Review Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 2024; 16(3):383-400
doi: 10.18863/pgy.1279927

Role of Glutamatergic Modulators in the Treatment of Obsessive Compulsive and Related Disorders

Obsesif Kompulsif ve İlişkili Bozuklukların Tedavisinde Glutamaterjik Modülatörlerin Rolü

Fatma Gül Helvacı Çelik[1], Çiçek Hocaoğlu[2]

[1]Giresun University, Giresun
[2]Recep Tayyip Erdoğan University, Rize

ABSTRACT

Due to the shared phenomenology and research findings related to disorders like obsessive-compulsive disorder (OCD), trichotillomania (TTM), body dysmorphic disorder (BDD), skin picking disorder (SPD), hoarding disorder (HD), and OCD, these conditions are collectively classified as Obsessive-Compulsive and Related Disorders (OCRDs) in the DSM-5. Despite having distinct features from OCD in terms of course and treatment outcomes, they are categorized together. The etiology of OCRDs remains incompletely understood, and information on their treatment is limited. Traditional pharmacological approaches often fall short in addressing the needs of many OCRD patients, necessitating alternative strategies. Recent research has shed light on a potential imbalance in glutamate, a crucial excitatory neurotransmitter in the brain, among certain patients with OCRDs. Findings from these studies suggest that glutamate modulators may be beneficial for individuals who do not respond to standard pharmacotherapeutic interventions. While no glutamate modulator has conclusively proven effective for OCD, promising results have been noted for memantine and riluzole. The evidence surrounding N-acetylcysteine (NAC) also positions it as a reasonable consideration for some patients. Noteworthy research on D-cycloserine (DCS) and ketamine has indicated potential benefits, and investigations into the off-label use of these pharmacological agents, originally approved for other indications, have been particularly focused on refractory OCRDs. It is essential to highlight that these drugs operate through diverse and, in some cases, opposing mechanisms. However, it is crucial to acknowledge that the existing studies on the use of these drugs in OCRDs are still insufficient. A more in-depth exploration of glutamate imbalance in the etiology of OCRDs is needed to better understand the role of glutamate modulators in treatment.

Keywords: Obsessive compulsive and related disorders, glutamate, D-cycloserine, ketamine, N-acetylcysteine

ÖZ

Obsesif kompulsif bozukluk (OKB) gibi bozuklukların fenomenoloji ve çalışma bulgularının benzer olması nedeniyle; trikotillomani (TTM), beden dismorfik bozukluğu (BDB), deri yolma bozukluğu (DYB) ve istifleme bozukluğu (İB) ile OKB, DSM-5'te Obsesif Kompulsif ve İlişkili Bozukluklar (OKİB) tanısal sınıflandırması altında yer almıştır. Bu psikiyatrik bozuklukların seyri ve tedavi sonuçları gibi OKB'den ayırt edici özellikleri olduğu için ayrı bir tanı olarak değerlendirilmiştir. OKİB'daki psikiyatrik bozuklukların etiyolojisi tam olarak aydınlatılamamıştır ve tedavilerine ilişkin bilgiler de sınırlıdır. Öte yandan, OKİB'lu birçok hastanın tedavisinde farmakolojik yaklaşımlar yetersiz kalmaktadır. Bu nedenle alternatif farmakolojik tedavi stratejilerine ihtiyaç vardır. Etiyoloji üzerine yapılan son araştırmalar, bazı hastalarda beynin en önemli eksitatör nörotransmitteri olan glutamattaki dengesizliğe dikkat çekmiştir. Bu çalışmaların sonuçları, standart farmakoterapötik yaklaşımlara yanıt vermeyen hastaların tedavisinde glutamat modülatörlerinin kullanımını desteklemektedir. Hiçbir glutamat modülatörünün OKB için etkili bir tedavi olduğu kanıtlanmamasına rağmen, memantin ve riluzol için umut verici olabileceği bildirilmiştir. N-asetil sistein (NAC) için kanıtlar da bu ilacı bazı hastalar için makul bir değerlendirme haline getirmektedir. D-sikloserin ve ketamin üzerine yapılan ilginç araştırmalarda da potansiyel bir faydadan söz edilmiştir. Diğer endikasyonlar için onaylanmış bu farmakolojik ajanların etiket dışı kullanımı, özellikle dirençli OKİB'da araştırılmıştır. Bu ilaçların hepsinin farklı ve bazı durumlarda zıt mekanizmalarla çalışması da dikkat çekicidir. Ancak bu ilaçların OKİB'da kullanımı ile ilgili çalışmaların halen yetersiz olduğu unutulmamalıdır. OKİB etiyolojisinde glutamat dengesizliğinin daha fazla araştırılması, glutamat modülatörlerinin tedavideki rolünü daha da aydınlatacaktır.

Anahtar sözcükler: Obsesif kompulsif ve ilişkili bozukluklar, glutamat, D-sikloserin, ketamin, N-asetilsistein

Address for Correspondence: Çiçek Hocaoğlu, Recep Tayyip Erdoğan University Faculty of Medicine Department of Psychiatry, Rize, Türkiye **E-mail:** cicekh@gmail.com
Received: 09.04.2023 | **Accepted:** 29.07.2023

Introduction

Obsessive Compulsive and Related Disorders (OCRDs) is newly added diagnostic group of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5) (APA 2013). There is a similar phenomenology of these disorders like obsessive compulsive disorder (OCD). Because of the different outcomes from anxiety disorders in course of illness, comorbidity, familial, genetic risk factors and biomarkers, personality correlates, cognitive-emotional processing, and treatment response, OCRDs were separated from anxiety disorders (Stein et al. 2010, Grünblatt 2021).

Obsessions (intrusive and unwanted recurrent and persistent thoughts, urges, or images) and compulsions (repetitive behaviors or mental acts to response an obsession) are the main symptoms of this group. In this group anxiety is an answer of these urges. In DSM-5, new specifications were added-good or fair insight, poor insight and absent insight/delusional beliefs. OCD, body dysmorphic disorder (BDD), skin picking disorder (SPD), trichotillomania (TTM), hoarding disorder (HD), substance/medication induced OCD, OCD due to another medical condition, other specified OCD, unspecified OCD (for example: exceptional jealousy) are the sub group disorders of OCRDs (Abramowitz et al. 2015). Repetitive behaviors are present in almost all disorders in OCRDs. While cognitive features are more prominent in some such as OCD, BDD and HD, body-oriented repetitive behaviors are observed more frequently in others such as TTM and SPD (Van Ameringen et al. 2014).

In addition to the common etiological features of OCD and OCRDs, there are similarities in treatment approaches. Accepted treatments such as serotonergic antidepressants for OCD are also used in the treatment of OCRDs. However, less is known about the treatment of OCRDs other than OCD and there are far fewer small studies. Serotonergic pharmacotherapy and clomipramine are first line pharmacotherapy for OCD is recommended in moderate-to-high doses and with a waiting period of at least 3 months until efficacy is seen. It has been determined that other OCRDs benefit from similar treatment options and serotonergic drugs are the first choice pharmacotherapy approaches for other OCRDs (Lochner et al. 2014). However, a significant number of current treatment approaches do not provide benefits in the treatment of OCD (Fineberg et al. 2010, Dougherty et al. 2018). Similarly, pharmacotherapy response is inadequate in OCRDs such as BDD, TTM, and HD (Borue et al. 2015, Parli et al. 2023). Certain common and accepted treatments for OCD are also used in the treatment of OCRDs. However, a significant number of current treatment approaches do not provide benefits in the treatment of OCRDs. Many patients with partial or no response to treatment continue to experience significant morbidity. This situation necessitated the development of new treatment strategies. Most of the recent studies in this area have focused on glutamate, which is a neurotransmitter (Pittenger 2015, Marinova et al. 2017).

Although a large number of neurochemical and genetic evidence points to glutamate dysregulation in the etiology of OCRDs, this situation has not been fully elucidated yet. A number of glutamatergic agents have been used off-label, especially in treatment-resistant cases (Grados et al. 2015, Borue et al. 2015, Pittenger 2015). Although there is evidence that glutamatergic modulators such as memantine, riluzole, ketamine, D-cycloserine (DCS), glycine, N-acetyl cysteine (NAC), topiramate and lamotrigine may be beneficial in some patients, none of these are yet considered as part of standard therapy. However, these agents may be a good option for individuals who are resistant to therapeutic strategies, although they have not been proven to be sufficiently effective. In this study, it is aimed to contribute to the current literature by reviewing the studies on the use of glutamate modulators in the treatment of OCRDs.

Glutamatergic System and OCRD

Glutamate, the main excitatory neurotransmitter in the brain, is also the precursor of gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter (Niciu et al. 2012). Glutamate release and reuptake are tightly regulated by Veziculer Glut-cystine antiporter and Excitatory amino acid transporters (EAAT). Glutamatergic neurons are spread to various parts of the brain such as the basal ganglia, cerebellum, brainstem circuits etc. (Pittenger et al. 2011).

Glutamate has two receptor subgroups, the ionotrophic (AMPA, kainate and NMDA) that are cation channels opened by glutamate and the metabotrophic (mGLU1-8) that are coupled to various intracellular signaling cascades. While ionotropic receptors show rapid effects, metabotropic receptors also cause cellular and nuclear changes, resulting in longer-lasting effects. There is a complex relationship between glutamate and other neurotransmitters too.

Glutamate is involved in the etiopathogenesis of many psychiatric disorders such as schizophrenia, mood disorders and OCD (Pittenger et al. 2011). The role of the glutamatergic system in OCRDs comes from OCD studies (neuroimaging, genomics, cerebrospinal fluid biochemical evaluation and animal modeling studies) and results have shown that glutamatergic agents may be effective in these disorders (Goodman et al. 2021). In particular, there is growing evidence that NAC is effective in TTM and SPD. Glutamatergic agents such as topiramate, lamotrigine, ketamine, and memantine are also evaluated in OCRDs treatments (Sani et al. 2019, Grant et al. 2023). Furthermore, neuroimaging studies have also detected subcortical region differences (striatal topography model) in OCRDs like TTM and BDD, that may indicate glutamatergic system changes (Rauch et al. 2003, Atmaca et al. 2010, Isobe et al. 2018).

Cortico-Striato-Thalamo-Cortical Circuit (CSTC) and OCRD

One of the well-known anomalies in OCD is dysfunction of the orbitofrontal cortex (OFC) and CSTC circuits. The OFC and CSTC play important roles in habit learning and goal-directed behavior control. In particular, dysfunction of the CSTC can result in disruptions in goal-directed and habitual behavioral control.

