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Treatment-resistant OCD: Pharmacotherapies in adults

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ABSTRACT

Serotonin reuptake inhibitor (SRI) medications are well established as first-line pharmacotherapeutic treatment for Obsessive-Compulsive Disorder (OCD). However, despite the excellent safety profile and demonstrated efficacy of these medications, a substantial proportion of individuals with OCD fail to attain sufficient benefit from SRIs.

In this narrative review, we discuss clinical features of OCD that have been associated with poorer response to SRIs, and we present pharmacotherapeutic interventions that have been explored as augmenting or alternative treatments for treatment-resistant OCD. We additionally highlight non-SRI interventions for OCD that are currently under investigation.

Pharmacotherapeutic interventions were identified via expert consensus. To assess the evidence base for individual pharmacotherapies, targeted searches for relevant English-language publications were performed on standard biomedical research databases, including MEDLINE. Information relevant to ongoing registered clinical trials in OCD was obtained by search of ClinicalTrials.gov. Pharmacotherapies are grouped for review in accordance with the general principles of Neuroscience-based Nomenclature (NbN).

Clinical features of OCD that may suggest poorer response to SRI treatment include early age of onset, severity of illness, duration of untreated illness, and the presence of symmetry/ordering or hoarding-related symptoms. Based on evolving pathophysiologic models of OCD, diverse agents engaging serotonin, dopamine, norepinephrine, glutamate, and anti-inflammatory pathways have been explored as alternative or adjunctive therapies for treatment-resistant OCD and have at least preliminary evidence of efficacy.

Medications with dopamine antagonist activity remain the most robustly evidence-based of augmenting interventions, yet dopamine antagonists benefit only a minority of those who try them and carry elevated risks of adverse effects. Interventions targeting glutamatergic and anti-inflammatory pathways are less well evidenced, but may offer more favorable benefit to risk profiles. Ongoing research should explore whether specific interventions may benefit individuals with particular features of treatment-resistant OCD.

1. Introduction

Obsessive-compulsive disorder (OCD) is a typically chronic condition characterized by repeated experience of unwanted, distressing, and intrusive thoughts (obsessions) and/or repetitive or ritualized behaviors (compulsions), usually performed to reduce obsession-associated anxiety. OCD was long considered highly difficult to treat [75] but emerged through the last decades of the 20th century as a paradigm of neuroscience-informed psychiatric medicine. In concert with developments in cognitive behavioral therapy (CBT) and brain imaging technologies, the development of pharmacologic treatments based on the role of serotonin [68,93] facilitated studies that powerfully illustrated how psychotherapeutic and psychopharmacologic treatments might change the brain, normalize aberrant patterns of neural

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activation, and relieve symptoms [24,214].

First-line pharmacologic treatment for OCD utilizing serotonin reuptake inhibitors (SRIs) and exposure and response prevention (ExRP)-based CBT is now strongly evidence based, well established in clinical practice internationally, and summarized in consensus guidelines [17,22,67,112]. Despite this significant progress, most individuals with OCD benefit incompletely—or not at all—from first-line treatment, and the quality of life for individuals with OCD, even after treatment, is diminished compared to that of individuals without the disorder [87,129,190]. As OCD is estimated to affect between 1% to 2% of the world population [63,202], the social and economic costs of the disorder remain significant [88].

Individuals with OCD may insufficiently benefit from first-line treatment for many reasons. Critically, inadequate benefit from pharmacologic treatment most commonly reflects gaps in care related to inaccurate diagnosis, inappropriate medication, or an insufficient pharmacologic trial [132,217]. Strategies for optimizing initial treatment of OCD in adults and for ensuring adequacy of treatment of OCD in youth are addressed in separate articles of this special edition of *Comprehensive Psychiatry*. For some patients, sexual or other adverse effects of SRIs are dose-limiting, or comorbidities such as bipolar disorder—a relative contraindication to SRI use—may preclude benefit from first-line pharmacologic treatment. Even with well-tolerated SRI treatment of sufficient dose and duration, individuals with OCD may not experience satisfactory resolution of symptoms. In clinical studies, approximately 40% to 60% of patients do not demonstrate an initial response to SRIs [82,130,167]. Furthermore, patients who are considered responders to initial treatment may continue to experience a significant ongoing symptom burden, reflecting the fact that in most clinical trials, OCD treatment response is defined as only a 25% to 35% improvement in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score [133]. For those patients who insufficiently benefit from first-line SRI treatment and are characterized as having treatment-resistant OCD, practice guidelines offer clear guidance on next steps, including recommendations for a trial of a second SRI and then potentially a trial of clomipramine [67]. However, patients whose symptoms are not adequately improved by SRI treatment remain a significant clinical challenge.

1.1. Clinical characteristics associated with treatment resistance

Recognizing the heterogeneity of OCD presentations, research has increasingly begun to characterize clinical manifestations of OCD and patient-specific factors that predict response or resistance to SRI treatment. More severe symptoms [135,191], early age of onset [4,53,200], longer duration of illness [228], and longer duration of untreated illness [11] have been associated with poorer response to SRI pharmacotherapy. The patient's dominant category of obsessions or compulsions may also influence treatment response rates. Patients with primary sexual, religious, or harm-based obsessions, for example, are more likely to respond to SRIs [123,226]; conversely, those with contamination/cleaning symptoms [191,226] and particularly symmetry/ordering and hoarding-related symptoms [135,226,227] are less likely to respond to treatment with SRIs. Male gender has been associated with earlier age of illness onset and has been considered a possible risk factor for treatment resistance. However, while gender differences in comorbidity and dimensional expression of OCD symptoms have been reported in the literature, current data do not support a consistent association between gender and illness severity or treatment outcome [26,136]. Similarly, although comorbid tic disorder was previously believed to be associated with poorer outcome to SRI treatment [124]—in line with evidence for the association of tic disorder with early onset of OCD symptoms [53] and with symmetry, ordering, and hoarding symptoms [123,135]—several more recent studies have shown that comorbid tics do *not* predict lower likelihood of acute or longer term SRI treatment response [50,90,94,223].

Neurocognitive and metacognitive aspects of patients' functioning may further influence likelihood of response to SRIs. Neurologic "soft signs" and fine motor deficits have been associated with poorer response to SRI treatment [85,86,145]. Patients' understanding and beliefs about their symptoms are also relevant. Studies exploring the predictive value of poor insight—like comorbid tics, a diagnostic specifier in OCD—have been mixed. Some studies have suggested that insight has no influence on outcome [12,58], however, subsequent reports have suggested that poor insight predicts poorer acute response to SRIs [39,91,108,161] and poorer long-term outcomes [38]. In line with the latter studies, the presence of positive metacognitive beliefs about obsessions (e.g., that one's worry is protective) has also been found to predict lower likelihood of response to SRI treatment [171]. Insight impairment may negatively predict SRI response in as much as it may correlate with other features associated with poorer response to SRI medications: it has been associated with symmetry/ordering and hoarding symptoms [49,70,95], greater severity of symptoms [38,58,95], earlier age of onset [38,108,137], and greater illness duration [91,108]. Lastly, poor insight has also been associated with the presence of comorbid schizotypal personality disorder [12,38,177,184], while schizotypy and other personality disorders have also been associated with poorer SRI treatment response [177,238].

Although many patient-specific factors may suggest lower likelihood of response to SRI medications, they do not preclude the possibility of significant benefit. It should be emphasized that SRI medications remain the first-line treatment even for patients who present with such factors. Nonetheless, that we generally lack evidence to guide alternative treatment choices when patients present with particular features suggestive of treatment resistance remains a challenge. For example, comorbid tics were previously thought to predict better response to augmentation with dopamine-blocking medications [34,140], however, this has not been supported in more recent meta-analytic review [246,254]. Pharmacogenetic markers may present a promising exception to this generalization, however, and are separately discussed in this *Comprehensive Psychiatry* special issue.

