Obsessive compulsive disorder and the glutamatergic system

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Purpose of review
Evidence-based pharmacological interventions for obsessive compulsive disorder (OCD) are targeted mainly at the serotonergic and dopaminergic pathways, and are not always effective. It is timely to review the growing evidence from animal models and clinical research (e.g., brain imaging, genetics) on the role of the glutamatergic system in OCD.

Recent findings
Emerging evidence from both animal models and clinical research (including brain imaging, neurogenetics) supports the glutamatergic system as a potential target for pharmacotherapy in OCD. Although there have been relatively few randomized controlled trials of glutamatergic agents in pediatric or adult OCD to date, there is some work on riluzole, memantine, ketamine, topiramate, lamotrigine, *N*-acetylcysteine, and D-cycloserine.

Summary
Given the need for more efficacious treatments in OCD, and given emergent findings on the role of the glutamatergic system in this disorder, there is a need for additional pharmacotherapy trials on glutamatergic agents in OCD. Possible research designs for such trials might include stand-alone approaches, pharmacotherapy augmentation, or psychotherapy augmentation.

Keywords
clinical trials, genetics, glutamate, obsessive-compulsive disorder

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic condition that is characterized by significant impairment and contributes to an estimated 3% global burden of disease [1,2]. Onset is often early in life, and subsequently a range of comorbid psychiatric disorders often occur. Presentation to health services may be delayed due to shame surrounding the distressing symptoms as well as low health literacy [3,4]. The Epidemiological Catchment Study estimated the lifetime prevalence in populations in the United States to be 2.5%, data that have been supported by the recent National Comorbidity Survey Replication (NCS-R) and other studies in the World Mental Health Surveys [2,5].

Evidence-based pharmacological interventions for OCD are targeted mainly at the serotonergic and dopaminergic pathways, and are not always efficacious. It is timely to review the growing evidence from animal models and clinical research (e.g., brain imaging, neurogenetics) on the role of the glutamatergic system in OCD. Before doing so, we briefly review the diagnosis and assessment of this condition, as there have been a number of recent changes to the classification and diagnosis of OCD and related disorders (OCRDs).

CLINICAL SYMPTOMS AND DIAGNOSIS

Core features of OCD include intrusive, distressing thoughts, images, or urges (obsessions) which may heighten anxiety and which are recognized by the individual as inappropriate products of his or her own mind. These obsessions are different in quality

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KEY POINTS

- While the standard neurobiological model of obsessive compulsive disorder has long focused on cortico-striatal-thalamic-cortical circuitry, work has mainly focused on serotonergic and dopaminergic systems.
- There is growing evidence from animal research that glutamatergic neurons are also important in stereotypic behavior. This evidence is supported by human brain imaging and neurogenetics research.
- There is also early evidence from clinical trials that glutamatergic agents may be useful in the treatment of OCD. However, additional work, using larger samples, is needed to expand and confirm these promising but preliminary signals.

from simple everyday worries. The person then tries to neutralize the obsessions with other thoughts or mental acts (compulsions) that are often performed in a ritualistic manner designed to prevent an untoward event and alleviate anxiety.

Common obsessions include fears of contamination with the compulsion of washing or cleaning, as well as fear of harm to self or others with repeated act of checking and rechecking [6,7]. A third major symptom dimension revolves around symmetry obsessions and compulsions. Although factor analyses have also indicated that hoarding is another major symptom dimension of OCD, given research indicating that the phenomenology and psychobiology of hoarding differs from that of other symptom dimensions, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) now includes a new diagnosis of hoarding disorder [8].

Another notable change in DSM-5 is the introduction of a new chapter on obsessive compulsive and related disorders. First, there are key differences in the phenomenology and psychobiology of OCD and other DSM-IV anxiety disorders [8]. Second, there are important overlaps in the phenomenology and psychobiology of OCD with several other disorders characterized by repetitive preoccupations and/or ritualistic, stereotypical behavior [9,10]. The DSM-5 OCRD chapter includes OCD, body dysmorphic disorder, hoarding disorder, trichotillomania (hair-pulling disorder), and excoriation (skin-picking) disorder [8].

