

# Current trends in drug treatment of obsessive–compulsive disorder

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**Abstract:** This article aims to highlight current trends in the pharmacologic management of obsessive–compulsive disorder (OCD). A systematic search of the electronic database MEDLINE was conducted. The first case report of clomipramine efficacy in the management OCD more than 40 years ago gave new hope for the treatment of this debilitating disorder. Selective serotonin reuptake inhibitors (SSRIs) proved to have a similar efficacy profile compared with clomipramine but had a superior tolerability profile. While many patients with OCD respond to SSRIs or clomipramine, the treatment of those with refractory OCD remains challenging. Different augmentation agents in treatment-resistant OCD have been explored, with antipsychotic agents having the largest supporting evidence base. Nevertheless, new pharmacologic treatment options are required and are under investigation.

**Keywords:** obsessive–compulsive disorder, pharmacology, treatment, drug

## Introduction

Obsessive–compulsive disorder (OCD) is a chronic condition characterized by obsessions or compulsions that cause distress or interfere with functioning. Obsessions are repetitive thoughts or urges that may lead to distress or anxiety. Compulsions are repetitive behaviors or thoughts that are performed according to rigorous rules, or in response to obsessions.<sup>1</sup> OCD is associated with significant suffering, leads to a great deal of morbidity, and is associated with major economic costs. Many aspects of quality of life are negatively impacted by OCD, and there is an association between increased OCD severity and worse quality of life.<sup>2</sup> A number of clinical trials have been conducted on OCD and several others are ongoing, so updated reviews of this work are useful for clinicians. The aim of this article is to highlight current trends in the pharmacologic management of OCD. We conducted a systematic search of the electronic database MEDLINE using the MeSH term “obsessive–compulsive disorder” for all available articles published up to and including 2009. We used the additional search terms “drug treatment” and “pharmacotherapy” to refine the search. We further limited the search using specific drug names, selecting English language publications only, and choosing only randomized or controlled trials, systematic reviews, and meta-analyses.

## Epidemiology

The lifetime prevalence estimate of OCD is 1%–3%, with older adolescents particularly prone to developing the disorder, and the incidence declining in older age groups.<sup>3–5</sup>

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Males comprise the majority of very early onset cases, while females comprise the majority of new cases after the age of 10 years.<sup>4</sup> In a five-decade prospective study of the course of OCD, only 20% of patients had complete recovery, although most had some improvement in both clinical symptoms and social functioning.<sup>6</sup> Early onset of OCD is associated with lower rates of recovery.<sup>4,6</sup> A recent community study indicated that more than 90% of patients with a lifetime Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) OCD diagnosis met criteria for another lifetime DSM-IV disorder, and the most common comorbid conditions were anxiety disorders (75.8%), followed by mood disorders (63.3%), impulse-control disorders (55.9%), and substance abuse disorders (38.6%).<sup>4</sup> In clinic patients, anxiety disorder is also the most common comorbid condition (76%), followed by major depressive disorder (33%).<sup>7</sup>

## Etiology

Functional imaging of the brain has allowed exploration of brain structure and function in OCD patients and has indicated hyperactivity in the orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus of patients with the disorder.<sup>8</sup> These findings suggest that abnormalities in the corticobasal ganglia-thalamo-cortical loops involving the orbitofrontal cortex and anterior cingulate cortex play a role in the pathogenesis of OCD.<sup>9</sup> The corticobasal ganglia-thalamo-cortical network is innervated by a variety of neurotransmitter pathways, and particular interest has been paid to the dopamine and serotonin (5-HT) neurotransmitter systems in OCD.

The exact etiology of OCD remains uncertain but systematic family and twin studies have demonstrated the moderate heritability of OCD.<sup>10</sup> A range of association studies to identify genetic components possibly involved in the etiology of OCD has been undertaken.<sup>11</sup> Disappointingly, however, gene association studies have often failed to replicate one another. For example, there are inconsistent findings with respect to polymorphisms in the genes responsible for the serotonin transporter, dopamine transporter, and serotonin and dopamine receptor subtypes in OCD.<sup>11–13</sup> It is possible that multiple genes, each with small effects, contribute to OCD.

