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MINIREVIEWS

Antiglutamatergic agents for obsessive-compulsive disorder: Where are we now and what are possible future prospects?

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Abstract

Recent data suggest that obsessive-compulsive disorder (OCD) is driven by an imbalance among the habit learning system and the goal-directed system. The frontostriatal loop termed cortico-striatal-thalamo-cortical (CSTC) circuitry loop is involved in habits and their dysfunction plays an important role in OCD. Glutamatergic neurotransmission is the principal neurotransmitter implicated in the CSTC model of OCD. Hyperactivity in the CSTC loop implies a high level of glutamate in the cortical-striatal pathways as well as a dysregulation of *GABA* ergic transmission, and could represent the pathophysiology of OCD. Moreover, the dysregulation of glutamate levels can lead to neurotoxicity, acting as a neuronal excitotoxin. The hypothesis of a role of neurotoxicity in the pathophysiology of OCD clinically correlates to the importance of an early intervention for patients. Indeed, some studies have shown that a reduction of duration of untreated illness is related to an earlier onset of remission. Although robust data supporting a progression of such brain changes are not available so far, an early intervention could help interrupt damage from neurotoxicity. Moreover, agents targeting glutamate neurotransmission may represent promising therapeutical option in OCD patients.

Key Words: Obsessive-compulsive disorder; Antiglutamatergic agents; Glutammate; Early intervention; Neurophysiopathology; Duration of untreated illness

Core Tip: In pathophysiology of obsessive-compulsive disorder (OCD), dysfunction of the cortico-striatal-thalamo-cortical (CSTC) loop could provoke an imbalance between goal-directed system and habit learning system. Glutamate is the principal neurotransmitter implicated in the CSTC model of OCD. Glutammate dysregulation and

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neurotoxicity seem to be correlated, thus, an early intervention and a reduction of duration of untreated illness appear central in treatment of OCD, as well as the use of glutamate-modulating drugs that could help to interrupt damage from neurotoxicity.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a severe and debilitating neuropsychiatric condition that affects 2.5%-3.0% of the general population[1,2].

OCD usually occurs in childhood or adolescence[3] and is associated with important distress, disability and suicidality[4]. Conventionally, OCD is driven by irrational beliefs (obsessions) considered as the product of a cognitive bias (including overestimation of threat, increased personal responsibility and thought-action fusion) and compulsions, which are rational avoidance responses triggered by these irrational beliefs that form a coping mechanism to neutralize anxiety and reduce the likelihood that fears will be realized. Preceding DSM-5[5], OCD was considered an anxiety disorder: Anxiety symptoms are indeed commonly expressed by patients[6]. Nevertheless, anxiety is not essential for OCD diagnosis and the condition was considered to be more similar to other disorders, therefore OCD was moved to a separated section of DSM-5[7].

First-line treatments include cognitive behavior therapy (CBT) and pharmacological treatment with serotonin reuptake inhibitors (SRIs)[8]. Unfortunately, around 40% of patients with OCD do not achieve remission of their symptoms with these therapies [6]. Even when an alternate selective serotonin re-uptake inhibitor or clomipramine treatment is given, or when an atypical antipsychotic is added, a considerable portion of refractory patients (30%) remain with the diagnosis, which is associated with serious social disability, patient's and family's suffering as well as a high suicide rate [9]. To understand the mechanisms underlying the development of OCD, a variety of hypothesis have been proposed, one of which is a dysfunction of the serotonergic and dopaminergic systems[10]. More recently, different studies focused their attention on the role of the glutamatergic system in OCD pathology[11]. Glutamate is the principal neurotransmitter involved in cortico-striatal-thalamic circuits (CSTC)[12] and, according to recent hypotheses (CSTC model of OCD), it would seem implicated in the pathogenesis of OCD. Moreover, there is consensus among experts on the importance of early intervention in OCD patients to reduce the duration of untreated illness (DUI) as well as to reduce the 'toxic' effect of an extended DUI in OCD[13]. The first aim of this mini review is an overview of the role of glutamate in CSTC models of OCD and the use of antiglutamatergic agents. Moreover we propose an intervention on the DUI in order to optimize fundamental time, due to the supposed toxic damages, and subsequently an early use of antiglutamatergic agents. Therefore, an early intervention could be both reduce the toxic effect of an extended DUI and, if necessary, encourage early use of antiglutamatergic agents.

WHAT DRIVES THE NEUROPHYSIOPATHOLOGY OF OCD?

As previously mentioned, conventionally OCD is driven by obsessions, while compulsions would be a rational avoidance response triggered by irrational beliefs. Patients report that, despite the repetitive and ritualistic nature of such behaviors, which are unproductive and frequently without any purpose, they are unable to discontinue them.

Recent data[14,15] suggest that OCD is driven by interference in the balance between the habit learning system and the goal-directed system. The habit learning system is based on historical information, regardless of past rewards, and it can lead to behavioural rigidity even in the face of rapid changes in the environment; on the other

hand, the goal-directed system applies control over habits in light of changes, including changes in response to the evaluation of actions and outcomes. A neurocomputational study[16] found that OCD patients made choices mostly based on model-free (*i.e.*, habit) rather than model-based (*i.e.*, executive control) learning. It is difficult for patients with OCD to modulate their future behavior based on immediate feedback. Therefore, in light of these hypotheses, habit formation appears to be abnormal in patients affected by OCD. According to the contemporary habit hypothesis, compulsive behaviours would not be driven by irrational and intrusive thoughts, but would be the consequences of a deficit in the control over goal-directed actions, leading to amplified reliance on habitual thoughts.

Orbitofrontal and cingulate cortices and the caudate nucleus are involved in habit learning[17,18] and in goal-directed control[19-21]. The frontostriatal loop termed CSTC circuitry is involved in habits and there is consensus that dysfunction of these areas plays an important role in OCD[22-24]. Dysfunction of the CSTC could cause disruptions between the goal-directed system and habitual control[25], which would cause an overreliance on the latter. Neuroimaging studies have shown that dysfunction of these areas has been implicated in OCD, including structural abnormalities, altered brain activation and connectivity[22,26]. The hypothesis is that in patients with OCD, the hyperactivation or hyperconnection of CSTC leads to a uncontrolled positive feedback loop[24,27]. This would trigger the impulse to perform compulsions, which would in turn consolidate the habit of executing compulsions, increasing the need to perform them[10].

In line with this behavioural hypothesis, OCD has been removed from anxiety disorders in DSM-5 and placed into its own category of "obsessive-compulsive and related disorders".

STATE OF ART ABOUT THE USE OF ANTIGLUTAMATERGIC AGENTS IN OCD

Traditionally, OCD medications have targeted serotonergic pathways. SRIs are commonly administered to treat patients with OCD and although the exact mechanism of their action remains elusive, SRIs are considered to exert their effects by influencing the CSTC[28]. However, the proportion of non-responder patients suggests a role of other neurotransmitter systems outside of the serotonergic in the pathophysiology of OCD[10].

