REVIEW ARTICLE

Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder

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Abstract: ***Objective***: Obsessive-compulsive disorder (OCD) is a mental disease commonly associated with severe distress and impairment of social functioning. Serotonin reuptake inhibitors and/or cognitive behavioural therapy are the therapy of choice, however up to 40% of patients do not respond to treatment. Glutamatergic signalling has also been implicated in OCD. The aim of the current study was to review the clinical evidence for therapeutic utility of glutamate-modulating drugs as an augmentation or monotherapy in OCD patients.

Methods: We conducted a search of the MEDLINE database for clinical studies evaluating the effect of glutamate-modulating drugs in OCD.

Results: Memantine is the compound most consistently showing a positive effect as an augmentation therapy in OCD. Anti-convulsant drugs (lamotrigine, topiramate) and riluzole may also provide therapeutic benefit to some OCD patients. Finally, ketamine may be of interest due to its potential for a rapid onset of action.

Conclusion: Further randomized placebo-controlled trials in larger study populations are necessary in order to draw definitive conclusions on the utility of glutamate-modulating drugs in OCD. Furthermore, genetic and epigenetic factors, clinical symptoms and subtypes predicting treatment response to glutamate-modulating drugs need to be investigated systematically.

Keywords: Obsessive-compulsive disorder, glutamate, glutamate-modulating drugs, treatment response, memantine, clinical subtypes.

1. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disease characterized by anxiety-provoking, unwanted and repetitive thoughts (obsessions) and repeated ritualistic behaviours aimed to decrease the anxiety (compulsions). Symptoms can cause severe distress and functional impairment [1]. OCD affects 2-3% of the population and is ranked within the ten leading neuropsychiatric causes of disability [2; WHO, 2008]. OCD comorbidity with depression, bipolar disorder, and substance use and impulse control disorders has been reported, and is associated with increased overall distress and suicidality rates as well as additional treatment challenges [3, 4].

1.1. Brain Circuits Implicated in Obsessive-Compulsive Disorder

Dysfunction of the cortico-striatal-thalamo-cortical circuitry has been implicated in OCD, including structural abnormalities, altered brain activation and connectivity [5, 6]. Meta-analyses of volumetric studies have implicated reduced orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and dorsal mediofrontal/anterior cingulate volume, as well as increased thalamic and lenticular nucleus extending to the caudate nucleus volume in OCD patients [7, 8]. On the other hand, meta-analyses of positron emission tomography (PET), single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) studies implicated the head of the caudate, the orbital gyrus and the dorsal frontoparietal network in OCD [9, 10].

Glutamate is the primary neurotransmitter within the implicated in OCD cortico-striatal-thalamic circuits [11]. Anatomical nodes of relevance within this circuitry include

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areas of the frontal and cingulate cortex, caudate, putamen and thalamus, comprising the direct cortico-striatal pathway, as well as the globus pallidus and subthalamic nucleus comprising the indirect loop [2]. Dysregulation of glutamatergic signaling within the cortico-striatal circuitry has been proposed in OCD, with reduced glutamatergic concentrations in the anterior cingulate cortex, combined with overactivity of glutamatergic signaling in the striatum and orbitofrontal cortex [12-15]. However, additional circuits, including the amygdalo-cortical circuitry may also be important for the pathophysiology of OCD [16]. Overall, the neuroimaging data implicate disruptions of glutamatergic signalling in OCD, which suggests glutamate-modulating drugs may be potentially useful for the disorder.

1.2. Dysregulation of Neurotransmitter Signalling in OCD

Serotonin reuptake inhibitors (SRIs) are considered to exert their effects by influencing the cortico-striato-thalamo-cortical circuit, even though the exact mechanism of action remains elusive. For example, escitalopram treatment has been associated with restoring imbalances in brain connectivity in OCD patients [17]. A meta-analysis of genetic polymorphisms previously implicated in OCD suggested a role of serotonergic genes (the serotonin transporter *SLC6A4* and the serotonin 2A receptor *HTR2A*) in OCD vulnerability [18]. On the other hand, recent genome-wide association studies (GWAS) have not identified involvement of serotonergic genes at genome-wide significant levels [19, 20]. However, in a GWAS investigating genetic polymorphisms influencing treatment response to SRIs in OCD, enrichment analysis suggested a role for serotonergic and glutamatergic genes polymorphisms [21].

Pathophysiological processes involving other neurotransmitter systems and signalling molecules, besides serotonin, may also be important in OCD. Notably, dopamine dysfunction has been found in some OCD cases [22, 23]. An autoimmune hypothesis for the development of an OCD subtype has also been suggested, implicating Group A Streptococcal infections. Accordingly, in a subgroup of OCD patients changes in anti-streptococcal, anti-neuronal or anti-basal ganglia antibody titers, immune cells and circulating cytokines have been detected [24, 25]. Additional systems implicated in OCD include neuropeptide neurotransmitters [26] and sex steroids [27, 28]. Second messenger pathways alterations in OCD have also been detected and are of interest due to the potential for their specific therapeutic targeting [29-31]. Finally, a rapidly increasing number of studies indicate that changes in glutamatergic neurotransmission may be involved in OCD pathophysiology, with glutamate-modulating agents presenting a potential therapeutic alternative [32] (see next section).

1.3. Glutamatergic Signalling

Glutamate is the major excitatory neurotransmitter in the brain, present in about 50% of synapses. Glutamatergic neurotransmission has a fundamental role for neuronal plasticity, learning, and memory [33]. However, in pathological conditions glutamate can act as a neuronal excitotoxin, leading to rapid or delayed neurotoxicity [34]. Dysregulation of gluta-

matergic signalling has been implicated in a number of neuropsychiatric illnesses, including OCD, depression, bipolar disorder and schizophrenia [35, 36]. Glutamate mediates its effects through ionotropic (NMDA, AMPA, kainate) and metabotropic (mGluRs) receptors [37]. The NMDA receptor requires in addition to glutamate also binding of glycine or D-serine to its glycine cofactor site, in order to ensure its activation. Overall, ionotropic glutamate receptors are a critical constituent of the core mechanisms of rapid neurotransmission, while metabotropic glutamate receptors participate in the slower modulation of neuronal function. Both ionotropic and metabotropic glutamate receptors are localized in the candidate brain circuitry of OCD. Glutamate receptors are involved in the processes of long term potentiation (LTP) and long term depression (LTD) of neuronal firing, which are forms of long term synaptic plasticity critically important for learning [38]. Glutamate receptors have been implicated in virtually every form of learning in the brain, including habit learning [38-40]. The relationship between activity levels at different glutamate receptor subtypes is currently not well understood in OCD. Interestingly, interactions with serotonergic signalling for both ionotropic and metabotropic glutamate receptors have been demonstrated [41, 42].

In addition, Na$^+$-dependent glutamate transporters (EAATs 1-5) and vesicular glutamate transporters (VGLUTs 1-3) mediate the reuptake of glutamate into glial and neuronal cells and thus terminate its action in the synaptic cleft [43]. EAAT1 and EAAT2 are the primary astrocyte glutamate transporters, while EAAT3 is the primary neuronal glutamate transporter. Astrocytes convert glutamate into glutamine and release it. Neurons in turn take up glutamine and convert it into glutamate [44]. The cystine/glutamate antiporter on astrocytes mediates the cellular uptake of cystine in exchange for simultaneous release of extrasynaptic glutamate. Overactivity of the cystine/glutamate transporter has been associated with glutamatergic excitotoxicity in several pathological conditions [45].

