

Investigational and Experimental Drugs to Treat Obsessive-Compulsive Disorder

This article was published in the following Dove Press journal:
Journal of Experimental Pharmacology

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Abstract: Treatment-resistance is a frequent condition for obsessive-compulsive disorder (OCD). Over the past decades, a lot of effort has been made to address this issue, and several augmentation strategies of serotonergic drugs have been investigated. Antidopaminergic drugs are considered the first choice as augmentation strategy for treatment-resistant OCD patients, but they seem to work only for a subset of patients, and none of them have been officially approved for OCD. Recently, the role of glutamate and inflammation in OCD pathophysiology clearly emerged, and this has led to several investigations on glutamatergic and anti-inflammatory agents. Results seem promising but still inconclusive. Probiotic interventions (considered to modulate the immune systems and the brain activity) are gaining attention in several psychiatric fields but are still at their early stages in the OCD field. Research on new treatment approaches for OCD is moving forward, and more than one hundred interventional trials are ongoing around the world. While the vast majority of these trials involve neuromodulation and psychotherapeutic approaches, only a small proportion (around 20%) involve the investigation of new pharmacological approaches (tolcapone, nabilone, psilocybin, troriluzole, nitrous oxide, rituximab, naproxen, and immunoglobulins). Here, we provide a comprehensive review of investigational and experimental drugs to treat OCD.

Keywords: OCD, glutamate, immune system, inflammation, probiotics, pharmacotherapy

Introduction

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder with a lifetime prevalence of 1–2% in the general population and is the fourth most frequent psychiatric disorder.¹ The story of OCD medications is relatively recent. In the mid-eighties, clomipramine (the most selective serotonergic drug among the tricyclic antidepressants) was seen to have a specific anti-obsessive effect compared to other antidepressants (with more noradrenergic effects).² From that discovery, in subsequent years, the role of the serotonergic system in OCD pathophysiology has become the center of investigation for the subsequent years and selective serotonin reuptake inhibitors (SSRIs) rapidly gained the role of first-line treatments for OCD patients.^{3,4} Although SRIs changed the natural history and treatment trajectory of OCD patients, up to 40–60% of patients, still do not respond to these treatments.^{5,6} Consequently, the mid-nineties research moved to investigating augmentation strategies for OCD. From that period on, several trials emerged in which antidopaminergic agents (eg, haloperidol, risperidone, etc.) were added to SRIs treatment. The results proved the effectiveness of this augmentation strategy, initially and mainly in tic-related and/or poor-insight OCD patients, but then in a broader cohort of

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treatment-resistant patients.⁷ After more than 20 years, as shown by recent meta-analyses, several antidopaminergic agents have been confirmed to be significantly superior to placebo as augmentation to SRIs in resistant-OCD patients.⁸ However, this is true, on average, for only one-third of resistant patients.⁷ Therefore, the research for new treatments beyond current guidelines is still mandatory.^{5,6}

In more recent years, pathophysiological studies moved beyond serotonin and dopamine and increasingly and consistently showed glutamate and inflammatory involvement in OCD pathophysiology.

The aim of this paper is to review current available data on investigational and experimental drugs for treating OCD. In the first sections, we will specifically focus on glutamate and anti-inflammatory agents since they represent the most promising areas of research and because we already have controlled trials that can inform us about their future role in the treatment of OCD. In the second section, we will focus on medications under investigation and for which there is still a lack of controlled studies.

Methods

A PubMed search was conducted using the terms “obsessive-compulsive disorder”, “OCD treatment”, “medications”, “augmentation”, “glutamate”, “OCD medications”, “glutamate system”, “glutamatergic agents”, “inflammation”, “PANDAS”, “PANS”, “anti-inflammatory agents”, “microbiome/microbiota”, “probiotics”. We also looked for still ongoing trials on the website www.clinicaltrials.gov (last update mid-September 2020). To conduct this research, the search term used was “obsessive-compulsive disorders”. The search filter used was “recruiting, not yet recruiting, active-not recruiting and enrolling by invitation” in order to find the still ongoing and non-published trials.