CSTC connects fronto-cortical and subcortical areas. These projections connect to cortical neurons, striatum (glutamatergic synapses onto GABA-ergic medium spiny neurons), globus pallidus pars internalis (GPi) and substantia nigra pars reticulata (SNr). This connection occurs two pathways, the 'direct pathway'(striato-nigral) is mediated by dopamine receptor type 1 (D1R), and 'indirect pathway' (striato-pallidal) is mediated by dopamine receptor type 2 (D2R). There is a balance between these pathways and they send an inhibitory tone to the thalamus with "accelerator-brake" activity. An imbalance of increased activity in the direct pathway removes the inhibitory effect of the thalamus and leads to repetitive behavior sequences (Ting and Feng 2008). The Baxter's model proposes that the imbalance of direct and indirect pathways controlled by glutamate and GABA is responsible for the etiopathogenesis of OCD and it is the most accepted model. Increased glutamatergic activity resulting in over activity of the direct pathway may underlie development of OCD (Wu et al. 2012). So that the hyperactivation or hyperconnection of CSTC may lead to a uncontrolled positive feedback loop and trigger the impulse to perform compulsions, which would in turn consolidate the habit of executing compulsions, increasing the need to perform them (Burguière et al. 2015, Dougherty et al. 2020)

Evidences of Glutamate Dysfunction in OCRD

Morphological and functional neuroimaging studies have shown abnormalities in CSTC in OCD. Some evidence of glutamate dysregulation in OCD has been found in proton magnetic resonance spectroscopy (MRS) studies (Maia et al. 2008, Rotge et al. 2010).

Genes coding glut transporters (EAAC1, EAAT3), NMDA subunits (GRIN2B), kainate subunits (GRIK2/3), and members of postsynaptic density units (DLGAP1) have been found to be related to OCD and variants. An association of SLC1A1 (glut transporter gene) gene mutations in male OCD patients has also been found (Arnold et al. 2004, Stewart et al. 2007, Alonso et al. 2012). In knockout mouse studies, abnormalities in genes controlling NMDA subunits have also been found to result in OCD-like behaviors (Wu et al. 2012). Although genetic studies have found links between glutamate-related genes and OCD, genetic studies have limitations and that findings may not be able to be generalized to all OCRDs cases.

This mechanism has been noted in human, animal and genetic studies. However, the exact nature of this relationship still remains unclear. Although neuroimaging, and neurophysiological studies have found associations between glutamate dysfunction and OCD, these findings cannot be generalized to all OCRDs with the current findings. While the evidence suggests that glutamate dysfunction is involved in the etiology of OCRDs, it is not yet clear how this dysfunction might be targeted therapeutically. Despite the available evidence, further studies are needed to glutamate dysfunction and its relationship to OCRDs.

Glutamatergic Agents in OCD

First-line treatments of OCD are cognitive behavior therapy (CBT) and pharmacological treatments with serotonin reuptake inhibitors (SRIs) (Reddy et al. 2017). However, despite administering appropriate treatment, 30-60% OCD patients do not respond adequately to treatment (Hadi et al. 2021).

Based on the glutamate hypothesis in the etiopathogenesis of OCD, glutamatergic agents have become the most exciting agents in the treatment of OCRDs. Glutamatergic agents act by multiple mechanisms and are defined as glutamate modulators. They can be receptor antagonists, glutamate co-agonists, reuptake inhibitors, and ion

channel modulators that act to induce changes in glutamate transmission. None of the glutamatergic modulators using in OCD treatment have U.S. Food and Drug Administration (FDA) approval (Hadi et al. 2021). Because the necessary steps to approve new treatments for OCRD have not yet been completed.

Memantine

Memantine is a non-competitive NMDA receptor antagonist. Memantine inhibits the effects of sustained elevated glutamate that may lead to neuronal dysfunction (Lu and Nasrallah 2018). It may regulate the abnormal communication between OFC, anterior cingulate cortex (ACC), hippocampus and amygdala by reducing direct pathway hyperactivity (Vlček et al. 2018). Open-label studies have demonstrated clear effect of adding memantine to SRI therapy (Stewart et al. 2010, Bakhla et al. 2013). In the first of these studies, memantine was added in the SRI treatment to 22 of 44 patients with OCD who received standard treatment, and a decrease in the severity of depression and obsessive symptoms was reported in the memantine-added group (Stewart et al. 2010). In the other study, 10mg/day memantine was added as an augmenting agent to twelve OCD patients who had been using various drugs for more than 5 years but revealed a poor response. In this 12-week open-label study, OCD symptoms and drug side effects were monitored. As a result of the study, the authors reported that 8 out of 12 patients achieved a net benefit with a 25% or greater reduction in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) and that the drug had no side effects (Bakhla et al. 2013).

Four randomized controlled trials (RCT) were evaluated memantine to placebo as an SRIs adjunctive treatment. Memantine adjunction showed a reduction in three of these. A 12-week placebo-controlled randomized double-blind study included 40 inpatients with a diagnosis of OCD. Memantine was added to the treatment of patients using selective serotonin reuptake inhibitors (SSRI) or clomipramine and compared with the group receiving the placebo. As a result of the study, it was stated that there was a decrease in disease severity and symptoms in the memantine added group (Haghighi et al. 2013). In another randomized placebo-controlled 8-week study, 42 patients with a Y-BOCS score ≥21 diagnosed with OCD according to DSM-IV-TR, were administered fluvoxamine plus given random memantine (10 mg/day or more for the first week) followed by 20 mg/day) or placebo. As a result of the study, no difference was found between the two groups in terms of side effects. The authors reported that memantine add-on to fluvoxamine was effective in controlling symptoms in the short-term in patients with moderate and severe OCD symptoms (Ghaleiha et al. 2013). In a double-blind, placebo-controlled study conducted with 32 SSRI-resistant patients with OCD, 20 mg/day memantine or placebo was added to treatment randomly. In the evaluation performed at the end of 12 weeks, it was stated that memantine is an effective and well tolerated augmentation agent in patients with severe OCD resistant to SSRI monotherapy. (Modarresi et al. 2018). In the last RCT, the addition of memantine, placebo, and gabapentin did not lead to a reduction in symptoms. Unlike the results of these studies, in a double-blind, placebo-controlled study that included 99 patients with OCD, memantine, gabapentin and placebo were administered in addition to the standard SSRI treatment. At the end of the a 12-week period, there was no difference in the treatment responses of all three groups. In addition, it has been reported that the addition of glutamatergic drugs such as gabapentin and memantine did not have an additional positive effect on patients with OCD. In addition, the authors reported side effects such as skin rash, drowsiness, anxiety, and dizziness (Farnia et al. 2018). A recent review concluded that memantine showed a positive effect as an augmentation therapy in OCD (Marinova et al. 2017).

A recent meta-analysis for memantine as an augmentation agent in adult OCD, which was identified as 3 small, open-label, uncontrolled trials; 1 small, single-blind, nonrandomized controlled trial and 4 small-to-medium, double-blind, randomized controlled trials; found a significant overall mean reduction. This meta-analysis evaluated four RCTs in categorical analysis and found that OCD patients receiving memantine augmentation were 3.61 times more likely to respond to treatment than those receiving placebo (Modarresi et al. 2019).

Ketamine

Ketamine is a "use-dependent" antagonist of the NMDA and it can augment glutamate release when NMDA is already active, blocks synaptic NMDA receptor activity under spontaneous glutamatergic neurotransmitter release and modulates downstream signaling (Aan et al. 2012, Suzuki and Kanzo 2020). Ketamine blocks the NMDA receptor, presumably on GABA interneurons, leading to disinhibition of pyramidal neural activity in cortex, subsequently increasing the glutamate release triggering a cascade of signaling pathways, including AMPA receptor activation, brain-derived neurotrophic factor (BDNF) secretion and activation of mammalian target of rapamycin (mTOR) signaling (Krystal et al. 2013).

The exact nature of the ketamine mechanism in OCD is unclear. There is only one RCT and open-label report of ketamine use for OCD in the related literature. In this randomized, double-blind, placebo-controlled trial, a total of 15 patients diagnosed with OCD (one with saline and the other with ketamine) were administered two 40-minute intravenous infusions, 1 week apart. Significant improvement in obsessions during infusion was reported in those taking ketamine (n=8) compared with subjects receiving placebo (n=7). One week after infusion, 50% of those receiving ketamine met criteria for treatment response (≥35% reduction in Y-BOCS). The authors noted that the rapid anti-OCD effects of a single intravenous dose of ketamine may persist for at least 1 week in some patients with OCD. This is the first randomized, controlled trial to show that a drug that affects glutamate neurotransmission can reduce OCD symptoms without an SRI, consistent with the glutamatergic hypothesis of OCD (Rodriguez et al. 2013).

Transient improvement lasting no more than one week was reported in an open-label study. In this open-label study, ketamine was administered to 10 patients (0.5 mg/kg IV in 40 minutes) who had a diagnosis of treatment-resistant OCD. It was found that more than 35% improvement in OCD symptoms and more than 50% improvement in depressive symptoms 1-3 days after treatment. However, it has been reported that improvement in OCD symptoms did not continue after the acute effects of ketamine disappeared (Bloch et al. 2012).

Another open-label study found some benefit of ketamine infusion augment to CBT. In this study, participants received a single 40-minute IV infusion of ketamine (dose = 0.5 mg/kg), followed by 10 sessions of one hour CBT over two weeks. Nine out of 10 patients who started ketamine completed the infusion. Patients reported a rapid reduction in obsessive symptom severity after infusion. The authors suggested that CBT sessions could help them maintain the improvement resulting from ketamine. However, it needs to be tested in a randomized controlled trial to determine whether the improvement seen after two weeks of CBT is due to the addition of CBT or whether the effects of ketamine persist longer than previously described (Rodriguez et al. 2016). Evidence suggests that ketamine might have additional benefits in untreated OCD patients, and more systematically researches are needed for OCD.

N-Acetyl Cysteine

N-acetyl cysteine (NAC) has antioxidant, hepatoprotective and mucolytic effects. NAC converted to cystine in CNS, cysteine exchanges to glutamate by cystine glutamate antiporter, so that activates mGLuR2/3 receptors. It leads to regulation of extracellular glutamate levels by inhibition of synaptic glutamate release. Due to the role of the cystine component of NAC in the glutamate cycle, NAC has prompted clinical investigations as a glutamate-modulating therapeutic agent for psychiatric conditions, including addiction, bipolar disorder, schizophrenia, autism and OCD augmentation therapy (Oliver et al. 2015, Ghaderi et al. 2019, Gadallah et al. 2020, Yolland et al. 2020, Nery et al. 2021, Lee et al. 2021).

In earlier studies, addition of NAC to SRIs exhibited a reduction in the severity of OCD symptoms. In this 12-week randomized, placebo-controlled study, NAC (up to 2400 mg/day) was added to the treatment of 48 patients (36 females; mean ± SD age, 30.93 ± 4.99) with OCD who did not respond to SRIs therapy. Accordingly, it was determined that the patients given NAC improved significantly in the mean Y-BOCS score and were significantly higher than the group receiving placebo. The authors stated that NAC may be a safe and effective option to increase standard treatment in patients with resistant OCD (Afshar et al. 2012). In another 10-week randomized placebo placebo-controlled study, NAC (2000 mg/day) was added to the treatment of 44 OCD patients with moderate to severe symptoms using 200 mg/day fluvoxamine and compared with the placebo group. The results of this study showed that NAC might be effective as an augmentative agent in the treatment of moderate-to-severe OCD (Paydary et al. 2016) In a 10-week, randomized, double-blind, placebo-controlled clinical study conducted with 34 pediatric and adolescent patients with OCD, NAC (2400mg/day) was added to patients receiving citalopram (20-40 mg/day) and compared with the group receiving placebo. This study suggests that NAC contributes to citalopram's effect of improving compulsions in OCD children and adolescents. The authors also reported that the drug was well tolerated (Ghanizadeh et al. 2017).

