal treatment; given the lifetime morbid risk of 2.7 % [2], this translates to over three million people in the USA. Furthermore, many who are

judged to be treatment responders have a partial response and/or a fluctuating course and thus continue to experience substantial morbidity. These numbers highlight the urgent need for new treatments.

Established pharmacological strategies in OCD target the brain's serotonin and dopamine neuromodulatory systems. Efforts to identify other neurochemical systems that may be involved in OCD and may represent fruitful therapeutic targets have led to investigations of other classes of medications in recent years. Increasing interest has focused on modulators of glutamate, the brain's primary excitatory neurotransmitter, as potential therapeutics in refractory disease [11•, 12–14]. While no such agent has been definitively proven to be efficacious, convergent evidence is increasingly lending credibility to this approach, and several well-tolerated agents represent reasonable alternatives once standard-of-care interventions have been exhausted.

## Glutamate in the central nervous system

A comprehensive review of glutamate in the brain is far beyond our scope here, but a review of basic concepts is useful to lay the groundwork for what follows; more detailed discussions are available in recent reviews [11•]. Glutamate is an amino acid that serves as the brain's primary excitatory neurotransmitter. Its role in the brain is thus fundamentally different from that of the monoaminergic neurotransmitters. Dopamine, serotonin, and other aminergic transmitters are used by a small minority of cells that are localized in a few brain regions, mostly in the brainstem and midbrain; these cells project broadly and have important modulatory effects on diverse functional circuits throughout the brain. Glutamatergic neurons, in contrast, are embedded in practically every brain circuit; rather than being modulatory, they are appropriately thought of as constituting the circuitry itself, in most cases. This being the case, it is simplistic to speak of a "glutamate system"; the glutamate system constitutes the entire brain. Similarly, it is problematic to ask whether glutamate is excessive or reduced in OCD, or any other condition, or to seek simply to increase or decrease it using pharmacotherapy. Globally increasing glutamate would be expected to lead to seizure and neurotoxicity and globally reducing it to anesthesia. Any abnormalities in psychiatric disease are likely to be more subtle and circuit specific, and any pharmacotherapy aimed at glutamate should be thought of as modulatory, rather than simply activating or antagonizing.

Glutamate is packaged into vesicles at the axonal presynaptic terminal and is released into the synaptic cleft upon arrival of an action potential. Synaptic glutamate binds to several classes of receptors. Key among these is the *N*-methyl-D-aspartate (NMDA) receptor, so named for the agonist used to identify it in early studies. The NMDA receptor has several unique characteristics, to

which we will return below, and is a target of several glutamatergic drugs [15]. Other glutamate receptors include the AMPA and kainate receptors and the metabotropic glutamate receptors, or mGluRs. Glutamate is efficiently removed from the area around the synaptic cleft by a group of transporters, collectively known as the excitatory amino acid transporters, or EAATs [16]. EAAT1 and EAAT2 are expressed on astrocytes and perform the majority of this glutamate reuptake; EAAT3 is expressed on neurons. Low levels of glutamate persist extrasynaptically due to spillover from the synaptic cleft as well as active regulation by glial cells. These various glutamate receptors and transporters all constitute potential targets for pharmacotherapeutic agents.

A primary function of glutamate in the central nervous system is the transmission of signals from one neuron to another, but it has other roles. Glutamate binding to the NMDA receptor, in particular, is critical for the initiation of important forms of synaptic plasticity; this is mediated by the influx of calcium ions through the activated receptor. Excessive calcium influx, however, can lead to neuronal damage and even death. Calcium influx through extrasynaptic NMDA receptors appears to be particularly pernicious in this regard, which is presumably one reason that extrasynaptic glutamate concentrations are so tightly regulated. Glutamate binding to mGluR receptors regulates a variety of cellular processes, including synaptic plasticity, negative feedback modulation of glutamate release, and the regulation of local protein synthesis in dendrites.