Glutamate is the principal neurotransmitter implicated in the CSTC model of OCD [12]. In the neuropathophysiology of OCD, a dysregulation of the glutamatergic signal within the cortico-striatal circuitry has been suggested, which would lead to a reduced concentration of glutamate in the anterior cingulate cortex on the one hand, and overactivity of glutamatergic signalling in the striatum and orbitofrontal cortex on the other[29]. Hyperactivity in the CSTC loop implies a high level of glutamate in the cortical-striatal pathways and a dysregulation of GABAergic transmission that could represent the pathophysiology of OCD[10]. Furthermore, both ionotropic and metabotropic glutamate receptors are located in the candidate brain circuits of OCD and have been virtually associated with every form of learning in the brain, including habit learning[14,30]. Additionally, several studies showed an increase in glutamate in the cerebrospinal fluid of OCD patients compared to controls[1,31,32]. Genetics studies have also found an association between glutamate genes and OCD[33-35]. A polymorphism encoding for *N*-methyl-D-aspartic acid receptor (NMDAR) has been associated with OCD in families[33].

In light of a possible role of glutamatergic signal dysregulation in OCD, it is possible to find in glutamatergic drugs candidates for the augmentation strategy of OCD's therapy. Glutamate-modulating drugs have shown promise as potential therapeutic agents in other psychiatric disorders with a high comorbidity with OCD such as depression, bipolar disorder and suicide[36-38]. Moreover, several studies suggested that neuromodulation techniques using noninvasive devices, such as transcranial magnetic stimulation (TMS), or invasive procedures, such as deep brain stimulation (DBS), could offer additional support for the CSTC model of OCD. Based on the results of a recent randomized controlled trials (RCT), the Food and Drug Administration approved deep TMS, for the treatment of OCD[39,40]. Also DBS, which involves implantation of electrodes that modulate specific brain function, is approved for treatment of refractory OCD[41]. The first trials on DBS for OCD were conducted in the 2003 by Gabriëls *et al*[42] showed that DBS targeted at striatal areas is effective and safe for patients with refractory OCD.

This background has motivated the interest in studying glutamate modulators in patients who are unresponsive to standard pharmacotherapeutic approaches. Several clinical studies were conducted to evaluate the effect of glutamate-modulating drugs in OCD, however, they differed significantly in terms of treatment resistance, comorbidities, age and gender of the patients[29].

In particular, some studies using memantine and riluzole reported promising benefits[43]. Other studies have explored the role of stimulants and nutritional supplements such as *N*-acetylcysteine (NAC) and glycine[44-46]. Glutamate-modulating RCT for refractory OCD are reported in Table 1. To be more precise we describe the principal studies reported in the literature:

Memantine

Memantine, a low-to-moderate affinity noncompetitive NMDAR antagonist[47] currently approved for the treatment of Alzheimer's disease, is used as an augmentative agent to SRIs in the treatment of moderate to severe OCD. Four RCTs [48-51] were conducted using memantine *vs* placebo as an adjunctive treatment to SRIs [48,50,51] or fluvoxamine[49]. In three of these, conducted on 40, 42 and 32 patients, respectively[48-50], the adjunction of memantine (in the target dose of 5-10 mg/d for 12 wk[48] or 20 mg/d for 8 wk[49] or 12 wk[50] showed a reduction in scores at the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). In the last RCT[51] conducted on 99 patients, the use of memantine (in the target dose of 10 mg/d for 8 wk) *vs* placebo and *vs* gabapentin did not lead to the reduction of Y-BOCS scores.

A recent review on the subject conducted by Marinova *et al*[29] concluded that memantine is the compound that most consistently showed a positive effect as an augmentation therapy in OCD. However, a critical letter[52], exposed some concern on this conclusion mainly due to some methodological gaps and because all four RCTs were conducted in the same geographic area. Andrade[52] concluded that, in the light of these limitations, it is still premature to recommend the use of memantine as an OCD augmentation therapy and that more studies are needed.

Amantadine

Amantadine, a weak noncompetitive NMDAR antagonist originally used in the treatment and prophylaxis of viral infections, has been used in the treatment of some neurological conditions including Parkinson's disease, dementia, multiple sclerosis, cocaine withdrawal, pain and depression[53-55]. In one RCT, conducted on 100 patients diagnosed with moderate to severe OCD[56] the use of amantadine *vs* placebo as an adjunctive treatment to SRIs, showed a significant effect on Y-BOCS compared to placebo.

Riluzole

Riluzole acts through voltage-gated ion channels modulating the outflow of glutamate and enhancing the reuptake of extracellular glutamate. It is approved for the treatment of amyotrophic lateral sclerosis and some data report benefit in the use of riluzole for depression and anxiety[57]. Three RCTs were conducted using riluzole *vs* placebo adjunctive to SRIs[58,59] or fluvoxamine[60]. Only one study, conducted on 50 patients [60], using riluzole at a final dose of 100 mg/d for 10 wk, showed a reduction in the Y-BOCS score; while the other two, conducted on 38[58] and 60 patients[59], respectively, both using riluzole at a final dose of 100 mg/d for 12 wk, did not lead to the reduction in the Y-BOCS scores.

Ketamine

Ketamine, a noncompetitive NMDA receptor antagonist, is approved for the treatment of depression. An RCT by Rodriguez and colleagues[61], conducted on 15 drug-free adults with OCD (intravenous infusions of ketamine 0.5 mg/kg *vs* placebo) reported significant improvement of OCD symptoms in patients that received ketamine *vs* placebo. This study was the first RCT that proved the effect of antiglutamatergic agents on OCD symptoms without the presence of an SRIs.

Glycine

Glycine is an amino acid, NMDA glutamate receptor agonist. Only one RCT[46] conducted on a sample of 24 patients with OCD used glycine augmentation (60 g/d for 12 wk) *vs* placebo. This study had a high dropout rate due to the adverse effects of glycine. However, nearly significant improvements in Y-BOCS scores were observed in evaluable patients.

Table 1 Glutamate-modulating randomized controlled trials for refractory obsessive-compulsive disorder