But the earlier studies on NAC augmentation therapy in OCD were generally small and lacked rigorous methodology. These findings have not been replicated and NAC did not show a reduction of OCD symptoms in placebo controlled trials. This 16-week, double-blind, placebo-controlled randomized study aimed to evaluate the efficacy and safety of NAC in the treatment of OCD, administered 3 g/day NAC (twice-daily) to 44 participants (18-70 years). At 16 weeks, only four (20%) participants were considered 'responders' (YBOCS ≥35% reduction at endpoint) versus four (27%) in the placebo group (Sarris et al. 2015). In the 16-week study in adults with treatment-resistant OCD, no significant difference was found between the NAC group and the placebo

group. The authors stated that the addition of NAC was superior to placebo in reducing anxiety symptoms. However, no change was observed in the severity of depression and OCD symptoms (Costa et al. 2017).

A recent meta-analysis which was evaluated NAC add on therapy in OCD, found that NAC was significantly superior compared to placebo. However, the meta-analysis highlighted that the small samples and limited number of clinical studies with methodological problems weakened the evidence for the use of NAC in OCD. In the meta-analysis, it was stated that there is a need for studies with larger samples, longer duration, better designed and evaluating the single use of NAC in OCD (Gadallah et al. 2020). Thus the use/augmentation of NAC in OCD trials are preliminary and have inconsistent findings; so that it needs to be more investigated.

Lamotrigine

Lamotrigine is an antiepileptic agent. It is also used as a mood stabilizer drug. By inhibiting voltage-sensitive sodium channels, lamotrigine stabilizes presynaptic neuronal membranes and inhibits glutamate release (Verrotti et al. 2018). Studies have examined lamotrigine augmentation to SRI treatment in treatment-resistant OCD. The efficacy of lamotrigine add-on therapy in OCD was initially reported in case reports and case series. A 59-year-old female patient with a diagnosis of treatment-resistant OCD who was successfully treated with the addition of lamotrigine (150 mg/day) to clomipramine (225 mg/day) is presented. After 10 weeks of this treatment, her clinical condition was reported to have improved markedly, as evidenced by a significant decrease in the Y-BOCS (Uzun 2010). Two cases of adding lamotrigine in treatment-resistant OCD, each using multiple SRIs for more than 10 years, are presented. Adding lamotrigine (100 mg/day) to paroxetine (60 mg/day) treatment in the first case resulted in a >50% reduction in Y-BOCS. The second patient had a 50% reduction in Y-BOCS by adding lamotrigine (200 mg/day) to clomipramine (225 mg/day) (Arrojo-Romero et al. 2013). Some benefits were also reported in schizophrenia/schizoaffective disorder and bipolar disorder whom presents with comorbid OCD (Bisol and Lara 2009, Poyurovsky et al. 2010). The efficacy of lamotrigine add-on therapy in OCD was also supported by two double-blind RCTs. In a 16-week double-blind, randomized, placebo-controlled study of 33 treatment-resistant OCD patients, 100 mg/day lamotrigine was added to the SRI treatment. At the end of the study, improvement was observed in OCD, mood symptoms, and only semantic fluency in terms of cognitive functions. The authors note that SRI therapy provides evidence that lamotrigine supplementation is well tolerated and can be recommended as an effective therapeutic strategy to ameliorate treatment-resistant OCD (Bruno et al. 2012). In another 12-week, double-blind, randomized, placebo-controlled study, lamotrigine (n = 26) and placebo (n = 27) were added to the SRI treatment of OCD patients. As a result of the study, the treatment response was better than the placebo in the lamotrigine added group (Khalkhali et al. 2016). There is evidence to support the efficacy of lamotrigine add-on therapy in OCD. However, this effectiveness needs to be supported by studies with larger samples and longer control periods.

Topiramate

Topiramate is an anti-epileptic molecule that inhibits glutamate release and increases GABA release via voltage-gated calcium channels. It is also thought that topiramate has other mechanisms of action, including blocking AMPA (Suppes 2002). Topiramate effects on OCD are inconclusive. Of the three RCT, two were negative and only the first one resulted positively. One of these RCTs reported a significant reduction in compulsions subscale only. The positive RCT had a sample size of 18, which is quite small (Berlin et al. 2011). Another RCT which was evaluated topiramate augmentation among treatment-refractory OCD patients with comorbid depression found that nearly 32% reduction OCD scores and also lower depression scores at the end of 12 weeks (Mowla et al. 2010). The last RCT in treatment-refractory OCD found a similar reduction in topiramate and the control group (Afshar et al. 2014). These findings are insufficient due to low tolerability, accompanying depression, and short-term data in small samples. On the other hand topiramate can cause cognitive side effects, such as word-finding difficulties and memory impairment, which may be particularly problematic for patients with OCD (Pietrzak et al. 2013).

Glycine

Glycine acts as an obligatory co-agonist at the NMDA receptor and essential for normal glutamate signaling. In a single controlled study evaluating glycine as an OCD add-on therapy, no statistically significant difference was found. The major adversity in this study was its poor tolerability resulting in high dropout rates (Greenberg et al. 2009). After this study, no other studies were conducted evaluating glycine in the treatment of OCD. However, studies using sarcosine (glycine reuptake inhibitor) and rapastinel (NMDA receptor glycine region co-

agonist) in OCD patients who have never received any treatment, have shown that they may be effective (Köse and Çetin 2017). There is insufficient evidence for the efficacy of glycine supplementation in treatment-resistant OCD, and further studies are needed.

Riluzole

Riluzole acts by modulating glutamate release via voltage-gated ion channels and increasing its reuptake from the extracellular area (Pittenger et al. 2015). In case reports and open-label studies, it has been reported that riluzole add-on therapy may be beneficial in refractory OCD (Coric et al. 2003, Coric et al. 2005, Grant et al. 2007a). Only one of the two RCTs comparing riluzole and placebo as add-on therapy to SRIs found reduction. In a 12-week, double-blind, randomized, placebo-controlled study, riluzole (final dose of 100 mg/day) or placebo was added to the SRI treatment of 60 treatment-resistant childhood-onset OCD patients. Although there was improvement in OCD symptoms at the end of the study, there was no difference from the placebo. Riluzole was fairly well tolerated, although it was associated with one case of pancreatitis and five instances of slight increases in transaminases. (Grant et al. 2014). In an 8-week, double-blind, randomized, placebo-controlled study, riluzole (50 mg twice daily) or placebo was added to fluvoxamine (200 mg/day) treatment in 50 treatment-resistant OCD patients. At the end of the study, the treatment response was superior to placebo in OCD symptoms in the riluzole added group. The authors stated that riluzole may be a suitable adjuvant agent for fluvoxamine in the treatment of moderate to severe OCD (Emamzadehfard et al. 2016). Hence, the results of studies evaluating the benefits of riluzole in OCD are mixed.

D-cycloserine

D-cycloserine (DCS) is an NMDA partial agonist in the amygdala and it has suggested a role in fear extinction and may increase the efficacy of exposure therapy (Lewin et al. 2014). Eight RCTs have been established comparing DCS and placebo as add-on therapy to the exposure and response prevention CBT approach. (1-2 hours before CBT, 125 mg IV infusion). Four of them reported a significant amelioration of OCD symptoms (Kushner et al. 2007, Wilhelm et al. 2008, Farrell et al. 2013, Andersson et al. 2015). The other four studies did not find any statistically significant improvement. In the light of these data, although there is not sufficient data on the additional benefits of DCS to OCD addition therapy, it may increase the effectiveness of CBT (Storch et al. 2007, Storch et al. 2010, Mataix-Cols et al. 2014, Storch et al. 2016).

In another meta-analysis on the subject, six studies were examined. The authors suggested that with the careful optimization of DCS-augmented exposure and response prevention (ERP) therapy by fine-tuning timing and dosing of DCS administration and number and frequency of ERP sessions, DCS may enhance the efficacy of ERP therapy in reducing the symptomatic severity of OCD patients, especially at early stage of the treatment; therefore, DCS augmentation could possibly reduce treatment cost, reduce treatment drop and refusal rate (Xia et al. 2015).

Glutamatergic Agents in Body Dysmorphic Disorder (BDD)

BDD was added to the OCRD class in DSM-5 because it has many features similar to OCD (repetitive behaviors, ruminations, etc.). There have been repetitive behaviors or mental acts in response to preoccupations a real or imagined defect in physical appearance and the concern is disproportionate to the physical abnormality in BDD. Ruminative thoughts about their perceived “flaws” are very persistent, intrusive and ranged from overestimated thinking to delusional belief. BDD has high comorbidity with major depression, OCD, social phobia and high rate of suicide. BDD is a difficult-to-treat patient group, there is a lack of insight and rejection of psychiatric treatment/referral (Castle et al. 2021). Despite the poor insight, CBT and SRIs have been found to be more effective than antipsychotics. There is a lack of data about glutamatergic agents in BDD. Augmentation in BDD is recommended for comorbid psychiatric disorders such as depression, anxiety or other OCRD (Castle et al. 2021). Pregabaline may be effective comorbid anxiety. NAC, esketamine (comorbid resistant depression) and memantine augmentation to SRI may be efficacious in BDD. BDD pharmacotherapy is still very weak and more research and evaluations are needed for its pharmacotherapy (Dong et al. 2019).

Glutamergic Agents in Skin Picking Disorder (SPD)

SPD usually follows a chronic course, beginning in childhood and adolescence. It is a psychiatric disorder in which repetitive skin-damaging behaviors are exhibited with triggers such as distress, stress, and sadness. Approximately three hours a day are spent resisting the urge to think or skin picking. OCD, mood disorders,

generalized anxiety disorder, BDD, substance use disorders, eating disorders, TTM, kleptomania, guilt, worthlessness and suicidal thoughts usually comorbid with SPD (Grados et al. 2015). The fact that it is located in OCRDs, has significant similarities with OCD and neuroimaging and genetic studies; suggests that glutamatergic agents may be effective for the treatment of SPD.

Several case reports have reported that NAC may be useful in the treatment of SPD (Odlaug and Grant 2007). In a recent study, it was reported that the use of NAC was beneficial in patients with Prader Willi Syndrome (PWS) and comorbid pervasive developmental disorder (PDD), and skin picking behaviors of all patients were significantly reduced or disappeared (Miller and Angulo 2014). In addition, two RCTs (NAC 1200–3000 mg/day for 12 weeks and 16 weeks) found that NAC significantly reduced symptoms compared to the placebo (Silva-Netto et al. 2014, Grant et al. 2016).