Environmental factors, especially adverse perinatal experiences, may be associated with the development of OCD. Compared with controls, mothers of children with OCD had significantly higher rates of illness requiring medical care during pregnancy, and had more birth difficulties (induced labor, forceps delivery, cord prolapse, or prolonged labor).<sup>14</sup> Group A  $\beta$ -hemolytic streptococcal throat infections

have been associated with childhood onset of OCD, and this has been termed PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection).<sup>15</sup> It has been suggested that PANDAS may be triggered by an autoimmune response whereby reactive lymphocytes and antibodies against Group A  $\beta$ -hemolytic Streptococcus cross the blood–brain barrier and cross-react with neural cells to produce dysfunction in the central nervous system, specifically the basal ganglia. Further work is needed to confirm this hypothesis.<sup>15</sup>

A range of animal models of OCD has been developed.<sup>16</sup> Such work aims ultimately to develop new treatments for OCD based on a better understanding of the basic mechanisms that contribute to the disorder. On the one hand, there have been significant advances in understanding such mechanisms and we arguably have a more rigorous understanding of the neuroanatomy and neurochemistry of this relatively homogeneous disorder than we have of many other more heterogeneous psychiatric disorders. At the same time, much remains to be understood, and work on animal models of OCD has not yet translated into novel findings in clinical studies.

## History of pharmacotherapy in OCD

The first case report indicating that the tricyclic antidepressant, clomipramine, might have some benefit in patients with OCD was published more than 40 years ago.<sup>17</sup> Since then, clomipramine has been studied thoroughly and was the first drug approved by the US Food and Drug Administration (FDA) for the treatment of OCD. Clomipramine acts by inhibiting the reuptake of norepinephrine and serotonin, but serotonin inhibition is more pronounced. The selectivity of clomipramine for serotonin led to the hypothesis that a serotonin deficit is responsible for the symptoms of OCD.<sup>18</sup> This hypothesis also gave impetus to the study of selective serotonin reuptake inhibitors (SSRIs) in OCD, in the hope that those agents would be more efficacious and better tolerated.<sup>19</sup>

## Best treatment: SSRIs or clomipramine?

The response of OCD patients to pharmacologic intervention can be measured using a range of scales. The Yale–Brown Obsessive Compulsive Scale (YBOCS) score is the most widely used clinician-rated severity scale in OCD research.<sup>20</sup> The score range of the YBOCS is 0–40, with higher scores representing more severe symptoms. A response to treatment is usually, but not always, defined as a 25% or more reduction

in YBOCS score after treatment initiation.<sup>21</sup> Another measure used to determine efficacy in OCD research is the Clinical Global Impression scale (CGI), which rates patients according to severity of illness, global improvement, and efficacy of treatment.<sup>22</sup>

Using the symptom severity scales, data can be meta-analyzed to quantify the efficacy of different agents in the pharmacotherapy of OCD. Table 1 summarizes published meta-analyses of short-term OCD treatment studies. Early meta-analyses suggested that both SSRIs and clomipramine were more effective than placebo. Of note is that when the data for the SSRIs were compared with clomipramine, clomipramine generally had greater effect sizes. However, head-to-head studies have found similar efficacy for clomipramine and SSRIs. This may partly be explained by the fact that clomipramine studies were typically conducted earlier; patients

were treatment-naïve (and so perhaps more responsive), and placebo response was low. In contrast, the SSRI studies may have included patients who had previously failed to respond to other agents, and placebo responses were higher.

As discussed above, individual studies comparing SSRIs with clomipramine demonstrate very little difference in efficacy. In a small study, fluoxetine (40 mg daily) showed similar efficacy compared with clomipramine (150 mg daily), and both treatments were well tolerated.<sup>23</sup> Comparisons between fluvoxamine and clomipramine demonstrated equal efficacy, although again both studies were small (clomipramine 100–250 mg versus fluvoxamine 100–250 mg, and clomipramine 150–300 mg versus fluvoxamine 150–300 mg, with both drugs administered daily).<sup>24,25</sup> In an adequately powered comparison of sertraline and clomipramine, no significant difference in efficacy was found.<sup>26</sup>