Ref.	Drugs	Adjunctive/ monotherapy	Subjects	Duration & dose	Results
Haghighi *et al*[48], 2013	Memantine	Adjunctive to SRIs	40 pt	12 wk. Dose: 5-10 mg/d	Significant reduction. Y-BOCS score
Ghaleiha *et al*[49], 2013	Memantine	Adjunctive to fluvoxamine	42 pt	8 wk. Dose: 20 mg/d	Significant reduction. Y-BOCS score
Modarresi *et al*[50], 2018	Memantine	Adjunctive to SRIs	32 pt	12 wk. Dose: 20 mg/d	Significant reduction. Y-BOCS score
Farnia *et al*[51], 2018	Memantine	Adjunctive to SRIs	99 pt	8 wk. Dose: 10 mg/d	No significant reduction. Y-BOCS score
Naderi *et al*[56] , 2019	Amantadine	Adjunctive to SRIs	100 pt	12 wk. Dose: 100 mg/d	Significant reduction. Y-BOCS score
Grant *et al*[59], 2014	Riluzole	Adjunctive to SRIs	60 pt	12 wk. Final dose: 100 mg/d	No significant reduction. Y-BOCS score
Pittenger *et al*[58], 2015	Riluzole	Adjunctive to SRIs	38 pt	12 wk. Final dose: 100 mg/d	No significant reduction. Y-BOCS score
Emamzadehfar *et al* [60], 2016	Riluzole	Adjunctive to fluvoxamine	50 pt	10 wk. Final dose: 100 mg/d	Significant reduction. Y-BOCS score
Rodriguez *et al*[61], 2013	Ketamine	Monotherapy	15 pt	Intravenous infusions dose: 0.5 mg/kg	Significant reduction. Y-BOCS score
Greenberg *et al*[46], 2009	Glycine	Adjunctive pharmacological or psychotherapeutic treatment	24 pt	12 wk. Dose: 60 mg/d	No significant reduction. Y-BOCS score
Afshar *et al*[44], 2012	N-acetylcysteine	Adjunctive to SRIs	48 pt	12 wk. Dose: 2.4 g/d	Significant reduction. Y-BOCS score
Sarris *et al*[68], 2015	N-acetylcysteine	Adjunctive to SRIs	44 pt	16 wk. Dose: 3 g/d	No significant reduction. Y-BOCS score
Paydary *et al*[45], 2016	N-acetylcysteine	Adjunctive to fluvoxamine	44 pt	10 wk. Dose: 2 g/d	Significant reduction. Y-BOCS score
Costa *et al*[69], 2017	N-acetylcysteine	Adjunctive to SRIs	40 pt	16 wk. Dose: 3 g/d	No significant reduction. Y-BOCS score
Ghanizadeh *et al*[70], 2017	N-acetylcysteine	Adjunctive to SRIs	34 pt	10 wk. Dose: 2.4 g/d	Significant reduction. Y-BOCS score
Li *et al*[71], 2020	N-acetylcysteine	Adjunctive to SRIs	11 pt	12 wk. Dose: 2.7 g/d	Significant reduction. Y-BOCS score
Esalatmanesh *et al*[75], 2016	Minocycline	Adjunctive to fluvoxamine	102 pt	10 wk. Dose: 200 mg/d	Significant reduction. Y-BOCS score
Kushner *et al*[78], 2007	D-cycloserine	Adjunctive to CBT	32 pt	125 mg	Significant reduction. Y-BOCS score
Wilhelm *et al*[79], 2008	D-cycloserine	Adjunctive to CBT	23 pt	100 mg	Significant reduction. Y-BOCS score
Farrell *et al*[80], 2013	D-cycloserine	Adjunctive to CBT	17 pt	25-50 mg	Significant reduction. Y-BOCS score
Andersson *et al*[81], 2015	D-cycloserine	Adjunctive to CBT	128 pt	12 wk. Dose: 50 mg	Significant reduction. Y-BOCS score
Mataix-Cols *et al*[82], 2014	D-cycloserine	Adjunctive to CBT	27 pt	50 mg	Significant reduction. Y-BOCS score
Storch *et al*[83], 2007	D-cycloserine	Adjunctive to CBT	24 pt	250 mg	No significant reduction. Y-BOCS score
Storch *et al*[85], 2010	D-cycloserine	Adjunctive to CBT	30 pt	25 mg	No significant reduction. Y-BOCS score
Storch *et al*[84], 2016	D-cycloserine	Adjunctive to CBT	142 pt	50 mg	No significant reduction. Y-BOCS score

RCT: Randomized controlled trials; OCD: Obsessive-compulsive disorder; SRIs: Serotonin reuptake inhibitors; CBT: Cognitive behaviour therapy; pt:

Patients; Y-BOCS: Yale-Brown Obsessive Compulsive Scale.

Nicotine

Some studies have also suggested that nicotine acts by promoting glutamatergic transmission as well as by stabilizing the glutamatergic hyperactivity of the loop running from the orbitofrontal cortex to the cyngulate gyrus, the striatum and the thalamus[62-65]. Nicotine acts on the desensitisation of nAChRs by increasing both glutamatergic transmission and, transiently, *GABA*ergic transmission. In particular, nAChR on GABA neurons are more desensitized then those on the glutamatergic system. This would lead to a shift toward excitation, reducing inhibitory inputs[65]. According to these data and with the complexity of OCD's pathophysiology, nicotine can be considered as a possible add-on therapeutic option in OCD resistant subjects, due to its peculiar mechanism of action. Only one study[66] was conducted on 5 patients using nicotine. Patients who received nicotine reported a reduction in Y-BOCS scores, especially in the compulsive score. A recent systematic review on the efficacy of nicotine administration suggested the need to test nicotine use in OCD in a large RCT. However, such suggestion raises ethical issues related to nicotine administration for its potential addiction effect[67].

NAC

NAC is a glutamate-modulating drug acting through the inhibition of the synaptic glutamate release. Five RCTs were conducted on adults[44,45,68-70] and one on children[71] using NAC *vs* placebo as an adjunctive therapy to SRIs[44,68-71] or fluvoxamine[45]. In three studies, conducted on 48, 44, 34 and 11 patients, respectively [44,45,70,71], the use of NAC (in the dose of 2.4 g/d for 12 wk[44] or 2 g/d for 10 wk [45] or of 2.4 g/d for 10 wk[70] or 2.7 g/d for 12 wk[71] showed improvement in the severity of OCD symptoms. On the other hands, in two studies conducted on 44[68] and 40 patients[69], respectively, the use of NAC (in the dose of 3 g/d for 16 wk)[68, 69] did not lead to a reduction of OCD symptoms.

Minocycline

Minocycline is an antibiotic that crosses the blood-brain barrier and has a neuroprotective effect that decreases glutamate-induced neurotoxicity[72]. It is used in some neurodegenerative diseases such as amyotrophic lateral sclerosis and Parkinson[73, 74]. Only one RCT was conducted on 102 patients using minocycline (200 mg/d for 10 wk) *vs* placebo as an adjunctive treatment to fluvoxamine. The results showed a reduction in Y-BOCS scores in the group that received minocycline[75].

D-cycloserine

D-cycloserine is a partial agonist at the *N*-methyl-d-aspartate receptor in the amygdala and some data have suggested a role of this receptor in fear extinction. For this reason, it was hypothesized that d-cycloserine may increase the efficacy of exposure therapy, a component of CBT for anxiety and OCD[76,77].

Eight RCTs were conducted on OCD patients using d-cycloserine *vs* placebo as an augmentation treatment of CBT with exposure and response prevention. Among these RCTs, four studies, conducted on 32[78], 23[79], 17[80] and 128 patients[81], respectively, used d-cycloserine in doses of 25[82] to 125 mg[78] close to each CBT session, reporting a significant amelioration of OCD symptom. In the other four studies, conducted on 27[82], 24[83], 30[45] and 142[84] patients, respectively, used d-cycloserine in doses of 25[85] to 250 mg[84] close to each CBT session, but did not show any statistically significant improvement.

In light of such contrasting results, it is not yet possible to give a clear answer on the use of glutamate-modulating drugs in OCD.

Therefore, further randomized placebo-controlled trials in larger study populations are essential to draw definitive indications on the efficacy of the use of antiglutamatergic agents in OCD.

THE REASON WHY EARLY INTERVENTION COULD BE IMPORTANT FOR OCD

As we underline, glutamate neurotransmission plays a crucial role in the CSTC of

OCD[12]. Furthermore, glutamate is also implicated in neuronal plasticity, learning, and memory[86]. Dysregulation of glutamate levels may bring glutamate receptor hyperactivity or even excitotoxicity in neurons and, in pathological situations, glutamate could lead to neurotoxicity by acting as a neuronal excitotoxin[87].

In support of this hypothesis, neuroimaging studies found changes in multiple sites of age-related brain structures suggesting that OCD is characterized by complex and nonlinear neurophysiopathological mechanisms[88,89].

The hypothesis of the role of neurotoxicity in the neurophysiopathology of OCD is clinically related to the importance of early intervention for patients. Indeed, some studies showed that a faster onset in the treatment of OCD correlates with an earlier onset of remission[90]. On the contrary, late intervention is associated with increased comorbidity, disability, reduced treatment response and remission[91-93].