In this narrative review, we cover the range of pharmacologic treatments that have been proposed as augmentations or alternatives to first-line SRI treatments. Given the breadth of pharmacologic interventions studied and the limited evidence suggesting superiority of any one strategy over another, potential pharmacotherapies are grouped according to principles of Neuroscience-based Nomenclature (NbN; https://nbn2r.com/) [255]. Treatment strategies falling outside of typical psychopharmacology domains (e.g., anti-inflammatory drugs) are discussed separately. To assess the evidence base for each of the interventions discussed, relevant English-language literature was gathered by means of targeted searches of biomedical research databases, including MEDLINE, via pubmed.org and europepmc.org, as well as by use of general internet search resources, including scholar.google.com. Information relevant to ongoing clinical trials in OCD was obtained by searches of clinicaltrials.gov. While no implication about the efficacy of treatments currently being explored in clinical trials is intended, references to these ongoing trials are included to convey the growing edge of pharmacotherapeutic research in OCD.

The last US Food and Drug Administration (FDA) approval of a medication for OCD was nearly 20 years ago. No non-SRI intervention discussed here has been approved for treatment of OCD by the FDA, the European Medicines Agency, or any other major regulatory body. The interventions described should be considered only with careful attention to the supporting evidence. While evidence is very limited for some interventions, the generally low rate of placebo response in OCD (Fenghua [64,107]) suggests optimism when considering positive results of preliminary or open-label studies. Table 1 lists proposed pharmacologic interventions for treatment-resistant OCD along with letter grades indicating the degree of supporting evidence. Table 2 lists pharmacologic interventions currently under investigation in clinical trials.

Table 1
Agents investigated in clinical trials for treatment-resistant OCD.

Class of drug	Agent	Proposed mechanism of action for OCD	Level of evidence	Dose range	Safety cautions monitoring
Serotonin agents	SRIs (high dose)	SERT inhibition	1	Depending on SRI agent	QTc prolongation; hyponatremia
	Intravenous Clomipramine	SERT inhibition	3	150–250 mg	QTc prolongation - arrhythmias; seizures; liver toxicity; anticholinergic effects
	Intravenous Citalopram	SERT inhibition	4	60–80 mg	QTc prolongation; hyponatremia
	Ondansetron	5-HT3 receptor antagonist	3	1–8 mg	QTc prolongation
	Buspirone	Full agonist at presynaptic and partial agonist at postsynaptic 5-HT1A receptors, D2 receptors antagonist	3	30–60 mg	Good tolerability in OCD trials
	Psilocibyn	5-HT1A and 5-HT2A/2C agonist	4	0.10–0.30 mg/kg	Transient hypertension
	Tryptophan	5HT precursor	4	6 g	Good tolerability in OCD trials
	Inositol	Intracellular modulator of serotonin receptor signalling	4	18 g	Good tolerability in OCD trials
Norepinephrine and Serotonin agents	Mirtazapine	Alpha-2 presynaptic adrenergic receptor antagonist / 5HT2A, 5HT2C, and 5HT3 receptors antagonist	3	30–60 mg	Metabolic impact
	Pindolol	Beta-blocker / presynaptic serotonin 5HT1A receptor antagonist	3	2.5–5 mg	Good tolerability in OCD trials
Norepinephrine Dopamine agents	d-amphetamine	DAT and NET reuptake inhibition / dopamine vescicole storage inhibition	3	30 mg	Blood pressure and heart rate increase
	Methylphenidate (extended release)	DAT and NET reuptake inhibition	3	30–40 mg	Blood pressure and heart rate increase
Dopamine Serotonin Norepinephrine multimodal agents	Risperidone	D2 and 5HT2A receptor antagonist	1	0.5–6 mg	QTc prolongation; metabolic impact
	Aripiprazole	D2/D3 and 5HT1A/5HT2A partial agonist	1	10–15 mg	QTc prolongation; metabolic impact
	Quetiapine	D2 and 5HT2A receptor antagonist, Alpha1 and H1 antagonist	2	25–400 mg	QTc prolongation; metabolic impact
	Olanzapine	D2 and 5HT2A receptor antagonist, H1 inverse agonist	2	5–20 mg	QTc prolongation; metabolic impact
	Paliperidone	D2 and 5HT2A receptor antagonist	3	3–9 mg	QTc prolongation; metabolic impact
	Haloperidol	D2 antagonist	3	2–10 mg	QTc prolongation; metabolic impact
Dopamine agents	Tolcapone	MAO inhibitor	3	200 mg	Liver enzymes monitoring
Glutamate agents	Memantine	Glutamate NMDA receptor antagonist	2	20 mg	Good tolerability in OCD trials
	Ketamine	Glutamate NMDA receptor antagonist	3	Single infusion	Transient blood pressure and heart rate increase; dissociation
	N-acetyl cysteine	Modulation of AMPA and NMDA receptors through the cystine-glutamate antiporter	3	2–3 g	Good tolerability in OCD trials
	Minocycline	Reduction of microglia activity and therefore microglia-mediated NMDA toxicity	3	200 mg	Sunlight sensitivity increase
	Lamotrigine	Glutamate AMPA receptor antagonist	3	100–200 mg	Skin reactions
	Pregabalin	Ca^{2+} channel modulation	3	75–225 mg	Good safety and tolerability in OCD trials
	Topiramate	Glutamate AMPA receptor antagonist	3	100–200 mg	Paresthesia; cognitive impairments
	Riluzole	Glutamate release inhibitor and glutamate glial uptake stimulator	3	50–100 mg	Increase aminotransferases
	Troriluzole	Glutamate release inhibitor and glutamate glial uptake stimulator	3	140–200 mg	AE not clearly reported in the OCD published study
Opioid agents	Morphine	μ receptor agonist	3	15–40 mg	Misuse risk
	Tramadol	μ receptor agonist	4	254 mg	Misuse risk
	Buprenorphine	μ receptor partial agonist	3	2–6 mg	Misuse risk
Anti-inflammatory agents	Celecoxib	COX-2 inhibitor	3	400 mg	Good tolerability in short-term OCD trials
Cannabinoids	Dronabinol	CB1/CB2 receptor agonist	4	20–30 mg	Cognitive and motor skills impairment; potential misuse
	Nabilone	CB1 receptor agonist	4	1–2 mg	Cognitive and motor skills impairment; potential misuse
Others	Lithium	Hypothesized to upregulate glutamatergic or inflammatory pathways via Wnt/beta-catenin signaling	4	900–1200 mg	Thyroid and kidney function impairments; QTc prolongation

SRI: serotonin reuptake inhibitor; SERT: serotonin transporter; DAT: dopamine transporter; NET: norepinephrine transporter; NMDA: N-methyl-D-aspartate; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; CB1/2: cannabinoid receptor 1 and 2; COX-2: Cyclooxygenase-2; MAO: Monoamine oxidase.

Definition for level of evidence rating:

Level of evidence: 1 - Meta-analysis with narrow confidence intervals and/or two or more double-blind (DB) randomized controlled trials (RCTs) with adequate sample size, including placebo-controlled or active-control comparison; 2 - Meta-analysis with wide confidence intervals and/or one or more DB RCTs with adequate sample size with placebo or active comparison; 3 - Small-sample DB RCTs or nonrandomized, controlled prospective studies or case series or high-quality retrospective studies or health system administrative date; 4 - Expert opinion/consensus/anecdotal reports/uncontrolled trial.

Table 2
Agents currently under investigation in clinical trials.