1.4. Glutamatergic Dysfunction in OCD

Glutamate is the primary neurotransmitter within the implicated in OCD cortico-striatal-thalamo-cortical circuits [11]. Increased glutamate levels have been measured in cerebrospinal fluid of OCD patients compared to healthy controls [46, 47]. Excessive glutamate levels could lead to glutamate receptor hyperactivity or even excitotoxicity in neurons.

Genetic studies have also implicated an association of glutamatergic genes with OCD. *SLC1A1* coding for the neuronal glutamate transporter EAAT3 and *GRIN2B* coding for the NR2B subunit of NMDARs have repeatedly shown association with OCD [48-50]. The 9p chromosome, in which *SLC1A1* is located, has also been implicated in OCD by linkage analysis [51].

Several animal studies have further corroborated the possible benefit of anti-glutamatergic drugs for reducing OCD resembling behaviours in animals. Thus, the uncompetitive NMDAR antagonists memantine and amantadine inhibited marble-burying without affecting locomotor activity in mice [52]. Furthermore, fluoxetine and memantine had a synergis-

tic effect in reducing compulsive scratching in mice, with the combination of both drugs exerting an effect at lower concentrations than each of them alone [53]. It has to be noted that there are significant limitations in the interpretation of animal data in relation to clinical OCD.

Thus, converging evidence from preclinical and clinical research suggests that glutamatergic signalling dysregulation, possibly involving the corpus striatum, is associated with OCD and is potentially reversible with treatment. This suggests possible therapeutic utility for glutamate-modulating drugs in OCD.

1.5. Current Treatment Strategies for Obsessive-Compulsive Disorder

The current first-line treatment for OCD includes cognitive behavioural therapy (CBT) applied in the form of expo-

sure and response prevention (ERP) and serotonin reuptake inhibitors (SRIs) [54]. SRIs include clomipramine and the selective serotonin reuptake inhibitors (SSRIs). In mild to moderate OCD cases monotherapy with CBT or SRIs is the treatment of choice, while severe OCD commonly requires a combination of CBT and SRIs [55, 56]. However, only about 60% of patients respond to current treatment and even among responders symptoms often persist to some degree [57]. SSRIs (fluoxetine, sertraline, *etc.*) are generally well tolerated (also better in comparison to clomipramine), but side effects can occur, most commonly gastrointestinal complaints, sexual dysfunction, sedation, and behavioural activation. In addition, in children and adolescents rare cases of suicidal ideation arising after SSRIs administration have been described [58].

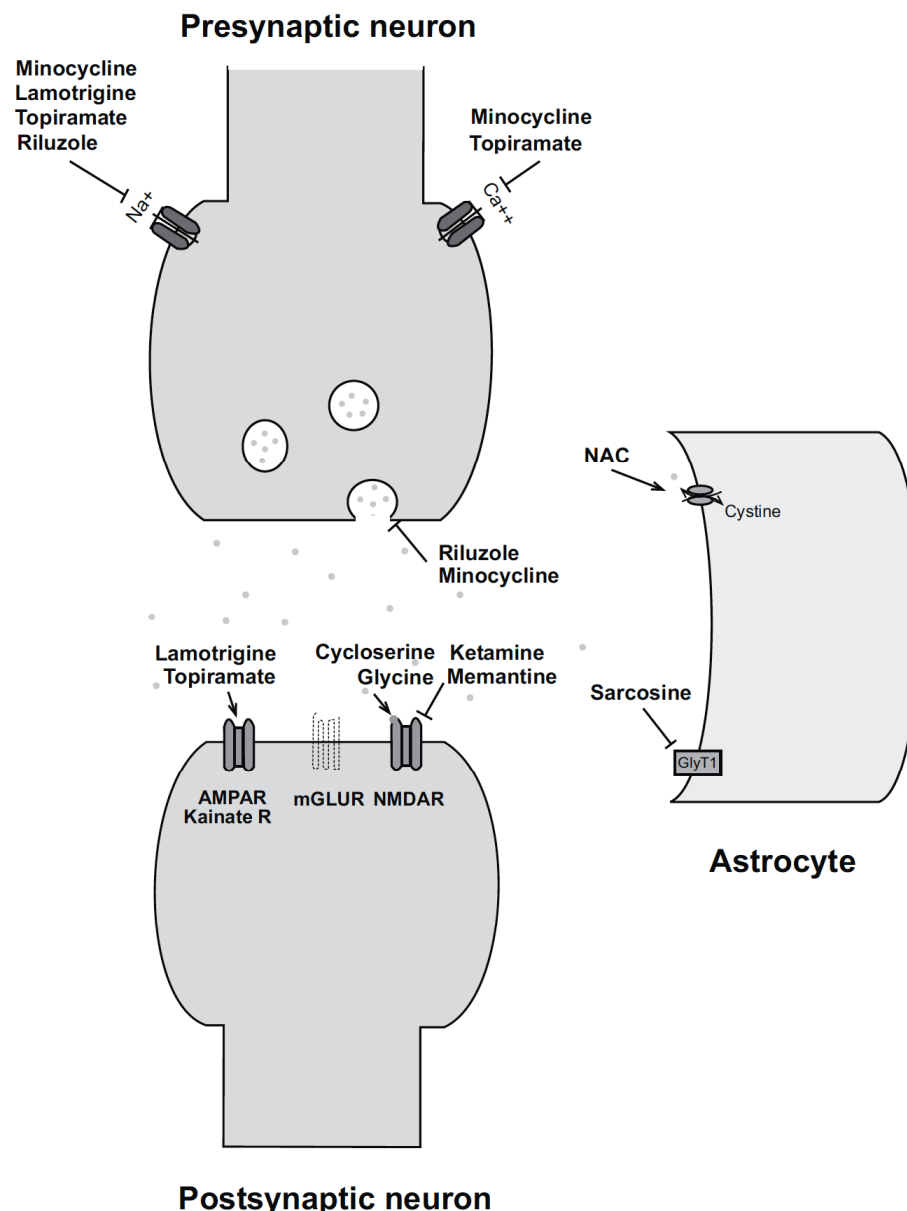In treatment-resistant OCD several augmentation strategies are available. The most extensively studied augmenta-

Fig. (1). Mechanisms of action of glutamate-modulating drugs at the glutamatergic synapse.

tion agents are antipsychotic drugs, which provide therapeutic benefit to a subgroup of OCD patients, but are associated with significant side effects [56, 59, 60]. Therefore, a need for the development of novel therapeutic agents for OCD exists. Glutamatergic drugs constitute one of the candidates for augmentation or monotherapy in OCD (including treatment-resistant OCD) in light of a possible role for glutamatergic signalling dysregulation in the disorder.

1.6. The Therapeutic Potential of Glutamate-Modulating Drugs in Other Psychiatric Disorders

Under the broad term of "glutamate-modulating" drugs compounds with different mechanisms of action are included (Fig. **1**). They differ significantly in their toxicity and safety profiles, as well as in the speed of onset and duration of the therapeutic effects.

Glutamate-modulating drugs have shown promise as potential therapeutic agents in other psychiatric disorders, including depression, bipolar disorder, suicidality, and self-injurious behaviour [61-63]. There is a high comorbidity between OCD and affective disorders [64], and comorbid OCD has been associated with increased overall distress and suicidality rates [65]. Thus, there are strong arguments to investigate the effect of glutamate-modulating drugs in co-morbid as well as in treatment-resistant OCD.