The DUI for OCD is very high compared to other mental disorders[94]. Most cases of OCD arise in childhood or adolescence[92] and symptoms are often ignored[95] extending the time for diagnosis (from 2 to 10 year) and consequently for starting treatment[92,96,97] with average DUI of two to three years[98,99]. Although there is a paucity of data to support a progression of such brain changes so far, it is assumed that early intervention, even with the use of glutamate-modulating drugs, could help to stop neurotoxic damage[13]. A crucial point may be the switch from a time-dependent neurotransmitter dysfunction to an irreversible structural damage. This may explain both refractory to SSRI and the unresponsiveness to anti-glutamatergic agents.

Identifying and confirming the efficacy and safety of new therapeutic approaches for OCD could also be very useful for early intervention in these patients. An international group of expert clinicians and scientists with extensive OCD experience are documenting the negative impact associated with the delayed treatment on clinical outcomes, suggesting the importance of a greater emphasis on targeted early intervention for OCD patients as is already is the case for psychotic disorders. Early intervention is more promising for reducing chronicity as well as the economic and social burdens associated with OCD.

CONCLUSION

The hypothesis of a hyperactive CSTC loop that implies a high level of glutamate in the cortical-striatal pathways and a dysregulation of *GABA*ergic transmission may represent the pathophysiology of OCD. Despite the effectiveness of SRIs in treating OCD, the treatment-resistant symptoms observed in 40% of patients present enormous clinical issues. The refractory to SRIs and the unresponsiveness to antiglutamatergic agents may be explained by a time-dependent neurotransmitter dysfunction, which may lead to an irreversible structural damage. There is a need to develop novel pharmacological strategies, which are not exclusively related to refractory subjects. If glutamate-neurotoxicity is extensively confirmed, the time from OCD onset will be the most important variable to take into consideration. In such a scenario, agents targeting glutamate neurotransmission may represent a promising treatment, especially in the case of a timely prescription.

REFERENCES

1 **Ruscio AM**, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 53-63 [PMID: 18725912 DOI: 10.1038/mp.2008.94]

2 **Kessler RC**, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 593-602 [PMID: 15939837 DOI: 10.1001/archpsyc.62.6.593]

3 **Dell'Osso B**, Benatti B, Hollander E, Fineberg N, Stein DJ, Lochner C, Nicolini H, Lanzagorta N, Palazzo C, Altamura AC, Marazziti D, Pallanti S, Van Ameringen M, Karamustafalioglu O, Drummond LM, Hranov L, Figee M, Grant JE, Zohar J, Denys D, Menchon JM. Childhood, adolescent and adult age at onset and related clinical correlates in obsessive-compulsive disorder: a report from the International College of Obsessive-Compulsive Spectrum Disorders (ICOCS). *Int J Psychiatry Clin Pract* 2016; **20**: 210-217 [PMID: 27433835 DOI: 10.1080/13651501.2016.1207087]

4 **Carmi L**, Fineberg N, Ben Arush O, Zohar J. Epidemiology of OCD. In: Geddes JR, Andreasen NC, Goodwin GM, editors. New Oxford Textbook of Psychiatry, Third Edition. Oxford: Oxford University Press, 2020

5 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Publishing, 2013

6 **Stein DJ**, Fineberg NA, Bienvenu OJ, Denys D, Lochner C, Nestadt G, Leckman JF, Rauch SL, Phillips KA. Should OCD be classified as an anxiety disorder in DSM-V? *Depress Anxiety* 2010; **27**: 495-506 [PMID: 20533366 DOI: 10.1002/da.20699]

7 **Phillips KA**, Stein DJ, Rauch SL, Hollander E, Fallon BA, Barsky A, Fineberg N, Mataix-Cols D, Ferrão YA, Saxena S, Wilhelm S, Kelly MM, Clark LA, Pinto A, Bienvenu OJ, Farrow J, Leckman J. Should an obsessive-compulsive spectrum grouping of disorders be included in DSM-V? *Depress Anxiety* 2010; **27**: 528-555 [PMID: 20533367 DOI: 10.1002/da.20705]

8 **Skapinakis P**, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, Welton NJ, Baxter H, Kessler D, Churchill R, Lewis G. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. *Lancet Psychiatry* 2016; **3**: 730-739 [PMID: 27318812 DOI: 10.1016/S2215-0366(16)30069-4]

9 **Hollander E**, Kwon JH, Stein DJ, Broatch J, Rowland CT, Himelein CA. Obsessive-compulsive and spectrum disorders: overview and quality of life issues. *J Clin Psychiatry* 1996; **57** Suppl 8: 3-6 [PMID: 8698678]

10 **Dougherty DD**, Brennan BP, Stewart SE, Wilhelm S, Widge AS, Rauch SL. Neuroscientifically Informed Formulation and Treatment Planning for Patients With Obsessive-Compulsive Disorder: A Review. *JAMA Psychiatry* 2018; **75**: 1081-1087 [PMID: 30140845 DOI: 10.1001/jamapsychiatry.2018.0930]

11 **Albelda N**, Bar-On N, Joel D. The role of NMDA receptors in the signal attenuation rat model of obsessive-compulsive disorder. *Psychopharmacology (Berl)* 2010; **210**: 13-24 [PMID: 20238210 DOI: 10.1007/s00213-010-1808-9]

12 **Ting JT**, Feng G. Neurobiology of obsessive-compulsive disorder: insights into neural circuitry dysfunction through mouse genetics. *Curr Opin Neurobiol* 2011; **21**: 842-848 [PMID: 21605970 DOI: 10.1016/j.conb.2011.04.010]

13 **Fineberg NA**, Dell'Osso B, Albert U, Maina G, Geller D, Carmi L, Sireau N, Walitza S, Grassi G, Pallanti S, Hollander E, Brakoulias V, Menchon JM, Marazziti D, Ioannidis K, Apergis-Schoute A, Stein DJ, Cath DC, Veltman DJ, Van Ameringen M, Fontenelle LF, Shavitt RG, Costa D, Diniz JB, Zohar J. Early intervention for obsessive compulsive disorder: An expert consensus statement. *Eur Neuropsychopharmacol* 2019; **29**: 549-565 [PMID: 30773387 DOI: 10.1016/j.euroneuro.2019.02.002]

14 **Gillan CM**, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, de Wit S. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry* 2011; **168**: 718-726 [PMID: 21572165 DOI: 10.1176/appi.ajp.2011.10071062]

15 **Gillan CM**, Morein-Zamir S, Urcelay GP, Sule A, Voon V, Apergis-Schoute AM, Fineberg NA, Sahakian BJ, Robbins TW. Enhanced avoidance habits in obsessive-compulsive disorder. *Biol Psychiatry* 2014; **75**: 631-638 [PMID: 23510580 DOI: 10.1016/j.biopsych.2013.02.002]

16 **Voon V**, Derbyshire K, Rück C, Irvine MA, Worbe Y, Enander J, Schreiber LR, Gillan C, Fineberg NA, Sahakian BJ, Robbins TW, Harrison NA, Wood J, Daw ND, Dayan P, Grant JE, Bullmore ET. Disorders of compulsivity: a common bias towards learning habits. *Mol Psychiatry* 2015; **20**: 345-352 [PMID: 24840709 DOI: 10.1038/mp.2014.44]

17 **Yin HH**, Knowlton BJ, Balleine BW. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur J Neurosci* 2004; **19**: 181-189 [PMID: 14750976 DOI: 10.1111/j.1460-9568.2004.03095.x]