As noted above, OCD often has early onset, and significant comorbidity. Without treatment, the course is somewhat variable, but is characterized by a long lag between symptom onset and formal diagnosis, and often by continued symptomatology. In the clinical setting, it is useful to assess symptom severity using a standardized symptom severity scale such as the Yale–Brown Obsessive Compulsive Scale (YBOCS), comorbid disorders, and functional impairment.

ANIMAL STUDIES

As noted, evidence-based treatments of OCD target the serotonergic and dopaminergic neurotransmitter systems. Similarly, animal models of and clinical research on OCD have focused on these systems, and their role in modulating the cortico-striatal-thalamic-cortical (CSTC) circuitry thought to underlie OCD symptoms. For example, in an exciting new line of research, optogenetic techniques have been used to repeatedly hyperstimulate corticostriatal neurons, resulting in excessive grooming behavior, which then responded to fluoxetine [11–13]. However, recent basic work has also provided insights into the role of glutamate in repetitive behavior [14,15▪▪]. We briefly review some of the key laboratory studies.

The D1CT-7 (cyclin D1 promoter controlling the expression of cholera toxin) model was the first genetic mouse model to test the CSTC theory of OCD. Cholera toxin activates signal transduction of stimulatory G-protein and synthesis of cyclic adenosine monophosphate (cAMP). Hyperactivation of the cortical–limbic glutamatergic neurons in these transgenic mice led to OCD-like stereotypical behavior and tics [14]. Furthermore, the D1CT-7 mice exposed to the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK 801 showed increased repetitive climbing and leaping, and stereotypical behavior [13].

A role for changes in glutamate signaling and transmission was found in two knockout mouse models characterized by compulsive behavior. These models focused on the disks large-associated protein 3 (DLGAP3), also known as SAP90/PSD95-associated protein 3 (SAPAP3), as well as on SLITRK5, which are the scaffold proteins in the postsynaptic membranes of neuronal synapses, predominantly in the striatum [15▪▪].

Genetic deletion of DLGAP3/SAPAP3 resulted in increased anxiety and compulsive grooming behaviors, perhaps analogous to those seen in human participants with trichotillomania (hair-pulling disorder) and in skin-picking disorder [16,17]. The DLGAP3-knockout mice were found to have changes in NMDA receptor composition, namely greater numbers of NR1 (GRIN1) and NR2B (GRIN2B) subunits, and fewer NR2A (GRIN2A) subunits of striatal neurons [15▪▪,16]. These changes suggest that glutamate dysfunction in CSTC circuitry also plays a role in compulsive behaviors [18]. Indeed, an association has been found between SAPAP3 variants and early-onset OCD in some work [15▪▪,17].

Deletion of the SLITRK5 gene resulted in behavioral phenotypes similar to those seen in the DLGAP3-knockout mice, with excessive grooming of facial hair and severe skin excoriations [19]. However, there were differences between the two models in the expression of the NR2A and NR2B glutamate receptor subunits in the striatum at postmortem. With SLITRK5 gene deletions, the striatal expression of both receptor subunits was reduced. In the mice with DLGAP3 deletions, striatal expression of only NR2A was decreased, whereas that of NR2B was increased [15▪▪,16]. Again, there is some evidence of an association between SLITRK5 variants and obsessive compulsive and related disorders, although not all studies are consistent [20].

The signal attenuation model is an intriguing rodent model based on classical conditioning principles, with rats developing lever-pressing initially in response to a food reward. A light stimulus is then introduced to encourage extinction of the stimulus-food correlation but some continue lever-pressing compulsively. Rats treated with D-cycloserine (DCS), a partial NMDA receptor agonist, showed reduced compulsive behavior compared with the control group [21].

Repetitive digging and marble-burying behavior is another model that can be used to study obsessive compulsive and related symptoms. Mice studies indicate that the NMDA antagonist amantadine inhibits this marble-burying behavior without affecting motor movement [22].

