Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2023 Mar-Apr;45(2):146-161
doi:10.47626/1516-4446-2022-2891
Brazilian Psychiatric Association

REVIEW ARTICLE

Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders guidelines for the treatment of adult obsessive-compulsive disorder. Part I: pharmacological treatment

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Objectives: To summarize evidence-based pharmacological treatments and provide guidance on clinical interventions for adult patients with obsessive-compulsive disorder (OCD).
Methods: The American Psychiatric Association (APA) guidelines for the treatment of OCD (2013) were updated with a systematic review assessing the efficacy of pharmacological treatments for adult OCD, comprising monotherapy with selective serotonin reuptake inhibitors (SSRIs), clomipramine, serotonin and norepinephrine reuptake inhibitors (SNRIs), and augmentation strategies with clomipramine, antipsychotics, and glutamate-modulating agents. We searched for the literature published from 2013-2020 in five databases, considering the design of the study, primary outcome measures, types of publication, and language. Selected articles had their quality assessed with validated tools. Treatment recommendations were classified according to levels of evidence developed by the American College of Cardiology and the American Heart Association (ACC/AHA).
Results: We examined 57 new studies to update the 2013 APA guidelines. High-quality evidence supports SSRIs for first-line pharmacological treatment of OCD. Moreover, augmentation of SSRIs with antipsychotics (risperidone, aripiprazole) is the most evidence-based pharmacological intervention for SSRI-resistant OCD.
Conclusion: SSRIs, in the highest recommended or tolerable doses for 8-12 weeks, remain the first-line treatment for adult OCD. Optimal augmentation strategies for SSRI-resistant OCD include low doses of risperidone or aripiprazole. Pharmacological treatments considered ineffective or potentially harmful, such as monotherapy with antipsychotics or augmentation with ketamine, lamotrigine, or N-acetylcysteine, have also been detailed.

Keywords: Obsessive-compulsive disorder; practice guidelines; drug therapy; systematic review

Introduction

Obsessive-compulsive disorder (OCD) is a relatively common and disabling neuropsychiatric disorder with a lifetime prevalence in adults ranging from 1.5 to 3%.[1] Obsessions and/or compulsions that are time-consuming, distressing, and impact daily function are the core manifestations of OCD.[2] Because OCD can severely

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Submitted Oct 03 2022, accepted Jan 05 2023.

How to cite this article: de Oliveira MVS, de Barros PMF, de Mathis MA, Boavista R, Chacon P, Echevarria MAN, et al. Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders guidelines for the treatment of adult obsessive-compulsive disorder. Part I: pharmacological treatment. Braz J Psychiatry. 2023;45:146-161. http://doi.org/10.47626/1516-4446-2022-2891

impair the quality of life of both patients and caregivers,[3-5] it is considered a severe mental health disorder whose public health significance has been underestimated.[6] The burden imposed by OCD-related symptomatology can be minimized by evidence-based treatments – specifically, selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioral therapy (CBT) are considered first-line treatments for OCD.[1] Nevertheless, lack of response or partial response to treatment are common; it is estimated that almost half of patients adequately treated with an SSRI or CBT do not achieve criteria for response.[7,8]

Clinical practice guidelines are recommendations for clinicians about the care of patients with specific conditions. They should be based upon the best available research evidence and practice experience. Moreover, clinical guidelines should be periodically updated in order to incorporate the most recent evidence. Although there are several clinical guidelines for the treatment of OCD, most were developed in high-income countries and thus may reflect clinical practice in those nations, which may vary according to the organization of the local health system and regulatory aspects (e.g., approved medications for OCD treatment may vary between countries).[9-13]

In the present study, the first of a series of four articles regarding the most frequent treatments delivered to patients with OCD (pharmacotherapy, psychotherapy, neuromodulation, and neurosurgery), we aimed to produce updated clinical guidelines for the pharmacological treatment of adult OCD using a rigorous methodology, which included a systematic review of the literature in five different databases, as well as a thorough evaluation of the quality of the studies used to answer the research questions presented in this review.

Methods

Overview

The present guideline was developed by mental health professionals (psychiatrists and psychologists) experienced in OCD from different Brazilian academic institutions. It was designed to guide the decision-making processes of psychologists, psychiatrists, and general practitioners who care for adult patients with OCD. The development of this guideline seemed justified considering the level of severity and impairment associated with OCD, as well as the relatively low rates of diagnosis and delivery of evidence-based treatments to patients with OCD worldwide.[14,15] Moreover, the latest Brazilian clinical guideline for the treatment of OCD was published more than 10 years ago, in 2011.[16]

We adopted the Methodological Guideline for Elaboration of Clinical Guidelines,[17] developed by the Brazilian Ministry of Health, to steer the development process of this guideline. A systematic review was conducted to update two previous international treatment guidelines, which included articles published from 1966 to 2013.[10,11] The proposal of the present guideline was registered in the PRACTICE Guidelines Registration Platform (IPGRP-2021CN324).

Definition and construction of research questions

We adopted the Population, Intervention, Comparator, and Outcome (PICO) strategy to develop our research questions, which were formulated by a pharmacotherapy working group composed of three psychiatrists. These questions were discussed in a forum with clinical experts in OCD from different Brazilian academic centers, and some original questions were included or modified based on their relevance. The research questions defined after the experts' forum are described in Box 1.

Search strategy

To answer the research questions, our starting point was the American Psychiatric Association (APA) treatment guidelines, which included articles published from 1966 to 2004, and its updated version, with articles published from 2004 to 2013.[10,11] Then, we conducted a search in PubMed, Cochrane, Embase, PsycINFO, and LILACS to obtain information on the state of the art in pharmacological treatment of OCD. We restricted the novel search to the period from 2013 to 2020. Search strategies used in each database can be found in detail in Table S1.

Inclusion criteria

The study design, primary outcome measure, type of publication, language, and year of publication determined our inclusion criteria. We selected meta-analyses, systematic reviews, and randomized controlled trials (RCTs) conducted with adult patients with OCD, published from 2013 to 2020. The primary outcome of the studies included in the review was the pre- to post-treatment change in OCD severity, as assessed by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS).[18] Only articles in English were included. For questions or databases that were not examined in the APA guidelines, the search comprised meta-analyses published from 1966 to 2013 in order to include studies that were not examined by the guidelines used as our starting points.[10,11]

Article selection

Two members of the pharmacotherapy working group independently screened titles and abstracts considering the inclusion criteria. Then, these authors screened all relevant full-text articles for eligibility. A third author was consulted to solve any discrepancies. Rayyan software was used for this step.[19]

Quality assessment

To assess the quality of the included systematic reviews and meta-analyses, we adopted the AMSTAR checklist criteria.[20] For randomized clinical trials, we adopted the PEDro scale.[21] Low-quality studies were not excluded. However, treatment recommendations were organized hierarchically based on the relevance and quality of the evidence.

Box 1 Research questions

Interventions	Research questions
Pharmacologic treatments as monotherapy	
SSRIs	Are SSRIs superior to placebo in improving the severity of OCD in adult patients? What are the recommended doses and duration of treatment to evaluate their efficacy? Are there differences in efficacy and safety among the different SSRIs? What are the main adverse events of SSRIs? What is the duration of maintenance treatment with SSRIs?
Clomipramine	Is clomipramine superior to placebo in reducing the severity of OCD in adult patients? What are the recommended doses and duration of treatment to evaluate its efficacy? Are there differences regarding efficacy and safety between clomipramine and SSRIs? What are the main adverse events of clomipramine? What is the duration of maintenance treatment with clomipramine?
SNRI	Is treatment with SNRI superior to placebo or control intervention in improving the severity of OCD in adult patients? What are the recommended doses and duration of treatment to evaluate the efficacy? Are there differences between the efficacy of SNRI and SSRIs or clomipramine?
Megadose SSRI	Is treatment with megadose SSRI superior to placebo or usual doses of SSRI in reducing OCD symptoms in adult patients with OCD? What are the doses and duration of treatment to evaluate the efficacy of megadose SSRI? Is treatment with megadose SSRI safe?
Pharmacological augmentation treatments	
Clomipramine	Is augmentation of SSRI treatment with clomipramine superior to placebo in improving the severity of OCD in adult patients? What are the recommended doses and duration of treatment to evaluate the efficacy of SSRI augmentation with clomipramine? What is the safety of the combination of SSRI and clomipramine?
Antipsychotics	Is augmentation of SSRI treatment with antipsychotics superior to placebo in improving the severity of OCD in adult patients? What antipsychotics can be used for SSRI augmentation? What are the recommended doses and duration of treatment to evaluate the efficacy of SSRI augmentation with antipsychotics? Is the combination of SSRI and antipsychotics safe?
Glutamatergic agents	Is augmentation of SSRI treatment with glutamatergic agents superior to placebo in improving the severity of OCD in adult patients? What glutamatergic agents can be used in combination with SSRIs? What are the recommended doses and duration of treatment to evaluate the efficacy of SSRI augmentation with glutamatergic agents?

OCD = obsessive-compulsive disorder; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors.

Recommendations and levels of evidence

After answering the research questions, the recommendations were classified according to levels of evidence using the American College of Cardiology and the American Heart Association (ACC/AHA) Recommendation System[22] (Box 2).

Results

We identified 2,058 records by searching the defined databases for pharmacologic therapy of OCD, of which 1,649 were screened, 95 were assessed for eligibility, and 57 articles were included in this review. Figure 1 presents the study selection flowchart, designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. Of the 95 reports assessed for eligibility, 38 did not meet the inclusion criteria and were excluded. Excluded studies and reasons for exclusion can be found in Table S2.