18 **Coutureau E**, Killcross S. Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. *Behav Brain Res* 2003; **146**: 167-174 [PMID: 14643469 DOI: 10.1016/j.bbr.2003.09.025]

19 **Killcross S**, Coutureau E. Coordination of actions and habits in the medial prefrontal cortex of rats. *Cereb Cortex* 2003; **13**: 400-408 [PMID: 12631569 DOI: 10.1093/cercor/13.4.400]

20 **Tricomi EM**, Delgado MR, Fiez JA. Modulation of caudate activity by action contingency. *Neuron* 2004; **41**: 281-292 [PMID: 14741108 DOI: 10.1016/s0896-6273(03)00848-1]

21 **Tanaka SC**, Balleine BW, O'Doherty JP. Calculating consequences: brain systems that encode the causal effects of actions. *J Neurosci* 2008; **28**: 6750-6755 [PMID: 18579749 DOI: 10.1523/JNEUROSCI.1808-08.2008]

22 **Saxena S**, Rauch SL. Functional neuroimaging and the neuroanatomy of obsessive-compulsive disorder. *Psychiatr Clin North Am* 2000; **23**: 563-586 [PMID: 10986728 DOI: 10.1016/s0193-953x(05)70181-7]

23 **Menzies L**, Williams GB, Chamberlain SR, Ooi C, Fineberg N, Suckling J, Sahakian BJ, Robbins TW, Bullmore ET. White matter abnormalities in patients with obsessive-compulsive disorder and their first-degree relatives. *Am J Psychiatry* 2008; **165**: 1308-1315 [PMID: 18519525 DOI: 10.1176/appi.ajp.2008.07101677]

24 **Graybiel AM**, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. *Neuron* 2000; **28**: 343-347 [PMID: 11144344 DOI: 10.1016/s0896-6273(00)00113-6]

25 **Alexander GE**, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; **9**: 357-381 [PMID: 3085570 DOI: 10.1146/annurev.ne.09.030186.002041]

26 **Burguière E**, Monteiro P, Mallet L, Feng G, Graybiel AM. Striatal circuits, habits, and implications for obsessive-compulsive disorder. *Curr Opin Neurobiol* 2015; **30**: 59-65 [PMID: 25241072 DOI: 10.1016/j.conb.2014.08.008]

27 **Milad MR**, Rauch SL. Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends Cogn Sci* 2012; **16**: 43-51 [PMID: 22138231 DOI: 10.1016/j.tics.2011.11.003]

28 **Shin DJ**, Jung WH, He Y, Wang J, Shim G, Byun MS, Jang JH, Kim SN, Lee TY, Park HY, Kwon JS. The effects of pharmacological treatment on functional brain connectome in obsessive-compulsive disorder. *Biol Psychiatry* 2014; **75**: 606-614 [PMID: 24099506 DOI: 10.1016/j.biopsych.2013.09.002]

29 **Marinova Z**, Chuang DM, Fineberg N. Glutamate-Modulating Drugs as a Potential Therapeutic Strategy in Obsessive-Compulsive Disorder. *Curr Neuropharmacol* 2017; **15**: 977-995 [PMID: 28322166 DOI: 10.2174/1570159X15666170320104237]

30 **Lovinger DM**. Neurotransmitter roles in synaptic modulation, plasticity and learning in the dorsal striatum. *Neuropharmacology* 2010; **58**: 951-961 [PMID: 20096294 DOI: 10.1016/j.neuropharm.2010.01.008]

31 **Chakrabarty K**, Bhattacharyya S, Christopher R, Khanna S. Glutamatergic dysfunction in OCD. *Neuropsychopharmacology* 2005; **30**: 1735-1740 [PMID: 15841109 DOI: 10.1038/sj.npp.1300733]

32 **Bhattacharyya S**, Khanna S, Chakrabarty K, Mahadevan A, Christopher R, Shankar SK. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder. *Neuropsychopharmacology* 2009; **34**: 2489-2496 [PMID: 19675532 DOI: 10.1038/npp.2009.77]

33 **Arnold PD**, Rosenberg DR, Mundo E, Tharmalingam S, Kennedy JL, Richter MA. Association of a glutamate (NMDA) subunit receptor gene (GRIN2B) with obsessive-compulsive disorder: a preliminary study. *Psychopharmacology (Berl)* 2004; **174**: 530-538 [PMID: 15083261 DOI: 10.1007/s00213-004-1847-1]

34 **Dickel DE**, Veenstra-VanderWeele J, Cox NJ, Wu X, Fischer DJ, Van Etten-Lee M, Himle JA, Leventhal BL, Cook EH Jr, Hanna GL. Association testing of the positional and functional candidate gene SLC1A1/EAAC1 in early-onset obsessive-compulsive disorder. *Arch Gen Psychiatry* 2006; **63**: 778-785 [PMID: 16818867 DOI: 10.1001/archpsyc.63.7.778]

35 **Hanna GL**, Veenstra-VanderWeele J, Cox NJ, Boehnke M, Himle JA, Curtis GC, Leventhal BL, Cook EH Jr. Genomewide linkage analysis of families with obsessive-compulsive disorder ascertained through pediatric probands. *Am J Med Genet* 2002; **114**: 541-552 [DOI: 10.1002/ajmg.10519]

36 **Niciu MJ**, Henter ID, Luckenbaugh DA, Zarate CA Jr, Charney DS. Glutamate receptor antagonists as fast-acting therapeutic alternatives for the treatment of depression: ketamine and other compounds. *Annu Rev Pharmacol Toxicol* 2014; **54**: 119-139 [PMID: 24392693 DOI: 10.1146/annurev-pharmtox-011613-135950]

37 **Price RB**, Nock MK, Charney DS, Mathew SJ. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. *Biol Psychiatry* 2009; **66**: 522-526 [PMID: 19545857 DOI: 10.1016/j.biopsych.2009.04.029]

38 **Murphy DL**, Moya PR, Fox MA, Rubenstein LM, Wendland JR, Timpano KR. Anxiety and affective disorder comorbidity related to serotonin and other neurotransmitter systems: obsessive-compulsive disorder as an example of overlapping clinical and genetic heterogeneity. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20120435 [PMID: 23440468 DOI: 10.1098/rstb.2012.0435]

39 **Carmi L**, Tendler A, Bystritsky A, Hollander E, Blumberger DM, Daskalakis J, Ward H, Lapidus K, Goodman W, Casuto L, Feifel D, Barnea-Ygael N, Roth Y, Zangen A, Zohar J. Efficacy and Safety of Deep Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Prospective Multicenter Randomized Double-Blind Placebo-Controlled Trial. *Am J Psychiatry* 2019; **176**: 931-938 [PMID: 31109199 DOI: 10.1176/appi.ajp.2019.18101180]

40 **Goodman WK**, Storch EA, Sheth SA. Harmonizing the Neurobiology and Treatment of Obsessive-Compulsive Disorder. *Am J Psychiatry* 2021; **178**: 17-29 [PMID: 33384007 DOI: 10.1176/appi.ajp.2020.20111601]

41 **Goodman WK**, Alterman RL. Deep brain stimulation for intractable psychiatric disorders. *Annu Rev Med* 2012; **63**: 511-524 [PMID: 22034866 DOI: 10.1146/annurev-med-052209-100401]

42 **Gabriëls L**, Cosyns P, Nuttin B, Demeulemeester H, Gybels J. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: psychopathological and neuropsychological outcome in three cases. *Acta Psychiatr Scand* 2003; **107**: 275-282 [PMID: 12662250]