An open-label study evaluated lamotrigine monotherapy in SPD and reported that two-thirds of patients showed improvement (Grant et al. 2007b). However, in another double-blind randomized placebo-controlled trial (RPCT) lamotrigine was not superior to placebo in the treatment of SPD. Thirty-two patients (29 women) with SPD were treated in a 12-week double-blind, RPCT of lamotrigine as monotherapy. Lamotrigine dosing ranged from 12.5 to 300 mg/day. No significant overall difference was noted between lamotrigine and placebo. Y-BOCS and psychosocial functionality measures were used in the evaluation of the patients. These findings suggest that, although safe and well tolerated, lamotrigine therapy as a whole may not be as effective compared to placebo in patients with SPD. However, the authors suggested that in terms of neurocognitive data, lamotrigine may be valuable in a subset of patients exhibiting relatively impaired cognitive flexibility (Grant et al. 2010).

Topiramate has been used for SPD accompanying developmental disorders such as PWS, autism spectrum disorders and mental retardation. Positive results were observed in an open-label pilot study. In an open-label pilot study, topiramate demonstrated promising results (Jafferany and Osuagwu 2017). A review which was evaluated psychopharmacological treatments for PWD reported that topiramate may be effective in self-harm, impulsivity, and aggressive behavior in PWD (Bonnot et al. 2016). In another an open-label study evaluating topiramate on skin picking behavior in pervasive developmental disorder not otherwise specified, it was also found to be effective in reducing lesions (Jafferany et al. 2010). In an 8-week open-label study, topiramate (200mg/day) decreased self-injurious behaviors in three patients with PWS (Shapira et al. 2002).

There is also anecdotal evidence that riluzole reduces these behaviors in patients with skin picking behavior comorbid with eating disorders (Sasso et al. 2006).

Glutamatergic Agents in Trichotillomania (TTM)

TTM is a devastating psychiatric disorder that causes significant disability and comorbid psychiatric disorders (Grant and Chamberlain 2016). There is a feeling of increased tension just before pulling the hair or trying to resist the behavior, relief from tension with pleasure, satisfaction, or relief while pulling and often followed by a rapid feeling of guilt and hopelessness in TTM. Sometimes the pulled hair is chewed, sucked and, swallowed or eaten. TTM is also associated with PDD, anxiety, depression, BDD, psychosocial triggers, family dysfunction (common), other skin habits such as nail biting and pulling, self-harm, eating disorders and addiction. Familial predisposition is quite common too (Lochner et al. 2017, Torales et al. 2021).

There is no FDA -approved first-line drugs and it is a difficult-to-treat psychiatric condition. Evidence of efficacy for NAC in the treatment of TTM specifically has varied. The evidence has been promising in non placebo controlled studies (Özcan and Seçkin, 2016, Barroso et al. 2017). NAC was found to significantly reduce TTM symptoms compared to placebo in an early double-blind placebo-controlled trial. In a 12-week, double-blind, placebo-controlled study, fifty subjects (45 females and 5 males) with trichotillomania were administered NAC (dose range, 1200-2400 mg/day) or placebo. Patients were evaluated using the Massachusetts General Hospital Hair Pulling Scale, the Clinical Global Impression scale, the Institute of Psychiatry Trichotillomania Scale, and measures of depression, anxiety, and psychosocial functioning. The authors found that NAC showed statistically significant reductions in TTM symptoms. No side effects occurred in the NAC group and it was reported that NAC was well tolerated (Grant et al. 2009). In another double-blind placebo-controlled trial with 8-17 ages did not find significant benefit compared to the placebo. A total of 39 children and adolescents with TTM were included in the study. Randomly assigned to receive NAC or matching placebo for 12 weeks. NAC (or placebo) was titrated up to a maximum dose of 2400 mg over the course of 4 weeks. No significant difference between NAC and placebo was found on any of the primary or secondary outcome measures (Bloch et al. 2013). Therefore, while NAC may be a promising treatment for TTM, the evidence for its efficacy is not yet conclusive.

Although there is a case series showing that riluzole is effective in TTM, no study has yet been conducted to evaluate this (Coric et al. 2007). In a study evaluating the efficacy of topiramate in TTM, approximately half of the patients showed improvement, although almost one-third of the participants had dropped out due to non tolerable side effects (Lochner et al. 2006). Dronabinol is FDA-approved cannabinoid agonist for the treatment of anorexia associated with Acquired Immune Deficiency Syndrome (AIDS) and chemotherapy. It may reduce the excitotoxic damage caused by glutamate release in the striatum (Beal et al. 1995) In an open-label study with TTM reported that 9 out of 14 women responded to dronabinol and its' tolerability was observed to be good (Grant et al. 2011). In another study, nine children and adolescents aged 6 to 18 years diagnosed with attention-deficit/hyperactivity disorder (ADHD) and TTM were treated with methylphenidate (MPH) for a period of 12 weeks. Despite a significant improvement in ADHD after MPH treatment, no significant change was observed in hair pulling behavior (Golubchik et al. 2011).

Glutamatergic Agents and Hoarding Disorder (HD)

About 20-40% of OCD patients have hoarding symptoms, which differ markedly from typical OCD symptoms. HD differs markedly from OCD in terms of age of onset, clinical course, insight, and response to treatment, and as a result, it has been replaced by DSM-5 as a separate OCRD from OCD (Mataix-Cols et al. 2010). Individuals with HD have difficulty disposing or throwing objects and cannot organize them. As a result, accumulations of items, garbage etc. occur at a level that can occupy a large part of the living space (Nakao and Kanba 2019). HD is a newly diagnosis and standard pharmacological treatment approaches are not yet available for HD. According to the results of many studies, HD treatment response is low. A higher hoarding score correlated with poorer treatment response (Kress et al. 2016). It is clear that there is a need for new studies and strategies for HD treatment. There are atypical antipsychotics, DCS, MPH and atomoxetine addition options, but data on their efficacy are not yet available (Nakao and Kanba 2019). In other words, there is insufficient evidence regarding the role and efficacy of glutamatergic agents in the treatment of HD. Many other features such as HD symptomatology, treatment response, and treatment options need to be investigated.

General Characteristics of Studies

When open-label and placebo-controlled double-blind studies on the use of glutamatergic drugs in the treatment of OCRD are examined, it is understood that there are critical limitations. The results obtained with different methods and measurement tools used in sample selection are not consistent. The most studies on the use of glutamatergic drugs in the treatment were conducted with patients diagnosed with OCD, TTM and SPD. There are few studies on BDD, especially HD. In addition, the results of short-term studies with small sample groups should be reconsidered with randomized placebo-controlled long-term trials in larger study populations are necessary in order to draw definitive conclusions on the utility of glutamate-modulating drugs in OCRD. The general characteristics of the open-label and double-blind, randomized, placebo-controlled studies that have been conducted so far are presented in Table 1..

Table 1. General characteristics of the studies

Reference	Study type	RC	Sample	Measure	Drugs(mg/day)	Outcomes
Stewart et al. (2010)	case-control study	-	N=44 patients with a diagnosis of OCD who received standard treatment.	Y-BOCS CGI	memantine 10mg/day (Memantine was added to SRI treatment in 22 of 44 patient with a diagnosis of OCD)	Y-BOCS score reductions were greater among cases than in the control group, and clinical improvement was higher in the patient group..
Bakhla et al. (2013)	12-week, an open-label trial		N=12 subjects of OCD who had been on various medications for over 5 years, but were poor responders	Y-BOCS:	memantine 10mg/day as an augmenting agent	Out of 12 subjects, eight had clear benefit, with reduction of 25% or more on Y-BOCS and there were no side-effects with the medication,
Haghighi et al. (2013)	12 week, A randomised, double-blind, pla-cebo-controlled trial	×	N=40 In patients with OCD	Y-BOCS CGI Liver enzymes	memantine 10mg/day All patients were treated with SSRI or clomipramine randomly assigned to a treatment (administration of memantine) or a control group (placebo)	The results of this study for the treatment of patients with OCD show that adjuvant memantine has a significant and positive effect on OCD.

Ghaleiha et al. (2013)	8 week, A randomised, double-blind, placebo-controlled trial	×	N=42 patients with OCD who had a Y-BOCS score of ≥21 were randomly assigned to memantine) or placebo in addition to fluvoxamine	DSM-IV-TR SCID Y-BOCS CGI	memantine (10 mg/day for the first week, and 20 mg/day for the rest of the trial)	It has been noted that the addition of memantine to fluvoxamine significantly improves short-term outcomes in patients with moderate to severe OCD.
Modarresi et al. (2018)	12 week, A randomised, double-blind, placebo-controlled trial	×	N=32 SRI refractory OCD patients	Y-BOCS	20 mg/day memantine or placebo	Memantine is an effective and well tolerated augmentation in patients with severe OCD who are resistant to SRI monotherapy.
Farnia et al. (2018)	8 week, A randomised, double-blind, placebo-controlled trial	×	N=99 outpatients diagnosed with OCD	Y-BOCS	FLU + gabapentin (FLU + GAB); FLU + memantine (FLU + MEM); FLU + placebo (FLU + PLA).	No group differences were observed. Addition of glutamatergic drugs such as gabapentin and memantine in addition to standard treatment with SSRI has no additional positive effect on patients with OCD.Side effects such as skin rash, drowsiness, anxiety, dizziness have also been reported.
Bloch et al. (2012)	One week an open-label trial		N=10 patients with a diagnosis of treatment-resistant OCD.	SCID HDRS-17 Y-BOCS CGI	Ketamine (0.5 mg/kg IV in 40 minutes)	Although improvement in OCD and depressive symptoms was reported in the first days after the infusion, no improvement was observed in OCD symptoms after 1 week after the acute effects of ketamine disappeared.
Rodriguez et al. (2013)	2 week a randomised, double-blind, placebo-controlled trial	×	N=15 patients with a diagnosis of OCD.	Y-BOCS	Ketamine (0.5 mg/kg IV in 40 minutes) (N: 8) Salin (N:7)	One week after infusion, 50% of those receiving ketamine met criteria for treatment response (≥35% reduction in Y-BOCS). The rapid anti-OCD effects of a single intravenous dose of ketamine may persist for at least 1 week in some OCD patients.
Rodriguez et al. (2016)	4 weeks open-label study		N=10 patients with a diagnosis of OCD.	Y-BOCS	Ketamine (0.5 mg/kg IV in 40 minutes) (n: 9) 10 sessions of one hour CBT	A rapid reduction in obsessive symptom severity after infusion. CBT sessions could help them maintain the improvement from ketamine.
Afshar et al. (2012)	12 week, A randomised, double-blind, placebo-controlled trial	×	N=48 patients (36 females; mean ± SD age, 30.93 ± 4.99) with OCD who did not respond to SRIs therapy.	Y-BOCS	NAC (up to 2400 mg/day) as an augmenting agent	NAC improved significantly in the mean Y-BOCS score and were significantly higher than the group placebo
Paydary et al. (2016)	10 week, A randomised, double-blind, placebo-controlled trial	X	N= 44 patients with moderate-to-severe OCD (22 in each group)	Y-BOCS	two parallel groups to receive fluvoxamine (200 mg/ day) plus placebo or fluvoxamine (200 mg/ day) plus NAC (2000 mg/day).	The results showed that NAC might be effective as an augmentative agent in the treatment of moderate-to-severe OCD.
Ghanizadeh et al.(2017)	10 week, A randomised, double-blind, placebo-controlled trial	X	N=34 patients with OCD(10 to 21 years from both genders	Y-BOCS PedsQL	NAC (2400 mg/day)was added citalopram (40 mg/day)	This trial suggests that NAC adds to the effect of citalopram in improving resistance/control to compulsions in OCD children and adolescents. In addition, it is well tolerated.
Sarris et al. (2015)	16-week, A randomised, double-blind, placebo-controlled trial	×	N=44 participants (aged 18-70 years) with DSM-5-diagnosed OCD	Y-BOCS	3 g/day of NAC (1.5 g twice daily)	At 16 weeks, only four (20%) participants were considered 'responders' (YBOCS ≥35% reduction at endpoint) versus four (27%) in the placebo group. The NAC was well-tolerated, aside from more cases of heartburn occurring compared with placebo.
Costa et al. (2017)	16-week, A randomised, double-blind, placebo-controlled trial	×	N=40 in adults (aged 18-65 years) with treatment-resistant OCD	Y-BOCS	NAC (3,000 mg daily)	This trial did not demonstrate a significant benefit of NAC in reducing OCD severity in treatment-resistant OCD adults.
Uzun (2010)	Case report		A 59-year-old woman with treatment-resistant OCD	Y-BOCS	lamotrigine (up to 150 mg/day) was added to clomipramine (225 mg/day)	After 10 weeks of this treatment, her clinical condition remarkably improved, as indicated by a significant decrease of the Y-BOCS