**Table 1** Summary of meta-analyses of clomipramine and selective serotonin reuptake inhibitors in OCD

Study	n	Design (number of trials)	Duration	Effect on OCD
Greist et al <sup>75</sup>	1520	PL-controlled (7) [CMI, FLX, FLV, SER]	10–13 weeks	CMI and SSRIs > PL CMI > SSRIs No significant difference in drop-outs because of adverse effects
Piccinelli et al <sup>76</sup>	1809	PL-controlled (26) [CMI, FLX, FLV, SER, TCA]	5–36 weeks	CMI and SSRIs > PL CMI > SSRIs
Stein et al <sup>77</sup>	1039	PL-controlled (12) [FLX, FLV, SER, TRZ, CMI] Head-to-head (10) Open trial (6)	6–13 weeks	CMI and SSRIs > PL CMI = SER > FLX
Abramowitz <sup>78</sup>	20 studies with a range of 10–519 participants in each study	PL-controlled (5) [FLX, FLV, SER, CMI] Head-to-head (4)	4–13 weeks	CMI and SSRIs > PL CMI > FLV > FLX > SER Adverse effects correlated with effect size
Kobak et al <sup>79</sup>	4641	PL-controlled (5) [FLX, FLV, SER, CMI, PAR] Head-to-head (7)	Not reported	CMI and SSRIs > PL CMI = FLV = FLX > other SSRIs No difference in drop-out rates
Ackerman et al <sup>80</sup>	1876	PL-controlled (18) [CMI, FLX, FLV, SER, PAR] Head-to-head (8)	8–13 weeks	CMI and SSRIs > PL CMI = FLV = FLX = PAR
Soomro <sup>21</sup>	3097	PL-controlled (17) [FLX, FLV, SER, PAR, CIT]	6–13 weeks	Overall RR 1.84 (95% CI 1.56–2.17) Citalopram RR 1.58 (95% CI 1.20–2.08) Fluoxetine RR 2.41 (95% CI 1.58–4.56) Paroxetine RR 1.74 (95% CI 1.28–2.36) Sertraline RR 1.54 (95% CI 1.20–1.99) NNT 6–12

**Abbreviations:** CMI, clomipramine; FLX, fluoxetine; FLV, fluvoxamine; SER, sertraline; TRZ, trazodone; TCA, tricyclic antidepressants; PAR, paroxetine; CIT, citalopram; PL, placebo; SSRI, selective serotonin reuptake inhibitor; RR, relative risk; NNT, number-needed-to-treat; OCD, obsessive-compulsive disorder.

A recent Cochrane review compared the SSRIs in terms of their efficacy and tolerability in OCD.<sup>21</sup> The SSRIs of interest were fluoxetine, fluvoxamine, sertraline, paroxetine, and citalopram. The SSRIs as a group were shown to be more effective for treating OCD symptoms compared with placebo, and individually all drugs showed effect sizes of reasonable magnitude. Narrow confidence intervals (CIs) were reported for citalopram, fluvoxamine, paroxetine, and sertraline, and with slightly wider CIs for fluoxetine studies. The overall relative risk (RR) for response rate across all five SSRI studies was 1.84 (95% CI: 1.56–2.17). The RR for response rate in the citalopram group was 1.58 (95% CI: 1.20–2.08), fluoxetine 2.41 (95% CI: 1.58–4.56), paroxetine 1.74 (95% CI: 1.28–2.36), and sertraline 1.54 (95% CI: 1.20–1.99). Citalopram, paroxetine, and sertraline showed similar effect sizes (in terms of improvement in Y-BOCS scores) of 1.54–1.74, while fluvoxamine and fluoxetine showed larger effect sizes. However, lower limits of the CIs of effect sizes of all five drugs individually were comparable and the difference between the individual drugs was not statistically significant. The numbers needed to treat were calculated assuming that a response rate without treatment would be between 10% and 20%. Should 10% of patients be expected to recover without treatment, 12 patients would need to be treated with an SSRI to achieve improvement for one additional patient and should 20% of patients be expected to recover without treatment, six patients would need to be treated to achieve improvements for one additional patient.

Similarly, a systematic review of long-term medication studies in OCD shows that agents that are effective in short-term treatment are typically effective during long-term treatment.<sup>17</sup> For example, studies of clomipramine, escitalopram, fluoxetine, and sertraline have found that treatment effect is maintained beyond 12 weeks. Relapse prevention trials have also tended to show significant advantages for patients remaining on medication.