43 **Pittenger C**, Krystal JH, Coric V. Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder. *NeuroRx* 2006; **3**: 69-81 [PMID: 16490414 DOI: 10.1016/j.nurx.2005.12.006]

44 **Afshar H**, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P, Sadeghi M, Hafezian H. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 2012; **32**: 797-803 [PMID: 23131885 DOI: 10.1097/JCP.0b013e318272677d]

45 **Paydary K**, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. *J Clin Pharm Ther* 2016; **41**: 214-219 [PMID: 26931055 DOI: 10.1111/jcpt.12370]

46 **Greenberg WM**, Benedict MM, Doerfer J, Perrin M, Panek L, Cleveland WL, Javitt DC. Adjunctive glycine in the treatment of obsessive-compulsive disorder in adults. *J Psychiatr Res* 2009; **43**: 664-

670 [PMID: 19046587 DOI: 10.1016/j.jpsychires.2008.10.007]
47 **Parsons CG**, Danysz W, Quack G. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist--a review of preclinical data. *Neuropharmacology* 1999; **38**: 735-767 [PMID: 10465680 DOI: 10.1016/s0028-3908(99)00019-2]
48 **Haghighi M**, Jahangard L, Mohammad-Beigi H, Bajoghli H, Hafezian H, Rahimi A, Afshar H, Holsboer-Trachsler E, Brand S. In a double-blind, randomized and placebo-controlled trial, adjuvant memantine improved symptoms in inpatients suffering from refractory obsessive-compulsive disorders (OCD). *Psychopharmacology (Berl)* 2013; **228**: 633-640 [PMID: 23525525 DOI: 10.1007/s00213-013-3067-z]
49 **Ghaleiha A**, Entezari N, Modabbernia A, Najand B, Askari N, Tabrizi M, Ashrafi M, Hajiaghaee R, Akhondzadeh S. Memantine add-on in moderate to severe obsessive-compulsive disorder: randomized double-blind placebo-controlled study. *J Psychiatr Res* 2013; **47**: 175-180 [PMID: 23063327 DOI: 10.1016/j.jpsychires.2012.09.015]
50 **Modarresi A**, Sayyah M, Razooghi S, Eslami K, Javadi M, Kouti L. Memantine Augmentation Improves Symptoms in Serotonin Reuptake Inhibitor-Refractory Obsessive-Compulsive Disorder: A Randomized Controlled Trial. *Pharmacopsychiatry* 2018; **51**: 263-269 [PMID: 29100251 DOI: 10.1055/s-0043-120268]
51 **Farnia V**, Gharehbaghi H, Alikhani M, Almasi A, Golshani S, Tatari F, Davarinejad O, Salemi S, Sadeghi Bahmani D, Holsboer-Trachsler E, Brand S. Efficacy and tolerability of adjunctive gabapentin and memantine in obsessive compulsive disorder: Double-blind, randomized, placebo-controlled trial. *J Psychiatr Res* 2018; **104**: 137-143 [PMID: 30044966 DOI: 10.1016/j.jpsychires.2018.07.008]
52 **Andrade C**. Augmentation With Memantine in Obsessive-Compulsive Disorder. *J Clin Psychiatry* 2019; **80** [PMID: 31846244 DOI: 10.4088/JCP.19f13163]
53 **Huber TJ**, Dietrich DE, Emrich HM. Possible use of amantadine in depression. *Pharmacopsychiatry* 1999; **32**: 47-55 [PMID: 10333162 DOI: 10.1055/s-2007-979191]
54 **Pud D**, Eisenberg E, Spitzer A, Adler R, Fried G, Yarnitsky D. The NMDA receptor antagonist amantadine reduces surgical neuropathic pain in cancer patients: a double blind, randomized, placebo controlled trial. *Pain* 1998; **75**: 349-354 [PMID: 9583771 DOI: 10.1016/s0304-3959(98)00014-1]
55 **Stryjer R**, Strous RD, Shaked G, Bar F, Feldman B, Kotler M, Polak L, Rosenzcwaig S, Weizman A. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol* 2003; **18**: 93-96 [PMID: 12598820 DOI: 10.1097/00004850-200303000-00005]
56 **Naderi S**, Faghih H, Aqamolaei A, Mortazavi SH, Mortezaei A, Sahebolzamani E, Rezaei F, Akhondzadeh S. Amantadine as adjuvant therapy in the treatment of moderate to severe obsessive-compulsive disorder: A double-blind randomized trial with placebo control. *Psychiatry Clin Neurosci* 2019; **73**: 169-174 [PMID: 30488617 DOI: 10.1111/pcn.12803]
57 **Pittenger C**, Coric V, Banasr M, Bloch M, Krystal JH, Sanacora G. Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs* 2008; **22**: 761-786 [PMID: 18698875 DOI: 10.2165/00023210-200822090-00004]
58 **Pittenger C**, Bloch MH, Wasylink S, Billingslea E, Simpson R, Jakubovski E, Kelmendi B, Sanacora G, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot randomized placebo-controlled trial. *J Clin Psychiatry* 2015; **76**: 1075-1084 [PMID: 26214725 DOI: 10.4088/JCP.14m09123]
59 **Grant PJ**, Joseph LA, Farmer CA, Luckenbaugh DA, Lougee LC, Zarate CA Jr, Swedo SE. 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. *Neuropsychopharmacology* 2014; **39**: 1453-1459 [PMID: 24356715 DOI: 10.1038/npp.2013.343]
60 **Emamzadehfard S**, Kamaloo A, Paydary K, Ahmadipour A, Zeinoddini A, Ghaleiha A, Mohammadinejad P, Akhondzadeh S. Riluzole in augmentation of fluvoxamine for moderate to severe obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study. *Psychiatry Clin Neurosci* 2016; **70**: 332-341 [PMID: 27106362 DOI: 10.1111/pcn.12394]
61 **Rodriguez CI**, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, Flood P, Simpson HB. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. *Neuropsychopharmacology* 2013; **38**: 2475-2483 [PMID: 23783065 DOI: 10.1038/npp.2013.150]
62 **Heresco-Levy U**, Javitt DC. The role of N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission in the pathophysiology and therapeutics of psychiatric syndromes. *Eur Neuropsychopharmacol* 1998; **8**: 141-152 [PMID: 9619693 DOI: 10.1016/s0924-977x(97)00050-3]
63 **Girod R**, Barazangi N, McGehee D, Role LW. Facilitation of glutamatergic neurotransmission by presynaptic nicotinic acetylcholine receptors. *Neuropharmacology* 2000; **39**: 2715-2725 [PMID: 11044742 DOI: 10.1016/s0028-3908(00)00145-3]
64 **Araki H**, Suemaru K, Gomita Y. Neuronal nicotinic receptor and psychiatric disorders: functional and behavioral effects of nicotine. *Jpn J Pharmacol* 2002; **88**: 133-138 [PMID: 11928712 DOI: 10.1254/jjp.88.133]
65 **Mansvelder HD**, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. *Neuron* 2002; **33**: 905-919 [PMID: 11906697 DOI: 10.1016/s0896-6273(02)00625-6]
66 **Lundberg S**, Carlsson A, Norfeldt P, Carlsson ML. Nicotine treatment of obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28**: 1195-1199 [PMID: 15610934 DOI:

10.1016/j.pnpbp.2004.06.014]