Selective serotonin reuptake inhibitors (SSRIs), clomipramine, and serotonin and norepinephrine reuptake inhibitors (SNRIs)

Efficacy of SSRIs

SSRI efficacy in OCD is well-established. This evidence is supported by well-conducted RCTs and meta-analyses. Since the publication of the APA guidelines for the treatment of OCD, more RCTs have been published confirming these positive findings.[24-26] A meta-analysis with high overall confidence according to the AMSTAR-2 criteria (Table S3) included 17 RCTs (n=3,097) and demonstrated that SSRIs are more effective than placebo in reducing OCD symptoms.[27] The overall relative risk for treatment response was 1.84 (95%CI 1.56-2.17) and the overall reduction in Y-BOCS scores against placebo was -3.21 (95%CI -3.84 to -2.57). Using the ACC/AHA Recommendation System, the class of recommendation (COR) for SSRI monotherapy is 1 and the level of evidence (LOE) is A.

Box 2 Classes of recommendation and levels of evidence according to the American College of Cardiology and the American Heart Association (ACC/AHA) Recommendation System

Strength of evidence		Benefit-risk ratio
1	Strong	Benefit >>> Risk
2a	Moderate	Benefit >> Risk
2b	Weak	Benefit > Risk
3	No benefit (moderate)	Benefit = Risk
3	Harm (strong)	Risk > Benefit
Levels (or quality) of evidence		**Definition**
A		High-quality evidence from more than one RCT Meta-analysis of high-quality RCTs One or more RCTs corroborated by high-quality registry studies
B-R		Moderate-quality evidence from one or more RCTs Meta-analysis of moderate-quality RCTs
B-NR		Moderate-quality evidence from one or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies Meta-analysis of such studies
C-LD		Randomized or nonrandomized observational or registry studies with limitations of design or execution Meta-analysis of such studies Physiological or mechanistic studies in human subjects
C-EO		Consensus of expert opinion based on clinical practice

RCT = randomized controlled trial.

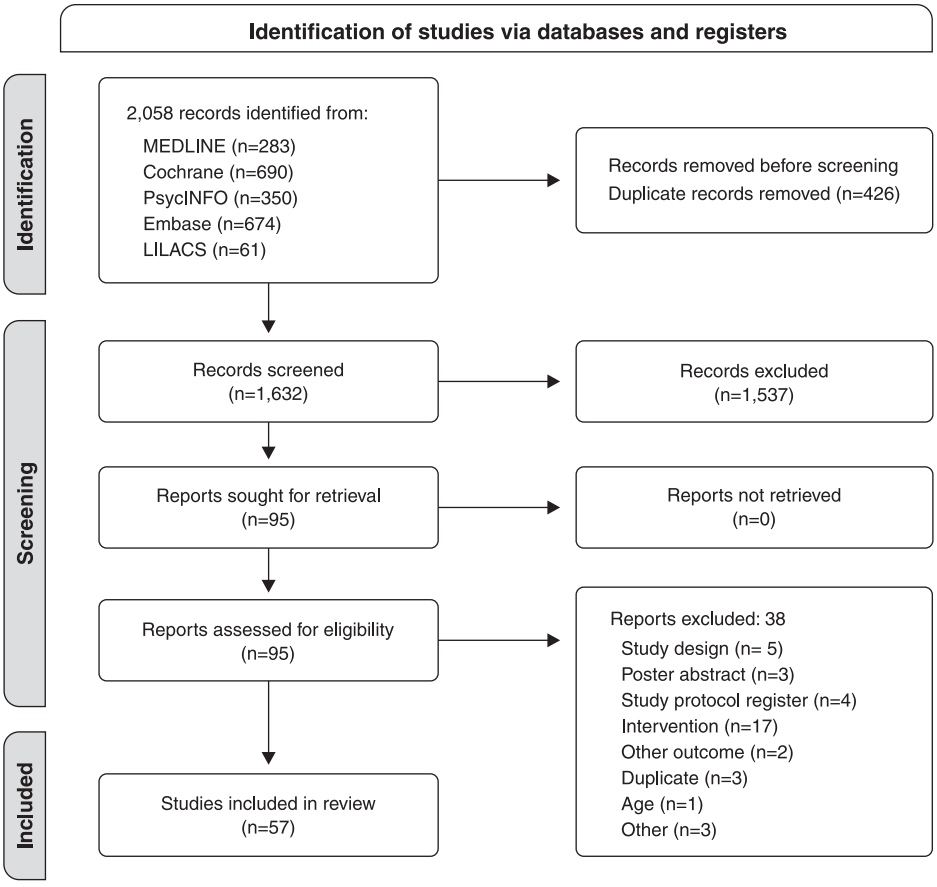

Figure 1. Flow diagram of study selection according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[23]

Comparisons between SSRIs

There is no evidence of superiority between individual SSRIs. Head-to-head comparisons have not shown statistically significant differences and the effect sizes were similar in a Cochrane meta-analysis.[27-29] A network meta-analysis including 37 trials of SSRIs with a total of 3,158 subjects also showed no significant differences between drugs when accounting for direct and indirect comparisons.[30] This meta-analysis, however, presented low overall confidence by the AMSTAR-2 criteria.

Efficacy of clomipramine

Clomipramine has also been found to be superior to placebo in reducing OCD symptoms in multiple RCTs and meta-analyses. While some reviews that did not directly compare clomipramine with SSRIs suggested that clomipramine's effect size was greater than that of SSRIs, head-to-head comparisons found no superiority between clomipramine and SSRIs.[31-37] A network meta-analysis showed that a nonsignificant trend favoring clomipramine disappeared when the sensitivity analysis accounted for the attrition rates observed in the clinical trials testing serotonergic medications – clomipramine studies, conducted earlier than those testing SSRIs, reported data only for subjects who completed the trials, overestimating efficacy despite lower rates of effectiveness. When all trials reporting intention-to-treat data were considered in the analyses, the effect sizes of SSRIs and clomipramine were found to be indistinguishable.[30] The COR for clomipramine monotherapy is 1 and the LOE is A.

Efficacy of serotonin-norepinephrine reuptake inhibitors (SNRIs)

Data on SNRIs is limited. There have been two trials comparing venlafaxine to other established treatments and one trial comparing venlafaxine to placebo. First, a randomized trial with 150 subjects comparing the efficacy of venlafaxine with paroxetine in the treatment of OCD demonstrated that there were no differences between groups.[38] Second, a randomized trial with 73 subjects comparing the efficacy of venlafaxine with clomipramine also found no difference between groups.[39] Finally, the single study comparing venlafaxine to placebo was a short (8-week) small randomized trial (n=30), which did not demonstrate the superiority of venlafaxine over placebo in reducing the severity of OCD.[40] In a network meta-analysis, venlafaxine was not superior to placebo.[30] Duloxetine, another SNRI, was only investigated as an augmentation treatment: Mowla et al.[41] published a brief report on an 8-week randomized trial with 46 subjects comparing augmentation of standard treatments with either sertraline or duloxetine. Patients had failed to respond to at least 12 weeks of SSRI treatment and were allocated to augment their current treatment with either sertraline or duloxetine. This RCT was rated 10 out of 11 in the PEDro scale (Table S4). Both groups showed similar rates of improvement. Despite the potential benefit of augmentation with duloxetine, combining a SSRI and a SNRI or two different SSRIs is unusual in clinical practice due to the risk of serotonin syndrome, a potentially life-threatening adverse event.[42] Therefore, to date there is no high-quality evidence supporting their use in the treatment of OCD. The COR for venlafaxine monotherapy is 2b and the LOE is C-LD. The COR for duloxetine augmentation is 2b and the LOE is C-LD.

Dosage of serotonergic agents

Most fixed-dose studies on serotonergic drugs point to the fact that higher doses lead to greater levels of improvement in patients with OCD when compared to lower doses.[43-46] This finding is supported by two dose-response meta-analyses.[47,48] However, these meta-analyses received a critically low overall rating by the AMSTAR-2 criteria. While higher doses are associated with increased improvement, they are also associated with increased levels of adverse effects. Recommended doses (to be achieved after gradual titration) are presented in Table 1.[11,13] For patients who have failed treatment with usual SSRI dosages, treatment with higher-than-recommended dosages has been proposed. A double-blind, multicenter RCT randomized 66 non-responders to 200 mg of sertraline into two groups: one continued taking 200 mg of sertraline and the other received higher doses of sertraline (250-400 mg) for 12 weeks.[49] The average final dose was 357 mg in the high-dose group, which presented significant improvements in Y-BOCS, National Institute of Mental Health – Global Obsessive-Compulsive Scale (NIMH Global OC), and Clinical Global Impression – Improvement Subscale (CGI-I). However, the difference was clinically modest and there was no significant difference in response rates between groups (decrease in Y-BOCS $\geqslant$ 25% and CGI-I $\leqslant$ 3). Adverse event rates were similar between groups. Further data supporting higher-than-recommended doses of SSRIs for the treatment of OCD include case series and small open-label studies.[29,50,51] Although it is not

Table 1 Recommended doses of serotonergic drugs for the treatment of OCD in adults

Medication	Recommended dose range (mg)
Selective SSRIs	
Fluoxetine	60-80
Sertraline	150-200
Fluvoxamine	200-300
Paroxetine	40-60
Citalopram	40-60[†]
Escitalopram	20-40
Clomipramine	100-250
Selective SNRI	
Venlafaxine	225-350

OCD = obsessive-compulsive disorder; SNRI = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.
The benefits of titration to higher doses must be weighed against the incidence of adverse effects on an individual basis.
[†] 20 mg in patients older than 60 years.

backed by robust evidence, the use of higher-than-recommended doses might be considered when dealing with nonresponders. The COR for higher-than-recommended doses of SSRIs is 2b and the LOE is C-LD.