## Glutamate in OCD

Several lines of evidence suggest that glutamate imbalance may contribute to the pathophysiology of OCD. We will not review these exhaustively here, as our focus is on therapeutics; we present a brief discussion of the major themes in this literature. No single line of evidence is sufficiently clear to constitute proof that glutamate dysregulation is a major contributor to obsessions and compulsions. The pathophysiology of OCD is sure to be heterogeneous, and glutamate dysregulation may be only one contributor among many. The ability to characterize this heterogeneity may, in the future, permit informed choices of targeted pharmacological strategies.

A pair of studies examining cerebrospinal fluid (CSF) in unmedicated adult patients indicates that glutamate is excessive in a subset [17, 18]. This is the most direct evidence for altered glutamate homeostasis in OCD. Several caveats are in order, however. First, glutamate excess was present in a minority of patients; though this was sufficient to produce a statistically significant effect of diagnosis, it may suggest that glutamate imbalance is present in only a subset of cases of OCD. If so, this may indicate that pharmacological approaches targeting glutamate may be appropriate only for that subset. Second, elevated glutamate in CSF cannot inform us as to where in the brain this glutamate comes from—it could be indicative of globally altered glutamate reuptake or some other aspect of homeostasis or of regionally specific abnormalities. Importantly, since glutamate is the principle neurotransmitter of many brain circuits, elevated glutamate could plausibly be a consequence of elevated neuronal activity that overwhelms local buffering capacity and not indicative of specific pathology in glutamatergic regulatory or signaling mechanisms.

A second line of evidence suggesting glutamate dysregulation in OCD derives from imaging studies using magnetic resonance spectroscopy, or MRS [19•]. Early MRS studies in unmedicated pediatric OCD suggested that glutamate and related compounds are elevated in the basal ganglia and reduced in the anterior cingulate cortex [20, 21]. Unfortunately here, too, the story has become more ambiguous with time and caveats abound. MRS has the advantage of allowing specific brain regions to be probed, but it is more difficult to interpret than direct glutamate measurement in CSF. MRS measures total tissue glutamate, including intrasynaptic and extrasynaptic as well as intracellular pools. Most studies do not distinguish between glutamate and related amino acids such as glutamine and aspartate; sometimes, even the inhibitory transmitter GABA contaminates the glutamate measure [11•]. More recent studies have reported variable results, with the majority reporting no significant differences between patients and controls [19•]. It remains unclear whether this is because of methodological heterogeneity, clinical variability, limited statistical power, false positives in the early studies, or some other consideration.

Genetics has the potential to provide the clearest demonstration of an etiological role for glutamate dysregulation in OCD. The genetics of neuropsychiatric disorders are complex and are only slowly coming into focus [22], but several promising leads implicate polymorphisms in regulators of glutamate homeostasis and neurotransmission as risk factors. Early interest focused on the gene *Slc1a1*, which encodes the principle neuronal glutamate transporter, EAAT3 [23, 24]. Mutations in this gene could plausibly alter glutamate clearance from the extrasynaptic space and thus contribute to altered neurotransmission. However, a meta-analysis of studies of the *Slc1a1* gene in OCD has called the initially reported association into doubt [25], and recent genome-wide association studies, though underpowered, have not identified it as a major genetic contributor [26•, 27••]. In those studies that do suggest an association, multiple alleles have been identified; they may have distinct effects on glutamate reuptake, and such effects may be developmentally and regionally restricted [28]. EAAT3 is responsible for a small fraction of total glutamate clearance, and so alterations in this transporter are not likely to have a major quantitative impact on brain glutamate levels [16]. On the other hand, EAAT3 has an important role in the production of antioxidants in neurons, and knockout mice exhibit cortical degeneration due to oxidative stress; this implies that abnormalities in EAAT3 or its expression may have effects other than glutamate dysregulation [29].