67 **Piacentino D**, Maraone A, Roselli V, Berardelli I, Biondi M, Kotzalidis GD, Pasquini M. Efficacy of nicotine administration on obsessions and compulsions in OCD: a systematic review. *Ann Gen Psychiatry* 2020; **19**: 57 [PMID: 33014119 DOI: 10.1186/s12991-020-00309-z]

68 **Sarris J**, Oliver G, Camfield DA, Dean OM, Dowling N, Smith DJ, Murphy J, Menon R, Berk M, Blair-West S, Ng CH. N-Acetyl Cysteine (NAC) in the Treatment of Obsessive-Compulsive Disorder: A 16-Week, Double-Blind, Randomised, Placebo-Controlled Study. *CNS Drugs* 2015; **29**: 801-809 [PMID: 26374743 DOI: 10.1007/s40263-015-0272-9]

69 **Costa DLC**, Diniz JB, Requena G, Joaquim MA, Pittenger C, Bloch MH, Miguel EC, Shavitt RG. Randomized, Double-Blind, Placebo-Controlled Trial of N-Acetylcysteine Augmentation for Treatment-Resistant Obsessive-Compulsive Disorder. *J Clin Psychiatry* 2017; **78**: e766-e773 [PMID: 28617566 DOI: 10.4088/JCP.16m11101]

70 **Ghanizadeh A**, Mohammadi MR, Bahraini S, Keshavarzi Z, Firoozabadi A, Alavi Shoshtari A. Efficacy of N-Acetylcysteine Augmentation on Obsessive Compulsive Disorder: A Multicenter Randomized Double Blind Placebo Controlled Clinical Trial. *Iran J Psychiatry* 2017; **12**: 134-141 [PMID: 28659986]

71 **Li F**, Welling MC, Johnson JA, Coughlin C, Mulqueen J, Jakubovski E, Coury S, Landeros-Weisenberger A, Bloch MH. N-Acetylcysteine for Pediatric Obsessive-Compulsive Disorder: A Small Pilot Study. *J Child Adolesc Psychopharmacol* 2020; **30**: 32-37 [PMID: 31800306 DOI: 10.1089/cap.2019.0041]

72 **Pi R**, Li W, Lee NT, Chan HH, Pu Y, Chan LN, Sucher NJ, Chang DC, Li M, Han Y. Minocycline prevents glutamate-induced apoptosis of cerebellar granule neurons by differential regulation of p38 and Akt pathways. *J Neurochem* 2004; **91**: 1219-1230 [PMID: 15569265 DOI: 10.1111/j.1471-4159.2004.02796.x]

73 **Traynor BJ**, Bruijn L, Conwit R, Beal F, O'Neill G, Fagan SC, Cudkowicz ME. Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; **67**: 20-27 [PMID: 16832072 DOI: 10.1212/01.wnl.0000223353.34006.54]

74 **NINDS NET-PD Investigators**. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology* 2006; **66**: 664-671 [PMID: 16481597 DOI: 10.1212/01.wnl.0000201252.57661.e1]

75 **Esalatmanesh S**, Abrishami Z, Zeinoddini A, Rahiminejad F, Sadeghi M, Najarzadegan MR, Shalbafan MR, Akhondzadeh S. Minocycline combination therapy with fluvoxamine in moderate-to-severe obsessive-compulsive disorder: A placebo-controlled, double-blind, randomized trial. *Psychiatry Clin Neurosci* 2016; **70**: 517-526 [PMID: 27488081 DOI: 10.1111/pcn.12430]

76 **Davis M**, Ressler K, Rothbaum BO, Richardson R. Effects of D-cycloserine on extinction: translation from preclinical to clinical work. *Biol Psychiatry* 2006; **60**: 369-375 [PMID: 16919524 DOI: 10.1016/j.biopsych.2006.03.084]

77 **Lewin AB**, Wu MS, McGuire JF, Storch EA. Cognitive behavior therapy for obsessive-compulsive and related disorders. *Psychiatr Clin North Am* 2014; **37**: 415-445 [PMID: 25150570 DOI: 10.1016/j.psc.2014.05.002]

78 **Kushner MG**, Kim SW, Donahue C, Thuras P, Adson D, Kotlyar M, McCabe J, Peterson J, Foa EB. D-cycloserine augmented exposure therapy for obsessive-compulsive disorder. *Biol Psychiatry* 2007; **62**: 835-838 [PMID: 17588545 DOI: 10.1016/j.biopsych.2006.12.020]

79 **Wilhelm S**, Buhlmann U, Tolin DF, Meunier SA, Pearlson GD, Reese HE, Cannistraro P, Jenike MA, Rauch SL. Augmentation of behavior therapy with D-cycloserine for obsessive-compulsive disorder. *Am J Psychiatry* 2008; **165**: 335-41; quiz 409 [PMID: 18245177 DOI: 10.1176/appi.ajp.2007.07050776]

80 **Farrell LJ**, Waters AM, Boschen MJ, Hattingh L, McConnell H, Milliner EL, Collings N, Zimmer-Gembeck M, Shelton D, Ollendick TH, Testa C, Storch EA. Difficult-to-treat pediatric obsessive-compulsive disorder: feasibility and preliminary results of a randomized pilot trial of D-cycloserine-augmented behavior therapy. *Depress Anxiety* 2013; **30**: 723-731 [PMID: 23722990 DOI: 10.1002/da.22132]

81 **Andersson E**, Hedman E, Enander J, Radu Djurfeldt D, Ljótsson B, Cervenka S, Isung J, Svanborg C, Mataix-Cols D, Kaldo V, Andersson G, Lindefors N, Rück C. D-Cycloserine vs Placebo as Adjunct to Cognitive Behavioral Therapy for Obsessive-Compulsive Disorder and Interaction With Antidepressants: A Randomized Clinical Trial. *JAMA Psychiatry* 2015; **72**: 659-667 [PMID: 25970252 DOI: 10.1001/jamapsychiatry.2015.0546]

82 **Mataix-Cols D**, Turner C, Monzani B, Isomura K, Murphy C, Krebs G, Heyman I. Cognitive-behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive-compulsive disorder: pilot randomised controlled trial. *Br J Psychiatry* 2014; **204**: 77-78 [PMID: 24262813 DOI: 10.1192/bjp.bp.113.126284]

83 **Storch EA**, Merlo LJ, Bengtson M, Murphy TK, Lewis MH, Yang MC, Jacob ML, Larson M, Hirsh A, Fernandez M, Geffken GR, Goodman WK. D-cycloserine does not enhance exposure-response prevention therapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 2007; **22**: 230-237 [PMID: 17519647 DOI: 10.1097/YIC.0b013e32819f8480]

84 **Storch EA**, Wilhelm S, Sprich S, Henin A, Micco J, Small BJ, McGuire J, Mutch PJ, Lewin AB, Murphy TK, Geller DA. 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* 2016; **73**: 779-788 [PMID: 27367832 DOI:

10.1001/jamapsychiatry.2016.1128]

85 **Storch EA**, Murphy TK, Goodman WK, Geffken GR, Lewin AB, Henin A, Micco JA, Sprich S, Wilhelm S, Bengtson M, Geller DA. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *Biol Psychiatry* 2010; **68**: 1073-1076 [PMID: 20817153 DOI: 10.1016/j.biopsych.2010.07.015]

86 **Javitt DC**, Schoepp D, Kalivas PW, Volkow ND, Zarate C, Merchant K, Bear MF, Umbricht D, Hajos M, Potter WZ, Lee CM. Translating glutamate: from pathophysiology to treatment. *Sci Transl Med* 2011; **3**: 102mr2 [PMID: 21957170 DOI: 10.1126/scitranslmed.3002804]