Timing of reassessment and duration of maintenance with serotonergic agents

A meta-analysis of treatment response curves demonstrated that response followed an exponential curve, with most patients presenting response at the beginning of treatment.[47] This study included 17 trials with a total of 3,275 subjects. More than 50% of subjects presented evident improvement within the first 4 weeks of treatment, while more than 80% of patients experienced evident improvement by week 6. Moreover, an open-label trial of fluoxetine in treatment-naive patients indicated that reduction of OCD severity (as indicated by a 20% reduction of baseline Y-BOCS scores) at 4 weeks was the best predictor of treatment response at 12 weeks.[52] These findings are in line with the APA Practice Guideline, which stated that an adequate trial should include "4-6 weeks at the highest comfortably tolerated dose."[11]

Most clinical trials for OCD had duration between 6 and 13 weeks. However, the extended trials that were conducted with SSRIs and clomipramine have generally found that discontinuation is associated with higher rates of relapse.[44,53-56] Relapse rates vary considerably between the studies (differences in methodology should account for part of this variance). The question as to how long the treatment should be continued remains to be clarified; however, most clinical guidelines, including the APA's, suggest at least 1-2 years after achieving remission.[11]

Recommendations and adverse effects of serotonergic drugs

Evidence up until this point corroborates current guidance to keep SSRIs as first-line treatment. SSRIs have substantially higher evidence to support their efficacy than SNRIs. Moreover, individual RCTs and meta-analysis demonstrate that SSRIs are better tolerated than clomipramine in the treatment of OCD.[29,57] Common side effects of SSRIs include gastrointestinal complaints (e.g., nausea, diarrhea), disturbed sleep (e.g., insomnia, somnolence, vivid dreams), increased sweating, agitation, and sexual dysfunction (e.g., decreased libido, delayed orgasm). It is worth noting that the FDA recommends a maximum dosage of 20 mg per day of citalopram for patients older than 60 years because of the risk of cardiac arrhythmias, and that it should also be avoided in patients with a risk of QT prolongation.[58] Common side effects of SNRIs include gastrointestinal complaints (e.g., nausea, constipation), dizziness, sleep disturbances (insomnia, sedation), agitation, and sexual complaints. Common side effects of clomipramine include gastrointestinal complaints (e.g., dry mouth, constipation, nausea), sexual complaints, sleep complaints (somnolence, sedation), urinary delay, orthostatic hypotension, and cardiac conduction delay.[11]

SSRI augmentation with clomipramine

We found one double-blind RCTs that compared three pharmacological strategies in patients with SSRI-resistant OCD – fluoxetine 80 mg per day plus placebo, fluoxetine up to 40 mg per day plus clomipramine up to 75 mg, and fluoxetine up to 40 mg per day plus quetiapine up to 200 mg per day. The first two strategies significantly reduced the severity of OCD and were both significantly superior to fluoxetine plus quetiapine.[59] Of note, the effect of time spent on fluoxetine monotherapy (6 months) was the most important factor associated with response at the endpoint. The greatest concern associated with clomipramine and SSRI combination therapy is the increment in the blood levels of both drugs, which can increase the risk of severe and potentially life-threatening events such as seizures, heart arrhythmia, and the serotonin syndrome.[60] The COR for clomipramine augmentation is 2b and the LOE is C-LD.

SSRI augmentation with antipsychotics

The search strategy retrieved 10 articles: six RCTs, three meta-analyses, one systematic review, and one narrative review. These studies aimed to investigate the efficacy of five second-generation antipsychotics (risperidone, paliperidone, aripiprazole, quetiapine, and olanzapine) as an augmentation strategy for treatment-resistant patients with OCD. We included trials testing the efficacy of haloperidol considering its relevance as a treatment alternative in low- and middle-income countries, such as Brazil. The systematic review and meta-analyses had variable quality as assessed by AMSTAR, ranging from critically low to high. Though published in 2010, one meta-analysis had not been included in the updated version of the APA guidelines, published in 2013,[61] and has been considered to answer the questions presented in this review. Out of the six RCTs selected for inclusion in this review, only one was assessed, as two had already been included in the reviews used as our starting point, while the remaining three were excluded from our final analysis, as explained below.

Risperidone

The updated version of the APA treatment guidelines stated that mixed study results provided inconclusive evidence that pointed towards only modest benefit of the adjuvant use of risperidone, possibly more relevant for specific groups (SSRI-resistant OCD or with tic comorbidity).[11] A high-quality meta-analysis as assessed by the AMSTAR criteria and which had not been included in that guideline concluded that risperidone was efficacious, though available data were small.[61] Subsequent studies demonstrated that the mean reduction in the Y-BOCS scores was 3.89 points, a significantly greater improvement as compared to placebo, according to a moderate-quality meta-analysis.[62] Moreover, this augmentation strategy produced moderate effect size (Hedges' g = 0.59), according to a low-quality meta-analysis.[63]

Finally, another review found there is strong evidence to support its use as an adjuvant treatment for SSRI-resistant OCD, although the quality of this review has been considered critically low by the AMSTAR criteria.[64]

Despite its well-known adverse effects such as sedation, weight gain, metabolic syndrome, and hyperprolactinemia, risperidone appears to be well tolerated, but most studies had a short duration (up to 8 weeks) and reported adverse effects insufficiently.[61] In a follow-up study which included eight patients who had responded to risperidone augmentation in an 8-week RCT comparing augmentation of SSRIs with either risperidone, exposure and ritual prevention (ERP), or placebo, only three patients in the risperidone arm completed the follow-up and had small, nonsignificant improvement after 6 months.[65] There were no studies evaluating the time to assess treatment response. Doses ranged from 0.5 to 6 mg/day, with mean doses between 0.5-2.2 mg, providing support for the prescription of lower doses than those used in the treatment of patients with psychotic disorders.[64] Another meta-analysis demonstrated that fixed doses of 0.5 mg produced a greater effect size than higher doses.[62] The COR for this augmentation strategy is 2a and the LOE is A.

Paliperidone

There was no mention of the use of paliperidone in either version of the APA guidelines. Our search retrieved two systematic reviews on the use of paliperidone as an adjuvant treatment for OCD; articles included in these reviews comprised one case report and one small RCT (n=34).[63,64,66] Though this RCT showed a trend favoring paliperidone as an augmentation strategy, there was no significant superiority of adjunctive paliperidone over placebo.[66] The COR for this augmentation strategy is 3 (no benefit) and the LOE is B-R.

Quetiapine

Both the original and updated versions of the APA guidelines included trials published prior to 2013 and concluded that adjuvant quetiapine treatment produced mixed results. Therefore, augmentation with quetiapine was regarded as a possible treatment, a recommendation corroborated by a systematic review which included more than 200 participants.[61] However, two meta-analyses concluded that quetiapine (dose range: 25-600 mg/day) showed no difference from placebo and studies had high heterogeneity.[62,63] A single-blind RCT of 33 SSRI-refractory patients with OCD who received either quetiapine or aripiprazole for 12 weeks demonstrated that adjuvant quetiapine was effective, with relevant response as measured by a Y-BOCS score decrease occurring as early as 8 weeks.[67] Moreover, 60% of patients achieved response at 12 weeks and there was a large effect size (r = 0.62). The mean dose was 110 mg/day (SD = 47.1), and one patient in the quetiapine group dropped out, because of excessive sedation. Although the study's quality could be considered good, as assessed using the PEDro scale, conclusions are limited because of the small sample size and the single-blind design. Weight gain has also been reported as a cause of treatment discontinuation.[61] Three other publications consisted of the same study published by a group of authors in 2015 and 2019 with slightly different phrasing in separate journals and therefore were not included in this review.[68-70] The COR for this augmentation strategy is 3 (no benefit) and the LOE is B-R.

Aripiprazole

The updated version of the APA guidelines considered there was some support for aripiprazole augmentation; this recommendation was supported by one double-blind RCT.[71] Subsequent meta-analyses included an additional RCT and concluded that this treatment strategy was significantly superior to placebo with a large effect size, though sample sizes were small (n=79) and the longest follow-up duration was 16 weeks.[62,64,72] One of the meta-analyses found no new RCTs of aripiprazole for OCD, observed that studies with low-quality methodology were not enough to change the recommendation status of this augmentation strategy, and considered the evidence for the use of aripiprazole at best only promising.[64] The single-blind RCT mentioned above comparing adjuvant quetiapine with adjuvant aripiprazole (mean dose 13.2 mg/day, SD = 5.7 mg/day) for OCD demonstrated that 86% of patients on the aripiprazole group responded by 12 weeks, with a large effect size (r = 0.80).[67] Aripiprazole is better tolerated than other antipsychotics and is associated with less adverse effects such as weight gain, sedation, or hyperprolactinemia, as well as a lower risk of akathisia than risperidone.[62,64] The COR for this augmentation strategy is 2b and the LOE is B-R.