Arrojo-Romero et al. (2013)	Case series		24-year-old Spanish woman 46-year-old Spanish woman	Y-BOCS	lamotrigine (100 mg/day) was added to paroxetine (60 mg/day), Lamotrigine 200mg/day was added to clomipramine 225 mg/day	Significant improvement in symptoms was observed with the addition of lamotrigine in two women who were resistant to treatment and did not respond to multiple antidepressant and antipsychotic augmentation for many years.
Bruno et al.(2012)	16-week, A randomised, double-blind, placebo-controlled trial	×	N=33 patients with treatment-resistant OCD	Y-BOCS HDRS	Lamotrigine (100 mg/day) was added to stable SRI treatment	The findings provide evidence that lamotrigine augmentation of SRI treatment is well tolerated and may be proposed as an effective therapeutic strategy to improve outcome in treatment-resistant OCD
Khalkhali et al.(2016)	12-week, A randomised, double-blind, placebo-controlled trial	×	N=53 patients with treatment-resistant OCD	Y-BOCS	Lamotrigine (100 mg/day) was added to stable SRI treatment	This augmentation is well tolerated and may be an effective strategy for patients with refractory obsessive-compulsive disorder.
Berlin et al. (2011)	12-week, A randomised, double-blind, placebo-controlled trial	×	N=36 adult patients with DSM-IV-defined OCD	Y-BOCS	topiramate (n = 18) (topiramate group (mean endpoint dose = 177.8 ± 134.2 mg/d; range, 50-400 mg/day) and placebo (n = 18) groups	The results of this first double-blind, placebo-controlled trial of topiramate augmentation for treatment-resistant OCD suggest that topiramate may be beneficial for compulsions, but not obsessions
Mowla et al. (2010)	12-week , A randomised, double-blind, placebo-controlled trial	×	N=49 patients with treatment-resistant OCD	Y-BOCS	topiramate was added to stable SSRI treatment. The mean dosage of topiramate was 180.15 mg/day (range 100-200 mg/day).	The results of this study demonstrated that topiramate may augment the therapeutic effect of SSRIs in treatment-resistant OCD patients.
Afshar et al. (2014)	12 week, A randomised, double-blind, placebo-controlled trial	×	N=27 patients with refractory OCD	Y-BOCS CGI	A total of 13 patients in the topiramate group and 14 ones in the placebo group	This study didn't show efficacy of topiramate as an agent to augment SRIs in treatment-resistant OCD patients.
Grant et al. (2007a)	12 week an open-label trial		N=6 subjects, ages 8-16 years patients with with OCD.	CY-BOCS CGI CGI	riluzole for OCD symptoms that had resisted prior treatments. OCD symptoms and adverse effects of drug were monitored.	Four of 6 subjects had clear benefit, with reduction of more than 46% (39% overall) on CY-BOCS Riluzole may be beneficial for treatment-resistant OCD in young subjects and seems well tolerated.
Coric et al. (2005)	an open-label trial		N=13 patients aged between 18 and 65 years with a primary diagnosis of OCD.	Y-BOCS CGI HAM-D HAM-A	riluzole 50 mg twice a day	Y-BOCS scores improved significantly over time. Of 13 patients, 7 (54%) demonstrated a >35% reduction in Y-BOCS scores, and 5 (39%) were categorized as treatment responders. HAM-D and HAM-A scores for the group also significantly improved over time. Riluzole was well tolerated with no serious adverse effects noted.
Grant et al.(2014)	12-week, A randomised, double-blind, placebo-controlled trial	×	N=60 treatment-resistant children and adolescents (mean age=14.5 ± 2.4 years)	CY-BOCS CGI	riluzole (final dose of 100 mg/day) or placebo	All subjects showed significant reductions in CY-BOCS scores during treatment; however, there was no significant difference between placebo and riluzole on any of the primary or secondary outcome measures
Emamzadeh-fard et al. (2016)	8-week , a randomised, double-blind, placebo-controlled trial	×	N=50 (25 in each group)	Y-BOCS	Fluvoxamine (200 mg/day) plus placebo or fluvoxamine plus riluzole (50 mg twice daily)	Riluzole augmentation therapy demonstrated higher treatment response according to the Y-BOCS total scores. Riluzole may be of clinical use as an adjuvant agent to fluvoxamine in treatment of moderate to severe obsessive-compulsive disorder.
Kurshner et al. (2007)	12 week, a randomised, double-blind, placebo-controlled trial	×	N=25 patients with DSM-IV-defined OCD Y-BOCS score ≥18	DSM-IV Y-BOCS	DCS (125 mg/day) or placebo (14/11) in a double-blind fashion to individuals with OCD approximately 2 hours before each exposure session.	DCS augmentation has the potential to increase the efficiency, palatability, and overall effectiveness of standard exposure therapy for OCD.
Wilhelm et al. (2008)	5 week a randomised, double-	×	N=23 patients with OCD	Y-BOCS	DCS (100 mg), versus placebo (10/13) 1	Relative to the placebo group, the DCS group's OCD symptoms were significantly more

	blind, placebo-controlled trial				hour before each of the ten exposure-based behavioral therapy sessions	improved at mid-treatment, and the DCS group's depressive symptoms were significantly more improved at posttreatment.
Farrell et al. (2013)	12 week a randomised, double-blind, placebo-controlled trial	×	N= 16 (Caucasian, 1 Asian) children and adolescents (aged 8-18 years) with a primary diagnosis of OCD	Y-BOCS	DCS or placebo (9/8) doses (25 or 50 mg) were taken 1 hour before ERP sessions.	In this preliminary study, DCS-augmented ERP produced significant improvements in OCD severity from posttreatment to 1-month follow-up, relative to a placebo control condition, in severe and difficult-to-treat pediatric OCD.
Andersson et al. (2015)	12 week a randomised, double-blind, placebo-controlled trial	×	N=128 adult outpatients with a primary diagnosis of OCD	Y-BOCS	50 mg of DCS or placebo, administered 1 hour before each of 5 ERP tasks.	Use of DCS may be a promising CBT augmentation strategy but only in antidepressant-free patients with OCD
Storch et al. (2007)	12 week a randomised, double-blind, placebo-controlled trial	×	N=24 (22 Caucasian; 1 African; 1 Asian)adults meeting DSM-IV criteria for OCD	Y-BOCS	ERP therapy+ DCS 100 mg, versus ERP +placebo. (12/12)	No significant group differences were found across outcome variables. The rate of improvement did not differ between groups. The present results fail to support the use of DCS with ERP therapy for adult OCD.
Storch et al. (2010)	12 week a randomised, double-blind, placebo-controlled trial trial	×	N=30 (97% Caucasian; 3% Hispanic) youth (aged 8-17) with a primary diagnosis of OCD.	Y-BOCS	CBT + DCS 100 mg, versus CBT + Placebo (15/15) All patients received seven ERP sessions paired with DCS or placebo taken 1 hour before sessions.	Although not significantly different, compared with the CBT + Placebo group, youth in the CBT + DCS arm showed small-to-moderate treatment effects (d = .31-.47 on primary outcomes). No adverse events were recorded.
Mataix-Cols et al. (2014)	1-year follow-up a randomised, double-blind, placebo-controlled trial	×	N=27 youth with OCD	Y-BOCS	randomised to either 50 mg DCS or placebo (13/14) administered immediately after each of ten CBT sessions,	Both groups improved significantly and maintained their gains at 1-year follow-up, with no significant advantage of DCS over placebo at any time point. The effects of CBT may not be augmented or accelerated when DCS is administered after sessions.
Storch et al. (2016)	a randomised, double-blind, placebo-controlled trial	×	N=142 youths (age range, 7-17 years) with a primary diagnosis of OCD	C Y-BOCS CGI, CDRS MASC	randomized in a double-blind fashion to DCS plus CBT or placebo plus CBT. Intent-to-treat analysis was performed.	DCS augmentation of CBT did not confer additional benefit relative to placebo among youth with OCD.
Grant et al. (2007b)	12-week an open-label trial		N=24 subjects (19 women) with PSP		lamotrigine as monotherapy. Lamotrigine dosing ranged from 25 mg every other day to 300 mg/day.	Lamotrigine was associated with improvements in two thirds of subjects with PSP.
Grant et al. (2010)	12-week A randomised, double-blind, placebo-controlled trial	×	N=32 subjects (29 female subjects [90.6%]; mean age, 32.8 +/- 13.3 years) with PSP	Y-BOCS	lamotrigine as monotherapy. Lamotrigine dosing ranged from 12.5 to 300 mg/d	No significant overall differences were noted between lamotrigine and placebo.
Jafferany &Osuagwu, (2017)	12-week an open-label trial		N= 10 patients (8 women and 2 men) with SPD (per DSM-5 criteria)	SPS-Y-BOCS, SPIS, (CGI-I) BAI, BDI	topiramate in a titrating-upward dose (25-200 mg/d).	Topiramate improved time spent skin picking from 85 minutes to 30 minutes per day. Topiramate appears to be a promising agent in the treatment of skin-picking symptoms.
Jafferany et al. (2010)	12-week an open-label trial		N=2 patients with severe SPD	SP-SAS RBS-R	topiramate in a gradually titrating dose up to 200 mg/day for 12 weeks.	In both of two cases, topiramate was not found helpful in reducing skin-picking behavior, as evidenced by subjective and objective measures
Shapira et al. (2002)	8-week an open-label trial		N=3 PWS adults treated with topiramate		topiramate in a gradually titrating dose up to 200 mg/d for 8 weeks.	Three PWS adults treated with topiramate had a reduction in lesions and self-injury.
Miller and Angulo (2014)	12 week An open-label trial		N=35 individuals with confirmed PWS (ages 5-39 years, 23 females/12 males) and SPD		NAC (dose of 450-1,200 mg/day)	All 35 individuals had improvement in skin-picking behaviors. Ten (29%) individuals (six males and four females) did not have complete resolution of skin-picking behavior, but had significant reduction in the number of active lesions.
Grant et al. (2016)	12-week A randomised, double-	×	N=66	YBOCS.	NAC (dosing range, 1200-3000 mg/day) or placebo	Compared with placebo, NAC treatment was associated with significant improvements in the YBOCS. NAC treatment resulted in significant