87 **Sanacora G**, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. *Nat Rev Drug Discov* 2008; **7**: 426-437 [PMID: 18425072 DOI: 10.1038/nrd2462]

88 **Boedhoe PS**, Schmaal L, Abe Y, Ameis SH, Arnold PD, Batistuzzo MC, Benedetti F, Beucke JC, Bollettini I, Bose A, Brem S, Calvo A, Cheng Y, Cho KI, Dallaspezia S, Denys D, Fitzgerald KD, Fouche JP, Giménez M, Gruner P, Hanna GL, Hibar DP, Hoexter MQ, Hu H, Huyser C, Ikari K, Jahanshad N, Kathmann N, Kaufmann C, Koch K, Kwon JS, Lazaro L, Liu Y, Lochner C, Marsh R, Martínez-Zalacaín I, Mataix-Cols D, Menchón JM, Minuzzi L, Nakamae T, Nakao T, Narayanaswamy JC, Piras F, Pittenger C, Reddy YC, Sato JR, Simpson HB, Soreni N, Soriano-Mas C, Spalletta G, Stevens MC, Szeszko PR, Tolin DF, Venkatasubramanian G, Walitza S, Wang Z, van Wingen GA, Xu J, Xu X, Yun JY, Zhao Q; ENIGMA OCD Working Group, Thompson PM, Stein DJ, van den Heuvel OA. Distinct Subcortical Volume Alterations in Pediatric and Adult OCD: A Worldwide Meta- and Mega-Analysis. *Am J Psychiatry* 2017; **174**: 60-69 [PMID: 27609241 DOI: 10.1176/appi.ajp.2016.16020201]

89 **Boedhoe PSW**, Schmaal L, Abe Y, Alonso P, Ameis SH, Anticevic A, Arnold PD, Batistuzzo MC, Benedetti F, Beucke JC, Bollettini I, Bose A, Brem S, Calvo A, Calvo R, Cheng Y, Cho KIK, Ciullo V, Dallaspezia S, Denys D, Feusner JD, Fitzgerald KD, Fouche JP, Fridgeirsson EA, Gruner P, Hanna GL, Hibar DP, Hoexter MQ, Hu H, Huyser C, Jahanshad N, James A, Kathmann N, Kaufmann C, Koch K, Kwon JS, Lazaro L, Lochner C, Marsh R, Martínez-Zalacaín I, Mataix-Cols D, Menchón JM, Minuzzi L, Morer A, Nakamae T, Nakao T, Narayanaswamy JC, Nishida S, Nurmi E, O'Neill J, Piacentini J, Piras F, Reddy YCJ, Reess TJ, Sakai Y, Sato JR, Simpson HB, Soreni N, Soriano-Mas C, Spalletta G, Stevens MC, Szeszko PR, Tolin DF, van Wingen GA, Venkatasubramanian G, Walitza S, Wang Z, Yun JY; ENIGMA-OCD Working Group, Thompson PM, Stein DJ, van den Heuvel OA; ENIGMA OCD Working Group. Cortical Abnormalities Associated With Pediatric and Adult Obsessive-Compulsive Disorder: Findings From the ENIGMA Obsessive-Compulsive Disorder Working Group. *Am J Psychiatry* 2018; **175**: 453-462 [PMID: 29377733 DOI: 10.1176/appi.ajp.2017.17050485]

90 **Mancebo MC**, Boisseau CL, Garnaat SL, Eisen JL, Greenberg BD, Sibrava NJ, Stout RL, Rasmussen SA. Long-term course of pediatric obsessive-compulsive disorder: 3 years of prospective follow-up. *Compr Psychiatry* 2014; **55**: 1498-1504 [PMID: 24952937 DOI: 10.1016/j.comppsych.2014.04.010]

91 **Dell'Osso B**, Benatti B, Buoli M, Altamura AC, Marazziti D, Hollander E, Fineberg N, Stein DJ, Pallanti S, Nicolini H, Van Ameringen M, Lochner C, Hranov G, Karamustafalioglu O, Hranov L, Menchon JM, Zohar J; ICOCS group. The influence of age at onset and duration of illness on long-term outcome in patients with obsessive-compulsive disorder: a report from the International College of Obsessive Compulsive Spectrum Disorders (ICOCS). *Eur Neuropsychopharmacol* 2013; **23**: 865-871 [PMID: 23791074 DOI: 10.1016/j.euroneuro.2013.05.004]

92 **Albert U**, Barbaro F, Bramante S, Rosso G, De Ronchi D, Maina G. Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder. *Eur Psychiatry* 2019; **58**: 19-26 [PMID: 30763828 DOI: 10.1016/j.eurpsy.2019.01.017]

93 **Rufer M**, Hand I, Alsleben H, Braatz A, Ortmann J, Katenkamp B, Fricke S, Peter H. Long-term course and outcome of obsessive-compulsive patients after cognitive-behavioral therapy in combination with either fluvoxamine or placebo: a 7-year follow-up of a randomized double-blind trial. *Eur Arch Psychiatry Clin Neurosci* 2005; **255**: 121-128 [PMID: 15812606 DOI: 10.1007/s00406-004-0544-8]

94 **Altamura AC**, Buoli M, Albano A, Dell'Osso B. Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study. *Int Clin Psychopharmacol* 2010; **25**: 172-179 [PMID: 20305566 DOI: 10.1097/YIC.0b013e3283384c74]

95 **Rapoport JL**, Inoff-Germain G, Weissman MM, Greenwald S, Narrow WE, Jensen PS, Lahey BB, Canino G. Childhood obsessive-compulsive disorder in the NIMH MECA study: parent versus child identification of cases. Methods for the Epidemiology of Child and Adolescent Mental Disorders. *J Anxiety Disord* 2000; **14**: 535-548 [PMID: 11918090 DOI: 10.1016/s0887-6185(00)00048-7]

96 **Geller D**, Biederman J, Faraone SV, Frazier J, Coffey BJ, Kim G, Bellordre CA. Clinical correlates of obsessive compulsive disorder in children and adolescents referred to specialized and non-specialized clinical settings. *Depress Anxiety* 2000; **11**: 163-168 [PMID: 10945136 DOI: 10.1002/1520-6394(2000)11:4<163::AID-DA3>3.0.CO;2-3]

97 **García-Soriano G**, Rufer M, Delsignore A, Weidt S. Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature. *Psychiatry Res* 2014; **220**: 1-10 [PMID: 25108591 DOI: 10.1016/j.psychres.2014.07.009]

98 **Walitza S**, Zellmann H, Irblich B, Lange KW, Tucha O, Hemminger U, Wucherer K, Rost V, Reinecker H, Wewetzer C, Warnke A. Children and adolescents with obsessive-compulsive disorder and comorbid attention-deficit/hyperactivity disorder: preliminary results of a prospective follow-up

study. *J Neural Transm (Vienna)* 2008; **115**: 187-190 [PMID: 18200431 DOI: 10.1007/s00702-007-0841-2]

99 **Zellmann H**, Jans T, Irblich B, Hemminger U, Reinecker H, Sauer C, Lange KW, Tucha O, Wewetzer C, Warnke A, Walitza S. [Children and adolescents with obsessive-compulsive disorders]. *Z Kinder Jugendpsychiatr Psychother* 2009; **37**: 173-182 [PMID: 19415602 DOI: 10.1024/1422-4917.37.3.173]

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