Glutamatergic Agents in OCD

A glutamatergic dysfunction in OCD patients emerged in the last years and was supported by preclinical, imaging, and genetic studies. Functional studies converged on the presence of a hyperglutamatergic state in the so-called cortico-striatal-thalamo-cortical circuit of OCD patients.^{9–14} Recent studies on both pediatric and adult OCD patients demonstrated a link between the response to fear-extinction during cognitive-behavioral therapy and glutamate levels.^{15–17} However, establishing a clear relation between glutamatergic dysfunction and OCD and understanding its exact functional meaning, is not an easy task, for several reasons. Firstly, glutamatergic

neurons are present in almost all brain circuitries and are therefore difficult to specifically localize a glutamatergic dysfunction in a specific brain area.¹⁸ Secondly, while most studies converged on a hyper-glutamatergic state in OCD patients, it is noted that also pro-glutamatergic agents show some positive effects for OCD symptoms.¹⁹ Summarized here is current evidence on glutamatergic agents for OCD.

Ketamine

In recent years, ketamine (a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, usually administered intravenously) gained much attention due to its rapid-onset antidepressant effect on treatment-resistant depressed patients.²⁰ This interest grew up when subsequent studies indicated the short-term effect reported in the first infusive trials could be sustained with repeated doses.²⁰ After these reports, some researchers studied ketamine also for OCD. In fact, early reports demonstrated rapid-onset but short-term anti-obsessional effects of a single intravenous dose of ketamine infusion.^{21–23} Furthermore, a randomized cross-over trial, conducted by the group of Carolyn Rodriguez at the Stanford University on 15 OCD patients, showed the significant anti-obsessional effect of a ketamine's single-infusion both immediately after the first infusion and after a 1 week follow-up.²⁴ Interestingly, their study revealed the anti-obsessional effect (almost 50% of responders) was not driven by the ketamine's antidepressant effect, but its mechanism of action appeared to be related to GABA reduction in the medial cortex.²⁵ In order to extend the observed anti-obsessional effects of ketamine, the same group investigated two different approaches in two subsequent studies: adding intensive cognitive behavioral therapy (CBT) (10 sessions in 2 weeks after ketamine infusion) or adding memantine after a ketamine infusion. Results of these studies showed that ketamine's anti-obsessional effects in responder patients are sustained over time when adding CBT but not when adding memantine.^{26,27}

Rapastinel (GLYX-13)

Rapastinel (formal name GLYX-13) is a partial agonist at the glycine site of the glutamate NMDA receptor and, as is the case for ketamine, it is usually administered intravenously. Rapastinel has been shown to have both an antidepressant and a cognitive-enhancing activity without the typical side effects seen with ketamine.²⁸ Rodriguez et al

showed a rapid but short-term improvement on OCD, anxiety, and depressive symptoms in a small sample of treatment-resistant OCD patients.²⁹ Interestingly, in a separate paper on the same OCD sample, the rapastinel's effect, contrary to what had been observed for ketamine, appeared to be correlated to a reduction of the Brain-Derived Neurotrophic Factor (BDNF).³⁰

Memantine

Memantine is non-competitive NMDA receptor blockers that have been approved for the treatment of Alzheimer's disease. Compared to ketamine, memantine exerts a weak block of the ion channel pore of the NMDA receptor.¹⁹ Due to its glutamate-modulating properties and its tolerability, memantine has been investigated for treatment-resistant OCD across several studies by different research groups. After some initial positive case studies and small open trials, between 2013 and 2018, three independent placebo-controlled trials showed a significantly positive effect on OCD symptoms when used as an addition to SRIs medications.^{31–41} A recent meta-analysis in 2019 put together these controlled studies and confirmed the efficacy of memantine in both moderate and severe treatment-resistant OCD.⁴² Thus, memantine is one of the most promising glutamatergic agents for the treatment of OCD. Further multicenter trials are warranted to extend its use to the resistant-OCD population.