2. METHOD

We systematically searched the database PubMed (http://www.ncbi.nlm.nih.gov/pubmed) for articles investigating the effect of glutamate-modulating drugs in OCD using the search terms "obsessive-compulsive disorder" or "OCD" AND "glutamate" or "riluzole" or "memantine" or "ketamine" or "glycine" or "sarcosine" or "topiramate" or "lamotrigine" or "N-acetylcysteine" or "minocycline" or "D-cycloserine". Papers published until February 15th, 2017 were retrieved and clinical trials or case reports were included in the analysis.

3. RESULTS

A growing number of clinical investigations have assessed the utility of glutamate-modulating drugs as an augmentation or monotherapy in OCD, including difficult to treat OCD. However, there are significant variations in between studies in terms of treatment-resistance, comorbidity, age and gender of the patients. Many were open-label trials with small sample sizes and no placebo controls or case reports. Recently, several small double-blind, placebo-controlled trials on glutamate-modulating drugs as monotherapy or augmentation of an existing psychotropic regimen (summarized in Table **1**) or as augmentation of psychotherapy (summarized in Table **2**) have also been conducted and due to their theoretically superior study design have provided more reliable data on the drugs' efficacy.

3.1. Riluzole

Riluzole, a drug approved for the treatment of amyotrophic lateral sclerosis, inhibits synaptic glutamate release and stimulates glutamate uptake by astrocytes [66, 67]. Side effects reported with riluzole are usually mild: diarrhea and

reversible after discontinuation transaminases elevation. More serious rare potential side effects include hepatotoxicity and pancreatitis in children and adolescents [68, 69].

Results on riluzole efficacy in OCD so far have been mixed. The first encouraging data on its potential utility came from a case report of an adult OCD patient [70]. Small open-label studies suggested therapeutic efficacy of riluzole as an adjunctive therapy in treatment-resistant OCD, including one investigation in children and adolescents [71] and two in adults [72, 73]. Interestingly, 2 of the 5 responders in the Coric *et al.* study [72] showed predominantly hoarding phenotypes. However, the open-label design and small study numbers require caution in the data interpretation.

A double-blind, placebo-controlled trial with riluzole was conducted in 60 treatment-resistant children and adolescents with OCD [69]. The sample group in this study was characterized by treatment resistance, high degree of comorbidity with other psychiatric disorders (including 17 patients with autism spectrum disorder) and additional pharmacological treatment in 92% of the cases. In this 12 weeks trial riluzole did not show superior effect as an add-on medication to the existing therapeutic regimen on any of the primary (CY-BOCS, CGAS, CGI-I and CGI-S) or secondary outcome measures [69]. Most patients tolerated riluzole well; however there was one case of pancreatitis.

A second randomized placebo-controlled trial of riluzole augmentation was conducted in treatment-refractory adult OCD patients, including both outpatients and inpatients [74]. Riluzole or placebo was added to the existing SRI treatment regimen for 12 weeks after a 2 weeks placebo lead-on phase. No significance was achieved in the study sample as a whole on the primary outcome measure (Y-BOCS score), even though Y-BOCS scores change after riluzole augmentation was nominally greater. Riluzole showed some benefit in outpatients, where significantly more patients achieved at least partial treatment response in comparison to the placebo [74].

Finally, in a double-blind, placebo-controlled trial of 50 adult OCD patients adjunctive therapy with riluzole in addition to fluvoxamine treatment for 10 weeks resulted in greater reduction of total and compulsions subscale Y-BOCS scores compared to the fluvoxamine group [75].

The results to date suggest that riluzole may have the potential for efficacy in a less severe or treatment-resistant OCD population, however tolerability and acceptability issues may impact on its further development as a treatment for OCD.

3.2. Memantine

The uncompetitive NMDAR antagonist memantine is approved for the treatment of moderately severe Alzheimer's disease. Memantine is generally well tolerated even in the elderly population and has a relatively low propensity for drug-drug interactions [76]. Side effects most commonly include fatigue, headache, increase in blood pressure and dizziness. Memantine has been tested in treatment-resistant OCD. Positive results from a few case-reports [77-80] suggested memantine may be associated with clinical

Table 1.　Placebo-controlled, randomized, double-blind clinical trials of glutamate-modulating drugs as monotherapy or augmentation of the existing psychotropic regimen in OCD.

Study & Drug	Duration & Dose	Adjunctive/ Monotherapy	Subjects	Treatment Resistance at Baseline	Endpoint Results on Efficacy	Side Effects	Effect on Primary Outcome: (Yes/no)
Riluzole							
Grant *et al.*, 2014	12 weeks Final dose: 100 mg/day	Adjunctive Initial treatment: SRI	60 pediatric OCD patients (17 with co-morbid ASD)	Yes	No significant differences in change of CY-BOCS, CGAS, CGI-I and CGI-S scores between the placebo and riluzole groups at the end of the trial	Mainly well tolerated 1 pancreatitis case 5 transaminases elevation cases	CY-BOCS score change: no CGI-I score change: no CGI-S score change: no CGAS score change: no
Pittenger *et al.*, 2015	12 weeks + 2 weeks lead-on placebo Final dose: 100 mg/day	Adjunctive Initial treatment: SRI	38 adult OCD patients (27 outpatients and 11 inpatients)	Yes	No significant difference in Y-BOCS scores change between the placebo and riluzole groups at the end of the trial Among OCD outpatients only significantly more achieved at least partial treatment response with adjunctive riluzole.	Well tolerated	Y-BOCS score change: no
Emamzadehfard *et al.*, 2016	10 weeks Final dose: 100 mg/day	Adjunctive Initial treatment: fluvoxamine	50 adult OCD patients		Significant greater reduction of Y-BOCS total and compulsions scores between the placebo and riluzole groups at the end of the trial	Well tolerated	Y-BOCS score change: yes
Memantine							
Ghaleiha *et al.*, 2013	8 weeks Final dose: 20 mg/day	Adjunctive Initial treatment: fluvoxamine	42 adult OCD patients	No	Greater reduction of Y-BOCS scores in the memantine group at the end of the trial ($p = 0.006$)	Well tolerated	Y-BOCS score change: yes
Haghighi *et al.*, 2013	12 weeks Dose: 5-10 mg/day	Adjunctive Initial treatment: SRI	40 adult OCD patients	No	Greater reduction of Y-BOCS scores in the memantine group at the end of the trial ($p = 0.005$)	Well tolerated	Not predefined Y-BOCS score change: yes
Ketamine							
Rodriguez *et al.*, 2013	Ketamine & saline i.v. infused at least 1 week apart in random order Dose: 0.5 mg/kg	Monotherapy	15 adult OCD patients (2 with mild or moderate co-morbid depression)	Part of the sample	Greater reduction in Y-BOCS scores for subjects receiving ketamine as first infusion at 7 days post infusion ($p < 0.01$) Obsession symptoms severity (OCD-VAS score) with ketamine significantly lower at mid-infusion, 230 min and 7 days post infusion compared to the saline group	Mild increase in blood pressure and pulse Dissociation, psychotic and manic symptoms, time perception distortion, dizziness, nausea, vomiting, headache	Not predefined Y-BOCS score change: yes for ketamine as first infusion OCD-VAS score change: yes
Glycine							
Greenberg *et al.*, 2009	12 weeks Final dose: 60 g/day	Adjunctive Initial treatment: stable psycho-pharmacological or psychotherapeutic treatment	24 adult OCD patients	Not specified	Reduction of Y-BOCS scores in the glycine compared to the placebo group at the endpoint showed a trend towards significance ($p = 0.053$)	High drop-out rate related to glycine's unpleasant taste and nausea	Y-BOCS score change: no (strong trend towards significance)