Class of drug	Agent	Proposed mechanism of action for OCD	Current ongoing trials (design)
Glutamate agents	Ketamine	Glutamate NMDA receptor antagonist	1 DBPC
	Dextromethorphan	NMDA antagonist / SERT and NET inhibition / sigma-1 agonist activity	1 open-label randomized crossover
	Nitrous Oxide	NMDA antagonist and opioid receptor agonist	1 DBPC
	Troriluzole	Glutamate release inhibitor and glutamate glial uptake stimulation	1 DBPC
	Pregabalin	Ca^{2+} channel modulation	1 DBPC
Anti-inflammatory / immunomodulators agents	Rituximab	Monoclonal antibody that binds a surface protein of B-lymphocytes	1 DBPC (single infusion)
	Naproxen	Non-selective COX-1/2 inhibition	1 DBPC
	Octagam 5%®	Set of intravenous immunoglobulins	1 open-label (only PANDAS/ PANS patients)
Probiotics	*Lactobacillus helveticus* + *Bifidobacterium longum*	Enrichment of the anti-inflammatory microbiota	1 DBPC
Cannabinoids	Nabilone	CB1 receptor agonist	1 open-label; 1 DBPC (single dose)

DBPC: double-blind placebo-controlled; SERT: serotonin transporter; NET: norepinephrine transporter; NMDA: N-methyl-D-aspartate; CB1/2: cannabinoid receptor 1 and 2; COX-1/2: Cyclooxygenase 1 and 2.

2. Serotonin agents

2.1. Serotonin reuptake inhibitors (SRIs)

2.1.1. High-dose oral serotonin reuptake inhibitors

High doses of SRIs have been explored as a novel treatment for treatment-resistant OCD. Results of a meta-analysis of 9 RCTs examining different doses of SSRIs demonstrated that compared with medium and low doses, high-dose SSRI use led to significantly greater reduction in the total Y-BOCS score [35]. High-dose SSRI use also significantly increased the probability of treatment response, although it was associated with an increased likelihood of dropout due to adverse events. Therefore, tolerability is of concern when considering the potential benefits of higher dose SRI treatment. A systematic retrospective case review of treatment-resistant OCD patients treated with high-dose SSRIs (doses beyond the upper limit of approved dose ranges) in a specialty clinic found that baseline and endpoint Y-BOCS scores were significantly higher for patients receiving this treatment than for a control group (patients receiving a standard dose of SSRIs), consistent with these patients representing a particularly treatment-resistant cohort; nonetheless, Y-BOCS scores significantly improved in these patients over the period of high-dose SRI use [169]. These promising results suggested both tolerability and benefit of this strategy. Further support for use of supra-maximum SRI dose comes from two prospective studies: one randomized, double-blind continuation study exploring sertraline at doses of up to 400 mg daily (versus continuation at 200 mg) in patients who had not previously responded to 200 mg [163], and one open-label study exploring escitalopram at doses up to 50 mg daily in patients who had not responded to 20 mg daily [187]. Both studies suggested supra-maximum doses were well tolerated and helpful.

2.1.2. Intravenous serotonin reuptake inhibitors

Early studies suggested a greater efficacy of clomipramine in OCD compared to its more noradrenergic metabolite desmethylclomipramine [139,229]. Several case series then described the successful treatment of OCD refractory to oral clomipramine and/or other SRIs with **intravenous clomipramine** (IV CMI). IV CMI bypasses first-pass hepatoenteric metabolism, thereby reaching a higher clomipramine/desmethylclomipramine plasma level ratio [61,102,116,237,247]. These reports were corroborated by a double-blind placebo-controlled trial involving highly treatment-resistant patients that found both good tolerability and a greater response to repeated administration of IV CMI (gradually titrated to 250 mg) compared with placebo. Responder patients responded rapidly (relative to oral treatments), and the response rate exceeded 50% after 1 month [62]. Other studies investigated whether a "pulse-loading" regimen (reaching a high dose in a short period of time) of IV clomipramine would achieve a faster clinical response. A pilot double-blind, placebo-controlled study comparing IV vs. oral clomipramine pulse-loading treatment (150 mg the first day followed by 200 mg the second day) reported a significant response 4.5 days after the second "pulse-loaded" infusion [119]. These results are consistent with a subsequent open-label study of drug-naïve patients that showed a faster response onset for IV pulse-loaded treatment (evident after 1–2 weeks) compared to gradual dosing IV treatment (evident after 5–8 weeks) [118]. However, a subsequent controlled study directly comparing IV vs. oral clomipramine pulse-loading in treatment-resistant patients failed to find differences in response onset (evident after 2 weeks for both arms) or a correlation between clomipramine/desmethylclomipramine plasma levels and clinical response (as had been observed in the previous trial by Fallon and colleagues) [115].

An open-label study of **IV citalopram** in 39 treatment-resistant patients reported a 59% response rate after only 3 weeks of IV treatment that was maintained at 12 weeks [165]. Also, a small case series of 5 severe, treatment-resistant OCD patients reported that IV pulse-loading (40 mg IV for 3 days followed by 80 mg IV for 18 days, then switching to oral 80 mg/day) was rapidly and lastingly effective in 3 out of the 5 patients, with no significant side effects (QTc prolongation or sodium plasma levels increase), both during the acute and the 1-year follow-up period [81].

In summary, IV SRI treatments (clomipramine and citalopram) may represent an effective and safe strategy for patients insufficiently responsive to oral SRIs. However, despite several studies over the last 20 years that reported promising results of this approach, further controlled trials comparing IV SRI treatment to other more evidence-based strategies, such as augmentation with dopamine-blocking medications or psychotherapy, are required to clarify where this strategy might stand in a sequential approach to treatment-resistant OCD.

2.2. Serotonin receptor modulators

2.2.1. Serotonin receptor antagonists

Although primarily used as an antiemetic, the serotonin 5-HT3 receptor antagonist **ondansetron** has been examined as an augmentation treatment in OCD. Mechanistically, ondansetron has been suggested to indirectly inhibit cortico-mesolimbic dopamine release, as 5-HT3 receptors are co-localized with gamma-aminobutyric acid (GABA) interneurons in the ventral tegmental area [36,166]. A single-blind 12-week study of ondansetron in combination with SSRIs and antipsychotics found that 64.3% of patients examined (9/14) responded to treatment (≥25% reduction in total Y-BOCS score and Clinical Global Impression Scale-Improvement (CGI-I) score of 1 or 2), and no worsening of OCD symptoms or serious adverse events were reported [166].

In addition, evidence from a randomized control trial has demonstrated superiority of ondansetron over **granisetron** (another serotonin 5-HT3 receptor antagonist) as an adjunctive treatment to SSRIs augmented with an antipsychotic [221].

Ondansetron has also been examined in RCTs as an augmentation treatment for patients receiving SSRI monotherapy. Two studies found significant increases in improvement with ondansetron vs. placebo when used as an adjunct to fluoxetine [224] or fluvoxamine [84]. In an 8-week RCT examining the efficacy of ondansetron in combination with fluoxetine, ondansetron—compared to placebo—significantly reduced Y-BOCS scores at weeks 2 and 8 [224]. A similar 12-week RCT reported a significantly higher response rate at 8 and 12 weeks in patients augmented with ondansetron compared to placebo [218]. Critiques of these studies—noting for example the lack of information about the treatment history of enrolled participants given the high response rates reported—have suggested cautious skepticism about these results [15] and a 'real world' case series reported disappointing outcomes with ondansetron augmentation [101]. Nonetheless, current evidence suggests that ondansetron has the potential to be a novel adjunctive medication for treatment-resistant OCD. A placebo-controlled trial of higher dose ondansetron in OCD and tic disorder patients is ongoing (NCT03239210).

Notably, although ondansetron has been well tolerated in these studies, prescribing clinicians should be aware that it may contribute to QTc prolongation; it should be used with caution in patients at risk for arrhythmia or when combined with other medications that may prolong the QTc interval.