	blind, placebo-controlled trial		59 (89%) were women; mean (SD) age was 34.8 (11.0) years		(participants (31 randomized to placebo and 35 to NAC)	reductions in skin-picking symptoms and was well tolerated.
Özcan and Seç-kin, (2016)	Case series		N= 2 (a 30-year-old female, and a 14-year-old girl) both who were diagnosed with TTM		NAC (1200 mg/day, p.o.).	Hair pulling behaviour subsided within 2 months and 2 weeks of initiating NAC in the first and second patient, respectively. No side-effects related to NAC were noted.
Grant et al. (2009)	12-week A ran-domised, double-blind, placebo-controlled trial	×	N=50 individuals with TTM (45 women and 5 men)	MGH-HPS, CGI, PITS	NAC (dosing range, 1200-2400 mg/day) or placebo was administered for 12 weeks.	NAC demonstrated statistically significant reductions in TTM symptoms. No adverse events occurred in the NAC group, and NAC was well tolerated
Bloch et al. (2013)	12-week A ran-domised, double-blind, placebo-controlled trial	×	N=39 children and adolescents aged 8 to 17 years with pediatric TTM		NAC (or placebo) was titrated up to a maximum dose of 2400 mg over the course of 4 weeks	No significant difference between NAC and placebo was found
Lochner et al.(2006)	16-week an open-label pilot study		N=14 adults with TTM	MGH-HPS, CGI,	Topiramate (50-250 mg/day)	The primary outcome measure (HPS) indicated that the severity of hair-pulling in adults with TTM who completed the 16-week study (n=9) decreased significantly from baseline to the treatment endpoint (F=5.05; P=0.0002). Five patients dropped out owing to adverse effects.
Grant et al. (2011)	12-week an open-label		N=14 female subjects (mean age = 33.3 ± 8.9) with DSM-IV TTM	MGH-HPS,	dronabinol (dose ranging from 2.5-15 mg/day).	Twelve of the 14 subjects (85.7%) completed the 12-week study. Dronabinol demonstrated statistically significant reductions in TTM symptoms
Golubchik et al. (2011)	12-week an open-label trial		N=9 children and adolescents, aged 6 to 18 years, diagnosed with ADHD and TTM,	ADHD Rating Scale, MGH-HPS	methylphenidate (MPH)	Significant improvement was detected in ADHD after MPH treatment (P < 0.003), but no significant change was observed in pulling.

RC: Randomized control, CGI : Clinical Global Impression, Y-BOCS : Yale-Brown Obsessive-Compulsive Scale, SRI: serotonin reuptake inhibitors, SSRI: Selective serotonin reuptake inhibitors, PWS: Prader-Willi Syndrome, OCD: obsessive compulsive disorder, PSP:pathologic skin picking, SPD: skin picking disorder, TTM: Trichotillomania, ADHD: Attention deficit hyperactivity disorder FLU: Fluoxetine, SCID: Structured Clinical Interview for DSM Disorders , HDRS-17: The 17-item Hamilton Depression Rating Scale, DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th edition, CBT: Cognitive behavioural therapy, ERP: exposure and response prevention, NAC: N-acetylcysteine, DCS: D-cycloserine, MPH: methylphenidate CY-BOCS: Children's Yale-Brown Obsessive-Compulsive Scale, CDRS: Children's Depression Rating Scale, SPS-Y-BOCS: Skin Picking Scale modified after the Yale-Brown Obsessive-Compulsive Scale (SPS-Y-BOCS), SPIS: Skin Picking Impact Scale MASC: Multidimensional Anxiety Scale for Children, SP-SAS :Skin Picking Symptom Assessment Scale, RBS-R: Repetitive Behavior Scale-Revised, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, MGH-HPS: Massachusetts General Hospital Hair Pulling Scale, PITS: Psychiatric Institute Trichotillomania Scale, PedsQL: Pediatric Quality of Life Inventory

Table 2. Results of studies on the use of glutamatergic modulators in the treatment of OCRD

Drug	OCD	BDD	TTM	SPD	HD
Memantine	+	+			
Ketamine	+	+			
N-Acetyl Cysteine	+/-	+	++	++	
Lamotrigine	++		+	+	
Topiramate	+		+	+	
Glycine	+/-				
D- cycloserine	+				+?
Sarkosine	+				
Rapastinel	+		+	+	
Riluzole	+		+?	+?	
Dronabinol			+		

+=RCT, RPCT; +/-= RCT, RPCT, pozitive and negative results; +?= insufficient data for effectiveness; RCT: randomised controlled trial ; RPCT: randomized placebo-controlled trial; OCRD: Obsessive Compulsive and Related Disorders, OCD:obsessive compulsive disorder, TTM: trichotillomania, BDD: body dysmorphic disorder, SPD:skin picking disorder, HD: hoarding disorder; Memantine: non-competitive antagonist of transmembrane ion channel pore of the NMDA receptor., Ketamine: non-competitive antagonist of NMDA receptors.N-Acetyl Cysteine: precursor of cysteine and modulates the cystine-glutamate anti porter. Topiramate: AMPA receptor modulator (inhibitory).Lamotrigine: AMPA receptor modulator (inhibitory).Glycine, D-cycloserine, sarcosine: Glycine-site of NMDA receptor modulators. Rapastinel: NMDA receptor glycine-site partial agonist. Riluzole: reduces glutamatergic transmission by inhibiting synaptic glutamate release and increasing glial glut uptake. Dronabinol: canabinoid agonist and may reduce the exocitotoxic damage caused by glutamate realease in the striatum.

In this study, a review of glutamate modulating drugs used in the treatment of OCRD is presented. In studies on the subject, the role of riluzole, NAC, DCS, glycine, ketamine and memantine in treatment has been investigated. Currently, OCD has the most support at present for the use of glutamate modulators. The results of studies on the use of glutamatergic modulators in the treatment of OCRDs are summarized in Table 2.

Conclusion

OCRDs are serious mental disorders that can lead to significant psychosocial problems that are frequently seen in the general population. A significant number of cases do not respond to standard treatment approaches. Therefore, new treatment approaches are needed. Glutamate modulators have long been of increasing interest in the treatment of treatment-resistant OCD. While this is the case, it is worth noting that their use in the treatment of OCRD remains unclear and is based on small studies. However, the evidence is gaining strength to support some significant degradation of glutamate in disease. This new perspective on the pathophysiology of OCD, complementing the older focus on monoaminergic neurotransmission, constitutes an important focus of current research and a promising area for the continued development of new therapeutics. Glutamate modulators can be a good alternative, especially in treatment-resistant cases. As reviewed above, memantine, NAC, riluzole, and lamotrigine are options that may be beneficial for some patients. Especially in the treatment of OCD resistant to standard treatment approaches, studies with positive effect as an augmentation with lamotrigine, riluzole and memantine draw attention. NAC is the leading option for the treatment of TTM and SPD. Further investigation of all these agents and the disorders underlying normal glutamate neurotransmission or homeostasis are needed to clarify which agents benefit most in which patients. In addition, genetic and epigenetic factors, clinical symptoms, and subtypes that predict treatment response to glutamate-modulating drugs should be systematically investigated.

References

Aan Het Rot M, Zarate CA, Charney DS, Mathew SJ (2012) Ketamine for depression: where do we go from here? Biol Psychiatry, 72:537–547.

Abramowitz JS, Jacoby RJ (2015) Obsessive-compulsive and related disorders: a critical review of the new diagnostic class. Annu Rev Clin Psychol, 11:165-186.

Afshar H, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P et al. (2012) N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol, 32:797–803.

Afshar H, Akuchekian S, Mahaky B, Zarean E (2014) Topiramate augmentation in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial. J Res Med Sci, 19:976–981.

Alonso P, Gratacós M, Segalàs C, Escaramís G, Real E, Bayés M et al. (2012) Association between the NMDA glutamate receptor GRIN2B gene and obsessive-compulsive disorder. J Psychiatry Neurosci, 37:273–281.

Andersson E, Hedman E, Enander J, Radu Djurfeldt D, Ljótsson B, Cervenka S et al. (2015) D-Cycloserine vs placebo as adjunct to cognitive behavioral therapy for obsessive-compulsive disorder and interaction with antidepressants: A randomized clinical trial. JAMA Psychiatry, 72:659-667.

Andrade C (2019) Augmentation with memantine in obsessive-compulsive disorder. J Clin Psychiatry, 80:19f13163.

APA (2013) Diagnostic and Statistical Manual of Mental Disorders Fifth edition (DSM-5). Washington DC, American Psychiatric Association.

Arnold PD, Rosenberg DR, Mundo E, Tharmalingam S, Kennedy JL, Richter MA (2004) Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive-compulsive disorder: a preliminary study. Psychopharmacology (Berl), 174:530-538.

Arrojo-Romero M, Tajes Alonso M, de Leon J (2013) Lamotrigine augmentation of serotonin reuptake inhibitors in severe and long-term treatment-resistant obsessive-compulsive disorder. Case Rep Psychiatry, 2013:612459.

Atmaca M, Bingol I, Aydin A, Yıldırım H, Okur I, Yıldırım MA et al. (2010) Brain morphology of patients with body dysmorphic disorder. J Affect Disord, 123:258-263.

Bakhla AK, Verma V, Soren S, Sarkhel S, Chaudhury S (2013) An open-label trial of memantine in treatment-resistant obsessive-compulsive disorder. Ind Psychiatry J, 22:149-152.

Barroso L, Sternberg F, Souza M, Nunes G (2017) Trichotillomania: a good response to treatment with N-acetylcysteine. An Bras Dermatol, 92:537–539.

Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, et al. (1995) Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage, 10:89-97.

Berlin HA, Koran LM, Jenike MA, Shapira NA, Chaplin W, Pallanti S et al. (2011) Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry, 72:716–721.

Bisol LW, Lara DR (2009) Improvement of obsessive-compulsive disorder with divalproex and lamotrigine in two patients with bipolar II disorder. Pharmacopsychiatry, 42:37–39.

Bloch MH, Wasylink S, Landeros-Weisenberger A, Panza KE, Billingslea E, Leckman JF et al. (2012) Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol Psychiatry, 72:964–970.