N-Acetylcysteine (NAC) and L-Carnosine

Meanwhile, NAC (a precursor of the amino acid cysteine) and l-carnosine (a dipeptide made up of the two amino acids beta-alanine and histidine) are usually thought to have in common only an antioxidant activity, they also share an interesting glutamate-modulating activity that has been investigated for the treatment of different psychiatric disorders.^{43,52–54} NAC modulates glutamatergic transmission by the cystine-glutamate antiporter, while l-carnosine reduces glutamatergic activity by upregulating the glutamate transporter 1.^{43,52} For the OCD spectrum, NAC showed clear benefits in placebo-controlled trials for both trichotillomania and excoriation disorder.^{44,45} However, its usefulness for OCD patients is still controversial. In fact, of the 5 available controlled trials of NAC augmentation of SRIs for treatment-resistant OCD patients, 3 showed positive results while 2 showed negative results.^{46–50} Of note, a recent small open trial on pediatric OCD patients showed some initial positive effects of NAC on OCD symptoms.⁵¹ On the other hand, L-carnosine has been

less investigated for OCD, but the only available controlled trial (1 g of L-carnosine as add on to fluvoxamine) showed good results.^{55,56}

Lamotrigine and Topiramate

Lamotrigine and topiramate are two inhibitors of the glutamate AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) receptors.⁵⁷ Lamotrigine showed a significant effect on OCD symptoms in two different placebo-controlled trials as add-on to SRIs. It also showed some effectiveness on OCD symptoms in patients with comorbid schizophrenia and OCD (the so-called “schizo-obsessive” population).^{58–60} However, a recent naturalistic study on bipolar patients showed the onset of de-novo OCD symptoms in patients treated with lamotrigine. For most of these patients, OCD symptoms disappeared after 1 month of lamotrigine discontinuation.⁶¹ On the other hand, topiramate effects on OCD are still inconclusive. Of the 3 available controlled trials, 2 has been negative and only the first one resulted positive.^{62–64}

Other Glutamatergic Agents

Some other glutamatergic agents have been investigated for OCD: three modulators of the glycine-cite in the NMDA receptors (glycine, d-cycloserine, and sarcosine) and riluzole, a glutamate release inhibitor and glutamate glial uptake stimulator. While glycine showed a clear lack of anti-OCD effects and poor tolerability in controlled trials,⁶⁵ d-cycloserine (DCS) data is more controversial. DCS has gained attention as an augmentation strategy for exposure and response prevention therapy due to its ability to enhance fear extinction in animal models. However, controlled trials on adults and children with OCD produced mixed results, and recent meta-analyses showed minimal benefits.^{66–69} Sarcosine showed some promising results in an open trial, but with a small sample size.⁷⁰ Finally, riluzole showed good results in only one of the three available controlled trials.^{71–73}

Anti-Inflammatory Agents in OCD

Today, we can talk about the so-called “immunopsychiatry”, since the role of autoimmunity and inflammation has been recognized to play a role in the pathophysiology of several psychiatric disorders including depression and schizophrenia.⁷⁴ Autoimmunity was initially implicated in the OCD pathophysiology in the early nineties, with the so-called pediatric autoimmune neuropsychiatric disorder associated with group A beta-hemolytic streptococcus