2.2.2. Serotonin receptor agonists

Buspirone is an azapirone compound with complex actions mainly on serotonergic and dopaminergic receptors. It is a full agonist at presynaptic 5-HT1A autoreceptors, a partial agonist at postsynaptic 5-HT1A receptors, and an antagonist of the D2 subtype of the dopamine receptor. Its use in OCD has typically been as an augmentation strategy aimed at enhancing 5-HT transmission. A very early open trial [96] did not find buspirone useful in OCD, but a later double-blind, randomized study [173] found efficacy similar to that of clomipramine. Two open-label trials found that buspirone as adjunctive therapy to fluoxetine seemed effective in the treatment of patients unresponsive to fluoxetine alone [97,131]. However, subsequent studies in treatment-resistant OCD (two of them double-blind), did not replicate these findings, and showed no significant differences with buspirone added to fluoxetine [76], fluvoxamine [142], or clomipramine [178]—although in the latter study the authors suggested that it could be useful for a subgroup of patients.

Beginning in the mid 1990's, anecdotal reports have suggested potential beneficial effects of **psilocybin** (a potent 5-HT_{1A} and 5-$HT_{2A/2C}$ agonist) on obsessive-compulsive symptoms [127,250]. The only available open-label trial showed a marked reduction during the 24 h of the study procedure, with different doses of psilocybin in each of the 9 OCD patients [150]. Three trials of psilocybin for OCD are ongoing: two active-comparator controlled trials (NCT03300947; NCT03356483) and one trial of psilocybin-assisted psychotherapy (NCT04882839). The latter protocol will include 15 therapeutic sessions: 12 for psychological preparation and three experiential sessions under the influence of psilocybin.

2.3. Supplements and phytochemicals with putative serotonergic action

Tryptophan is the amino acid precursor of the neurotransmitter serotonin. Studies of tryptophan depletion in OCD patients have generally not found a specific worsening of obsessional symptoms, although patients have experienced feelings of distress or worsening mood [29,120]. On the other hand, IV tryptophan administration elicited neuroendocrine responses in OCD subjects, such as increased plasma growth hormone [66], and an open-label study found improvement in clomipramine-resistant OCD patients when treated with L-tryptophan augmentation [189]. Another open-label report [33] found that tryptophan significantly reduced obsessive-compulsive symptoms when added to a combination of pindolol and an SRI, however, the evidence for its efficacy in OCD remains very weak.

Inositol is a precursor in the phosphatidylinositol second-messenger cycle, and has been proposed as a potential intracellular modulator of serotonin receptor signaling [188]. An early double-blind, controlled, crossover trial of 18 g/day inositol vs. placebo suggested that it was effective in OCD [72]. However, two subsequent studies in more treatment-resistant patients—an open-label trial [215] and a double-blind trial [72] using inositol as an adjunctive treatment—did not find this augmentation strategy effective.

Different herbal remedies or phytochemicals (*Crocus sativus* and crocin in general, *Silybum marianum* or milk thistle, Echium amoenum, *Hypericum perforatum* or St. John's wort, *Withania somnifera*, curcumin, *Citrus aurantium*, *Benincasa hispida*, *Colocasia esculenta*, *Valeriana officinalis*, *Lagenaria siceraria*, Echium amoenum) that purportedly act on the serotonergic system have been suggested as therapies for OCD, although evidence for their efficacy is very slim or nonexistent [20,206,234]. Among these, one, **St. John's wort** (*Hypericum perforatum*) has received somewhat more attention. Although an open-label study found significant improvement with St. John's wort (L. vH. [236]), a subsequent double-blind, placebo-controlled study by the same authors found no significant difference in efficacy between St. John's wort and placebo [109].

3. Norepinephrine serotonin agents

Mirtazapine is an antidepressant that increases noradrenergic transmission by blocking the presynaptic alpha-2 adrenergic receptor of noradrenergic neurons. It additionally increases serotonin neurotransmission by blocking alpha-2 receptors on serotonin neurons (where they function as presynaptic heteroreceptors) and serves as a serotonin 5HT2A, 5HT2C, and 5HT3 receptor antagonist. Pallanti et al. [168] conducted a single-blind trial that found an earlier onset of response in OCD patients receiving citalopram plus mirtazapine compared to citalopram plus placebo, At 12 weeks, however, there was no significant efficacy difference between the two groups. A subsequent open-label study with a double-blind discontinuation phase [113,117], however, found that mirtazapine monotherapy was superior to placebo.

Pindolol is a beta-adrenergic blocking agent, but also a potent presynaptic serotonin 5HT1A receptor antagonist that can increase serotonin transmission. An open-label report [33] found pindolol augmentation of an SRI ineffective, but that a combination of pindolol and tryptophan significantly reduced obsessive-compulsive symptoms when added to an SRI. One double-blind, placebo-controlled study found pindolol effective when added to paroxetine [47], while another double-blind, placebo-controlled study with pindolol added to fluvoxamine found no significant differences compared to placebo and no shortening of the latency of the anti-obsessional response to fluvoxamine [154]. A recent meta-analysis [208] suggested that pindolol might nonetheless be useful as an OCD treatment augmentation strategy.

4. Norepinephrinedopamine agents

Recent years have brought significant research attention to the potential for psychedelic and other abusable drugs to produce rapid therapeutic effects in mental disorders [240]. This literature also extends back several decades and includes psychostimulant drugs. Since the early 1980s, four double-blind, controlled studies have explored the use of psychostimulants in OCD, and all have shown meaningful and fast symptom relief. The first, a double-blind placebo-controlled crossover study published in 1983, involved single doses of **d-amphetamine** (30 mg/d) and placebo administered to 12 subjects (mean age = 33.1 years) with severe OCD [92]. Significant, almost immediate improvement was

observed in 11 subjects, as measured by self and clinician ratings conducted 5 h after study drug administration.

A second double-blind placebo-controlled crossover study involved 11 subjects (mean age = 33.5 years) with OCD who were treated with randomly ordered d-amphetamine (30 mg/d), **methylphenidate** (40 mg/d), or placebo [98]. At 4 h post study drug administration, d-amphetamine produced a statistically significant reduction in the Comprehensive Psychopathological Rating Scale - Obsessive-Compulsive Subscale score compared to methylphenidate and placebo (47% vs. 27% vs. 17%).

A third double-blind study compared augmentation with d-amphetamine (30 mg/d) to high-dose **caffeine** (300 mg/d) in 24 subjects (mean age = 40) with treatment-resistant OCD who were on a stable, adequate dose of a SRI for at least 12 weeks [114]. At the end of week 1, 50% of subjects in the d-amphetamine group and 58% of subjects in the caffeine group responded (≥ 20% reduction in Y-BOCS score). Further, 33% of subjects in the d-amphetamine group and 42% in the caffeine group met criteria for full response (≥35% reduction in Y-BOCS score and CGI-I of much improved or very much improved). At the end of week 5, 33% and 50%, respectively, were full responders. The study drugs were well tolerated: no subject discontinued due to side effects, and none reported a euphoric 'high' or cravings. In explaining how both medications might have produced a response, the authors argue that both increase dopamine neurotransmission in the brain and that caffeine also increases tryptophan and serotonin levels. Finally, the authors argue that the response is unlikely to represent a placebo effect, because it was much more robust than the documented placebo effect in OCD trials and was sustained over the course of the study.