Bloch MH, Panza KE, Grant JE, Pittenger C, Leckman JF (2013) N-Acetylcysteine in the treatment of pediatric trichotillomania: a randomized, double-blind, placebo-controlled add-on trial. J Am Acad Child Adolesc Psychiatry, 52:231-240.

Bonnot O, Cohen D, Thuilleaux D, Consoli A, Cabal S, Tauber M (2016) Psychotropic treatments in Prader-Willi syndrome: a critical review of published literature. Eur J Pediatr, 175:9-18.

Borue X, Sharma M, Hudak R (2015) Biological treatments for obsessive-compulsive and related disorders. J Obsessive Compuls Relat Disord, 6:7-26.

Bruno A, Micò U, Pandolfo G, Mallamace D, Abenavoli E, Di Nardo F et al. (2012) Lamotrigine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive–compulsive disorder: a double-blind, placebo-controlled study. J Psychopharmacol, 26:1456–1462.

Burguière E, Monteiro P, Mallet L, Feng G, Graybiel AM (2015) Striatal circuits, habits, and implications for obsessive-compulsive disorder. Curr Opin Neurobiol, 30:59-65.

Castle D, Beilharz F, Phillips KA , Brakoulias V, Drummond LM , Hollander E et al. (2021) Body dysmorphic disorder: a treatment synthesis and consensus on behalf of the International College of Obsessive-Compulsive Spectrum Disorders and the Obsessive Compulsive and Related Disorders Network of the European College of Neuropsychopharmacology. Int Clin Psychopharmacol, 36:61-75.

Coric V, Milanovic S, Wasylink S, Patel P, Malison R, Krystal JH et al. (2003) Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with obsessive-compulsive disorder and major depressive disorder. Psychopharmacology (Berl), 167:219–220.

Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G et al. (2005) Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: An open-label trial. Biol Psychiatry, 58:424–428.

Coric V, Kelmendi B, Pittenger C, Wasylink S, Bloch MH, Green J (2007) Beneficial effects of the antiglutamatergic agent riluzole in a patient diagnosed with trichotillomania. J Clin Psychiatry, 68:170-171.

Costa DLC, Diniz JB, Requena G, Joaquim MA, Pittenger C, Bloch MH et al. (2017) Randomized, double-blind, placebo-controlled trial of N-Acetylcysteine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry, 78:e766-e773.

de Salles Andrade JB, Giori IG, Melo-Felippe FB, Vieira-Fonseca T, Fontenelle LF, Kohlrausch FB (2019) Glutamate transporter gene polymorphisms and obsessive-compulsive disorder: A case-control association study. J Clin Neurosci, 62:53-59.

Dong N, Nezgovorova V, Hong K, Hollander E (2019) Pharmacotherapy in body dysmorphic disorder: relapse prevention and novel treatments. Expert Opin Pharmacother, 20:1211–1219.

Dougherty DD, Brennan BP, Stewart SE, Wilhelm S, Widge AS, Rauch SL (2018) Neuroscientifically informed formulation and treatment planning for patients with obsessive-compulsive disorder: A review. JAMA Psychiatry, 75:1081-1087.

Dougherty D, Rauch S, Greenberg BD (2020) Pathophysiology of obsessive-compulsive and related disorders. In The American Psychiatric Association Publishing Textbook of Anxiety, Trauma and OCD-Related Disorders (Eds N Simon, E Hollander, BO Rothbaum, DJ Stein) 265-284. Washington DC, American Psychiatric Association Publishing.

Emamzadehfard S, Kamaloo A, Paydary K, Ahmadipour A, Zeinoddini A, Ghaleiha A et al. (2016) Riluzole in augmentation of fluvoxamine for moderate to severe obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study. Psychiatry Clin Neurosci, 70:332-341.

Farnia V, Gharehbaghi H, Alikhani M, Almasi A, Golshani S, Tatari F et al. (2018) Efficacy and tolerability of adjunctive gabapentin and memantine in obsessive compulsive disorder: Double-blind, randomized, placebo controlled trial. J Psychiatr Res, 104:137-143.

Farrell LJ, Waters AM, Boschen MJ, Hattingh L, McConnell H, Milliner EL et al. (2013) Difficult-to-treat pediatric obsessive compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-cycloserine augmented behavior therapy. Depress Anxiety, 30:723-731.

Fineberg NA, Bienvenu OJ, Denys D, Lochner C, Nestadt G, Leckman JF et al. (2010) Should OCD be classified as an anxiety disorder in DSM-V? Depress Anxiety, 27:495-506.

Gadallah AHA, Ebada MA, Gadallah A, Ahmed H, Rashad W, Eid KA et al. (2020) Efficacy and safety of N-acetylcysteine as add-on therapy in the treatment of obsessive-compulsive disorder: A systematic review and meta-analysis. J Obsessive Compuls Relat Disord, 25: 100529.

Ghaderi A, Vahed N, Ghayoomi R, Ostadmohammadi V, Gholami M, Dehkohneh S (2019) N-acetylcysteine in addiction management: Current knowledge and future perspectives. International Journal of Pharmaceutical Research, 11:13-24.

Ghaleiha A, Entezari N, Modabbernia A, Najand B, Askari N, Tabrizi M et al. (2013) Memantine add-on in moderate to severe obsessive-compulsive disorder: randomized double-blind placebo-controlled study. J Psychiatr Res, 47:175-180.

Ghanizadeh A, Mohammadi MR, Bahraini S, Keshavarzi Z, Firoozabadi A, Alavi Shoshtari A (2017) Efficacy of N-Acetylcysteine augmentation on obsessive compulsive disorder: A multicenter randomized double blind placebo controlled clinical trial. Iran J Psychiatry, 12:134-141.

Grant P, Lougee L, Hirschtritt M, Swedo SE (2007a) An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. J Child Adolesc Psychopharmacol, 17:761–767.

Grant JE, Odlaug BL, Kim SW (2007b) Lamotrigine treatment of pathologic skin picking: an open label study. J Clin Psychiatry, 68:1384–1391.

Grant JE, Odlaug BL, Kim SW (2009) N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. Arch Gen Psychiatry, 66:756-763.

Grant JE, Odlaug BL, Chamberlain SR, Kim SW (2010) A double-blind, placebo-controlled trial of lamotrigine for pathological skin picking: treatment efficacy and neurocognitive predictors of response. J Clin Psychopharmacol, 30:396-403.

Grant JE, Odlaug BL, Chamberlain S, Kim SW (2011) Dronabinol, a cannabinoid agonist reduces hair pulling in trichotillomania: A pilot study. Psychopharmacology, 218:493–502.

Grant PJ, Joseph LA, Farmer CA, Luckenbaugh DA, Lougee LC, Zarate CA Jr et al. (2014) 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. Neuropsychopharmacology, 39:1453-1459.

Grant JE, Chamberlain SR, Redden SA, Leppink EW, Odlaug BL, Kim SW (2016) N-Acetylcysteine in the treatment of excoriation disorder: a randomized clinical trial. JAMA Psychiatry, 73:490–496.

Grant JE, Chamberlain SR (2016) Trichotillomania. Am J Psychiatry, 173:868-874.

Grant JE, Chesivoir E, Valle S, Ehsan D, Chamberlain SR (2023) Double-blind placebo-controlled study of memantine in trichotillomania and skin-picking disorder. Am J Psychiatry, 180:348-356.

Golubchik P, Sever J, Weizman A, Zalsman G (2011) Methylphenidate treatment in pediatric patients with attention-deficit/hyperactivity disorder and comorbid trichotillomania: a preliminary report. Clin Neuropharmacol, 34:108–110.

Grados MA, Atkins EB, Kovacikova GI, McVicar E (2015) A selective review of glutamate pharmacological therapy in obsessive-compulsive and related disorders. Psychol Res Behav Manag, 8:115-131.

Greenberg WM, Benedict MM, Doerfer J, Perrin M, Panek L, Cleveland WL et al. (2009) Adjunctive glycine in the treatment of obsessive-compulsive disorder in adults. J Psychiatr Res, 43:664–670.

Goodman WK, Storch EA, Sheth SA (2021) Harmonizing the neurobiology and treatment of obsessive-compulsive disorder. Am J Psychiatry, 178:17-29.

Grünblatt E (2021) Genetics of OCD and related disorders; searching for shared factors. Curr Top Behav Neurosci, 49:1-16.

Hadi F, Kashefinejad S, Kamalzadeh L, Hoobehfekr S, Shalbafan M (2021) Glutamatergic medications as adjunctive therapy for moderate to severe obsessive-compulsive disorder in adults: a systematic review and meta-analysis. BMC Pharmacol Toxicol, 22:69.

Haghighi M, Jahangard L, Mohammad-Beigi H, Bajoghli H, Hafezian H, Rahimi A et al. (2013) In a double-blind, randomized and placebo-controlled trial, adjuvant memantine improved symptoms in inpatients suffering from refractory obsessive-compulsive disorders (OCD). Psychopharmacology (Berl), 228:633-640.

Isobe M, Redden SA, Keuthen NJ, Stein DJ, Lochner C, Grant JE, Chamberlain SR (2018) Striatal abnormalities in trichotillomania: a multi-site MRI analysis. Neuroimage Clin, 17:893-898.

Jafferany M, Shireen F, Ibrahim A (2010) An open-label trial of topiramate in the treatment of skin picking in pervasive developmental disorder not otherwise specified. Prim Care Companion J Clin Psychiatry, 12:PCC.09l00829.

Jafferany M, Osuagwu FC (2017) Use of topiramate in skin picking disorder: a pilot study. Prim Care Companion CNS Disord, 19:16m01961.

Khalkhali M, Aram S, Zarrabi H, Kafie M, Heidarzadeh A (2016) Lamotrigine augmentation versus placebo in serotonin reuptake inhibitors-resistant obsessive-compulsive disorder: a randomized controlled trial. Iran J Psychiatry, 11:104–114.

Kress VE, Stargell NA, Zoldan CA, Paylo MJ (2016) Hoarding disorder: Diagnosis, assessment, and treatment. J Couns Dev, 94:83-90.

Köse S, Çetin M (2017) Ketamine and rapastinel: NMDA receptor modulators in the rapid treatment of obsessivecompulsive disorder. Psychiatry Clin Psychopharmacol, 27:213–214.

Kushner MG, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M (2007) D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. Biol Psychiatry, 62:835-838.

Lee TM, Lee KM, Lee CY, Lee HC, Tam KW, Loh EW (2021) Effectiveness of N-acetylcysteine in autism spectrum disorders: A meta-analysis of randomized controlled trials. Aust N Z J Psychiatry, 55:196-206.

Lewin AB, Wu MS, McGuire JF, Storch EA (2014) Cognitive behavior therapy for obsessive-compulsive and related disorders. Psychiatr Clin North Am, 37:415-445.

Lochner C, Seedat S, Niehaus DJ, Stein DJ (2006) Topiramate in the treatment of trichotillomania: an open-label pilot study. Int Clin Psychopharmacol, 21:255-259.