(GABHS) (PANDAS), then renamed pediatric acute neuropsychiatric syndrome (PANS).^{75–78} After that, a putative role of neuroinflammation and autoimmunity in OCD pathophysiology emerged also in adults. Autoimmune disorders, such as lupus erythematosus and multiple sclerosis, are highly prevalent in OCD patients, and nationwide studies on OCD and their healthy relatives reported up to 43% of comorbid autoimmune diseases.^{79–81} Also, several studies and recent meta-analyses consistently showed a fivefold higher rate of anti-basal ganglia antibodies in OCD patients compared to controls.⁷⁸ Finally, while the presence of cytokines levels abnormalities in OCD patients is still controversial according to the most recent meta-analyses,⁸² a recent paper shows the presence of inflammation markers in the adult OCD brain (specifically within the cortico-striatal-thalamo-cortical regions supposed to be involved in OCD pathophysiology).⁸³ Despite early investigations suggested a positive effect of antibiotics on PANS patients, current literature did not support their use but showed promising effects of the non-steroidal anti-inflammatory drugs (NSAID).^{84,85} Thus, anti-inflammatory agents have also been investigated on adults with OCD. Here, we will review current literature on anti-inflammatory agents for adults with OCD.

Celecoxib

Celecoxib is an NSAID that exerts its anti-inflammatory activity by inhibiting the cyclooxygenase-2 (COX-2) enzyme. COX-2 inhibitors showed a protective effect on glutamate-mediated neural death and they exert an anti-inflammatory action by inhibiting the production of pro-inflammatory cytokines (especially TNF- α and IL-6).^{86,87} Celecoxib showed an antidepressant effect, correlated to IL-6 levels reduction, in a controlled trial on patients with major depressive disorder.⁸⁸ Two double-blind controlled trials by two different research groups in the same country investigated the effectiveness of celecoxib 400 mg augmentation of SSRIs (fluoxetine and fluvoxamine, respectively) for 8 weeks vs placebo.^{89,90} In both trials, celecoxib was well tolerated and was found to be superior to placebo. However, results of both studies have serious limitations considering in both cases SSRIs were administered at a low dose (under the recommended ones) and for a non-adequate treatment period before adding celecoxib. This fact poses difficulties in distinguishing a direct effect of celecoxib vs a carry-over effect of SSRIs.^{89,90} Thus, despite these preliminary results are intriguing in the view of an inflammation-mediated pathophysiology of

OCD, further and larger multicenter trials are needed to generalize these results.

Minocycline

Minocycline is a tetracycline antibiotic with both anti-glutamatergic and anti-inflammatory activities.⁹¹ While the first open study on OCD patients was negative a recent double-blind controlled study on more than hundred OCD patients showed a significant anti-obsessional effect when added to fluvoxamine.^{92,93}

Probiotics

Probiotics can help in regulating the human immunological system and the brain through the so-called “microbiota-gut-brain axis” (the set of hormonal, immunological, and neural connections between the brain and the gut-microbiota).^{94,98–101} A putative role of the microbiota-gut-brain axis has already been suggested for several psychiatric disorders (depression, ADHD, autism spectrum disorders, bipolar disorder, psychosis, and post-traumatic stress disorder).^{95–97} However, this field of research is still at its early stages in the world of OCD research. In 2020, a group of researchers showed that the natural compulsive-like behavior in the deer mouse is associated with altered gut microbiota composition.¹⁰² In 2018, an Italian group of researchers demonstrated that children with the PANS and PANDAS showed an altered bacterial community structure, in particular showing the presence of a high increase in Bacteroidetes.¹⁰³ Interestingly, a recent Canadian study was the first to show that adult OCD patients have less richness/evenness of gut microbiota compared to controls and in particular they display a lower presence of three butyrate-producing genera (namely Oscillospira, Odoribacter, and Anaerostipes).⁹⁵ These latter results are of special interest since butyrate-producing species seem to have an anti-inflammatory effect on human immunological state.⁹⁵ To the best of our knowledge, there are still no available trials on probiotics interventions for OCD patients. Only studies on animal models of OCD and on healthy volunteers with OCD symptoms showed intriguing results.^{104,105} According to our research on clinicaltrials.gov (mid-September 2020), there is an ongoing trial on the probiotic formula Lactobacillus Helveticus and Bifidobacterium Longum (two probiotic agents that showed anxiolytic properties on human studies).