Recent genetic studies have suggested that polymorphisms in other glutamate-associated genes may contribute to OCD risk [22]. The synapse-associated protein 90/postsynaptic density-95-associated proteins (SAPAPs)/disks large-associated proteins (DLGAPs), which are key components of the postsynaptic complex that anchors and spatially organizes glutamate receptors, have been a focus of significant interest. The *DLGAP1* gene has emerged from recent genetic studies as a leading candidate risk gene, though it is not yet considered proven [26•, 27••]. Knockout of another member of this gene family, *SAPAP3*, leads to phenotypes in mice that have been interpreted as recapitulating aspects of OCD [30]. Suggestive genetic associations have also been reported with the gene *PTPRD*, a regulator of the development of glutamatergic synapses, and with the glutamate receptor gene *GRIK2* [27••]. None of these genetic associations are yet proven, but the fact that so many glutamate-

associated genes are emerging from genetic studies has the potential to provide perhaps the strongest evidence for a causal role for underlying abnormalities in glutamate homeostasis or neurotransmission in the pathophysiology of OCD.

## Glutamate pharmacology: the NMDA receptor

With this background, we now turn to a consideration of the various glutamate modulators that have been investigated in the treatment of OCD. It is important to emphasize that in no case has the efficacy of these agents been conclusively proven, in general or in a subset of patients, in multiple well-controlled trials, and thus they should not be considered first-line treatment in place of better-proven approaches such as SSRI pharmacotherapy or expert CBT. But in the substantial fraction of patients who do not respond to conventional treatments—which is regrettably large—glutamate modulators represent an increasingly viable alternative [7, 10, 11•]. In the treatment of refractory patients, the evidence of benefit is limited but other therapeutic options are readily exhausted; clinical decisions must be made through careful balancing of risks and uncertain, but plausible, benefits.

### *Memantine*

Memantine is a noncompetitive antagonist that blocks the transmembrane ion channel pore of the NMDA receptor; it binds with relatively weak affinity and a rapid on-off rate, thus attenuating the passage of current through the channel but not blocking it as completely as agents such as ketamine and phencyclidine. Memantine is of modest benefit in intermediate Alzheimer's dementia, and it is approved in the USA and elsewhere for this purpose [31].

Evidence from CSF [17, 18] and MRS studies [21] suggesting elevated glutamate in OCD motivates the use of a glutamate antagonist in refractory disease; memantine has been investigated in this context. Early case reports and case series suggested benefit from the addition of memantine to standard treatment [11•, 32]. Effects have been reported in children as well as adults [33]. Some diagnostic specificity to this effect is suggested by the observation, in an open-label study, that response rates are greater in OCD than in generalized anxiety disorder [34]. Two recent placebo-controlled studies of memantine have been published by groups in Iran, one in inpatients and one in outpatients, both showing very large and statistically significant treatment effects [35, 36]. These controlled studies, while promising, must be interpreted with caution; the effect sizes and response rates reported—100 % in one study—exceed what has been seen in open-label studies of memantine or in controlled studies of any other medication in OCD, and placebo response rates were also extremely high. The generalizability of these results must be established through careful studies from other centers.

With these caveats, memantine is increasingly seen as an alternative in refractory OCD, and it is often used in this context at specialty centers [37]. Dosing has typically followed what is standard in Alzheimer's disease (10 mg twice daily), although lower doses are used in pediatric patients.

Reported tolerability has generally been good, with no reported severe adverse events in OCD patients.

### *Glycine and glycine reuptake inhibitors*

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The NMDA receptor has an obligatory coagonist site that is bound in vivo by the amino acids glycine or D-serine; regulation of the concentration of these coagonists represents an alternative mechanism by which receptor activity can be physiologically modulated [38, 39] and thus a pharmacological target.

Glycine itself was investigated in a single placebo-controlled study of patients with refractory OCD [40]. Results of an analysis of completers suggested benefit of adjunctive glycine ( $p=0.053$ ). However, tolerability of glycine is poor, because it must be taken in very large quantities (~60 g/day), has an unpleasant odor and taste, and frequently causes nausea.

While these characteristics make glycine a difficult agent to use clinically, the results of this pilot study suggest that other strategies modulating the coagonist site may have therapeutic potential.

Concentrations of brain glycine are regulated in part by its reuptake by the transporters, GLY-T1 and GLY-T2. Inhibitors of these transporters can increase local glycine concentrations. Sarcosine, or N-methylglycine, a naturally occurring low-affinity GLY-T inhibitor that is available as a dietary supplement [41], has been investigated in OCD in a single uncontrolled study [42]. Improvement was seen in three different cohorts of patients, either alone or as augmentation of stable SSRI therapy.