Study & Drug	Duration & Dose	Adjunctive/ Monotherapy	Subjects	Treatment Resistance at Baseline	Endpoint Results on Efficacy	Side Effects	Effect on Primary Outcome: (Yes/no)
Topiramate							
Mowla *et al.*, 2010	12 weeks Dose: 100-200 mg/day	Adjunctive Initial treatment: existing treatment regimen	49 adult OCD patients	Yes	Y-BOCS score mean decrease 32.0% in the topiramate group vs. 2.4% in the placebo group (p < 0.05)		Y-BOCS score change: yes
Berlin *et al.*, 2011	12 weeks Dose: 50-400 mg/day	Adjunctive Initial treatment: SSRI	36 adult OCD patients	Yes	No significant treatment effect of topiramate on total Y-BOCS scores (p = 0.11) or obsessions subscores (p = 0.99) Significant treatment effect of topiramate on Y-BOCS compulsions subscores (p = 0.014).	Due to adverse effects 28% discontinuation and 39% dose reduction in the topiramate group Weight loss, influenza-like symptoms, taste perversion, paresthesia, memory difficulty	Y-BOCS total score change: no Y-BOCS obsessions subscore change: no Y-BOCS compulsions subscore change: yes
Afshar *et al.*, 2014	12 weeks Dose range: 100-200 mg/day	Adjunctive Initial treatment: SRI	38 adult OCD patients	Yes	No significant difference in Y-BOCS scores between the topiramate and placebo group at the end of the study (p = 0.058) Y-BOCS scores were significantly lower in the topiramate vs. the placebo group at weeks 4 (p = 0.01) and 8 (p = 0.01) of the trial.	2 patients dropped out due to adverse effects. Paresthesia, cognitive problems, weight loss, micturition frequency, renal stone, decreased appetite	Y-BOCS score change at the end of the trial: no (strong trend towards significance) Treatment response: no (strong trend)
Lamotrigine							
Bruno *et al.*, 2012	16 weeks Final dose: 100 mg/day	Adjunctive Initial treatment: SRI	40 (final sample 33) adult OCD patients	Yes	Lamotrigine was associated with greater reduction of Y-BOCS (p < 0.0001) and HDRS scores (p < 0.0001) at endpoint. Lamotrigine was associated with lower CGI-S scores at the end of the trial (p < 0.0001).	Well tolerated Sedation, fatigue, headache, skin rash	Y-BOCS score change: yes CGI-S score difference: yes HDRS score change: yes
Khalkhali *et al.*, 2016	12 weeks Final dose: 100 mg/day	Adjunctive Initial treatment: SRI	53 adult OCD patients	Yes	Lamotrigine was associated with greater reduction of the total Y-BOCS score (p = 0.007), as well as the obsessions (p = 0.01) and compulsions subscales (p = 0.005).	Well tolerated Headache, skin rash	Y-BOCS score change: yes
N-acetylcysteine							
Afshar *et al.*, 2012	12 weeks Dose: up to 2.4 g/day	Adjunctive Initial treatment: SRI	48 adult OCD patients	Yes	Greater reduction of Y-BOCS scores in the NAC compared to the placebo group at the end of the trial (p = 0.003) Significantly more patients in the NAC compared to the placebo group were responders (p = 0.013).	Well tolerated Nausea, vomiting, diarrhea	Y-BOCS change: yes Treatment response rate: yes

(Table 1) contd….

Study & Drug	Duration & Dose	Adjunctive/ Monotherapy	Subjects	Treatment Resistance at Baseline	Endpoint Results on Efficacy	Side Effects	Effect on Primary Outcome: (Yes/no)
N-acetylcysteine							
Sarris *et al.*, 2015	16 weeks Dose: 3 g/day	Monotherapy or adjunctive Initial treatment: existing stable treatment regimen or monotherapy	44 adult OCD patients	Not specified	No significant difference in Y-BOCS scores changes between the NAC and placebo group at the end of the study	Well tolerated Heartburn	Y-BOCS change: no
Paydary *et al.*, 2016	10 weeks Dose: 2 g/d	Adjunctive Initial treatment: fluvoxamine	44 adult OCD patients		Greater reduction of Y-BOCS total scores (p = 0.012) and obsessions subscale (p = 0.011) in the NAC compared to the placebo group at the end of the trial	Well tolerated	Y-BOCS change: yes
Costa *et al.*, 2017	16 weeks Dose: 3 g/d	Adjunctive Initial treatment: SRI	40 adult OCD patients	Yes	No significant difference in Y-BOCS scores changes between the NAC and placebo group at the end of the study Some benefit in reducing anxiety symptoms in the NAC group	Well tolerated Abdominal pain	Y-BOCS change: no
Minocycline							
Esalatmanesh *et al.*, 2016	10 weeks Dose: 200 mg/d	Adjunctive Initial treatment: fluvoxamine	102 adult OCD patients	No	Greater reduction of Y-BOCS total scores (p = 0.003), the obsession subscale (p = 0.001) and greater response rate in the minocycline group at the end of the trial	Well tolerated	Y-BOCS change: yes

Abbreviations: ADIS = Anxiety Disorders Interview Schedule, ASD = autism spectrum disorder, CBT = cognitive behavioural therapy, CSR = clinical severity rating, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impression – Improvement, CGI-S = Clinical Global Impression - Severity, GOCS = Global Obsessive-Compulsive Scale, HDRS = Hamilton Rating Scale for Depression, NAC = N-acetylcysteine, OCD-VAS = OCD visual analog scale, SSRI = selective serotonin reuptake inhibitor, SUDS = Subjective Units of Distress Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

improvement, which in one case was sustained up to 9 months. Three small, open label trials of memantine, administered either as monotherapy or adjunctive to SRI [81-83], were also performed. They showed promise of efficacy with approximately 45% to 60% of entrants showing some sign of clinical response using the Y-BOCS and good tolerability. In the study by Feusner *et al.* [82], memantine had a preferential efficacy in OCD compared to a group of generalized anxiety disorder patients.

Recently, two double-blind, placebo-controlled trials have also demonstrated promising results. In the study by Ghaleiha *et al.* [84] 42 OCD patients without psychiatric comorbidity and without psychotropic medication use in the 6 weeks preceding the screening, were randomized to memantine or placebo as an add-on treatment to fluvoxamine. After 8 weeks patients from the memantine-assigned group showed higher rate of remission (p < 0.001) and greater improvement in both the obsession and compulsion subscales of the Y-BOCS. A limitation of the study was the relatively short duration of the trial (8 weeks). Thus, it could not be definitely concluded whether the advantage over fluvoxamine treatment would have been sustained in a longer trial.

In the trial by Haghighi *et al.* [85], 40 adult OCD patients were randomized to memantine or placebo as an add-on treatment to their SRIs regimen. All OCD patients in this study had no psychiatric comorbidities, were not defined as treatment-resistant, and for the week before and during the trial were on SRI regimen. After 12 weeks significant beneficial effect of memantine on OCD symptoms severity was observed measured by greater decrease in Y-BOCS scores (p = 0.005). In addition, 9 patients from the SRI + memantine group were full responders in comparison to 0 patients from the SRI group. A limitation of this study was that symptoms of depression and anxiety were not measured throughout the study, not accounting for a possible effect of memantine on them [85].