Thus, the evidence does not support superior efficacy of clomipramine over the SSRIs or of one SSRI over others in the same drug class for the treatment of OCD. However, the drugs have differences in tolerability and the potential to cause interactions.

## Tolerability of serotonin reuptake inhibitors and clomipramine

SSRIs increase synaptic availability of serotonin, and a number of postsynaptic 5-HT receptor types, including those for 5-HT<sub>3</sub>, are stimulated. Stimulation of such receptors is suspected to be responsible for some of the adverse

effects of SSRIs. Although reported adverse effect data were limited in the Cochrane review,<sup>21</sup> the overall and individual adverse effects for the different SSRIs were always worse than for placebo, and in the majority of cases the difference was statistically significant. Nausea, headache, and insomnia were consistently reported amongst the most common adverse effects in trials of each of the drugs. SSRIs were particularly prone to cause sexual side effects and the relative risk ranged from 5.74 to 18.64 for the individual drugs compared with placebo. The reviewers concluded that the modest OCD symptom improvement achieved by utilizing SSRIs should be weighed against the adverse effects, particularly those that impact on quality of life, such as sexual adverse effects.

Epileptic seizures have been reported during treatment with almost all antidepressants, including clomipramine and the SSRIs. The bulk of evidence suggests that clomipramine has a relatively high seizure risk, while SSRIs have a lower seizure risk. The seizure risk seems to be dose-related.<sup>27</sup>

Both clomipramine and the SSRIs are associated with weight gain in the long-term (more than two years) treatment of patients with OCD.<sup>28</sup> Clomipramine appears to have the greatest potential to induce weight gain, and sertraline and fluoxetine the least. Weight gain seems to be more significant for females. The small sample studied in OCD limits rigorous comparisons between SSRIs, but a meta-analysis of second-generation antidepressants for the treatment of major depressive disorder indicated that paroxetine might have the greatest propensity to cause weight gain.<sup>29</sup>

Clomipramine blockade of muscarinic, histaminergic, and adrenergic receptors decreases tolerability. Common adverse effects include blurred vision, xerostomia, urinary retention, constipation, orthostatic hypotension, and sedation. The major safety concern with the use of clomipramine is the drug's ability to slow cardiac conduction, which may precipitate life-threatening arrhythmias in overdose. The increased toxicity in overdose might be due to modulation of ion channel function, particularly for potassium and sodium, within the myocardium. UK mortality data show that tricyclic antidepressants are associated with a significantly higher number of accidental and intentional deaths than SSRIs.<sup>30</sup> Clomipramine was responsible for 11 deaths per million prescriptions, while SSRIs as a class were responsible for two deaths per million prescriptions, confirming that SSRIs are rarely fatal in overdose. When fatal, the SSRI was mostly taken in combination with other drugs, particularly tricyclic antidepressants. Very high doses of SSRIs (>75 times the normal daily dose) may

cause more serious adverse effects, including seizures and decreased consciousness.<sup>31</sup>

In head-to-head studies, clomipramine discontinuation rates were higher than those for SSRIs. When fluvoxamine was compared with clomipramine, fluvoxamine was better tolerated, with clomipramine having twice the amount of withdrawals owing to adverse effects.<sup>25</sup> In an adequately powered comparison between sertraline and clomipramine, significantly more patients withdrew from the clomipramine group due to adverse effects.<sup>26</sup>

In summary, as with all pharmacologic interventions, both clomipramine and SSRIs cause adverse effects, but the evidence suggests that SSRIs have a more favorable tolerability profile than clomipramine.

## Interactions with cytochrome P450 isoenzymes

The metabolism of most antidepressants is highly dependent on the activity of hepatic cytochrome P450 (CYP450) enzymes. Some antidepressants are not only substrates for CYP450 metabolism, but are also inhibitors of the metabolic clearance of other drugs, sometimes producing clinically significant drug–drug interactions.<sup>32</sup> Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C9, while fluoxetine and paroxetine potently inhibit CYP2D6. Citalopram and escitalopram are weak inhibitors of CYP450 isoenzymes and are less likely than other second-generation antidepressants to interact with coadministered medications.<sup>33</sup> Clomipramine significantly inhibits CYP2C19.<sup>34</sup>

Interactions with CYP450 isoenzymes should be kept in mind when combining antidepressant treatment with other drugs, especially when augmenting treatment-resistant OCD patients.