More specific GLY-T1 inhibitors have been developed, though they are not widely available. A recently completed phase 2 study of one of these, bitopertin [43], examined efficacy in patients with OCD, as augmentation of stable SSRI treatment (NCT01674361); results have not yet been reported.

### *Ketamine*

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Ketamine is a noncompetitive pore-blocking antagonist of the NMDA receptor, like memantine, but with much tighter binding and very different clinical effects. It has been used clinically as an anesthetic and in pain control since the 1970s [44]; it is also used recreationally and has abuse potential. Interest in ketamine as a treatment for psychiatric disease stems from the unexpected observation that it produces rapid (though short-lived) antidepressant effects, even in severely ill and refractory patients [45, 46]. A full review of this fascinating effect, which has become a major focus in the pharmacology of depression, is beyond our scope here, but the observation has motivated interest in whether a similar effect might be seen in OCD.

An initial case report documented improvement in a medication-free patient with severe OCD after intravenous ketamine infusion [47]. A subsequent uncontrolled study in patients with severe disease, many of whom had comorbidities and were medicated, found a statistically significant but clinically trivial 8 % improvement 24 h after ketamine infusion; among those patients with comorbid depression, there was a 72 % response rate



for depressive symptoms, providing an internal control for the efficacy of the pharmacological treatment [48•]. Subsequently, a randomized placebo-controlled study in unmedicated patients with less severe symptoms but a pattern of continuous obsessions showed a clear and clinically significant response [49••]. In aggregate, these observations suggest that there may be some benefit from ketamine treatment in OCD, perhaps in a particular subset of patients, but whether this effect will prove to be as robust as in major depressive disorder remains to be seen.

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### *D-Cycloserine*

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D-Cycloserine (DCS) is a partial agonist at the glycine/D-serine site on the NMDA receptor. It has proven to be of limited benefit (in schizophrenia, where it has been extensively studied [50]) using a traditional pharmacological approach with daily dosing, perhaps because of the development of tachyphylaxis [51]. However, acute treatment has been shown to enhance certain forms of learning, by augmenting the NMDA receptor's key function in initiating mechanisms of synaptic plasticity [52]. Since cognitive-behavioral therapy, a first-line treatment for OCD and a range of other anxiety and mood disorders, represents a form of structured learning, this observation motivated the hypothesis that phasic D-cycloserine treatment in conjunction with CBT might lead to synergistic benefit [53]. Such synergy has now been demonstrated in a variety of clinical contexts [54].

Several studies have attempted the augmentation of CBT with D-cycloserine in OCD. The results have been mixed. In four early studies, three suggested benefit of D-cycloserine augmentation (not always reaching statistical significance [55–57]), while one did not [58]. Where benefit has been reported, it has generally been in the rapidity of CBT response or the efficacy of low-intensity treatment, not in the asymptotic efficacy of robust CBT; nevertheless, acceleration of CBT's effects could be of substantial clinical importance, if it facilitates engagement or reduces treatment dropouts. Details such as DCS dose and timing may critically affect the efficacy of this approach [59]. A more recent study suggests another modulator of efficacy, with significant benefit from DCS augmentation of CBT in unmedicated adults with OCD, but not in those on stable SSRI pharmacotherapy [60••]. More work is needed to clarify the appropriate role of DCS in OCD treatment.

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### *The heterogeneity of NMDA-targeting strategies*

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These four pharmacological strategies for targeting the NMDA receptor in OCD are striking for their heterogeneity. Memantine pharmacotherapy entails chronic NMDA antagonism. Ketamine, in contrast, has been used as a single infusion and thus entails acute or phasic antagonism. Glycine and GLT1 receptor blockers are presumed to augment NMDA function by increasing the availability of

coagonist glycine and thus entail a chronic indirect enhancement of NMDA function, while D-cycloserine used in conjunction with CBT is an example of acute or phasic NMDA enhancement. It is possible that all of these varied strategies will indeed prove to be of benefit. However, it is important to note that none of these strategies are supported by unequivocal evidence, and it is equally possible that one or more of them will prove, with more data, to be inefficacious. Alternatively, it may be that all four strategies are of potential benefit, but not in the same patients. Much more research is needed to clarify these issues.