Olanzapine

The APA guidelines and subsequent systematic reviews and meta-analysis took into consideration only two double-blind RCTs published in 2004, with a combined total sample of 70 participants.[10,11,61-63] One trial produced positive results (mean doses: 11.2 mg/day; maximum 20 mg/day), while the other demonstrated no benefit of augmentation with olanzapine (mean doses: 6.1 mg/day; maximum 10.0 mg/day).[73,74] Taken together, the lack of replication of the positive results in the pivotal trial and the profile of associated adverse events, notably weight gain,[61] SSRI augmentation with olanzapine is not recommended. The COR for this augmentation strategy is 3 (no benefit) and the LOE is B-R.

Haloperidol

The updated version of the APA guidelines made no change from its original stance, which supported the adjunctive use of haloperidol, and no original trials testing this augmentation strategy were found in our search.[10,11] Nonetheless, this first-generation antipsychotic (FGA) will be mentioned considering its wide availability in the Brazilian public health system, being one of the most accessible in the country and probably in other countries with similar levels of development and health system organization.

An RCT testing the combination of haloperidol 2 to 10 mg/day (mean = 6.2, SD = 3.0) or placebo in patients with OCD not responsive to fluvoxamine for 4 weeks demonstrated that those with comorbid tic disorders greatly benefited from the association, as compared to those without tic disorders, who had no benefit.[75]

A crossover RCT, in which haloperidol 2 mg/day or risperidone 1 mg/day for 2 weeks was added to treatment with SSRIs, concluded that adjunctive haloperidol and risperidone might have a role in the treatment of OCD, even though more than 40% of patients who received haloperidol dropped out due to poor tolerability.[76] The COR for this augmentation strategy is 2b and the LOE is C-LD.

Augmentation with glutamate-modulating agents

Our search retrieved trials testing the efficacy of the following glutamate-modulating agents: amantadine, gabapentin, ketamine, L-carnosine, lamotrigine, mavoglurant, memantine, *N*-acetylcysteine (NAC), pregabalin, riluzole, and topiramate. Below, we provide details of the articles included in our review for each medication.

Amantadine

One RCT testing the augmentation of fluvoxamine with amantadine, an uncompetitive antagonist of the *N*-methyl-D-aspartate receptor (NMDA)-type glutamate receptor, was included among the articles selected to answer the questions regarding the efficacy of glutamate-modulating agents in the treatment of OCD.[77] This trial included 106 treatment-free patients, who were randomized to receive fluvoxamine up to 200 mg per day plus amantadine 100 mg per day or placebo for 12 weeks. The results of this study demonstrated a significant superiority of the combination of SSRI plus amantadine over placebo in reducing the severity of OCD. This RCT received the maximum score in the PEDro scale, indicating high methodological quality. However, the dose of fluvoxamine used in this study was below that recommended for OCD treatment, which contrasts with different guidelines on the initial treatment of OCD. Therefore, amantadine can be used for SSRI augmentation, but further trials are needed to confirm this recommendation. The COR for this augmentation strategy is 2b and the LOE is C-LD.

Gabapentin

One three-arm RCT was identified among the selected articles to answer the question regarding the efficacy of gabapentin as an augmentation strategy for OCD treatment.[78] This study included 99 patients with SSRI-resistant OCD who were randomized to receive fluoxetine + gabapentin up to 300 mg per day, fluoxetine + memantine up to 10 mg per day, or fluoxetine + placebo for 8 weeks. The results of this study did not demonstrate a significant superiority of the active interventions over placebo. This study scored 8 out of 11 points in the PEDro scale, indicating moderate-to-high methodological quality. Considering these results, augmentation of SSRIs with gabapentin in patients with treatment-resistant OCD is not supported by the available literature. The COR for this augmentation strategy is 3 (no benefit) and the LOE is B-R.

Ketamine

Two RCTs assessing the efficacy of ketamine for OCD treatment were identified among the selected articles and included in this review.[79,80] The first study consisted of a crossover RCT in which 15 treatment-free OCD adults with near-constant obsessions were randomized to receive two 40-minute intravenous infusions, one of saline and one of ketamine (0.5 mg/kg), spaced at least 1 week apart – the order of each infusion pair was randomized.[79] However, as ketamine showed significant carryover effects, the authors reported only the first-phase data in their statistical analyses. The results demonstrated that 1 week post-infusion, 50% of those receiving ketamine (n=8) met criteria for treatment response vs. 0% of those receiving placebo (n=7). This study scored 8 out of 11 points in the PEDro scale, indicating moderate-to-high methodological quality.

The second study was designed as an RCT aimed at assessing the efficacy of intranasal ketamine 50 mg or intranasal midazolam 4 mg.[80] However, this study was discontinued after only two participants completed it due to a low enrollment rate and poor tolerability.

Based on the aspects cited above, the use of ketamine either by intravenous or intranasal routes for OCD treatment is not supported by the available literature. The COR for this augmentation strategy is 3 (harm) and the LOE is A.

L-carnosine

One RCT assessing the efficacy of L-carnosine, a natural dipeptide with antiglutamatergic and antioxidative properties, for OCD treatment was identified among the selected records and included in this review.[81] Fifty treatment-free patients with OCD were randomized to receive fluvoxamine up to 200 mg per day + L-carnosine up to 1,000 mg per day or placebo for 10 weeks. The combination of fluvoxamine with L-carnosine resulted in a significantly greater improvement of OCD severity, as compared to placebo. This RCT received the maximum score in the PEDro scale, indicating high methodological quality. However, a more comprehensive and individualized review of this manuscript allowed identification of quality aspects not assessed by the PEDro scale. For example, the period over which this study was conducted was surprisingly short – the authors stated that 92 patients were screened, 50 were randomized, and 44 completed the trial from March 2016 to June 2016. This information strikingly contrasts with the duration of recruitment reported in studies with similar designs. Moreover, the alleged significant efficacy of this augmentation strategy in reducing the severity of obsessions, as stated in the results and discussion sections of the manuscript, diverges from the information presented in figures and tables. Similar to what was observed in the amantadine trial, this study consisted of delivering an initial

pharmacological intervention in treatment-naive patients. Moreover, the dose of fluvoxamine used in this study was below that recommended for OCD treatment. Considering all aspects mentioned above, in addition to the absence of other studies replicating these findings, augmentation of SSRIs with L-carnosine can be used, but this recommendation is not supported by high-quality scientific evidence (COR = 2b; LOE = C-LD).

Lamotrigine

One RCT testing the efficacy of augmenting SSRIs with lamotrigine or placebo in treatment-resistant patients with OCD met the inclusion criteria and was included in this review.[82] Sixty patients with OCD resistant to an adequate trial with SSRIs were included in the study and were randomized to receive adjunctive fixed doses (100 mg) of lamotrigine per day or placebo for 12 weeks. The combination of lamotrigine with SSRI was significantly superior in reducing the severity of OCD as compared to placebo, with a moderate effect size (Cohen's d = 0.54). This RCT scored 10 out of 11 in the PEDro scale, indicating an alleged high methodological quality. However, prescription of lamotrigine without careful dose titration, as described in this study, is in striking contrast to the conventional recommendation. It is known that the major barrier to lamotrigine administration is the potential for life-threatening skin rash, which increases if the starting dose is too high or if escalation is done too rapidly.[83-86] Thus, the conventional titration protocol has been recommended as a slower-is-safer approach, taking more than 8 weeks to reach the usual maintenance dose.[85] Therefore, although showing positive results in a small RCT, the clinical trial demonstrating the efficacy of lamotrigine for OCD should not be considered high-quality evidence to support its use. The COR for this augmentation strategy is 3 (harm) and the LOE is C-LD.

Mavoglurant

One RCT testing the augmentation of SSRI with mavoglurant, an antagonist of mGluR5 receptors, aimed at reducing the severity of OCD in treatment-resistant patients was included in this review.[87] This study was terminated because of a lack of efficacy at interim analysis and, therefore, does not support the use of an mGluR5 receptor antagonist for OCD treatment. The COR for this augmentation strategy is 3 (no benefit) and the LOE is B-R.

Memantine

Two meta-analyses were included in this review to answer the questions regarding the efficacy of memantine as an augmentation strategy in the treatment of patients with OCD.[88,89] In the study conducted by Kishi et al.,[88] three RCTs comprising 114 patients were included in the analysis, whereas the study conducted by Modarresi et al.[89] included eight trials with different designs (four double-blind RCTs, one single-blind case-control trial, and three open-label studies), comprising 125 subjects. The daily dose of memantine used in the trials included in both reviews ranged from 5 to 20 mg per day, and the duration of the trials varied from 8 to 16 weeks. Both meta-analyses demonstrated a significant benefit of augmenting SSRI with memantine in reducing the severity of OCD, as compared to placebo. However, both systematic reviews had their quality classified as critically low per the AMSTAR criteria. Therefore, memantine can be used as an augmentation strategy in treatment-resistant patients with OCD, but this intervention is not supported by high-quality scientific evidence (COR = 2b; LOE = C-LD).