More recently, an 8-week augmentation RCT compared extended-release methylphenidate (MPH-ER) (36 mg/d) vs. placebo in 44 adults (mean age = 24.7 years; 66% males) with OCD insufficiently responsive to at least 8 weeks of adequately dosed fluvoxamine [252]. Baseline Y-BOCS scores were greater than 20, and the average duration of symptoms was 5.7 years. Intent to-treat analysis revealed significantly superior response rates (Y-BOCS reduction ≥25%) in the MPH-ER + fluvoxamine group vs. placebo + fluvoxamine group (59% vs. 5%; $P < .001$). Additionally, a significant decrease in Y-BOCS scores in the MPH-ER + fluvoxamine group vs. MPH-ER + placebo group was detected from the second week ($F = 8.16$; $p = .005$). Overall, MPH-ER was well tolerated.

Taken together, these studies suggest that stimulants can be a safe, effective, fast-acting pharmacotherapy augmentation option in treatment-resistant OCD, although larger and longer-term studies are required, including to assess continued efficacy and misuse potential over time. That stimulants may be helpful in OCD seems counterintuitive; compared to ADHD, a condition well known to respond to stimulants, OCD shows the opposite frontostriatal activity pattern (hyperactivation vs. hypoactivation) and sits on the opposite end of the compulsivity-impulsivity behavioral spectrum [3]. Still, the neuropsychological literature has shown that the two conditions display similar executive function deficits, including in response inhibition, attention allocation, and cognitive set-shifting [3], possibly pointing to some shared pathophysiology. Such deficits in OCD may underlie the beneficial effects of stimulant medications. For example, caffeine has recently been shown to mitigate experimentally-induced distress and compulsive cleaning urges in individuals with high contamination fears, and this effect is hypothesized to reflect a beneficial impact of caffeine-induced arousal on inhibitory control [157]. Lastly, evidence suggests dysregulated dopamine neurotransmission in cortico-striatal-thalamo-cortical pathways in OCD, and stimulants' effects include dopamine reuptake inhibition [111,252] and stimulation of presynaptic autoreceptors [216]. In clinical practice, patients with OCD who benefit from stimulants often describe feeling less distracted by intrusive thoughts and an enhanced ability to concentrate on non-OCD matters, perhaps mirroring the clinical effect seen in ADHD treatment.

5. Dopamine serotonin norepinephrine multimodal agents

If OCD patients are resistant to SRIs, evidence supports augmentation with atypical antipsychotics as a treatment [79,80]. This approach reflects the hypothesis that OCD is characterized by excessive striatal dopamine signaling, supported by multiple studies reporting reduced D2/D3 receptor binding in the striatum of OCD patients [51,52,176,213]. Drugs classified as atypical antipsychotics have numerous mechanisms of action, including dopamine blockade, antagonism at 5-HT_{2A} and other serotonin receptors, and adrenergic, muscarinic and histaminergic effects, yet their efficacy in OCD appears attributable primarily to their shared dopamine receptor D2/D3 antagonist effects [57].

Several meta-analyses examining antipsychotic augmentation have demonstrated the superiority of antipsychotics over placebo [34,55,56,110,253,254]. Of the atypical antipsychotics, **risperidone** has been demonstrated as the most effective in treating OCD symptoms in meta-analyses [55,110,253,254]. **Aripiprazole** has also been shown to be effective vs. placebo [56,253,254], and a meta-analysis by Veale et al. [246] showed higher efficacy for aripiprazole over risperidone as augmentation therapy for OCD. **Quetiapine** and **olanzapine** have been examined, although the results are inconsistent and multiple meta-analyses have been unable to demonstrate their efficacy vs. placebo [34,55,56,110]. **Paliperidone** has been studied in treatment-resistant OCD patients in one randomized, placebo-controlled trial of 8 weeks; paliperidone-treated individuals showed significant baseline to post-treatment reductions in Y-BOCS, yet while paliperidone-treated participants had numerically greater reductions in Y-BOCS scores than placebo-treated individuals (reduction of nearly 8 points vs. 4 points), between group differences did not meet the threshold for significance [231]. **Clozapine** has not been tested in placebo-controlled trials, and was found ineffective as monotherapy for treatment-resistant OCD in an open label study [141]. The evidence for **haloperidol** in OCD is conflicting, as several studies have demonstrated superiority to placebo [34,56,253,254], but others have produced inconsistent findings [55]. Of note, case report, experimental, and epidemiologic evidence supports the possible precipitation of obsessive-compulsive symptoms by atypical antipsychotics, particularly clozapine, in individuals with primary psychotic disorders [69,128,170]. However, systematic reviews have not found atypical antipsychotic medications to worsen symptoms in individuals with OCD, and as such this risk appears relevant to patients with a primary psychotic disorder diagnosis [205].

When considering patients with comorbid tic disorders, several of the aforementioned meta-analyses demonstrated the effectiveness of antipsychotic augmentation, independent of whether patients had tics [55,110]. Dold and colleagues [56] did not include patients with comorbid tic disorders in their analysis. With the exception of two meta-analyses—one where antipsychotics were not significantly effective in patients with tics [253,254]; and another where patients with tics responded more positively to antipsychotics [34]—the evidence overall suggests that antipsychotic augmentation is an effective treatment strategy for treatment-resistant OCD, regardless of tic comorbidity.

Although antipsychotic augmentation is currently the first-line treatment for patients who are resistant to SRIs [67], augmentation with antidopaminergic agents such as antipsychotics has only been found effective in one-third of patients with treatment-resistant OCD [79,80]. Considering the limited availability of long term data on the safety or efficacy of antidopaminergic medication in OCD, and given the significant long term risks of dopamine blocking medications, including particularly cardiometabolic risks and risk of tardive extrapyramidal symptoms, care should be taken not to prolong medication trials in the absence of clear evidence of benefit. Alternative approaches for treatment-resistant OCD remain needed.

6. Dopamine agents

The literature on augmentation treatment of OCD with dopamine antagonists vastly surpasses literature on interventions that might increase dopamine signaling; yet, together with evidence of benefit from psychostimulant treatments, a trial of the directly pro-dopaminergic intervention **tolcapone** further suggests that dopamine agonist approaches may offer OCD symptom relief. Tolcapone is a catechol-O-methyltransferase (COMT) inhibitor used in the treatment of Parkinson's disease and enhances dopamine signaling of prefrontal cortical networks. Tolcapone has been studied in OCD in a double-blind, placebo-controlled crossover trial. The study found that tolcapone 200 mg was significantly superior to placebo (16.4% vs. 3.6% symptom reduction) and was equally well tolerated. Of note, 25% of the included patients were concurrently receiving stable medications (SSRIs or venlafaxine) and 80% had had treatment for OCD (SSRI or psychotherapy) in the past [77].

The experimental literature suggests some basis for the paradoxical observation that both dopamine agonist and antagonist drugs may benefit OCD. Enhanced error-signaling is associated with OCD across a number of imaging and electroencephalography (EEG) paradigms and is thought to originate with striatal dopaminergic responses [193]. In a neuroimaging study of anterior cingulate cortex prediction error responses in individuals with OCD, strikingly, both a dopamine antagonist medication (amisulpride) and a dopamine agonist medication (pramipexole) normalized exaggerated error response [155]. While pramipexole has not been studied for clinical effects in OCD and, like other D3 agonist drugs, has been associated with treatment-emergent impulse control disorders, the observation that dopamine modulators other than the atypical antipsychotics may address pathophysiologic mechanisms relevant to OCD raises the hope that dopaminergic treatments with less risk of adverse effects may ultimately be viable options for treatment-resistant OCD.