## Other glutamatergic agents

### *Riluzole*

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Riluzole is a multifunctional glutamate modulator that is used in the treatment of amyotrophic lateral sclerosis [61]. Two of its mechanisms are inhibition of glutamate release through inhibition of presynaptic voltage-gated cation channels—a mechanism similar to that of anticonvulsant drugs such as lamotrigine and topiramate—and potentiation of glial reuptake of perisynaptic or extrasynaptic glutamate via glial transporters [61]. Riluzole was the first glutamate modulator to be used in refractory OCD [62], and several open-label reports have suggested substantial benefit [63, 64]. More recent controlled studies, however, are less promising. A blinded placebo-controlled study of children with OCD, some of whom were medicated and some of whom had comorbid autism, found no evidence of benefit [65]. And a controlled study of adults, all of whom were stably medicated and some of whom were treated as inpatients, found only a modest benefit in outpatients (and none in inpatients) that did not reach statistical significance in the primary analysis [66•]. What benefit there was appeared to be most significant in obsessions, not compulsions. More studies are needed to clarify whether riluzole is of substantial benefit in a subset of patients.

### *N-Acetylcysteine*

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N-Acetylcysteine, or NAC, is a modified amino acid with both glutamate-modulating and antioxidant properties [67]. Its low cost and relatively benign side effect profile have motivated interest in its utility across a range of neuropsychiatric conditions [68].

Data in OCD remain very thin. An early case report suggested benefit when NAC was added to standard pharmacotherapy [69]. More recently, a controlled trial from Iran has reported a large and statistically significant benefit [70]. Corroborative results from other



sites are needed.

*N*-Acetylcysteine has also been investigated in trichotillomania, an OCD-related disorder, with mixed results. A high-quality blinded placebo-controlled trial in adults suggested clear benefit with a large effect size [71], but a similar trial in adolescents found no evidence for benefit [72]. Despite this relatively sparse evidence, interest in NAC remains strong in many quarters, because of its low cost and benign side-effect profile.

### Anticonvulsants

Anticonvulsant drugs work by a range of mechanisms, several acts by modulating glutamate outflow.

Topiramate interacts with voltage-gated calcium channels and thereby modulates glutamate release from axon terminals. Controlled trials have suggested modest benefit from topiramate; this may be greater for compulsions than for obsessions [73, 74]. Side effects, especially cognitive slowing, can be problematic with this agent, which has not entered widespread use for OCD.

Lamotrigine is another anticonvulsant that has been used for a range of other indications. It reduces glutamate outflow through inhibition of certain voltage-gated sodium channels, overlapping mechanistically with one of the mechanisms of action of riluzole. Early work with lamotrigine suggested no benefit in OCD [75], but a more recent controlled trial has suggested clear benefit [76]. More research is needed.

## Conclusion

Glutamate modulators have been a focus of increasing interest in the treatment of refractory OCD for over 10 years [11•, 62]. This being the case, it is frustrating that their appropriate use in this population remains murky and based on small studies. In refractory patients, however, in whom better-proven strategies have been exhausted, they represent a viable alternative. The evidence for benefit is perhaps strongest for memantine, as reviewed above; riluzole and lamotrigine are also viable considerations that may be of benefit for some patients. More studies of all of these agents, and of the underlying perturbations of normal glutamate neurotransmission or homeostasis, are needed to clarify which agents are of the most benefit and in which patients.

## Compliance with Ethics Guidelines

### Conflict of Interest

Christopher Pittenger declares no financial conflict of interest. He was site PI for a study funded by F. Hoffman La Roche, Ltd., investigating the use of the drug bitopertin in refractory OCD; this study ([www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT01674361) is briefly mentioned in the manuscript.

## Human and Animal Rights and Informed Consent

This article presents no new human or animal data, but it summarizes published work done by the author in human subjects, as described in references 63, 64, 66, 69, and 72. In all cases, these studies were overseen and approved by the Yale University Human Investigations Committee, and all participants gave written informed consent prior to participation.

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