## Optimal dose of treatment

There is evidence to suggest that OCD drug response is better at higher doses.<sup>35</sup> Paroxetine was shown to have a positive dose–response relationship, with higher doses of 40 mg and 60 mg daily showing a significant improvement compared with placebo.<sup>36</sup> No significant difference was demonstrated between the 20 mg daily dose and placebo. Fluoxetine was evaluated in three fixed doses (20, 40, and 60 mg daily) and, although all doses were effective, the highest dose tended to give the greatest benefit. This finding did not reach statistical significance and adverse effects were dose-related.<sup>37</sup> A dose-finding study of escitalopram in nonresistant OCD suggested a dose–response effect with 20 mg daily which was numerically more robust than 10 mg daily on some secondary measures.<sup>38</sup>

There were no significant adverse event differences between the two dosage groups.

Success with doses greater than those recommended in the summary of product characteristics has been shown in treatment-refractory patients. A multicenter, randomized, double-blind, nonplacebo trial was performed to evaluate the efficacy and safety of 12 additional weeks of high-dose sertraline (250–400 mg, mean 357 mg daily) in 30 OCD patients who had failed to respond to 16 weeks of standard-dose sertraline treatment.<sup>39</sup> High doses of sertraline resulted in significantly greater and more rapid improvement in OCD symptoms compared with the maximal labeled dose of sertraline (200 mg daily). Obsessive, but not compulsive symptoms, also responded faster to high-dose sertraline compared with sertraline 200 mg daily. The higher doses of sertraline were well tolerated and produced similar rates of adverse effects compared with 200 mg, although patients had higher rates of tremor and agitation at higher doses. Pampaloni et al described the frequency and outcome of off-label doses of SSRIs prescribed in treatment-refractory patients.<sup>40</sup> Patients on high-dose treatment showed significant within-group improvements, although Y-BOCS scores for the high-dose group remained significantly higher than control patients treated for a matched period, suggesting enduring treatment resistance. No differences were found between the cases and controls with respect to the adverse effects, although the sample size was small and the findings limited by the retrospective study design.

Currently, expert consensus guidelines recommend gradually increasing the SSRI dose to the maximum, and do not recommend doses above the limit specified in the summary of product characteristics. Should patients not respond after an adequate medication trial, medication should be changed or augmented with another agent.<sup>41,42</sup>

## Resistant obsessive–compulsive disorder

Despite the substantial clinical improvements provided by the pharmacologic treatment of OCD with clomipramine and SSRIs, it has been estimated that 40%–60% of patients do not respond completely.<sup>43</sup> Various alternative strategies have been proposed for the treatment of resistant OCD.

## Increased dose of serotonin reuptake inhibitor

As discussed above, SSRIs have been used beyond the recommended maximum dose for patients who responded poorly to treatment and who tolerated supratherapeutic

doses. An open-label, prospective, 16-week, high-dose escitalopram study demonstrated statistically significant improvement in Y-BOCS score compared with baseline in patients receiving high doses.<sup>44</sup> Patients with resistant OCD received a mean dose of escitalopram 33.8 mg daily that was well tolerated with no treatment discontinuations. In a multicenter, double-blind trial, 66 nonresponders to 16 weeks of sertraline 50–200 mg daily were randomized to sertraline 200 and 250–400 mg daily. The high-dose group demonstrated significantly greater improvement compared with the 200 mg daily group. None of the patients in the high dose group discontinued due to adverse effects.<sup>39</sup>

A retrospective folder review matched 192 patients receiving high-dose SSRIs (fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline, and escitalopram) with a matched number of cases receiving the standard-dose treatment.<sup>40</sup> Patients on the high-dose treatment showed significant within-group improvements (mean Y-BOCS score 25.35 at baseline versus 20.95 at endpoint), although endpoint scores for the high-dose group remained significantly higher than for the control patients for a matched period, suggesting enduring treatment resistance. Frequency of adverse effects did not significantly differ between the two groups, although this finding is limited by the retrospective design of the study.