7. Glutamate agents

Glutamate is a chemical messenger that sends signals to nerve cells by binding to AMPA (alpha-methyl propionic acid), NMDA (N-methyl-D-aspartate), or metabotropic receptors. Glutamate is important in key cellular processes, including development, learning and memory, and neurodegeneration. Several lines of evidence suggest that dysregulation of glutamate—the main excitatory neurotransmitter in the brain—may contribute to OCD [67,182]. Significantly elevated levels of glutamate have been reported in the cerebrospinal fluid levels of treatment-naïve OCD participants compared with controls [31,40]. Increases in glutamatergic compounds in the caudate, detected using magnetic resonance spectroscopy, normalized with successful SRI treatment in pediatric OCD participants [199]. Human genetic studies have associated OCD with genes that code for proteins important in glutamatergic transmission (e.g., SLC1A1 and GRIN2B) [180]. Animal model systems have been applied to studying underlying pathologic repetitive behaviors [10,41]. A noncompetitive antagonist of NMDA, MK-801, exacerbates perseverative behaviors in a transgenic mouse model of OCD [144]. By disrupting glutamatergic transmission (i.e., by deleting a postsynaptic scaffolding protein called SAPAP3) [32,125], SRI treatment reduced compulsive grooming behavior in mice [249] as did the NMDA receptor antagonist ketamine [48]. Finally, agents that modulate glutamate ameliorate OCD symptoms in open and controlled trials, as summarized below.

7.1. Glutamate NMDA antagonist drugs

Although primarily used to treat Alzheimer's disease dementia, the NMDA receptor antagonist **memantine** has been tested as an augmentation treatment in OCD. Early case studies and open-label trials reported benefit [2,21,65,172,185,230]. At the same time, four small RCTs of memantine conducted in Iran showed high response rates (100% in one study), which are inconsistent with the literature [73,83,149,203]. Larger studies in diverse geographical areas are needed to reconcile these findings and guide consideration of memantine treatment [16].

Ketamine, a dissociative anesthetic drug and noncompetitive antagonist of the NMDA receptor, has generated enthusiasm in psychiatry due to the discovery of its rapid-onset antidepressant effect [28,251]. A review and meta-analysis encompassing 147 ketamine-treated participants reported that the ketamine antidepressant effect is rapid, but transient [160]. Ketamine has higher affinity for the NMDA receptor and shorter half-life than memantine [99]. A single intravenous dose of low-dose ketamine had rapid (in hours) and robust benefit in a case report [195]. A subsequent randomized controlled crossover study reported a single intravenous infusion of low dose ketamine benefitted unmedicated OCD participants [196]. In contrast, in an open-label trial of OCD adults with multiple comorbidities, depression symptoms improved while OCD symptom improvement was minimal [256]; two patients developed suicidal ideation [162]. A larger Stanford Medical School RCT of ketamine in unmedicated OCD patients has been completed (NCT02624596), but results are not yet published. A retrospective chart review of the clinical utility of repeated intravenous ketamine infusions showed benefit for a subset of patients [222]. Limited data exist for intranasal ketamine in OCD [5,197]. A small open-label study explored whether exposure-based CBT could extend the effects of a single IV dose of ketamine [198]. Given that the long-term effects of ketamine are unknown and ketamine is a drug of abuse, appropriate safeguards are needed, including side effect monitoring and screening for history of substance abuse [204].

The morphinan-class drug **dextromethorphan** is a noncompetitive NMDA antagonist, similar to memantine in receptor affinity, and is available over-the-counter in most countries for indicated use as a cough suppressant. In addition to its NMDA antagonist activity, dextromethorphan is a weak serotonin and norepinephrine reuptake inhibitor, and, like fluvoxamine, has significant sigma-1 agonist activity. Dextromethorphan is used in veterinary practice to treat compulsive behavior [54,192], but use in humans is complicated by dextromethorphan's rapid CYP2D6-mediated metabolism into dextrorphan, a metabolite which is rapidly gluconuridated and thus unavailable to the central nervous system (CNS). The prescription drug Neudexta—approved in Europe and the US for the neurologic indication of pseudobulbar affect—preserves dextromethorphan levels by combining dextromethorphan with low doses of the potent CYP2D6 inhibitor quinidine [235]. While no data yet support use of dextromethorphan in OCD, an open-label pilot study testing the combination of dextromethorphan and fluoxetine—also a potent CYP2D6 inhibitor—as a therapy for OCD and related disorders is currently recruiting (NCT04899687).

Like ketamine, the inhaled dissociative anesthetic gas **nitrous oxide** has both NMDA antagonist and opioid agonist effects [100]. Further suggesting similarity to ketamine, nitrous oxide has rapid antidepressant effects when inhaled for one hour at 50% concentration [158]. A recent replication study confirmed this antidepressant effect and demonstrated efficacy even at 25%, a gas concentration resulting in minimal subjective effects [159]. Given nitrous oxide's favorable safety profile, tolerability, and widespread acceptance in dental and obstetric anesthesia, a randomized placebo-controlled clinical trial (NCT03826693) is testing a one-hour 50% nitrous oxide inhalation as a rapid-acting intervention in OCD.

7.2. Glutamate NMDA receptor modulating drugs

N-acetylcysteine is an orally bioavailable precursor to L-cysteine that increases levels of the antioxidant molecule glutathione, which may bind to and modulate AMPA and NMDA receptors. N-acetylcysteine has been reported to be of benefit in some cases of refractory OCD [122]; outcomes in four RCTs, however, have been mixed [7,46,174,207].

Minocycline is a tetracycline antibiotic (commonly prescribed for acne) possessing anti-glutamatergic and anti-inflammatory activities in the brain. These activities are possibly achieved through diverse mechanisms involving both microglia and microbiota modulation. Indeed, minocycline reduces microglia activity and therefore microglia-mediated NMDA toxicity, and also enriches anti-inflammatory species in the gut microbiome [23,212,239]. The first open-label study in OCD did not find significant effects in a small sample of adult patients with the exception of two patients with early-onset OCD, one with comorbid hoarding disorder [194]; a more recent 10-week controlled study of minocycline 200 mg augmentation of fluvoxamine found significant superiority compared with placebo [60]. Notably, two unpublished trials are reported in the US clinicaltrials.gov register: a small open-label trial in adolescents ended without results being reported (NCT00515255), and a controlled trial in adolescent and young adults with OCD concluded in 2019 (NCT01695291).

7.3. Glutamate channel blocker drugs

Lamotrigine is a sodium channel blocker that is a first-line drug for seizures and approved for treatment of bipolar I and II. In OCD case reports, lamotrigine augmentation produced mixed benefit [18,89,121,242]. Two small RCTs report benefit of lamotrigine augmentation in OCD participants [37,106]. Of note, lamotrigine carries a black box warning about life-threatening dermatologic reactions, including Stevens-Johnson syndrome, and patients should be instructed to seek medical attention for any unexpected skin rash.

Pregabalin is a gamma-aminobutyric acid analog approved for epilepsy, neuropathic pain, fibromyalgia, and generalized anxiety disorder. It binds the $\alpha_2\delta$ subunit of voltage-gated calcium channels with high affinity, reducing calcium currents and thereby the release of several neurotransmitters, including glutamate [147]. Because of this putative anti-glutamatergic effect, pregabalin has been tested anecdotally in OCD patients. It produced high response rates in a small 8-week, open-label trial involving 10 treatment-resistant patients (with a dose range of 225–675 mg) [164]. Recently, a 12-week double-blind placebo-controlled trial of pregabalin augmentation (mean dose of 185 mg) to sertraline in 42 treatment-resistant OCD patients reported good tolerability and significant superiority to placebo (57% vs. 7% responders) [151]. Another controlled trial of pregabalin for OCD patients has been completed at the McMaster University in Canada, but results are not yet published.

7.4. Drugs with mixed anti-glutamate activity

Topiramate, a carbonic anhydrase inhibitor, is used to treat epilepsy and migraine headache. In OCD, initial case studies and open-label trials of topiramate augmentation were promising [201,244,245]; subsequent small RCTs, however, have had mixed outcomes [6,27,152].