Although conducting studies and interpreting data on rodents is clearly different from human participants due to the absence of language to describe the experience of the obsessive behaviors from the individual's perspective [23], such work provides an important foundation for moving from bench to bedside. In the next section, we review clinical research focused on alterations in the glutamatergic system in OCD.

CLINICAL STUDIES

Cognitive-affective research on OCD has indicated that this disorder is characterized by abnormalities in reversal learning, and perhaps by disturbances in the processing of particular affects such as disgust [24,25]. OCD has also been conceptualized in terms of excessive release of procedural strategies presumably reflecting disorder either in the striatum (which plays an important role in mediating such habitual behaviors) or in cortical structures (which play an important role in modifying activity in relevant subcortical structures).

Early cases of OCD after cortico-striatal neurological damage gave impetus to a cortico-striatal model of OCD, and this has been supported by brain imaging research. Both structural and functional studies have emphasized the role of ventral CSTC circuitry in OCD [26–29]. Structural studies have shown evidence of alterations in the volume of the relevant structures, as well as abnormalities in the relevant white matter structures, whereas functional studies have demonstrated hyperactivation of these circuits during exposure to feared stimuli as well as abnormalities in functional connectivity [30–33].

Thus, for example, early PET and single-photon emission computed tomography (SPECT) studies indicated increased glucose metabolism in CSTC circuitry, comprising the orbitofrontal cortex, anterior cingulate cortex, caudate, and thalamus [34,35]. Key neurotransmitter systems in these regions include the serotonin and dopamine systems, and both molecular imaging studies and pharmacotherapy studies have pointed to their involvement in OCD [36]. Thus, there was a reduction of glucose metabolism in the same regions after treatment with selective serotonin reuptake inhibitors (SSRIs) [37,38].

There are, however, two main types of glutamate receptors in many cortical and subcortical circuits [38]. Glutamatergic cortical tracts descend to act directly on the striatum with synapses on medium spiny neurons [15▪▪]. Inhibitory neurons connect to the basal ganglia structures in two pathways with opposite complex actions: the direct striatonigral pathway and the indirect striatopallidal pathway [36]. Magnetic resonance spectroscopy (MRS) studies in OCD have found reduced glutamate concentration in the anterior cingulate of patients with OCD [15▪▪,28,39].

Other clinical research methods support the role of the glutamatergic system in OCD [36]. Two studies examining the cerebrospinal fluid (CSF) of people with OCD reported increased concentrations of glutamate [40,41]. One of the studies looked at the association between OCD and CSF autoantibodies binding to the proteins in the thalamus and basal ganglia and found significantly more binding of these autoantibodies to thalamic and basal ganglia homogenates, and higher CSF glutamine and glycine levels, in individuals with OCD than in healthy controls [3,41]. This finding is consistent with a theory of abnormal excitatory neurotransmitter transmission in treatment-refractory OCD.

Genetic studies further confirm a role for the glutamatergic system in OCD. Solute carrier 1 (SLC1A1) encodes for the main neuronal excitatory amino acid transporter 3 (EAAT3), also known as excitatory amino acid carrier 1, EAAC1. Several family studies have shown significant associations between single nucleotide polymorphisms (SNPs) of

this gene and OCD susceptibility [42–46]. Other genes to show associations between SNPs and OCD are GRIN2B, which encodes for the NR2B receptor subunits, GRIK2 and GRIK, and DLGAP3 [16,47,48]. Gene variants in the glutamatergic system have been associated with specific alterations in brain imaging studies, including lower concentrations of glutamate in the anterior cingulate associated with GRIN2B, and higher glutamate concentrations in the caudate nuclei of pediatric patients with OCD [23,33]. Although not all data are consistent, findings pointing to glutamatergic involvement in OCD are some of the most widely replicated of the candidate gene studies in OCD [36,48,49]. Furthermore, a genome-wide association study of OCD found that in a case–control analysis, the lowest two *P* values were found within DLGAP1, another member of the neuronal postsynaptic density complex [50].