Drugs Under Investigation

In the following section, we will report the results of a systematic search on clinicaltrials.gov website database (updated at mid-September 2020) in order to propose an

overview of the ongoing drugs under investigations for OCD. The search resulted in a total of 129 recorded studies. Out of these, 113 studies involved interventional treatment arms. However, only 19.5% involved pharmacological treatments. The remaining 80.5% of the trials involved psychological treatments (internet-based psychotherapy, new cognitive-behavioral and mindfulness-based protocols) and neuromodulation techniques (deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and other neuromodulation interventions). These search results are interesting since they point out the fact that in the last years the pharmacological research for new treatments for OCD became the minority part of this field. Moreover, just a few of the pharmacological treatments investigated are “really” new agents or agents without previous investigations in the OCD field (here we will present these latter agents).

Considering that for most of the drugs presented in this section there are still no controlled trials available, we will report the rationale for their investigation in OCD treatment

and a brief summary of their proposed mechanisms of action (for a summary see Table 1).

Tolcapone

Catechol-O-methyltransferase (COMT) is an enzyme implicated in the degradation of catecholamines (eg, noradrenaline, dopamine) by transferring a methyl group to their hydroxyl group.¹⁰⁶ Several studies implicated COMT in the pathophysiology of psychiatric disorders such as schizophrenia, bipolar disorders, Parkinson's disease, depression, ADHD, addictions and also OCD.¹⁰⁷ The COMT gene is present on chromosome 22 q11 and several polymorphisms have been reported. Val158Met (G to A) polymorphism is the most studied and clinically important.¹⁰⁸ Substitution of Val by Met at 158th position reduces COMT activity. Since COMT inactivates dopamine in the prefrontal cortex, subjects with the low-activity allele showed lower COMT and higher dopamine levels.^{109–112} COMT gene Val158Met polymorphism has been consistently linked to several psychiatric disorders such as schizophrenia, panic disorders, bipolar disorder, ADHD, suicide, and addiction disorders.¹¹³ In the OCD field,

Table 1 Drugs Under Investigations for OCD

	Proposed Mechanism of Action for OCD	Trial Design	Drug Dose and Duration of Treatment
Tolcapone	COMT-inhibitor	QB cross-over	Tolcapone 200 mg/2 weeks
Nabilone	CBI receptor agonist	Randomized, two arms: nabilone “alone” vs nabilone + ERP	Nabilone 1 mg/4 weeks
Psilocybin	5-HT _{1A} and 5-HT _{2A/2C} receptors agonist	QB active-placebo-controlled (Niacine 250 mg)	Psilocybin 0.25 mg/Kg/single dose
Troriluzole (BHV-4157)	Augmenting the expression and function of excitatory amino acid transporters (ie, EAAT2)	DBPC	Troriluzole 140 mg/12 weeks
Nitrous oxide gas	Glutamate NMDA and AMPA receptors antagonist/ Low voltage calcium channels inhibitor	QBPC	50% oxygen + 50% nitrous oxide admixture/60 minutes
Rituximab	Antibodies against CD20, cluster of differentiation	Open label	1000 mg/single dose
Naproxen (for PANDAS/PANS)	Non selective COX-1 and COX-2 inhibitor	QBPC	10 mg/Kg/8 weeks
Octagam 5% (for PANDAS/PANS)	Immunoglobulines	Open label	1g/Kg (6 infusions)/18 weeks
Pregabalin	Ca ²⁺ channels modulation	QBPC	Up to 600 mg/8 weeks
Ondansetron (for tic-related OCD)	5HT ₃ receptors antagonist	QBPC	24 mg/4 weeks

Abbreviations: OCD, obsessive-compulsive disorder; DBPC, double-blind placebo-controlled; QBPC, quadruple blind placebo controlled; COMT, catechol-O-methyltransferase; 5HT, serotonin; CBI R, cannabinoid receptor type 1; ERP, exposure and response prevention; EAAT2, excitatory amino acid transporter 2; NMDA, N-methyl-D-aspartate receptor; AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; COX-1/2, cyclo-oxygenase.