In a further single-blind case-control study of 44 adult patients with severe, treatment-resistant OCD 22 received memantine augmentation to their treatment regimen [86], while 22 served as controls. Mean decreases in Y-BOCS scores at discharge compared to admission were significant in the memantine augmented group (27%) but not in the control group (16.5%), implying beneficial therapeutic effect of memantine augmentation. In addition, 50% decrease in Y-BOCS score was more likely in the memantine than in the

Table 2. Placebo-controlled, randomized, double-blind clinical trials of d-cycloserie as augmentation of psychotherapy in OCD patients

Study & Drug	Duration, dose and Temporal Relationship to CBT Sessions	Subjects	Mode of Therapy	Endpoint Results on Efficacy	Side Effects	Effect on Primary Outcome: (yes/no)
Studies in adults						
Storch *et al.*, 2007	12 CBT sessions with DCS 4 h prior to each session Dose: 250 mg/CBT session	24 adult OCD patients	In person 1 session hierarchy and education, 1 session practice exposure and 9 sessions exposure and response prevention exercises	No significant difference between the DCS and placebo groups in terms of OCD severity post-treatment.	Well tolerated	Y-BOCS change: no
Kushner *et al.*, 2007	10 CBT sessions with DCS 2 h prior to each session Dose: 125 mg/CBT session	25 adult OCD patients	In person Hierarchy at baseline, 10 sessions of exposure/ritual prevention techniques	No differences in Y-BOCS scores or between the DCS and placebo groups at the end of the trial. The DCS group achieved > 50% SUDS scores reduction significantly faster and showed improved compliance.	Well tolerated Mild gastrointestinal distress, fatigue, anxiety and dizziness	Y-BOCS change: no
Wilhelm *et al.*, 2008	10 CBT sessions with DCS 1 h before each session Dose: 100 mg/CBT session	23 adult OCD patients (Including patients with continuing stable psychotropic treatment regimen)	In person 1 psychoeducational /treatment planning session, 10 behavior therapy sessions	No significant differences in Y-BOCS scores between the DCS and placebo groups at post-treatment ($p = 0.14$) or 1 month follow up ($p = 0.12$) Significantly lower Y-BOCS scores in the DCS group at mid-treatment ($p = 0.009$) Significantly fewer depressive symptoms at post-treatment ($p=0.04$)	Well tolerated	Y-BOCS change: no at post-treatment or 1 mo follow up; yes at mid-treatment
Andersson *et al.*, 2015	DCS 1 h before 5 CBT tasks during a 12 weeks internet-based CBT Dose: 50 mg/CBT task	128 adult OCD outpatients (In some stable antidepressant regimen)	Therapist-supported internet 12 weeks of therapist-supported internet-based CBT	No difference between the DCS and placebo group in Y-BOCS scores at the trial end and 3 months follow up In the DCS group significantly more antidepressant-free patients achieved remission at the trial's end compared to antidepressant-medicated patients ($p = 0.008$).	Well tolerated	Y-BOCS change: no
de Leeuw *et al.*, 2017	6 guided exposure sessions with DCS 1 h before each session Dose: 125 mg/session	39 adult OCD patients	In person 6 weekly guided exposure sessions	No significant difference in the Y-BOCS score change between the groups at the end of the trial, although decrease in DCS group was numerically greater ($p = 0.076$). A significant effect of DCS in the "cleaning/contamination" subgroup ($p = 0.033$).	Well tolerated	Y-BOCS change: no
Studies in children and adolescents						
Storch *et al.*, 2010	10 CBT sessions with DCS 1 h before each session for 7 of the sessions Dose: weight-adjusted	30 children and adolescents with OCD	In person 10 CBT sessions including psychoeducation, cognitive therapy, hierarchy development, and ERP	No significant differences in CY-BOCS and ADIS-CSR scores changes at the end of the trial.	Well tolerated	CY-BOCS: no CGI-S: significant time and group, but no significant time by group interaction ADIS-CSR: no

(Table 2) contd….

Study & Drug	Duration, dose and Temporal Relationship to CBT Sessions	Subjects	Mode of Therapy	Endpoint Results on Efficacy	Side Effects	Effect on Primary Outcome: (yes/no)
Studies in children and adolescents						
Farrell *et al.*, 2013	9 CBT sessions with DCS 1 h before each of 5 sessions Dose: weight-adjusted	17 children and adolescents with OCD	In person 9 CBT sessions, including 4 sessions with instruction on cognitive-behavioural techniques and 5 ERP sessions	No significant difference in CY-BOCS between the DCS and placebo groups at the end of the trial Greater improvement from end of the trial until 1 month follow up in the DCS compared to the placebo group was detected for CY-BOCS obsessions subscale (p < 0.05), GOCS scale (p < 0.05) and CGI-S (p = 0.05).	Well tolerated	CY-BOCS scores: no at post treatment or 2 mo follow up; yes at 1 mo follow up for some of the measures CSR: no GOCS: yes at 1 mo follow up; no at post treatment or 3 mo follow up CGI-S: yes at 1 mo follow up; no at post treatment or 3 mo follow up
Mataix-Cols *et al.*, 2014	14 CBT sessions, 10 of them with DCS immediately after each session Dose: 50 mg	27 children and adolescents with OCD (In some patients stable psychotropic regimen)	In person 14-session manualised treatment, including 2 sessions psychoeducation, 10 sessions ERP and 2 sessions relapse prevention.	No significant differences in CY-BOCS scores between the DCS and placebo group at any time point	Well tolerated	CY-BOCS change: no
Storch *et al.*, 2016	10 CBT sessions with DCS administered 1 h prior to 7 of the sessions Dose: weight-adjusted	142 children and adolescents with OCD	In person 10 CBT sessions	No significant difference in the rate of CY-BOCS scores decline between the groups. No moderation effect for antidepressant medication observed.	Well tolerated	CY-BOCS change: no

Abbreviations: ADIS = Anxiety Disorders Interview Schedule, ASD = autism spectrum disorder, CBT = cognitive behavioural therapy, CSR = clinical severity rating, CY-BOCS = Children's Yale-Brown Obsessive Compulsive Scale, CGAS = Children's Global Assessment Scale, CGI-I = Clinical Global Impression – Improvement, CGI-S = Clinical Global Impression - Severity, GOCS = Global Obsessive-Compulsive Scale, HDRS = Hamilton Rating Scale for Depression, NAC = N-acetylcysteine, OCD-VAS = OCD visual analog scale, SSRI = selective serotonin reuptake inhibitor, SUDS = Subjective Units of Distress Scale, Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

placebo group (p = 0.04). A limitation of this study was the fact that randomization to the treatment groups was not performed and the decision to match cases and controls was taken only after the patients' discharge [86].

In summary, a beneficial therapeutic effect of memantine in OCD patients with or without treatment resistance has been consistently observed in these reports. However, there are currently no clear indications predicting which OCD patients would respond beneficially to memantine treatment augmentation.

3.3. Ketamine

Ketamine is a non-competitive NMDAR antagonist, which has been used as an anaesthetic and is currently being investigated for its rapid antidepressant effect [61, 63]. In a case report Rodriguez *et al.* [87] found that in a treatment-resistant patient with severe OCD a blinded ketamine intravenous infusion caused a complete cessation of obsessions with return to baseline after one week [87].

A placebo-controlled, double-blind, cross-over trial with ketamine as monotherapy was subsequently conducted by Rodriguez *et al.* [88] in 15 adult OCD patients with near constant obsession symptoms. Patients received two intravenous infusions (one with saline and one with ketamine) spaced at least one week apart in randomized order. After the first infusion those receiving ketamine (n=8) showed significantly lower obsession symptoms severity at mid-infusion (p < 0.005), 230 min post infusion (p < 0.05) and 7 days post infusion (p < 0.05) compared to the saline group (n=7). In addition 50% of the OCD subjects receiving ketamine met the treatment response criteria at one week compared to 0% from the saline group. Due to the substantial carry-over effect of ketamine at one week, the cross over arm of the study was not analyzed. Side effects with ketamine administration were significant and included dissociation, time perception distortions, positive psychotic and manic symptoms, dizziness, nausea or vomiting and headache. Overall the results of the study suggested a rapid effect of ketamine infusion as a monotherapy in OCD, which was sustained at one week post treatment. A limitation was the difficulty to blinding the patients to the infusion due to the psychoactive effects of ketamine, which in turn may influence self-rating scales as OCD-VAS [88].