Riluzole is a benzothiazole derivative used to treat amyotrophic lateral sclerosis. Riluzole is hypothesized to modulate glutamate through several mechanisms, including reducing presynaptic glutamate release and stimulating glutamate reuptake [183]. In OCD adults, riluzole augmentation showed promise in a case, in a retrospective case series, and in an open-label trial [43,44,183] Two subsequent small controlled studies have reported mixed results [59,181]. In pediatric OCD, a controlled study did not show efficacy [78]. Given the small size of these studies, large-scale controlled studies are needed before drawing firm conclusions on riluzole augmentation efficacy in pediatric and adult OCD populations.

A prodrug of riluzole, called **troriluzole**, was designed to improve bioavailability, safety, and dosing. Troriluzole can be actively absorbed in the stomach, eliminating the need for fasting, enabling once-daily dosing, and bypassing first-pass metabolism, thereby reducing burden on the liver. Troriluzole is hypothesized to modulate glutamate levels by enhancing the expression and function of excitatory amino acid transporters and decreasing presynaptic glutamate release. In a proof-of-concept study, 248 OCD outpatients with inadequate response to standard-of-care medications were randomized to receive troriluzole or placebo in addition to their OCD medications. Statistically significant differences were not present at the week-12 primary outcome time; however, an efficacy signal as early as week 8 ($p < .05$) was observed. Improved treatment effects and larger effect sizes were reported in patients with higher baseline disease severity [8]. Together, these data encouraged the sponsors to launch a Phase III multisite study (NCT04693351).

8. Opioid agents

8.1. Opioid agonists

The striatal system has been implicated in the pathophysiology OCD and possesses a high concentration of opioid receptors [156]. This helps explain the interest, now over two decades old, in testing mu receptor agonists in treatment-resistant OCD. A 1997 report [248] described five treatment-resistant OCD patients who responded to oral **morphine** (20–40 mg/d), dosed every 5 to 8 days. This inspired a double-blind crossover trial comparing once-weekly oral morphine (15–45 mg/d), lorazepam (0.5–2 mg/d) and placebo in patients with OCD who had a Y-BOCS score $\geq$ 20 and had failed at least two adequate SRI trials [113,117]. Thirty percent of subjects assigned to oral morphine responded ($\geq$ 25% reduction in Y-BOCS score), compared to 17% of subjects assigned to lorazepam and 0% of subjects assigned to placebo. The morphine responders described noticing improvement the day after taking morphine and reported it lasting for 2 to 5 days. No euphoria, disinhibition, or medication-seeking behavior was noted, although one subject, a responder, confessed after study-end to long-standing hydrocodone use disorder.

An open-label trial of the opioid medication **tramadol** enrolled seven subjects who had failed a mean of 2.9 adequate SRI trials [220]. The mean Y-BOCS score decreased 26%, with several subjects responding within 1 week. Among completers, the mean tramadol dose was 254 mg/d. Tramadol was well tolerated, although one subject dropped out due to nausea. Other cases of successful treatment with tramadol were subsequently reported [74]. Given reports of serotonin syndrome when tramadol (itself a modest SRI) is combined with SSRIs [25], caution should be exercised when using tramadol for augmentation purposes.

The partial mu receptor agonist **buprenorphine** has also received research attention. An open-label study reported that four of seven subjects with treatment-refractory OCD experienced a $\geq$ 40% decrease in Y-BOCS score when sublingual buprenorphine (400–600 μg/d) was added to their SRI [126]. Response was typically observed within two days of drug initiation. Of note, responders' symptoms rapidly worsened when buprenorphine was stopped, and improved again after it was resumed. A subsequent 12-week RCT [9] randomized 43 participants with refractory OCD on stable and adequately dosed SRIs to either adjuvant sublingual buprenorphine (2–4 mg) or placebo. The Y-BOCS, obtained at baseline and weeks 3, 9, and 12, revealed substantial improvements at weeks 3 and 9 in the buprenorphine group compared to placebo, without further improvement at week 12. The Y-BOCS reductions in the placebo group were not statistically significant.

8.2. Opioid antagonists

How opiates might rapidly alleviate OCD remains unknown, but putative explanations include mu-opioid receptor-mediated disinhibition of midbrain serotonergic neurons in the dorsal raphe nucleus and periaqueductal gray via suppression of inhibitory GABA-ergic transmission, inhibition of serotonin-induced glutamate release in the medial prefrontal cortex, rapid activation of c-fos and jun-B genes in the dorsal raphe, caudate nucleus, and thalamus, and rapid upregulation of medial striatum proteins involved in mitochondrial respiration and cytoskeletal

functions [113,117]. It is worth noting that opioid antagonist approaches have not appeared to be helpful in OCD. While naltrexone has been suggested to have potential benefit in a range of impulse control disorders, and thus possibly in OCD [71], only one small double-blind crossover study has explored this intervention, and in this study naltrexone did not offer clinical benefit [14].

Taken together, the opiate literature in OCD does not suggest a high risk for medication-seeking behavior or de novo prescription drug use disorders in the populations studied, but long-term data are lacking, and carefully excluding patients with a history of substance use disorders as well as closely monitoring for misuse during treatment would seem crucial. In OCD patients with are on replacement therapy with buprenorphine for comorbid opiate use disorder, monitoring for any opiate-mediated effects on OCD and adjusting OCD medications accordingly would seem indicated.

9. Anti-inflammatory agents

Autoimmunity was initially implicated in the OCD pathophysiology in the early 1990s, with the pediatric autoimmune neuropsychiatric disorder associated with group A beta-hemolytic streptococcus (GABHS), initially named PANDAS, then renamed pediatric acute neuropsychiatric syndrome (PANS) [257,258]. The nature of these conditions is still debated; however, several studies and meta-analyses consistently showed a fivefold higher rate of anti-basal ganglia antibodies in both pediatric and adult OCD patients compared to controls [175]. Also, a recent Swedish nationwide survey including more than 30,000 OCD patients reported up to 43% increased risk for comorbid autoimmune disease (not limited to Streptococcus-related conditions) and a higher prevalence of auto-immunity even in first-, second-, and third-degree healthy relatives of individuals with OCD compared to the general population [134]. Finally, while the presence of abnormal cytokine levels in OCD patients is controversial, recent studies confirm the presence of inflammatory markers in the adult OCD brain, specifically within the cortico-striatal-thalamo-cortical regions implicated in OCD pathophysiology [19,45]. While early studies of antibiotics for PANS patients were not encouraging, research on anti-inflammatory and immune-modulating agents has shown promising initial results in both adults and children with OCD.

9.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

Celecoxib is an NSAID that acts by inhibiting cyclooxygenase-2 (COX-2), the enzyme responsible for oxidation of arachidonic acid to prostaglandins. COX-2 is expressed by glutamatergic neurons across the brain, and its inhibition by COX-inhibitors exerts neuroprotective actions by suppressing neuroinflammatory responses that produce oxidative stress and neuronal apoptosis [225]. Double-blind placebo-controlled trials from different groups in Iran showed greater efficacy of celecoxib compared to placebo and good tolerability of celecoxib (400 mg) as an augmentation to SSRIs (fluvoxamine and fluoxetine) [209,219]. However, these results have some limitations: in both trials, patients started SSRIs and celecoxib at the same time, SSRIs were underdosed, and the trial duration was too short (8–10 weeks) to draw firm conclusions about celecoxib's effect compared to SSRIs alone [80]. Interestingly, two trials of celecoxib for OCD are ongoing (NCT04673578; NCT04786548). The first is a 12-week controlled trial in children and youth with OCD, while the second is an open-label trial in adult OCD patients; both aim to identify inflammatory biomarkers predictive of celecoxib response.