investigation of Val158Met polymorphism produced mixed results across studies, but in recent years evidence has become more consistent in favor of a link between OCD and this polymorphism.¹⁰⁸ Also, several studies suggest that COMT allelic variants might have an effect on cognitive domains such as memory, executive functions, and decision-making.¹⁰⁸ Dysfunctional decision-making and executive functions have been associated with OCD and some of these have been proposed as OCD endophenotype.^{7,114} Finally, dopaminergic circuitries dysfunction has been highly replicated across OCD studies and dopaminergic agents have been proposed as augmentation strategies for almost ten years.¹¹⁵

Tolcapone is a selective and reversible COMT inhibitor and is widely used in the treatment of Parkinson disease.¹¹⁶ Tolcapone inhibits the methylation of levodopa preventing the formation of its metabolite methyl dopa (a competitor of levodopa in crossing the blood-brain barrier).¹¹⁶ By doing this, tolcapone enhances the brain availability of levodopa.¹¹⁶

The Chicago University is running a randomized controlled trial in order to investigate the putative therapeutic effects of tolcapone in a clinical sample of OCD subjects. According to the trial status in clinicaltrials.gov website (mid-September 2020), the trial is yet recruiting participants.

Nabilone

An anti-obsessional and anti-anxiety effect of cannabis has been reported anecdotally by some OCD patients who smoke cannabis.¹¹⁷ Interestingly, the endocannabinoid system could be relevant to OCD pathophysiology. Indeed, the type 1 cannabinoid receptors (CB1R) are highly expressed in several brain areas involved in OCD (eg, prefrontal cortex, amygdala, and the striatum) and preclinical studies highlighted their role in fear-extinction and the balance between goal-directed vs habitual behaviors (two cognitive functions implicated in OCD pathophysiology).^{117,118} Furthermore, cannabinoids also proved to relieve anxiety and compulsive behaviors in animal models.¹¹⁷

In the OCD field, two case reports showed that dronabinol (tetrahydrocannabinol, THC), an agonist at central cannabinoid CB1 receptors, improved OCD symptoms in treatment-resistant patients, and a recent case report showed the efficacy of medical cannabis in a 22-year-old men with both OCD and comorbid depression.¹¹⁹ These reports are in line with current literature on Tourette syndrome showing positive effects on both tics and comorbid

OCD symptoms of several forms of cannabis agents (THC, cannabis extracts, and flowers).¹¹⁹

Nabilone is a synthetic cannabinoid that is thought to be a CB1R agonist. Recently, an open label two arms trial (sponsored by the New York State Psychiatric Institute) investigated the effects of nabilone 1 mg for 4 weeks vs nabilone associated to exposure and response prevention (ERP) therapy for 4 weeks on medication-free adults diagnosed with OCD. The study, to the best of our knowledge, is still not available on a peer-reviewed journal, but its results are reported on the clinicaltrials.gov website. According to these available data, 11 OCD patients have been recruited and divided in the two groups. None of the patients reported major side effects and only 3 patients reported anxiety as side effect. In the reported results the nabilone “alone” group reported a mean Y-BOCS score reduction of 2.5 points after 4 weeks of treatment while the nabilone+ERP reported a mean Y-BOCS score reduction of 11.2 points. Of course, we need to see the entire study results and statistical analysis in order to draw any conclusions.

Psilocybin

Psychedelic agents have gained a lot of attention in psychiatry after several investigations showed their putative improvement effects on depression, anxiety, addictions, and OCD, as we will see.¹²⁰ Psychedelic agents usually act as serotonin 2A receptor agonists and recently several preclinical studies highlighted their role in modulating the immune system by inducing an anti-inflammatory effect.¹²⁰ Psilocybin, a potent 5-HT_{1A} and 5-HT_{2A/2C} agonist, is one of the most studied compounds in this category of drugs. A small series of case reports suggested some putative beneficial effects of psychedelic agents on OCD patients since the early nineties.¹²¹ To the best of our knowledge, there is only one available open trial in the current literature. In 2006, an early small open trial assessed the acute effect of several different doses of psilocybin on OCD patients.¹²² Results of this study showed that all patients reported a marked reduction of OCD symptoms at some point during the 24 hours of the study. Psilocybin was well tolerated by almost all patients and only 1 out of the 9 subjects experienced transient hypertension non-related to anxiety or somatic symptoms.¹²²