N-Acetylcysteine (NAC)

Four RCTs testing the augmentation of SSRIs with NAC were included in this review and showed divergent results; two demonstrated a significant superiority of supplementation with NAC over placebo in reducing the severity of OCD, while two showed negative results.[90-93] The daily dose of NAC ranged from 2,000 to 3,000 mg per day and the duration of the trials varied from 10 to 16 weeks. Trials that demonstrated a benefit of NAC had a shorter duration, employed lower doses of NAC, and included subjects who were less treatment-resistant. Afshar et al.[90] included patients who failed to respond to SRI treatment, while Paydary et al.[92] included patients who did not receive any psychotropic medications 6 weeks prior to the study, i.e., SSRI and NAC or placebo were initiated at the same time.[90,92] On the other hand, RCTs that did not demonstrate any benefit of this intervention included patients with a higher degree of resistance to treatment.[91,93]

Regarding the quality assessment of the RCTs using the PEDro scale, all RCTs included in the review received high scores (range: 8-10), demonstrating high methodological quality. However, methodological issues that are not fully captured by the tool were detected in at least three trials.[90-92] For example, pre- and post-treatment CGI scores, an ordinal variable, were reported as means and SDs, rather than as absolute and relative frequencies.[90,91] Moreover, the target dose of fluvoxamine used in one positive study was below that recommended for OCD treatment.[92]

Considering the aforementioned aspects, specifically the divergent results, the different profile of patients with OCD included in the RCTs and the concerns regarding the methodological quality of some trials, the recommendation of using NAC in the treatment of OCD is not supported by the existing literature. The COR for this augmentation strategy is 3 (no benefit) and the LOE is B-R.

Pregabalin

One RCT assessing the efficacy of pregabalin for OCD treatment was identified among the selected records and included in this review.[94] Fifty-six SSRI-resistant patients with OCD were included in the trial and were randomized to receive either pregabalin up to 225 mg per day or placebo as augmenting agents for 12 weeks. The results

of this study demonstrated that pregabalin was significantly more effective than placebo as an augmentation strategy for treatment-resistant OCD – nearly 60% of patients allocated to the pregabalin group responded to treatment (reduction of baseline Y-BOCS scores $\geqslant$ 35%), while only 7.14% of those who received placebo were considered responders to treatment. This magnitude of treatment effect is similar to that produced by SSRIs, the first-line pharmacological treatment for OCD, and contrasts with the effect sizes produced by augmentation with antipsychotics, the most well-established pharmacological augmentation strategy for treatment-resistant OCD. This study scored 8 out of 11 in the PEDro scale, indicating moderate-to-high methodological quality. Therefore, the use of pregabalin may be considered as an adjuvant treatment for OCD, but this recommendation should be taken considering the aforementioned methodological concerns (COR = 2b; LOE = C-LD).

Riluzole

Two RCTs evaluating the efficacy of riluzole or placebo in reducing the severity of OCD met the criteria for inclusion in the present review.[95,96] One study included 39 SSRI-resistant patients with OCD, who were randomized to receive riluzole up to 100 mg or placebo and followed for 12 weeks, after a 2-week placebo lead-in.[95] The results of this trial did not demonstrate a significant difference between groups regarding the reduction of Y-BOCS scores. Another study included 54 treatment-free patients who were randomized to receive either fluvoxamine 200 mg per day + riluzole 100 mg per day or fluvoxamine 200 mg per day + placebo.[96] The results of this trial demonstrated a significantly greater improvement of OCD severity in patients allocated to receive fluvoxamine + riluzole, as compared to fluvoxamine + placebo. However, similar to the trials testing the efficacy of amantadine and pregabalin, the dose of fluvoxamine used in this study was below that recommended for OCD treatment. Both studies scored high (range: 10-11) on the PEDro scale, indicating high methodological quality. Considering the divergent results of these RCTs, riluzole in the treatment of OCD is not supported by the available literature. The COR for this augmentation strategy is 3 (no benefit) and the LOE is A.

Topiramate

One RCT testing the efficacy of augmenting SSRI with topiramate or placebo in treatment-resistant patients with OCD met the criteria for inclusion in this review.[97] In this study, 38 patients were randomized to receive topiramate up to 200 mg per day or placebo for 12 weeks. The results of this trial demonstrated a significant superiority of topiramate in reducing OCD severity as compared to placebo after 8 weeks, but not at week 12. Moreover, CGI subscale scores were not significantly different between groups. This study scored 10 on the PEDro scale, indicating high methodological quality. However, methodological issues that are not fully captured by this tool were identified after a thorough review of the manuscript. Similar to what we observed in two RCTs testing NAC, pre- and post-treatment CGI scores, an ordinal variable, were reported as means and SDs, rather than as absolute and relative frequencies. Based on the aforementioned aspects, topiramate can be used as an SSRI-augmentation agent in treatment-resistant OCD patients, but its use is supported by only one study with low overall methodological quality. The COR for this augmentation strategy is 2b and the LOE is C-LD.

Discussion

This article describes the process and results of development of international clinical guidelines on the pharmacological treatment of adult patients with OCD in a developing country. As our starting point, we reviewed the APA guidelines, which were last published in 2013, and updated them by conducting a systematic review of the literature published between 2013 and 2020. Methodological strengths of our study include performing a search in five relevant databases of the medical literature, as well as a rigorous assessment of the methodological quality of the articles selected to answer our research questions.

SSRIs/clomipramine and CBT with ERP are both established treatments for OCD.[1] The results of an RCT demonstrated that the effects of ERP and the combination of ERP plus clomipramine for OCD were similar, and both were superior to clomipramine only.[98] Different reviews corroborate this finding.[30,99] Therefore, treatment of OCD should always encompass ERP sessions. In situations where referral to ERP is not possible, medical treatment should include psychoeducation regarding the importance of implementing ERP techniques aimed at improving the severity of OCD. This topic – CBT with ERP for OCD – will be discussed in detail in the next article of this series comprising guidelines for the treatment of OCD. Considering the low availability of trained CBT therapists and the high rates of comorbid disorders that may require pharmacological treatment, an updated review of the best evidence-based pharmacological treatments for OCD seemed justified.[100,101] Below, we discuss the main findings of our systematic review and provide recommendations regarding the pharmacological treatment to be delivered for patients with OCD. These recommendations have been summarized in Table 2.

First-line pharmacological treatment

There is robust evidence supporting the efficacy of SSRIs for the treatment of OCD (COR = 1; LOE = A). Among specific SSRIs, there is no evidence of superiority of any particular drug. The efficacy of clomipramine for the treatment of OCD has also been demonstrated (COR = 1; LOE = A). Some reviews have suggested that the effect size of clomipramine was superior as compared to SSRIs, but head-to-head comparisons conducted more recently did not corroborate this finding.[31-37] However, it might be reasonable to indicate a trial with clomipramine in patients who did not respond adequately to SSRIs (COR = 2b;

Table 2 Pharmacological treatments for OCD in adults – classes of recommendations and levels of evidence

Pharmacological treatments for OCD	COR	LOE	Recommendations
Monotherapy with			
SSRIs	1	A	Efficacy well established in multiple RCTs and meta-analyses.
Clomipramine	1	A	Efficacy well established in multiple RCTs and meta-analyses. Due to lower tolerability in comparison to SSRIs, clomipramine is not recommended as first-line pharmacotherapy.
Venlafaxine	2b	C-LD	Similar results to SSRIs in two RCTs, no difference from placebo in one RCT and in high-quality meta-analysis. Its use may be considered when other strategies have failed.
Higher-than-recommended doses of SSRIs	2b	C-LD	Limited evidence. Its use may provide some benefit compared to standard dosages.
Antipsychotics	3 (no benefit)	C-LD	Limited evidence does not support this strategy.
SSRI augmentation strategies			
SRIs			
Clomipramine	2b	C-LD	Limited evidence. Its use may provide some benefit compared to SSRI monotherapy. Caution with adverse effects and potential drug-drug interactions is warranted.
Duloxetine	2b	C-LD	Evidence derived from one RCT with low overall quality. Therefore, its effectiveness is not well-established.
Antipsychotics			
Haloperidol	2b	B-R	Efficacious as an adjuvant compared to placebo, with poor adverse-effect profile. May be used with caution.
Risperidone	2a	A	Well-established efficacy as an adjuvant compared to placebo, but poor short- and long-term tolerability. Can be used.
Paliperidone	3 (no benefit)	B-R	No difference in efficacy from placebo. Use not recommended.
Quetiapine	3 (no benefit)	B-R	No difference in efficacy from placebo, unfavorable short- and long- term tolerability profile. Use not recommended.
Aripiprazole	2a	B-R	Efficacy significantly superior to placebo, fair tolerability. Can be used.
Olanzapine	3 (no benefit)	B-R	No difference in efficacy from placebo and many short- and long- term tolerability issues. Use not recommended.
Glutamate-modulating agents			
Amantadine	2b	C-LD	Evidence derived from one small RCT. Although its effectiveness is not definitely established, it can be used.
Gabapentin	3 (no benefit)	B-R	One RCT with moderate-to-high quality demonstrated no superiority over placebo. Use not recommended.
Ketamine	3 (harm)	A	Evidence derived from two RCTs, one of which was interrupted due to the low rate of enrollment and adverse events. Use not recommended.
L-carnosine	2b	C-LD	Evidence derived from one RCT with low overall quality. Although its effectiveness is not well-established, it can be used.
Lamotrigine	3 (harm)	C-LD	Not recommended due to potential for serious adverse events.
Mavoglurant	3 (no benefit)	B-R	Not recommended due to lack of efficacy.
Memantine	2b	C-LD	Evidence derived from two meta-analyses with low overall quality. Although its effectiveness is not well established, it can be used.
N-Acetylcysteine	3 (no benefit)	B-R	Divergent results of four RCTs, but serious methodological issues were detected in the positive trials. Considering the superior methodological quality of the negative trials, its use is not recommended.
Pregabalin	2b	C-LD	Evidence derived from one RCT with low overall quality. Although its effectiveness is not well-established, it can be used.
Riluzole	3 (no benefit)	A	Evidence derived from two RCTs with divergent results. Considering the superior methodological quality of the negative trial, its use is not recommended.
Topiramate	2b	C-LD	Evidence derived from one RCT with low overall quality. Although its effectiveness is not well-established, it can be used.