PHARMACOTHERAPY

SSRIs have been well studied in OCD, and are considered a first-line pharmacotherapy. A meta-analysis of SSRI studies suggested that higher doses are associated with a greater effect size [51]. Compared with the highly serotonergic tricyclic antidepressant clomipramine, SSRIs are better tolerated and safer [51,52]. The best studied SRI augmentation strategy for treatment-refractory OCD is the use of low-dose dopamine blockers [52,53]. However, a substantial proportion of OCD individuals fail to response to SSRIs, or to augmentation treatment.

Given the evidence from animal models and human research that the glutamatergic system is involved in OCD, it seems reasonable to target this system in pharmacotherapy. Potential glutamatergic agents include riluzole, memantine, and other NMDA-receptor antagonists (e.g., amantadine and ketamine), and certain anticonvulsants with glutamatergic properties (e.g., topiramate and lamotrigine), *N*-acetylcysteine (NAC), and DCS [15▪▪,54].

Riluzole is a calcium and sodium-channel blocker, which inhibits synaptic glutamate release and enhances glutamate uptake by astrocytes. Open-label trials have indicated that riluzole is effective in reducing OCD symptoms in more than half the pediatric and adult samples studied [55,56]. However, no randomized controlled trial (RCT) of riluzole in OCD has yet been published.

The NMDA receptor antagonist memantine has US Food and Drug Administration (FDA) approval for the treatment of moderate Alzheimer's dementia. One open-label study indicated its potential value as an augmentation strategy in treatment-resistant OCD [57]. Another open-label trial indicated efficacy of memantine treatment in OCD, but not in generalized anxiety disorder [58]. These findings suggest that further work with this agent in OCD may be warranted.

To date, there are no studies of treatment of OCD in humans with another NMDA antagonist, amantadine [22,28]. Ketamine is a glutamate modulator demonstrated in one open-label trial to have short-lived effects on treatment-resistant OCD symptoms without any sustained improvement [58]. In a recent randomized controlled cross-over trial, a single dose of ketamine resulted in improved symptoms in individuals not on any other treatment for OCD [59,60].

Small trials of other glutamatergic agents such as the anticonvulsants topiramate and lamotrigine have shown promise as monotherapy or augmenting agents in OCD [61–64]. A small RCT reported improvement of OCD symptoms with topiramate augmentation of SSRI medication [62]. Several case reports suggest that lamotrigine may be efficacious in augmenting SSRI treatments, although there are no RCTs [65,66]. However, one small study of lamotrigine augmentation of SSRI treatment of OCD did not demonstrate statistically significant symptom improvement [67].

NAC is a nutraceutical that increases extracellular glutamate by its action on the cystine oxidative pathway. A case study examining augmentation of fluoxetine with NAC suggested that this agent may be efficacious in OCD [68]. However, a more recent case series of patients with refractory OCD did not provide support for this augmentation strategy [69]. Notably, however, NAC was effective in a RCT of trichotillomania in adults [70] with some case reports of efficacy in skin picking [71]. On the other hand, NAC was ineffective in a RCT of trichotillomania in children [72].

There has been increasing interest, emerging from laboratory work on fear extinction, on the use of DCS to augment the effects of cognitive-behavioral therapy in anxiety and related disorders [52]. Two well designed trials have suggested that DCS is effective in the augmentation of exposure therapy for OCD [73,74]. However, one study did not show any improvement with DCS-enhanced exposure response prevention therapy [75]. A range of methological issues may contribute to explaining these inconsistent findings, and additional work on DCS as augmentation for cognitive-behavioral therapy is required [52].

CONCLUSION

Animal studies and clinical research (including brain imaging and neurogenetic studies) have

pointed to the role of the glutamatergic system in OCD. Although further work is needed to consolidate and extend this early work, it is notable there is already some preliminary evidence for the efficacy of various glutamatergic drugs in OCD. However, there are few well designed, randomized placebo-controlled trials of such agents. Such trials are sorely needed, given the chronicity and severity of OCD, and the fact that many individuals with this disorder fail to respond to first-line agents.

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Conflicts of interest

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