Interestingly, Yale University has now an ongoing trial on psilocybin for OCD. The study is a double-blind controlled trial that will involve 30 patients. Patients will be randomized to receive psilocybin (0.25mg/kg) or the

active comparator niacin (250 mg). According to clinicaltrials.gov (last update mid-September 2020), the trial is still in the recruiting phase.

Troriluzole (BHV-4157)

Troriluzole is a precursor of riluzole and, as this latter, is a glutamate modulator. Specifically, it reduces the synaptic levels of glutamate by augmenting the expression and function of the glial glutamate transporters (ie, EAAT2) responsible for glutamate synaptic clearance.

Phase 2–3 clinical trials are now investigating troriluzole as a treatment for Alzheimer's disease and spinocerebellar ataxia. According to clinicaltrials.gov register (mid-September 2020), there is a phase 2–3 controlled trial sponsored by the Biohaven Pharmaceuticals, Inc., assessing its efficacy on treatment-resistant OCD patients. The trial is active but not recruiting.

Nitrous Oxide Gas

Nitrous oxide is a colorless and nearly odorless anesthetic gas. It is often used for surgical anesthesia in association with other agents, since it is one of the weakest anesthetic drugs. It has a low blood-gas solubility, which means a rapid on- and offset of actions; therefore, patients usually completely recover within a few minutes. Moreover, it is not metabolized and its uptake and elimination are via the lungs.¹²³ Nitrous oxide's mechanism of action is supposed to be complex but mostly related to glutamatergic modulation. Indeed, it has an inhibitory action on both NMDA, AMPA, and kainite receptors, and it has an antagonist action on low voltage-activated calcium channels (LVA, T-type), and certain nicotinic acetylcholine receptors and potassium channels (TREK-1).¹²³ Nitrous oxide is widely considered as very tolerable and safe (main side effects are nausea and vomiting, headaches, dizziness, and euphoria).¹²³ Due to its anti-glutamatergic effect (as is the case for ketamine), it has been tested in treatment-resistant depressed patients. A recent randomized controlled trial showed that nitrous oxide significantly improved depression symptoms compared to placebo at 2 hours and after 24 hours from its administration.¹²⁴ In this trial, no serious adverse events occurred; all adverse events were brief and of mild to moderate severity.¹²⁴

As is the case for ketamine (firstly investigated in depression and subsequently in OCD), nitrous oxide has now gained attention also in the OCD field (mainly for its anti-glutamatergic effects). According to the register of clinicaltrials.gov register (mid-September 2020), a phase

2 double-blind controlled trial at the Stanford University is ongoing (not yet recruiting). This study seeks to explore whether a single inhalation of nitrous oxide gas may bring about rapid symptom relief in OCD. Nitrogen is used as active comparator.

Rituximab

Rituximab is a monoclonal antibody that binds the surface protein CD-20, widely expressed on B-lymphocyte. It triggers cell death and it has been used in the last 20 years for several CD20-expressing lymphoid malignancies.¹²⁵ It is administered intravenously. Due to its positive effects on autoimmune and dys-immunological diseases, it is gained attention also for psychiatric disorders with a probable immunological etiology. Given the overmentioned evidence about a possible role of inflammation in OCD pathophysiology, rituximab is now under consideration for its use in OCD patients. According to the register of clinicaltrials.gov (mid-September 2020), an open trial for treatment-resistant OCD patients is ongoing (and in a recruiting phase) in Sweden.