COR = class (strength) of recommendation; LOE = level (quality) of evidence; OCD = obsessive-compulsive disorder; RCT = randomized clinical trial; SNRIs = serotonin-norepinephrine reuptake inhibitors; SRIs = serotonin reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

LOE = C-LD). While evidence is not as compelling as for other agents, venlafaxine may be useful for treating OCD[38,39] (COR = 2b; LOE = C-LD). Duloxetine was only studied for augmentation of treatment as usual in a small trial, showing similar response as augmenting the patients' current regimen with sertraline.[41] Since it is not usual practice to augment one SSRI with another SSRI or SNRI, further data is needed to support this intervention.

Regarding dosage, most fixed-dose studies point to higher doses leading to greater improvement.[43-46] Thus, it is recommended that patients try high-dose serotonergic treatment before concluding that the treatment has failed (COR = 1; LOE = B-R). Because higher doses are not only associated with higher response rates, but also with higher rates of side effects, it is recommended that dosages be titrated gradually and taking individual tolerability in consideration (COR = 2a; LOE = B-R).

Recommendations for the timing of reassessment and the duration of maintenance treatment with serotonergic agents remain largely similar to those in the APA Practice Guideline.[11] Issari et al.[47] performed a meta-analysis of response curves of 17 trials, showing that 50% of subjects presented evident improvement within the first 4 weeks of treatment, and more than 80% presented evident improvement within the first 6 weeks of treatment. We corroborate the APA Practice Guideline recommendation that an adequate trial should include 4-6 weeks at the highest tolerated dosage (COR = 1; LOE = A). The duration of medication treatment, however, is much less clear. The great majority of trials were short-term, so most trials fail to provide guidance on when medication should be discontinued. The extended trials available have generally pointed that discontinuation of medication is associated with higher rates of relapse.[44,53-56] We corroborate the APA Practice Guideline recommendation of maintaining treatment for at least 1-2 years after achieving remission (COR = 2b; LOE = C-LD).

Pharmacological augmentation strategies

Serotonergic agents

For patients who have failed first-line therapies, it is possible to consider higher-than-recommended doses of SSRIs or augmenting SSRI with clomipramine. There is a limited number of studies investigating these strategies. Higher-than-recommended doses have been tested in a double-blind, multicenter RCT of 66 subjects comparing 200 mg of sertraline to 250-400 mg of sertraline (average final dose, 357 mg/day). There were significant improvements in Y-BOCS, NIMH Global OC Scale, and CGI-I, but the difference was clinically modest and there was no significant difference in response rates between groups. Further data supporting higher-than-recommended doses of SSRIs for the treatment of OCD include case series[29] and small open-label studies.[50,51] Thus, a trial of higher-than-recommended doses of SSRI might be reasonable in nonresponders (COR = 2b; LOE = C-LD).

Another strategy that has been investigated by a small body of research is augmenting SSRI with clomipramine. Diniz et al.[59] randomized 54 patients who had failed to respond to fluoxetine monotherapy (highest tolerated dose up to 80 mg/day) into one of three arms: clomipramine augmentation (75 mg/day), quetiapine augmentation (200 mg/day), or placebo augmentation. There was significant reduction in Y-BOCS in the clomipramine augmentation group, with a response rate of 44%. However, the treatment response was similar in the placebo augmentation group. Of note, patients in the fluoxetine + quetiapine arm did not show significant improvement over baseline. SSRI augmentation with clomipramine was also explored in case series and small open-label trials, with mostly positive experiences, but some reported negative results.[102,103] Despite a lack of robust evidence, in treatment-resistant patients it might be reasonable to try augmenting SSRIs with clomipramine (COR = 2b; LOE = C-LD). Nonetheless, caution regarding adverse effects and drug interactions is warranted.

Antipsychotics

While these guidelines focus on the adjuvant use of antipsychotics for OCD, we would like to highlight that no new research on the treatment of OCD with antipsychotics as monotherapy resulted from our search. Thus, no changes to the APA recommendations have been made and, at present, there is no evidence of the benefit of treating OCD patients with antipsychotics as monotherapy[104] (COR = 3; LOE = C-LD).

Antipsychotics, as a class, have been used as augmenting agents for patients with OCD unresponsive to SSRI monotherapy and have shown encouraging results in some cases. The majority of studies were short-term, between 4 and 16 weeks of duration, with the exception of one 6-month follow-up study mentioned earlier.[65] This precludes any recommendations regarding long-term treatment with these agents. Moreover, it has been clearly demonstrated that long-term treatment with antipsychotics is associated with serious adverse effects.[105] A systematic review demonstrated there was insufficient reporting of side effects in several trials, such that sexual dysfunction, a well-known reason for treatment discontinuation, was not mentioned as an adverse effect in any of the studies retrieved by our search.[61,106]

Though no new studies on haloperidol have been found following the 2007 guidelines recommendation, it may be prescribed judiciously as an adjunct in SSRI-resistant patients and its use should be considered when other antipsychotics are not available or affordable. Tolerability must be regularly assessed, since adverse effects such as parkinsonism and tardive dyskinesia are more frequent than with second-generation antipsychotics. Doses of haloperidol should be the lowest possible, starting from 0.5 mg up to 5 mg/day, and only in exceptional cases reaching 10 mg per day (COR = 2b; LOE = B-R).

Risperidone has been the most studied antipsychotic for this purpose and evidence suggests its superiority over placebo, though adverse effects such as sedation and weight gain may jeopardize tolerability. Close, regular monitoring of side effects is mandatory. Doses should mainly be kept in lower ranges (up to 2 mg per day, generally not exceeding 4 mg per day) (COR = 2a; LOE = A).

Aripiprazole is a newly recommended augmentation strategy for treatment-resistant OCD. Its doses should be kept in a low range, not exceeding 15 mg per day (COR = 2a; LOE = B-R).

Regarding paliperidone, quetiapine, and olanzapine, there is no evidence supporting their use as augmenting agents for treatment-resistant OCD (COR = 3; LOE = B-R).

Glutamate-modulating agents

To answer our questions regarding augmentation with glutamate-modulating agents in the treatment of OCD, we included 23 articles (two meta-analyses, one systematic review, and 20 RCTs). Our search retrieved trials testing the efficacy of the following glutamate-modulating agents: amantadine, gabapentin, ketamine, L-carnosine, lamotrigine, mavoglurant, memantine, NAC, pregabalin, riluzole, and topiramate. Although a few studies have demonstrated the efficacy of amantadine, L-carnosine, memantine, pregabalin, and topiramate (COR = 2b; LOE = C-LD), methodological concerns involving these studies preclude any definite conclusions favoring use of these medications. Therefore, we do not recommend the routine use of glutamate-modulating agents for treating patients with OCD.

Unexpected findings

During the development of the present guideline, we detected one RCT designed to determine the efficacy of SSRI-augmentation with either quetiapine or aripiprazole in treatment-resistant patients with OCD, which has been published in three different scientific journals from 2015 and 2019.[68-70] Despite reporting the same results, all articles were published as different original research.

Limitations

The results of our review should be interpreted in light of a few limitations. First, we restricted our search to the most frequent pharmacological treatments for OCD – SSRIs, clomipramine, SNRIs, antipsychotics, and specific glutamate-modulating agents. Other medications (e.g., celecoxib, ondansetron, minocycline) which may have a place in the pharmacotherapy of OCD were not covered by the present guidelines. Second, we only included trials using the Y-BOCS as primary outcome measure. An expert consensus derived from the results of a multi-round, web-based Delphi survey of experts in the field stated that treatment response should be defined by associating CGI-I scores with the relative reduction in baseline Y-BOCS scores after an adequate SSRI trial.[107] According to this consensus, successful treatment response has been defined as a Y-BOCS score reduction equal to or greater than 35% and a CGI-I score of 1 (very much improved) or 2 (much improved). Although this is the consensus optimal definition of treatment response, if we adopted it as an inclusion criterion for our review, very few articles would have been included to answer our research questions. Finally, despite our attempt to assess the methodological quality of the selected studies using validated instruments (AMSTAR-2 for systematic reviews and the PEDro scale for RCTs), we found that these instruments were not able to fully detect methodological flaws.[20,21] To address this issue, we based our recommendations not only on the scores provided by these tools, but also on qualitative assessment of the studies by experienced clinicians and researchers in the field of OCD.

Conclusions

The use of SSRIs in moderate-to-high doses for 8-12 weeks is supported by high-quality scientific evidence and remains the first-line pharmacological treatment of choice for OCD. Despite the well-established efficacy of clomipramine, as demonstrated in multiple RCTs and meta-analyses, it should be reserved for situations in which SSRIs are unavailable or ineffective, and tolerability and safety issues should be considered. For nonresponders to monotherapy with SSRIs or clomipramine, the most evidence-based next step is short-term augmentation of these agents with low doses of risperidone or aripiprazole. Finally, pharmacological strategies that have already been considered ineffective or potentially harmful include monotherapy with antipsychotics and augmentation with paliperidone, quetiapine, olanzapine, gabapentin, ketamine, lamotrigine, mavoglurant, NAC, or riluzole.