These results stand in contrast to an open-label trial carried out by Bloch *et al.* [89] in 10 adult patients with severe treatment-resistant OCD, high comorbidity rate of depression and high rate of concurrent psychotropic medication. All participants received single intravenous infusion with ketamine, which was associated only transiently (after 1-3 h post infusion) with substantial OCD symptoms improvement. Ketamine effect on Y-BOCS scores at days 1-3 post infusion did not reach the treatment response criteria, and Y-BOCS scores returned to baseline by day 7 after infusion. In contrast, depression symptoms were affected significantly in 4 of the 7 ketamine treated patients with comorbid depression, achieving treatment response in the first 1-3 days. Adverse effects of ketamine included dissociative symptoms, memory gaps, sensory distortions, and a transient systolic blood pressure increase in one subject. In two of the three OCD subjects without comorbid depression, both of which had trauma history, dysphoria, passive suicidal ideation and anxiety were observed, starting within the first two days after treatment [89, 90]. Thus, trauma history may be an indication for caution in ongoing investigations of ketamine in OCD patients.

The results from the initial small-sized trials on ketamine efficacy in OCD are contradictory – in both studies ketamine caused a rapid decrease in OCD symptoms, but the sustainability of its effect over a clinically meaningful period of time differed greatly. Two recent small, open label trials in adult OCD patients investigated the possibility to sustain the therapeutic effect after a single ketamine injection using either memantine treatment [91] or ERP therapy [92] and ERP showed overall more promising results. Ketamine was also associated with serious adverse effects, including dissociative symptoms, dysphoria, suicide ideation, psychotic or manic symptoms and anxiety, limiting its acceptability for clinical usage. However, its fast onset of action distinguishes it from most other glutamate-modulating compounds and makes it an interesting candidate for further investigations.

It has been proposed that the rapid antidepressant efficacy of ketamine involves inhibition of presynaptic NMDA receptors, causing increased release of glutamate from nerve endings and activation of postsynaptic AMPA receptors. These events are followed by activation of voltage-sensitive calcium channel, influx of calcium and secretion of brain-derived neurotrophic factor (BDNF). The BDNF-TrkB signaling triggers activation of the mTOR and its down-stream signaling pathways, causing enhanced synthesis of synaptic proteins and synaptogenesis [93]. Whether such a mechanisms is involved in the putative efficacy of ketamine in treating OCD is unknown and requires investigation. Interestingly, the mood stabilizer lithium at subtherapeutic or low therapeutic levels potentiates and prolongs the antidepressant effects of ketamine in a stress-induced mouse model of depression, likely by augmenting the BDNF-TrkB and mTOR signaling pathways [94]. Lithium inhibits excessive glutamate-induced, NMDA receptor-mediated calcium influx in neurons, presumably *via* reducing NR2B subunit tyrosine phosphorylation through the Src/Fyn kinase [reviewed in 95]. Together, it seems warranted to assess as to whether lithium can potentiate the putative efficacy of ketamine (and memantine) in OCD patients.

3.4. Glycine

Glycine is an NMDAR (co)-agonist. The occupancy of the glycine modulatory site by glycine, D-serine or D-alanine is a prerequisite for the activation of the cation channel by glutamate. In a double-blind, placebo-controlled trial 24 adult outpatient OCD subjects with stabilized treatment regimen were randomized to adjunctive glycine treatment or placebo for 12 weeks [96]. This study was characterized by high non-adherence rate, mainly due to nausea and the unpleasant taste of glycine. From the OCD patients who completed the study, 2 out of 5 subjects with adjunctive glycine were responders, while 0 out of 9 subjects with add-on placebo were responders. The decrease in Y-BOCS scores in the glycine compared to the placebo group showed a trend not reaching significance (p=0.053). Limitations of the study included the small sample size due to the high dropout rate and the heterogeneity of the initial treatment regimen [96]. In a case report of a patient comorbid for OCD and body dysmorphic disorder, who had failed multiple treatment trials, glycine treatment led to robust decrease in OCD/BDD symptoms and long term improved functioning [97].

3.5. Sarcosine

Sarcosine is an endogenous inhibitor of the glycine transporter-1. By blocking the glycine transporter it increases the synaptic availability of glycine. Sarcosine and glycine have shown promise also in clinical trials of schizophrenia [98]. Sarcosine was tested in a single open-label trial in 26 OCD patients as either monotherapy or as adjunctive therapy for 10 weeks. 8 OCD subjects met the criteria for responders in this study and sarcosine was overall well tolerated [99]. Limitations of the study included its open label design, and small sized and heterogeneous sample. Bitopertin, another inhibitor of the glycine transporter-1, has been investigated for its efficacy as augmentation of stable SSRI regimen in OCD patients, but no results have been reported so far (NCT01674361).

3.6. Topiramate

Topiramate is an anticonvulsant and anti-migraine drug. It is also an AMPA-receptor antagonist and interacts with voltage-gated sodium and calcium channels. Recognised adverse effects of topiramate (including paresthesia, cognitive problems, micturation frequency, renal stones, weight loss or psychiatric adverse events) limit its tolerability and acceptability. Evidence for potential benefit from topiramate in treatment-resistant OCD was suggested by a few open-label trials [100, 101] and case reports [102, 103]. However, in two other case reports, topiramate treatment was associated with the provocation of OCD symptoms in cases without prior OCD [104, 105]. In one case, OCD improved after topiramate discontinuation [105].

Three double-blind, placebo-controlled trials have since been conducted with topiramate in OCD, with mixed results. In the study of Mowla *et al.* [106], 49 treatment-resistant OCD patients were randomized to topiramate or placebo as an add-on to their current treatment regimen. At the end of the 12 weeks trial 12 from the 24 patients in the topiramate group (20 completers) were rated as responders versus no

patients from the placebo group. Significantly more improvement in the Y-BOCS scores was detected in the topiramate compared to the placebo group (p < 0.001) [106]. In the second placebo-controlled trial, 36 treatment-resistant adult OCD patients were randomly assigned for 12 weeks to topiramate or placebo as an adjunctive agent to their SSRI treatment regimen [107]. Topiramate significantly decreased compulsions subscale (p = 0.014), but not obsessions subscale (p = 0.99) or total Y-BOCS score (p = 0.11). Topiramate was not well tolerated (influenza-like symptoms, paresthesia, memory difficulties, taste perversions), which led to 28% drop-out and 39% dose reduction in the topiramate group [107]. In the third trial by Afshar *et al.* [108], 38 adult treatment refractory OCD patients were randomly assigned to topiramate or placebo as an adjunctive medication to their SRI treatment regimen for 12 weeks. Topiramate treatment led to statistically significant improvement of Y-BOCS scores in comparison to the control group at weeks 4 (p = 0.02) and 8 (p = 0.01), but not at the end point (week 12) (p = 0.058) and was associated with a number of side effects [108].