Naproxen and Immunoglobulins for PANS/PANDAS

As mentioned in the previous sections, a subset of pediatric-onset OCD is considered to be related to autoimmune phenomena (probably generated by a cross-reactivity between gangliosides in basal ganglia neurons with the GABHS and/or other agents cell). In this perspective, both anti-inflammatory agents and immunoglobulins gained much attention in the last years.

Based on the register of clinicaltrials.gov (mid-September 2020), there are two trials in an active phase, investigating these treatment approaches for this special population. The first is a multisite open-label trial (in the active-not recruiting stage) investigating the use of intravenous immunoglobulins (IVIG) at a dose of 1g/Kg/body weight given every 3 weeks for 6 infusions in pediatric subjects ages 4–16 years with moderate to severe PANS. The second is a double-blind placebo-controlled trial of Naproxen Sodium, a nonsteroidal anti-inflammatory drug (NSAID) (a non-selective COX-1 and 2 inhibitor) given to participants diagnosed with Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infections (PANDAS).

Other Agents Under Investigations

Ondansetron, a serotonin 5HT₃ receptor antagonist, usually prescribed to prevent nausea and vomiting, has been

investigated in OCD. Some promising results have been found (for a review see¹²⁶). However, a double-blind placebo-controlled trial of low daily dosages of ondansetron (0.5 and 0.75 mg) in a relatively large sample was negative.¹¹⁵ Now, a double-blind placebo-controlled trial with higher ondansetron doses on tic-related OCD patients is currently underway (clinicaltrials.gov, mid-September 2020).

Pregabalin, a gamma-aminobutyric acid analog, modulates calcium channels and has been approved for its use in epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorder. Anecdotal reports showed some efficacy of pregabalin for OCD and a recent placebo-controlled randomized trial showed positive results respect to placebo in a dose range between 75 and 225 mg.¹²⁷ A randomized controlled trial at the McMaster University in Canada investigated the effects of pregabalin in a flexible dose up to 600 mg for 8 weeks as an addition to SRIs treatment in resistant OCD. According to clinicaltrials.gov (last update mid-September 2020), the trial has concluded, but results are still not provided and, to the best of our knowledge, there are not available publications yet.

Conclusions

Treatment-resistance is a frequent condition for obsessive-compulsive disorder (OCD). More than a decade of investigations on augmentations strategies to serotonergic drugs, indicated antidopaminergic agents as the first choice for SRIs resistant patients. However, antidopaminergics seem to work only for one-third of patients and none of them have been officially approved for OCD.

On the other hand, over the last years OCD pathophysiology studies looked beyond serotonin and dopamine, and a role for glutamate and inflammation clearly emerged. This discovery has led to a large effort in the investigation of glutamatergic and anti-inflammatory agents. Results on anti-glutamatergic agents seem promising but still inconclusive. On the other hand, probiotic interventions (considered to modulate the immune systems and the brain activity) are gaining attention in several psychiatric fields but are still in their infancy in the OCD field. Research for new treatment approaches for OCD is moving forward, and more than one hundred interventional trials are ongoing around the world. While the vast majority of these trials involve neuromodulation and new psychotherapeutic approaches, only a small proportion (around 20%) involve the investigation of new pharmacological approaches. Most of these are glutamatergic modulators and/or immunomodulators (troriluzole, nitrous oxide, rituximab, naproxen, and immunoglobulins). COMT

inhibitors (tolcapone), endocannabinoid modulators (nabilone), and psychedelic agents (psilocybin) represent “new” pharmacological approaches for OCD.

However, in our opinion, more than discovering “new” agents, the goal for OCD pharmacological research in future years should be the application of a precision-medicine approach to OCD treatment. In other words, the imperative should be to individualize OCD treatments and find biomarkers in order to predict the treatment-response and in order to develop treatment approaches that are sub-type specific (both in terms of symptom dimensions and comorbidity patterns), phase specific (in a clinical staging perspective), multimodal and sequential, and, more importantly, dimensional.

Disclosure

The authors report no conflicts of interest for this work.

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