Acknowledgements

This study was supported by Instituto Nacional de Psiquiatria do Desenvolvimento para Crianças e Adolescente (INPD), Fundação de Amparo à Pesquisa do Estado de São Paulo [FAPESP; 2014/50917-0]), and Conselho Nacional de Desenvolvimento Científico e Tecnológico ([CNPq; 465550/2014-2]).

References

1 Stein DJ, Costa DLC, Lochner C, Miguel EC, Reddy YCJ, Shavitt RG, et al. Obsessive-compulsive disorder. Nat Rev Dis Primers. 2019;5:52.
2 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington: American Psychiatric Publishing; 2013.
3 Rosa AC, Diniz JB, Fossaluza V, Torres AR, Fontenelle LF, Mathis AS, et al. Clinical correlates of social adjustment in patients with obsessive-compulsive disorder. J Psychiatr Res. 2012;46:1286-92.
4 Velloso P, Piccinato C, Ferrão Y, Perin EA, Cesar R, Fontenelle LF, et al. Clinical predictors of quality of life in a large sample of adult obsessive-compulsive disorder outpatients. Compr Psychiatry. 2018; 86:82-90.
5 Ramos-Cerqueira AT, Torres AR, Torresan RC, Negreiros AP, Vitorino CN. Emotional burden in caregivers of patients with obsessive-compulsive disorder. Depress Anxiety. 2008;25:1020-7.
6 Torres AR, Prince MJ, Bebbington PE, Bhugra D, Brugha TS, Farrell M, et al. Obsessive-compulsive disorder: prevalence, comorbidity, impact, and help-seeking in the British National Psychiatric Morbidity Survey of 2000. Am J Psychiatry. 2006;163:1978-85.
7 Belotto-Silva C, Diniz JB, Malavazzi DM, Valério C, Fossaluza V, Borcato S, et al. Group cognitive-behavioral therapy versus selective serotonin reuptake inhibitors for obsessive-compulsive disorder: a practical clinical trial. J Anxiety Disord. 2012;26:25-31.
8 Erzegovesi S, Cavallini MC, Cavedini P, Diaferia G, Locatelli M, Bellodi L. Clinical predictors of drug response in obsessive-compulsive disorder. J Clin Psychopharmacol. 2001;21:488-92.

9 National Institute for Health and Care Excellence (NICE) [Internet]. Obsessive-compulsive disorder and body dysmorphic disorder: treatment. 2005 Nov 29. https://www.nice.org.uk/guidance/cg31.
10 American Psychiatric Association [Internet]. Practice guideline for the treatment of patients with obsessive-compulsive disorder. 2010. http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.
11 Koran LM, Simpson HB. APA Practice Guidelines [Internet]. Guideline watch (2013): Practice guideline for the treatment of patients with obsessive-compulsive disorder. March 2013. https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd-watch-1410457187510.pdf.
12 Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14Suppl 1:S1.
13 Reddy YCJ, Sundar AS, Narayanaswamy JC, Math SB. Clinical practice guidelines for Obsessive-Compulsive Disorder. Indian J Psychiatry. 2017;59:S74-90.
14 Perez MI, Limon DL, Candelari AE, Cepeda SL, Ramirez AC, Guzick AG, et al. Obsessive-compulsive disorder misdiagnosis among mental healthcare providers in Latin America. J Obsessive Compuls Relat Disord. 2022;32:100693.
15 Stahnke B. A systematic review of misdiagnosis in those with obsessive-compulsive disorder. J Affect Disord. 2021;6:100231.
16 Torres AR, Shavitt RG, Miguel EC, Fontenelle LF, Diniz JD, Belotto C, et al. Associação Brasileira de Psiquiatria [Internet]. Transtorno obsessivo compulsivo: tratamento. 2011 Jan 31. https://amb.org.br/files/ans/transtorno_obsessivo_compulsivo-tratamento.pdf.
17 CONITEC [Internet] Methodological Guideline for Elaboration of Clinical Guidelines. May 2016. http://conitec.gov.br/images/Relatorios/2016/Diretrizes_Metodologicas_WEB.pdf.
18 Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989;46:1006-11.
19 Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan – a web and mobile app for systematic reviews. Syst Rev. 2016;5:210.
20 Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
21 Cashin AG, McAuley JH. Clinimetrics: Physiotherapy Evidence Database (PEDro) Scale. J Physiother. 2020;66:59.
22 Jacobs AK, Kushner FG, Ettinger SM, Guyton RA, Anderson JL, Ohman EM, et al. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61:213-65.
23 Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
24 Fineberg NA, Baldwin DS, Drummond LM, Wyatt S, Hanson J, Gopi S, et al. Optimal treatment for obsessive compulsive disorder: a randomized controlled feasibility study of the clinical-effectiveness and cost-effectiveness of cognitive-behavioural therapy, selective serotonin reuptake inhibitors and their combination in the management of obsessive compulsive disorder. Int Clin Psychopharmacol. 2018;33:334-48.
25 Meng FQ, Han HY, Luo J, Liu J, Liu ZR, Tang Y, et al. Efficacy of cognitive behavioural therapy with medication for patients with obsessive-compulsive disorder: a multicentre randomised controlled trial in China. J Affect Disord. 2019;253:184-92.
26 Foa EB, Simpson HB, Liebowitz MR, Powers MB, Rosenfield D, Cahill SP, et al. Six-month follow-up of a randomized controlled trial augmenting serotonin reuptake inhibitor treatment with exposure and ritual prevention for obsessive-compulsive disorder. J Clin Psychiatry. 2013;74:464-9.
27 Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). Cochrane Database Syst Rev. 2008;2008:CD001765.
28 Mowla A, Modarresi F, Dastgheib SA. Comparing escitaloipram with sertraline for obsessive and compulsive symptoms in patients with obsessive compulsive disorder: a comparative double blind clinical trial. Asian J Psychiatr. 2018;38:92-5.
29 Fineberg NA, Reghunandanan S, Brown A, Pampaloni I. Pharmacotherapy of obsessive-compulsive disorder: evidence-based treatment and beyond. Aust N Z J Psychiatry. 2013;47:121-41.
30 Skapinakis P, Caldwell DM, Hollingworth W, Bryden P, Fineberg NA, Salkovskis P, et al. Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry. 2016;3:730-9.
31 Freeman CP, Trimble MR, Deakin JF, Stokes TM, Ashford JJ. Fluvoxamine versus clomipramine in the treatment of obsessive compulsive disorder: a multicenter, randomized, double-blind, parallel group comparison. J Clin Psychiatry. 1994;55:301-5.
32 Koran LM, McElroy SL, Davidson JR, Rasmussen SA, Hollander E, Jenike MA. Fluvoxamine versus clomipramine for obsessive-compulsive disorder: a double-blind comparison. J Clin Psychopharmacol. 1996;16:121-9.
33 Mundo E, Maina G, Uslenghi C. Multicentre, double-blind, comparison of fluvoxamine and clomipramine in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol. 2000;15:69-76.
34 Pigott TA, Pato MT, Bernstein SE, Grover GN, Hill JL, Tolliver TJ, et al. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Behavioral and biological results. Arch Gen Psychiatry. 1990;47:926-32.
35 López-Ibor Jr JJ, Saiz J, Cottraux J, Note I, Viñas R, Bourgeois M, et al. Double-blind comparison of fluoxetine versus clomipramine in the treatment of obsessive compulsive disorder. Eur Neuropsychopharmacol. 1996;6:111-8.
36 Zohar J, Judge R. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. OCD Paroxetine Study Investigators. Br J Psychiatry. 1996;169:468-74.
37 Bisserbe J, Lane R, Flament M; Franco-Belgian OCD Study Group. A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. Eur Psychiatry. 1997;12:82-93.
38 Denys D, van Megen HJ, van der Wee N, Westenberg HG. A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. J Clin Psychiatry. 2004;65:37-43.
39 Albert U, Aguglia E, Maina G, Bogetto F. Venlafaxine versus clomipramine in the treatment of obsessive-compulsive disorder: a preliminary single-blind, 12-week, controlled study. J Clin Psychiatry. 2002;63:1004-9.
40 Yaryura-Tobias JA, Neziroglu FA. Venlafaxine in obsessive-compulsive disorder. Arch Gen Psychiatry. 1996;53:653-4.
41 Mowla A, Boostani S, Dastgheib SA. Duloxetine augmentation in resistant obsessive-compulsive disorder: a double-blind controlled clinical trial. J Clin Psychopharmacol. 2016;36:720-3.
42 Prakash S, Rathore C, Rana K, Prakash A. Fatal serotonin syndrome: a systematic review of 56 cases in the literature. Clin Toxicol (Phila). 2021;59:89-100.
43 Stein DJ, Andersen EW, Tonnoir B, Fineberg N. Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. Curr Med Res Opin. 2007;23:701-11.
44 Hollander E, Allen A, Steiner M, Wheadon DE, Oakes R, Burnham DB, et al. Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. J Clin Psychiatry. 2003;64:1113-21.
45 Montgomery SA, McIntyre A, Osterheider M, Sarteschi P, Zitterl W, Zohar J, et al. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. The Lilly European OCD Study Group. Eur Neuropsychopharmacol. 1993;3:143-52.
46 Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry. 1995;52:289-95.
47 Issari Y, Jakubovski E, Bartley CA, Pittenger C, Bloch MH. Early onset of response with selective serotonin reuptake inhibitors in obsessive-compulsive disorder: a meta-analysis. J Clin Psychiatry. 2016;77:e605-11.
48 Bloch MH, McGuire J, Landeros-Weisenberger A, Leckman JF, Pittenger C. Meta-analysis of the dose-response relationship of