9.2. Other anti-inflammatory and immunomodulator agents

Other anti-inflammatory and immunomodulating agents are under investigation in ongoing clinical trials. **Rituximab** (a monoclonal antibody that binds a surface protein of B-lymphocytes prescribed for lymphoid malignancies and autoimmune diseases) is under investigation in a double-blind placebo-controlled single infusion trial in OCD patients with evidence of immune system alterations (NCT04323566). **Naproxen** (an NSAID with nonselective COX-1/2 inhibition activity) and **Octagam 5%®** (a set of intravenous immunoglobulins) are under investigation for children with PANS/PANDAS in an RCT and in an open trial, respectively (NCT04015596; NCT03348618).

The microbiota-gut-brain axis has been implicated in the pathophysiology of several neuropsychiatric disorders (mood disorders, psychoses, and autism spectrum disorders, among others), yet for OCD this research is still in its early stages [79]. A recent preclinical study found correlation between compulsive-like behaviors in the deer mouse and altered gut microbiota composition. Similarly, one clinical study in children with PANS/PANDAS and one in adult OCD patients showed increased pro-inflammatory and decreased anti-inflammatory bacteria species [186,210,241]. Although no studies have been published on **probiotics** supplementation in OCD, a pilot placebo-controlled study using healthy volunteers found that subjects taking *Lactobacillus helveticus* and *Bifidobacterium longum* (two bacteria having anti-inflammatory, anxiolytic, and anti-depressant effects in animal and clinical studies) reported a reduction of obsessive-compulsive symptoms compared to volunteers taking placebo [146]. A 12-week placebo-controlled trial of probiotic supplementation with this formula in OCD patients has been terminated, and to-date results have not been published (NCT02334644).

10. Lithium

Lithium is a modulator of intracellular signaling cascades, can increase serotonin and acetylcholine activity, and has neurotrophic and neuroprotective effects. However, which of these potential mechanisms mediates lithium's therapeutic effects in neuropsychiatric illness remains insufficiently understood. Recent speculation regarding lithium's action in OCD has emphasized the modulation of glumatergic or inflammatory pathways via Wnt/beta-catenin signaling, which lithium upregulates by inhibiting GSK3beta [243]. Although an early report [189] found lithium effective as adjunctive therapy to clomipramine in treatment-resistant OCD patients, two double-blind placebo-controlled trials of lithium augmentation of fluvoxamine in OCD patients unresponsive to fluvoxamine alone did not support its efficacy [143]. A double-blind crossover study of lithium adjunctive to clomipramine also found no meaningful improvement in OCD symptoms, but reported a 25% or greater reduction in depression scores in 44% of patients [179]. However, another study [232] found a good response in four cases of episodic OCD (characterized by acute onset, prominent feelings of shamefulness, short duration of OCD symptoms, and older age), and the authors suggested that episodic OCD might be a possible expression of bipolar disorder. They concluded that given the high comorbidity between OCD and bipolar disorder [13], which may reflect antidepressant use in OCD [30], mood stabilization should be the primary goal in the treatment of these patients. They suggest aripiprazole augmentation of lithium carbonate as the best option, and note that the addition of SRIs may be necessary only in a minority of bipolar disorder patients with treatment-resistant OCD. In these patients, where OCD is comorbid with bipolar disorder, CBT should be tried before antidepressants whenever possible.

11. Cannabinoid agents

Available data on cannabinoids for OCD are limited. Early studies reported a significant decrease in OCD symptoms after treatment with **dronabinol** (tetrahydrocannabinol, THC) in an anecdotal series of four patients, for two of whom it was added to clomipramine [42,211,233]. A recent 4-week open trial involving 11 drug-naïve OCD patients explored **nabilone** (a synthetic form of THC) as a monotherapy and as an add-on to exposure and response prevention (ExRP) therapy. This study found

the nabilone-ExRP combination superior to nabilone alone, which on its own led to very little symptom improvement [104]. Moreover, a recent placebo-controlled 14-patient study investigating the acute effect of a single administration of various smoked cannabis formulations (with different combinations of THC and cannabidiol) reported no difference compared to placebo [103]. Conversely, in a retrospective online survey, a majority of OCD patients who smoke cannabis reported subjective OCD symptom improvement, and patients using medical cannabis (auto-defining themselves as OCD patients in a mobile app) reported an acute positive effect of cannabis products on their OCD symptoms [105,138]. For patients with comorbid Tourette syndrome and OCD, available data are conflicting: retrospective studies reported positive effects of cannabis use on OCD symptoms while controlled trials did not [1,148,153]. Of note, two cannabinoid trials are ongoing: a 2-week open-label trial is evaluating the effects of cannabidiol in 15 OCD patients (NCT04978428), and a double-blind, placebo-controlled single-dose nabilone trial involving 60 OCD patients will assess the drug's cognitive, psychophysiological, and neuroimaging effects (NCT04880278).

12. Conclusions

No formal recommendation is made here as to which augmentation or alternative pharmacologic strategy for treatment-resistant OCD might best be tried, in which order, nor where in a potential sequence of escalating pharmacologic and non-pharmacologic care strategies these options might be employed. Dopamine antagonist medications remain the best evidenced intervention, yet they benefit only approximately one-third of patients who try them and have a complex long-term safety profile. The evidence base for the varied glutamatergic interventions is less robust, but a growing literature supports the safety profile and efficacy of many of these drugs. Finally, despite the very limited evidence to date, anti-inflammatory interventions are emerging as a potentially effective approach for treatment-resistant patients.

As in other areas of psychiatric medicine, clinical discretion is required when considering pharmacologic interventions for treatment-resistant OCD, as is clear communication with patients about rationales, risks, benefits, and alternatives. Patients will differ in their willingness to try less well-evidenced but potentially lower-risk treatments vs. better-evidenced but higher-risk medications. These factors, as well as potentially targetable comorbidities, adverse effects of concern, the prescriber's comfort and familiarity with an intervention, and other factors may reasonably influence treatment decisions.

This review highlights the potential for novel glutamatergic, anti-inflammatory and other currently experimental interventions to offer safe, effective and robustly evidence-based treatments for treatment-resistant OCD in the near future. Going forward, for treatments in development and for augmenting strategies currently in use, research may begin to parse out which treatments are helpful for individuals with particular OCD histories, symptom dimensions, comorbidities, or biomarkers, in line with the aims of personalized or precision psychiatric medicine. If pharmacologic therapies can be identified that better aid individuals with features of OCD associated with treatment resistance—such as insight impairment, symmetry/hoarding concerns, comorbid tics, or early disease onset—this would advance more effective and more comprehensive treatment for all individuals suffering with OCD. Identifying effective alternatives to first-line SRI treatments may also offer flexibility and freedom to those individuals for whom SRIs are effective, but poorly tolerated or otherwise unacceptable. Together, these advances will support the goal of developing expedient, safe, tolerable, and fully effective treatments for this common and often debilitating disorder.

Declaration of Competing Interest

Dr. Van Ameringen reports being on the Advisory Boards of Allergan, Almatica, Brainsway, Janssen, Lundbeck, Myriad Neuroscience, Otsuka and Purdue Pharma (Canada); Dr. Van Ameringen is on the Speaker's Bureau for Allergan, Lundbeck, Otsuka, Pfizer, Purdue Pharma (Canada) and Takeda; and has received research support from Janssen, Purdue Pharma (Canada), the Canadian Foundation for Innovation and Hamilton Academic Health Sciences Organization (HAHSO).

In the last 3 years, Dr. Rodriguez has served as a consultant for Biohaven Pharmaceuticals and Osmind, receives research grant support from Biohaven Pharmaceuticals and a stipend from APA Publishing for her role as Deputy Editor at The American Journal of Psychiatry.

There are no conflict of interest for the remaining authors (Drs. van Roessel, Grassi, Aboujaoude, and Menchon).

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