3.7. Lamotrigine

Lamotrigine is an anticonvulsant drug and has also antidepressant/mood-stabilizing properties utilized in the treatment of bipolar disorder. It blocks voltage-gated sodium channels, thus inhibiting glutamate release, inhibits AMPA receptors, is an indirect inhibitor of histone deacetylases (HDACs) and robustly induces the prominent neuroprotective protein Bcl-2 [109]. Positive results from case reports [110-112], and a retrospective open-label case series of 22 adult treatment-resistant OCD patients [113] suggested a possible therapeutic role for lamotrigine in OCD. On the other hand, in another case series of 8 treatment-resistant OCD patients, adjunctive lamotrigine resulted in significant improvement in only one patient [114].

Bruno *et al.* [115] conducted a 16 weeks double blind, placebo controlled study of adjunctive lamotrigine in 40 SRI-resistant OCD patients. At the end of the study the decrease in Y-BOCS scores was significantly more pronounced in the lamotgrine augmented group (p = 0.003). Furthermore, 35% of the patients assigned to the lamotrigine group showed a full and 50% - partial treatment response, while none of the patients in the placebo group reached the treatment response criteria. Lamotrigine was overall well tolerated with side effects including sedation, fatigue, headache, and in one patient skin rash [115]. Recently another 12 weeks double blind, placebo controlled trial with adjunctive lamotrigine in addition to stable SRI treatment regimen was conducted in 53 treatment-resistant adult OCD patients. At the end of the trial significantly greater reduction in total Y-BOCS scores (p = 0.007) was observed in the lamotrigine group [116]. Lamotrigine was overall well tolerated with skin rash and headache emerging as side effects.

An open-label trial by Poyurovsky *et al.* [117] provided information about the possible utility of lamotrigine in schizoaffective patients with obsessive-compulsive symptoms. Lamotrigine was added to the ongoing psychotropic treatment regimen of patients with schizophrenia (n = 5) and schizoaffective disorder (n = 6) and with clinically relevant obsessive-compulsive symptoms (OCS). Lamotrigine augmentation for 8 weeks was correlated with treatment response concerning the OCS in 5 of the patients, all of whom had schizoaffective disorder. Depressive symptoms were also improved with lamotrigine treatment, while schizophrenia symptoms were not affected [117].

However, accounts of OCD symptoms provocation after lamotrigine treatment have also emerged. Thus, Kemp *et al.* [118] described the development of obsessive symptoms in 5 patients suffering from bipolar II disorder after starting lamotrigine intake. In addition, Kuloglu *et al.* [119] described a case of a female bipolar disorder II patient in whom lamotrigine added to the treatment regimen was associated with the appearance of disruptive obsessive symptoms.

3.8. N-acetylcysteine

N-acetylcysteine (NAC) is an antioxidant, used as an antidote in acetaminophen overdose and the associated hepatotoxicity. NAC is a precursor of cysteine and modulates the cystine-glutamate antiporter [120]. An early report found benefits from NAC augmentation of fluvoxamine in an OCD case [121]. A subsequent randomized, double-blind, placebo-controlled trial was conducted in 48 adult treatment-resistant OCD patients, who were assigned to NAC or placebo adjunctive to SRI treatment for 12 weeks. At the end of the study significantly greater improvement of Y-BOCS scores in the NAC augmented group was detected (p = 0.003) and the response rate in the NAC group was higher. NAC was overall well tolerated with adverse effects including nausea, vomiting and diarrhoea [122]. A recent randomized, double-blind, placebo-controlled trial was carried out in 44 adult OCD patients who were randomized to NAC or placebo for 16 weeks [123]. Continuation of previously stable psychotropic regimen was allowed during the course of the trial. No difference in Y-BOCS scores was detected between the NAC and placebo groups at the end of the trial. At week 12 significant NAC was found to be significantly more effective in reducing the compulsions Y-BOCS subscale, however this difference dissipated by the end of the trial [123]. In addition, in a double-blind, randomized, placebo-controlled trial augmentation of fluvoxamine with NAC for 10 weeks led to greater reduction of total (p = 0.012) and obsessions (p = 0.011) subscale Y-BOCS scores compared to the fluvoxamine and placebo group [124]. Finally, Costa *et al.* conducted a double-blind, randomized, placebo-controlled trial in 40 treatment-resistant adult OCD patients, in whom augmentation of the existing SRI treatment regimen with NAC for 16 weeks did not lead to difference in the Y-BOCS score change in comparison to placebo, although some benefit in reducing anxiety symptoms was observed [125].

3.9. Minocycline

Minocycline is an antibiotic (a tetracycline derivative), which has been shown to inhibit Na^+- and Ca^{2+}-ionic currents and block glutamate release *in vitro* [126]. A prospective, open-label trial examined the efficacy of minocycline as an augmenting agent to the existing treatment regimen including SRI in 9 adult treatment-resistant OCD subjects for 12 weeks. While no treatment response was observed for the

group as a whole, two patients (both with early-onset OCD) were responders [127]. In a double blind, placebo controlled trial in 102 adult OCD patients minocycline or placebo were added to fluvoxamine treatment for 10 weeks. Greater reduction of Y-BOCS total scores (p = 0.003), the obsession sub-scale (p = 0.001) and greater response rate were observed in the minocycline group at the end of the trial [128]. Minocycline's relatively low cost and approved use in both children and adults suggests its further investigation in OCD could be warranted.

3.10. D-Cycloserine

D-cycloserine (DCS) is a partial NMDAR co-agonist that has been hypothesized to facilitate fear extinction [129]. DCS at varying doses has been tested for its effect in augmenting the treatment response to CBT (ERP) in several double-blind studies in adult OCD patients and younger people, with unimpressive results.

The first double-blind, placebo-controlled trial was conducted by Storch *et al.* [130] in 24 adult OCD patients, to whom DCS or placebo were administered 4 hours prior to each of 12 CBT sessions. No significant differences were found in this study between the two groups in terms of OCD severity or responder rate at post-treatment. In a second double-blind, placebo-controlled trial of 25 adult OCD patients, DCS or placebo was administered 2 hours prior to each of 10 CBT sessions [131]. There were no between-group differences in Y-BOCS scores or subjective units of distress scale (SUDS) scores at the last CBT session or at 3 months follow-up. However, the DCS group achieved > 50% reduction in SUDS scores significantly earlier than the placebo group. A third double blind, placebo-controlled trial by Wilhelm *et al.* [132] investigated 23 adult OCD patients. Participants received DCS or placebo one hour prior to each of 10 CBT sessions. No significant differences were detected in Y-BOCS scores at post-treatment or one month follow up. However, Y-BOCS scores in the DCS group were significantly lower at mid-treatment. On the other hand comorbid depression symptoms were significantly lower at post-treatment, but not at mid-treatment or 1 month follow-up. The data from the Wilhelm *et al.* [132] study were re-analyzed to elucidate the time-course of DCS effect and it was found to precipitate faster treatment-response to CBT [133]. Thus, DCS may accelerate the therapeutic effect of CBT in OCD patients and appears well tolerated, though its benefits are not sustained in terms of improved outcomes. A larger randomized, double blind, placebo controlled trial was recently conducted in 128 adult OCD outpatients [134] to whom placebo or DCS was administered 1 h before 5 CBT tasks during a 12 weeks course of internet-based CBT training. There was no difference on the Y-BOCS scores between the DCS and placebo groups at the end of the trial. Patients were allowed to continue their stable regimen of concurrent psychotropic medication and within the DCS group a significantly greater proportion of antidepressant-free patients achieved remission at the end of the study in comparison to antidepressant-treated patients, suggesting any possible benefit from DCS may be limited to otherwise unmedicated cases. There is a potential for pharmacological interaction between SSRIs and glutamatergic drugs, which is still not

definitively clarified and may be involved in the observed findings [135]. Finally, in a double-blind, placebo-controlled trial of 39 adult OCD patients DCS or placebo were administered 1 h before each of 6 weekly guided exposure sessions. There was no significant difference in the Y-BOCS score decrease at the end of the trial (p = 0.076), although the decrease in the DCS augmented group was numerically greater [136].