## Augmentation of SSRIs with antipsychotics

Evidence of the potential involvement of the dopamine system in OCD gave impetus to the study of whether antipsychotics could augment SSRIs in the treatment of the disorder. Addition of haloperidol was found to be particularly efficacious in SSRI-refractory OCD patients with comorbid chronic tic disorders, such as Tourette's disorder, although it was of little benefit in patients without tics.<sup>45</sup>

Risperidone is an atypical antipsychotic agent with potent dopaminergic and serotonergic antagonist activity.<sup>46</sup> A randomized, placebo-controlled augmentation trial of risperidone by McDougle demonstrated a 50% response rate, as defined by a  $\geq 35\%$  reduction in Y-BOCS score and "improved" or "much improved" CGI score, in patients receiving a six-week course of this agent. Risperidone was well tolerated with no treatment discontinuations. Erzegovesi investigated fluvoxamine-refractory patients, and 5/10 patients randomized to risperidone augmentation versus 2/9 patients receiving placebo had a significant response.<sup>47</sup> Risperidone was again well tolerated.

Results of placebo-controlled trials with another atypical antipsychotic, olanzapine, are conflicting. Shapira et al found no additional advantage of adding olanzapine in OCD patients refractory to fluoxetine, compared with extending the monotherapy trial,<sup>48</sup> while Bystritsky concluded that adding olanzapine to SSRIs is potentially efficacious in the short-term treatment of patients with refractory OCD.<sup>49</sup>

A randomized, placebo-controlled trial of quetiapine augmentation demonstrated significant improvement in the quetiapine arm, with 9/14 refractory patients showing significant improvement in the Y-BOCS score.<sup>50</sup> A larger randomized, placebo-controlled trial in 40 patients with treatment-resistant OCD demonstrated a significant difference in Y-BOCS score between quetiapine and placebo in favor of the antipsychotic. Eight patients in the quetiapine group compared with two in the placebo group had  $\geq 35\%$  decrease in Y-BOCS score after eight weeks' treatment.<sup>51</sup> While the antipsychotic was well tolerated, 30% of patients had an increase in weight. Carey et al found no difference in patients augmented with placebo or quetiapine, but pointed out that their findings might reflect a shorter trial of an SSRI before quetiapine augmentation and lower dosages of quetiapine compared with other trials.<sup>52</sup> The largest quetiapine placebo-controlled trial ( $n = 66$ ) to date concluded that quetiapine was significantly superior to placebo on Y-BOCS score and CGI scale score, but quetiapine augmentation was associated with more patients discontinuing treatment as a result of adverse events.<sup>53</sup> A meta-analysis of quetiapine studies suggests that this agent may be effective in the augmentation of SSRIs for the treatment of refractory OCD.<sup>54</sup>

Clozapine failed to show benefit when used as monotherapy for the treatment of OCD.<sup>5</sup> A series of basic science studies on the molecular effects of coadministration of SSRIs and atypical antipsychotics give support for the strategy of augmenting SSRIs with atypicals in refractory patients.

Until recently, all studies of atypical antipsychotic augmentation in OCD investigated only short-term response. A long-term follow-up of at least 1.5 years of patients receiving atypical antipsychotic augmentation raised concerns about the efficacy and metabolic effects of atypical antipsychotics.<sup>56</sup> Compared with SSRI responders, total Y-BOCS scores in those who required atypical antipsychotic augmentation were initially higher, and they remained at higher levels than those of SSRI responders after one year of treatment. This illustrates the disease severity in patients with resistant OCD but also the difficulty in obtaining an adequate response in these patients. Patients who received atypical

antipsychotic augmentation had significant increases in body mass index and fasting blood glucose, and demonstrated a trend towards increased cholesterol and triglycerides. Again, the advantages and disadvantages of pharmacotherapeutic intervention must be carefully weighed.