Lochner C, Stein DJ (2014)Treatment of obsessive-compulsive and related disorders. Curr Treat Options Psychiatry, 1:225-234.

Lochner C, Roos A, Stein DJ (2017) Excoriation (skin-picking) disorder: a systematic review of treatment options. Neuropsychiatr Dis Treat, 13:1867-1872.

Lu S, Nasrallah HA (2018) The use of memantine in neuropsychiatric disorders: an overview. Ann Clin Psychiatry, 30:234–248.

Maia TV, Cooney RE, Peterson BS (2008) The neural bases of obsessive - Compulsive disorder in children and adults. Dev Psychopathol, 20:1251–1283.

Mataix-Cols D, Frost RO, Pertusa A, Clark LA, Saxena S, Leckman JF et al. (2010) Hoarding disorder: a new diagnosis for DSM-V? Depress Anxiety, 27: 556–572.

Mataix-Cols D, Turner C, Monzani B, Isomura K, Murphy C, Krebs G et al. (2014) Cognitive behavioral therapy with post-session D-cycloserine augmentation for pediatric obsessive compulsive disorder: pilot randomised controlled trial. Br J Psychiatry, 204:77-78.

Marinova Z, Chuang DM, Fineberg N (2017) Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder. Curr Neuropharmacol, 15:977-995.

Miller JL, Angulo M (2014) An open-label pilot study of N-acetylcysteine for skin-picking in Prader-Willi syndrome. Am J Med Genet A, 164:421–424.

Modarresi A, Sayyah M, Razooghi S, Eslami K, Javadi M, Kouti L (2018) Memantine augmentation improves symptoms in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder: A randomized controlled trial. Pharmacopsychiatry, 51:263-269.

Modarresi A, Chaibakhsh S, Koulaeinejad N, Koupaei SR (2019) A systematic review and meta-analysis: memantine augmentation in moderate to severe obsessive-compulsive disorder. Psychiatry Res, 282:112602

Mowla A, Khajeian AM, Sahraian A, Chohedri AH, Kashkoli F (2010) Topiramate augmentation in resistant OCD: a double-blind placebo-controlled clinical trial. CNS Spectr, 15:613–617.

Nakao T, Kanba S (2019) Pathophysiology and treatment of hoarding disorder. Psychiatry Clin Neurosci, 73:370-375.

Nery FG, Li W, Del Bello MP, Welge JA (2021) N-acetylcysteine as an adjunctive treatment for bipolar depression: A systematic review and meta-analysis of randomized controlled trials. Bipolar Disord, 23:707-714.

Niciu MJ, Kelmendi B, Sanacora G (2012) Overview of glutamatergic neurotransmission in the nervous system. Pharmacol Biochem Behav, 100:656–664.

Nordstrom EJ, Burton FH (2002) A transgenic model of comorbid Tourette's syndrome and obsessive-compulsive disorder circuitry. Mol Psychiatry, 7:617–625.

Odlaug BL, Grant JE (2007) N-acetyl cysteine in the treatment of grooming disorders. J Clin Psychopharmacol, 27:227–229.

Oliver G, Dean O, Camfield D, Blair-West S, Ng C, Berk M et al. (2015) N-acetyl cysteine in the treatment of obsessive compulsive and related disorders: a systematic review. Clin Psychopharmacol Neurosci, 13:12–24.

Özcan D, Seçkin D (2016) N-Acetylcysteine in the treatment of trichotillomania: remarkable results in two patients. J Eur Acad Dermatol Venereol, 30:1606-1608.

Parli GM, Gales MA, Gales BJ (2023) N-Acetylcysteine for obsessive-compulsive and related disorders in children and adolescents: A review. Ann Pharmacother, 57:847-854.

Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S (2016) N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther, 41:214-219.

Pietrzak B, Konopka A, Wojcieszak J (2013) Effect of topiramate on hippocampus-dependent spatial memory in rats. Pharmacol Rep, 65:1152-1162.

Pittenger C, Bloch MH, Williams K (2011) Glutamate abnormalities in obsessive compulsive disorder: Neurobiology, pathophysiology, and treatment. Pharmacol Ther, 132:314–332.

Pittenger C, Bloch MH, Wasylink S, Billingslea E, Simpson R, Jakubovski E (2015) Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: A pilot randomized placebo-controlled trial. J Clin Psychiatry, 76:1075–1084.

Pittenger C (2015) Glutamatergic agents for OCD and related disorders. Curr Treat Options Psychiatry, 2:271-283.

Poyurovsky M, Glick I, Koran LM (2010) Lamotrigine augmentation in schizophrenia and schizoaffective patients with obsessive-compulsive symptoms. J Psychopharmacol, 24:861–866.

Rauch SL, Phillips KA, Segal E, Makris N, Shin LM, Whalen PJ et al. (2003) A preliminary morphometric magnetic resonance imaging study of regional brain volumes in body dysmorphic disorder. Psychiatry Res, 122:13-19.

Reddy YJ, Sundar AS, Narayanaswamy JC, Math SB (2017) Clinical practice guidelines for obsessive-compulsive disorder. Indian J Psychiatry, 59(Suppl 1):S74.

Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D et al. (2013) Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology, 38:2475–2483.

Rodriguez CI, Wheaton M, Zwerling J, Steinman SA, Sonnenfeld D, Galfalvy H et al. (2016) Can exposure-based CBT extend the effects of intravenous ketamine in obsessive-compulsive disorder? An open-label trial. J Clin Psychiatry, 77:408–409.

Rotge JY, Aouizerate B, Tignol J, Bioulac B, Burbaud P, Guehl D (2010) The glutamate-based genetic immune hypothesis in obsessive-compulsive disorder. An integrative approach from genes to symptoms. Neuroscience, 165:408–417.

Sani G, Gualtieri I, Paolini M, Bonanni L, Spinazzola E, Maggiora M et al. (2019) Drug treatment of trichotillomania (hair-pulling disorder), excoriation (skin-picking) disorder, and nail-biting (onychophagia). Curr Neuropharmacol, 17:775-786.

Sarris J, Oliver G, Camfield DA, Dean OM, Dowling N, Smith DJ et al. (2015) N-Acetyl Cysteine (NAC) in the treatment of obsessive-compulsive disorder: A 16-week, double-blind, randomised, placebo-controlled study. CNS Drugs, 29:801-809.

Sasso DA, Kalanithi PS, Trueblood KV, Pittenger C, Kelmendi B, Wayslink S et al (2006) Beneficial effects of the glutamate-modulating agent riluzole on disordered eating and pathological skin-picking behaviors. J Clin Psychopharmacol, 26:685–687.

Shapira NA, Lessig MC, Murphy TK, Driscoll DJ, Goodman WK (2002) Topiramate attenuate self-injurious behavior in Prader-Willi syndrome. Int J Neuropsychopharmacol, 5:141–145.

Shmelkov SV, Hormigo A, Jing D, Proenca CC, Bath KG, Milde T et al (2010) Slitrk5 deficiency impairs corticostriatal circuitry and leads to obsessive-compulsive-like behaviors in mice. Nat Med, 16:598-602.

Silva-Netto R, Jesus G, Nogueira M, Tavares H (2014) N-acetylcysteine in the treatment of skin picking disorder. Braz J Psychiatr, 36:101.

Suzuki K, Monteggia LM (2020) The role of eEF2 kinase in the rapid antidepressant actions of ketamine. Adv Pharmacol, 89:79-99.

Stein DJ, Fineberg NA, Bienvenu OJ, Denys D, Lochner C, Nestadt G et al. (2010) Should OCD be classified as an anxiety disorder in DSM-V? Depress Anxiety, 27:495–506.

Stewart SE, Fagerness JA, Platko J, Smoller JW, Scharf JM, Illmann C et al. (2007) Association of the SLC1A1 glutamate transporter gene and obsessive-compulsive disorder. Am J Med Genet B Neuropsychiatr Genet, 144B:1027–1033.

Stewart SE, Jenike EA, Hezel DM, Stack DE, Dodman NH, Shuster L et al. (2010) A single-blinded case-control study of memantine in severe obsessive-compulsive disorder. J Clin Psychopharmacol, 30:34–39.

Storch EA, Merlo LJ, Bengtson M, Murphy TK, Lewis MH, Yang MC et al. (2007) D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. Int Clin Psychopharmacol, 22:230-237.

Storch EA, Murphy TK, Goodman WK, Geffken GR, Lewin AB, Henin A et al. (2010) A preliminary study of D-cycloserine augmentation of cognitive behavioral therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry, 68:1073-1076.

Storch EA, Wilhelm S, Sprich S, Henin A, Micco J, Small BJ et al. (2016) Efficacy of augmentation of cognitive behavior therapy with weight- adjusted d-Cycloserine vs placebo in pediatric obsessive-compulsive disorder: A randomized clinical trial. JAMA Psychiatry, 73:779-788.

Suppes T (2002) Review of the use of topiramate for treatment of bipolar disorders. J Clin Psychopharmacol, 22:599–609.

Ting JT, Feng G (2008) Glutamatergic synaptic dysfunction and obsessive-compulsive disorder. Curr Chem Genomics, 2:62–75.

Torales J, Ruiz Díaz N, Ventriglio A, Castaldelli-Maia JM, Barrios I, García O et al. (2021) Hair-pulling disorder (Trichotillomania): Etiopathogenesis, diagnosis and treatment in a nutshell. Dermatol Ther, 34:e13466.

Uzun O (2010) Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: A case report. J Psychopharmacol, 24:425–427.

Van Ameringen M, Patterson B, Simpson W (2014) DSM-5 obsessive-compulsive and related disorders: Clinical implications of new criteria. Depress Anxiety, 31:487-493.

Verrotti A, Striano P, Iapadre G, Zagaroli L, Bonanni P, Coppola G et al. (2018) The pharmacological management of Lennox-Gastaut syndrome and critical literature review. Seizure, 63:17–25.

Vlček P, Polák J, Brunovský M, Horáček J (2018) Role of glutamatergic system in obsessive-compulsive disorder with possible therapeutic implications. Pharmacopsychiatry, 51:229-242.

Welch JM, Lu J, Rodriguiz RM, Trotta NC, Peca J, Ding JD et al. (2007) Cortico-striatal synaptic defects and OCD-like behaviours in Sapap3-mutant mice. Nature, 448:894–900.

Wilhelm S, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE et al. (2008) Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. Am J Psychiatry, 165: 335-341.

Wu K, Hanna GL, Rosenberg DR, Arnold PD (2012) The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder. Pharmacol Biochem Behav, 100:726–735.

Xia J, Du Y, Han J, Liu G, Wang X (2015) D-cycloserine augmentation in behavioral therapy for obsessive-compulsive disorder: a meta-analysis. Drug Des Devel Ther, 9:2101-2117.

Yolland CO, Hanratty D, Neill E, Rossell SL, Berk M, Dean OM et al. (2020) Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia. Aust N Z J Psychiatry, 54:453-466.

Authors Contributions: The author(s) have declared that they have made a significant scientific contribution to the study and have assisted in the preparation or revision of the manuscript

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared.

Financial Disclosure: No financial support was declared for this study.