Storch *et al.* [137] conducted a double-blind, randomized trial of DCS administered 1 hour prior to 7 out of 10 CBT sessions in 30 children and adolescents with OCD. There was no significant effect of DCS on OCD severity at post-treatment, even though DCS patients experienced numerically greater reduction in CY-BOCS scores. In a further double-blind, placebo-controlled, randomized trial, 17 paediatric patients with 'difficult to treat' OCD received 9 sessions CBT, 5 of which were augmented with DCS or placebo 1 hour before the session. A greater improvement in CY-BOCS scores in the DCS group compared to the placebo was detected at 1 month follow up post-treatment [138]. On the other hand, no therapeutic benefit was present when DCS (n = 12) in comparison to placebo (n = 12) was administered immediately after 10 CBT sessions in a double-blind, placebo-controlled trial of early-onset OCD patients [139]. A recent double-blind, placebo-controlled study in 30 early-onset OCD patients suggested that DCS augmentation of CBT was not associated with increased homework compliance, even though homework compliance by itself was associated with better outcome [140]. Finally, in a double-blind, placebo-controlled trial of 142 children and adolescents with OCD DCS was administered 1 h prior to 7 out of 10 CBT sessions. No difference on the CY-BOCS score change was observed between the groups [141].

4. DISUSSION

4.1. Summary

A number of glutamate-modulating drugs are being investigated for their potential therapeutic effect in OCD, however definitive conclusions are precluded by small sample sizes in the trials conducted so far (Tables **1** and **2**). To date, memantine is the compound most consistently showing a positive effect as an augmentation therapy to SRIs in OCD. Even though further randomized control trials are needed to better characterize memantine's effect, its use in OCD patients in whom other therapeutic agents have proven ineffective may be justified. Anti-convulsant drugs (lamotrigine, topiramate) have been associated with therapeutic effect in a subset of OCD patients. Riluzole may also provide some therapeutic benefit in less severe or treatment-resistant OCD patients. Ketamine remains an experimental treatment in OCD, in view of its adverse effect profile. Initial data on its effects in OCD are contradictory with one out of two studies showing clinical benefit for OCD symptoms. However, ketamine is of interest due to its potential for a rapid onset of action in specific clinical situations (see next section). N-acetylcysteine has shown contradictory results in four double-blind placebo-controlled trials up to date [142]. However, it has a particularly benign side effects profile, which provides motivation for its clinical

use in individual cases, despite the weakness of the data supporting it.

Data on glycine are limited with a trend towards a positive effect in a pilot randomized control trial, however problems with compliance due to its adverse effects profile make it a less likely candidate for further investigation. No randomized controlled trials are available for sarcosine and only a single double-blind, placebo-controlled trial is available for minocycline, but further studies are warranted due to their approved use for other indications and relatively low cost. Finally, DCS may accelerate the effect of CBT in some OCD patients, but the results supporting a clinically relevant effect for this compound are not convincing.

An important caveat to the current literature remains the commonly inconsistent results from different study sites. A clear explanation for this inconsistency is currently not available and may include differences in study design, method of assessment or study population. Independent replication of the data from more sites or a clear explanation for this heterogeneity would be needed to draw more conclusive conclusions.

4.2. OCD Comorbidity and the Potential Therapeutic Role of Glutamate-Modulating Drugs

The effect of glutamate-modulating drugs in comorbid OCD is of interest due to the high prevalence of comorbidity in the disorder. Available data up to date are very limited and not allowing to draw clear conclusions. Lamotrigine has been shown to improve both obsessive-compulsive symptoms and depressive symptoms in OCD patients [115] and thus warrants further investigation in patients with comorbid OCD and depression. So far no studies have been carried out in comorbid OCD and bipolar disorder. However, lamotrigine may be an interesting candidate to investigate in such cases, since it is approved for the prophylaxis and treatment of bipolar depression [143]. The first trials on the effect of ketamine in OCD patients, some of which with comorbid depression, showed contradictory results [88; 89]. However, due to its the rapid onset of action, ketamine may be interesting to investigate in specific clinical situations (for example in OCD patients with strong suicidal ideation).

4.3. Factors Predicting Treatment Response to Glutamate-Modulating Drugs in OCD Patients

OCD is a clinically heterogenous disorder and some subsets of patients might respond more favourably to certain drugs. Identification of factors predicting treatment response to glutamate-modulating drugs in OCD patients would facilitate the decision on their use as a therapeutic alternative. So far no studies have systematically assessed the correlation of response to glutamate-modulating drugs with symptom dimensions or clinical subtypes of OCD. However, we may get some clues from the existing limited study data [144]. For example, in an open-label trial with riluzole (a drug so far not overall found to be effective in OCD) OCD patients with prominent hoarding symptoms were noted to be particularly good responders [72]. In the study of Rodriguez *et al.* [127], OCD patients with early-onset of the disease or with hoarding symptoms were more likely to respond to minocycline augmentation. These findings are only preliminary and de-

rived from very small sample investigations. Future studies with larger cohorts need to systematically address this issue. A recent review article and meta-analysis of eight randomized, double-blind, placebo-controlled trials suggested benefit of add-on glutamate-modulating drugs in OCD, including treatment-resistant OCD [145]. Investigations with different glutamate-modulating compounds in clinically more homogenous study populations may advance the understanding of their potential therapeutic utility.

4.4. The Potential Role of Genetic and Epigenetic Factors for the Treatment Response to Glutamate-Modulating Drugs

Predisposition to OCD is determined by a combination of polygenic factors and environmental risk factors [14]. Epigenetic modifications, including DNA methylation, histone modifications and microRNAs, have not been specifically studied in OCD. However, they present a potential mechanism, through which environmental factors can lead to alterations in biological functions. Polymorphisms in glutamatergic genes or differences in their DNA methylation levels may affect the response of OCD patients to glutamate-modulating drugs. A recent study by Real *et al.* [146] suggested that a single nucleotide polymorphism in the *SLC1A1* gene and life stress at the time of OCD disease onset can interact to influence treatment resistance to SRIs in OCD patients. The potential effect of genetic polymorphisms and epigenetic modifications in glutamatergic genes on treatment response to glutamate-modulating drugs in OCD patients needs to be systematically evaluated.

CONCLUSION

Glutamatergic signalling has been implicated in the pathophysiology of OCD by genetic, imaging, biochemical and animal studies. Clinical investigations on the therapeutic utility of glutamate-modulating drugs in OCD (including treatment-resistant) patients are still limited in number and precluding definitive conclusions. Research progress has been delayed by the relatively few studies with double-blind design and by the small sample sizes. So far most data on potential utility in subsets of OCD patients have been collected for memantine, lamotrigine and riluzole. The effect of clinical symptoms and OCD subtypes (for example early-onset or comorbid for affective disorders OCD patients), as well as of genetic and epigenetic factors (modifications in glutamatergic genes) on treatment response to glutamate-modulating drugs needs to be further characterized. Analyzing larger and/or more clinically or neurobiologically homogenous study populations and using double-blind design would be informative. A combination of these approaches may help to identify a subgroup of OCD patients who would more effectively respond to glutamate-modulating drugs augmentation or monotherapy.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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