### Other drugs

Administration of the second messenger, inositol, in a small open-label study failed to produce a significant improvement in the majority of refractory patients.<sup>57</sup> Opioids are  $\mu$ -receptor agonists and in a placebo-controlled, double-blind study, oral morphine reduced the symptoms of OCD.<sup>58</sup> The evidence for anticonvulsants in patients with refractory OCD is mainly confined to anecdotal reports and uncontrolled trials.<sup>59</sup>

### Alternative mode of SSRI administration

In a randomized placebo-controlled trial ( $n = 54$ ), intravenous administration of clomipramine demonstrated superiority over placebo on outcome measures in patients who remained refractory to oral administration of clomipramine.<sup>60</sup>

### Augmentation of SSRI treatment with other agents

A number of clinical trials of augmentation strategies have failed to show any benefit in treatment-resistant OCD. In a double-blind, placebo-controlled trial, augmentation with lithium in treatment-resistant patients on fluvoxamine showed no clinical improvement in reducing obsessive-compulsive symptoms.<sup>61</sup> Buspirone added to fluvoxamine proved to be no better than placebo in reducing symptoms.<sup>62</sup> Adjunctive desipramine also showed no significant difference compared with placebo augmentation on OCD symptoms.<sup>63</sup>

A Cochrane review of the pharmacotherapy of treatment-resistant anxiety disorder concluded that more than twice as many treatment-resistant OCD patients respond to pharmacotherapy augmentation with various drugs than to placebo (31.8% versus 13.6%). The number needed to treat was found to be a clinically acceptable 5.5 and pharmacologic augmentation was tolerable insofar as there was no difference between medication and placebo dropout rate. Overall, superiority of a variety of drugs to placebo was demonstrated with a relative risk of nonresponse of 3.16 (95% CI: 1.08–9.23). A substantial proportion of the efficacy evidence was for augmentation with antipsychotic agents.<sup>64</sup>

## Future therapeutic options

Data for the efficacy of combining pharmacotherapy with cognitive behavioral therapy at the start of treatment is inconclusive, although patients who are resistant to pharmacotherapy may benefit from the addition of psychotherapy.<sup>65–67</sup>

New therapeutic options for OCD continue to be explored. D-cycloserine is an *N*-methyl-D-aspartic acid (NMDA) partial agonist, and NMDA receptor stimulation has been linked with amygdala neural plasticity and fear extinction effects.<sup>68,69</sup> D-cycloserine has been administered before an exposure task in various anxiety disorders, in the hope that stimulation of the NMDA receptor might help extinguish fear. In a randomized, double-blind, placebo-controlled trial of 23 OCD patients, D-cycloserine plus cognitive behavioral therapy improved OCD symptoms significantly at mid-treatment and depressive symptoms significantly post-treatment compared with placebo.<sup>68</sup> In another randomized, double-blind, placebo-controlled trial in 32 patients, D-cycloserine plus cognitive behavioral therapy decreased obsession-related distress significantly compared with placebo, but after additional exposure sessions, the difference was not seen. Patient drop-out rate was significantly higher in the placebo group.<sup>70</sup>

Riluzole, a glutamate antagonist, may hold promise for treatment-refractory patients.<sup>71</sup>

Treatment with modalities other than pharmacotherapy or psychotherapy has also been explored in patients with resistant OCD. Deep brain stimulation involves delivering a current via an implanted electrode that is connected to a battery-powered impulse generator that is implanted beneath the skin in the subclavicular region. The therapeutic mechanism of action is modulation of neuronal network activity using a pulse generator surgically placed in various regions, including the anterior internal capsule. Several clinical trials assessing the efficacy of deep brain stimulation in patients with OCD have shown promising results.<sup>72</sup>

Transcranial magnetic stimulation is a noninvasive technique that delivers magnetic pulses to the cortex by means of a hand-held stimulating coil applied directly to the head.<sup>73</sup> There is currently no reliable evidence to support the use of transcranial magnetic stimulation to treat OCD.<sup>74</sup>

## Conclusion

There have been significant advances in pharmacotherapy for OCD, but further work remains to be done. Extensive evidence exists to support the efficacy of clomipramine

and the SSRIs in the treatment of OCD. Clomipramine and the SSRIs are equally effective at relieving obsessions and compulsions, but the superior safety and tolerability of SSRIs make them the treatment of choice. However, SSRIs are not devoid of adverse effects which may significantly impact on patient quality of life. Treatment-refractory OCD remains an important clinical issue; antipsychotic augmentation is recommended, but is effective and well tolerated in a proportion of patients. There have been significant advances in uncovering the neurobiology of OCD, and ongoing work might ultimately be translated into novel approaches to the pharmacotherapy of OCD in the future.

## Disclosure

The authors report no conflicts of interest in this work.

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