SSRI in obsessive-compulsive disorder. Mol Psychiatry. 2010;15: 850-5.
49 Ninan PT, Koran LM, Kiev A, Davidson JR, Rasmussen SA, Zajecka JM, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. J Clin Psychiatry. 2006;67:15-22.
50 Dougherty DD, Jameson M, Deckersbach T, Loh R, Thompson-Hollands J, Jenike M, et al. Open-label study of high (30 mg) and moderate (20 mg) dose escitalopram for the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol. 2009;24:306-11.
51 Rabinowitz I, Baruch Y, Barak Y. High-dose escitalopram for the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol. 2008;23(1):49-53.
52 Costa DLC, Shavitt RG, Cesar RCC, Joaquim MA, Borcato S, Valério C, et al. Can early improvement be an indicator of treatment response in obsessive-compulsive disorder? Implications for early-treatment decision-making. J Psychiatr Res. 2013;47:1700-7.
53 Pato MT, Zohar-Kadouch R, Zohar J, Murphy DL. Return of symptoms after discontinuation of clomipramine in patients with obsessive-compulsive disorder. Am J Psychiatry. 1988;145:1521-5.
54 Koran LM, Hackett E, Rubin A, Wolkow R, Robinson D. Efficacy of sertraline in the long-term treatment of obsessive-compulsive disorder. Am J Psychiatry. 2002;159:88-95.
55 Romano S, Goodman W, Tamura R, Gonzales J. Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. J Clin Psychopharmacol. 2001;21:46-52.
56 Fineberg NA, Tonnoir B, Lemming O, Stein DJ. Escitalopram prevents relapse of obsessive-compulsive disorder. Eur Neuropsychopharmacol. 2007;17:430-9.
57 National Collaborating Centre for Mental Health (UK). Obsessive-compulsive disorder: core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder. Leicester: British Psychological Society; 2006.
58 US Food and Drugs Administration [Internet]. FDA Drug Safety Communication: abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). May Aug 24. [cited 2011 Aug 25]. http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm.
59 Diniz JB, Shavitt RG, Fossaluza V, Koran L, Pereira CA, Miguel EC. A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive-compulsive disorder. J Clin Psychopharmacol. 2011;31:763-8.
60 Popli AP, Baldessarini RJ, Cole JO. Interactions of Serotonin Reuptake Inhibitors With Tricyclic Antidepressants. Arch Gen Psychiatry. 1994;51:666-7.
61 Komossa K, Depping AM, Meyer M, Kissling W, Leucht S. Second-generation antipsychotics for obsessive compulsive disorder. Cochrane Database Syst Rev. 2010:CD008141.
62 Veale D, Miles S, Smallcombe N, Ghezai H, Goldacre B, Hodsoll J. Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis. BMC Psychiatry. 2014;14:317.
63 Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo-controlled trials. Int J Neuropsychopharmacol. 2015;18:pyv047.
64 Brakoulias V, Stockings E. A systematic review of the use of risperidone, paliperidone and aripiprazole as augmenting agents for obsessive-compulsive disorder. Expert Opin Pharmacother. 2019; 20:47-53.
65 Foa EB, Simpson HB, Rosenfield D, Liebowitz MR, Cahill SP, Huppert JD, et al. Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and response prevention or risperidone in adults with obsessive-compulsive disorder. J Clin Psychiatry. 2015;76:440-6.
66 Storch EA, Goddard AW, Grant JE, De Nadai AS, Goodman WK, Mutch PJ, et al. Double-blind, placebo-controlled, pilot trial of paliperidone augmentation in serotonin reuptake inhibitor-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2013;74:e527-32.
67 Talaei A, Hosseini FF, Aghili Z, Akhondzadeh S, Asadpour E, Mehramiz NJ, et al. A comparative, single-blind, randomized study on quetiapine and aripiperazole augmentation in treatment of selective serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Can J Physiol Pharmacol. 2020;98:236-42.
68 Shafti SS, Kaviani H. Aripiprazole versus quetiapine in treatment-resistant obsessive-compulsive disorder: a double-blind clinical trial. Ther Adv Psychopharmacol. 2015;5:32-7.
69 Shafti SS, Kaviani H. Adjunctive quetiapine may help fluvoxamine-resistant obsessive-compulsive disorder among female in-patients: a randomized-controlled study. Psychiatr Clin Psychopharmacol. 2019;29:171-7.
70 Shafti SS, Kaviani H. Evaluation of second generation antipsychotics, as augmentative plan, in treatment-resistant obsessive-compulsive disorder. Curr Psychopharmacol. 2019;8:146-54.
71 Muscatello MR, Bruno A, Pandolfo G, Micò U, Scimeca G, Romeo VM, et al. Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. J Clin Psychopharmacol. 2011;31:174-9.
72 Sayyah M, Sayyah M, Boostani H, Ghaffari SM, Hoseini A. Effects of aripiprazole augmentation in treatment-resistant obsessive-compulsive disorder (a double blind clinical trial). Depress Anxiety. 2012;29:850-4.
73 Bystritsky A, Ackerman DL, Rosen RM, Vapnik T, Gorbis E, Maidment KM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. J Clin Psychiatry. 2004;65: 565-8.
74 Shapira NA, Ward HE, Mandoki M, Murphy TK, Yang MC, Blier P, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. Biol Psychiatry. 2004;55:553-5.
75 McDougle CJ, Goodman WK, Leckman JF, Lee NC, Heninger GR, Price LH. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. A double-blind, placebo-controlled study in patients with and without tics. Arch Gen Psychiatry. 1994;51:302-8.
76 Li X, May RS, Tolbert LC, Jackson WT, Flournoy JM, Baxter LR. Risperidone and haloperidol augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder: a crossover study. J Clin Psychiatry. 2005;66:736-43.
77 Naderi S, Faghih H, Aqamolaei A, Mortazavi SH, Mortezaei A, Sahebolzamani E, et al. Amantadine as adjuvant therapy in the treatment of moderate to severe obsessive-compulsive disorder: A double-blind randomized trial with placebo control. Psychiatry Clin Neurosci. 2019;73:169-74.
78 Farnia V, Gharehbaghi H, Alikhani M, Almasi A, Golshani S, Tatari F, et al. Efficacy and tolerability of adjunctive gabapentin and memantine in obsessive compulsive disorder: Double-blind, randomized, placebo-controlled trial. J Psychiatr Res. 2018;104: 137-43.
79 Rodriguez CI, Kegeles LS, Levinson A, Feng T, Marcus SM, Vermes D, et al. Randomized controlled crossover trial of ketamine in obsessive-compulsive disorder: proof-of-concept. Neuropsychopharmacology. 2013;38:2475-83.
80 Rodriguez CI, Lapidus KAB, Zwerling J, Levinson A, Mahnke A, Steinman SA, et al. Challenges in testing intranasal ketamine in obsessive-compulsive disorder. J Clin Psychiatry. 2017;78:466-7.
81 Arabzadeh S, Shahhossenie M, Mesgarpour B, Rezaei F, Shalbafan MR, Ghiasi Z, et al. L-carnosine as an adjuvant to fluvoxamine in treatment of obsessive compulsive disorder: a randomized double-blind study. Hum Psychopharmacol.2017;32.
82 Khalkhali M, Aram S, Zarrabi H, Kafie M, Heidarzadeh A. Lamotrigine augmentation versus placebo in serotonin reuptake inhibitors-resistant obsessive-compulsive disorder: a randomized controlled trial. Iran J Psychiatry. 2016;11:104-14.
83 Moon J, Park HK, Chu K, Sunwoo JS, Byun JI, Lim JA, et al. The HLA-A*2402/Cw*0102 haplotype is associated with lamotrigine-induced maculopapular eruption in the Korean population. Epilepsia. 2015;56:e161-7.
84 Kim BK, Jung JW, Kim TB, Chang YS, Park HS, Moon J, et al. HLA-A*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population. Ann Allergy Asthma Immunol. 2017;118(5):629-30.
85 Wong IC, Mawer GE, Sander JW. Factors influencing the incidence of lamotrigine-related skin rash. Ann Pharmacother. 1999;33: 1037-42.

86 Guberman AH, Besag FM, Brodie MJ, Dooley JM, Duchowny MS, Pellock JM, et al. Lamotrigine-associated rash: risk/benefit considerations in adults and children. Epilepsia. 1999;40:985-91.
87 Rutrick D, Stein DJ, Subramanian G, Smith B, Fava M, Hasler G, et al. Mavoglurant augmentation in OCD patients resistant to selective serotonin reuptake inhibitors: a proof-of-concept, randomized, placebo-controlled, phase 2 study. Adv Ther. 2017;34: 524-41.
88 Kishi T, Matsuda Y, Iwata N. Combination Therapy of serotonin reuptake inhibitors and memantine for obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. J Alzheimers Dis. 2018;64:43-8.
89 Modarresi A, Chaibakhsh S, Koulaeinejad N, Koupaei SR. A systematic review and meta-analysis: Memantine augmentation in moderate to severe obsessive-compulsive disorder. Psychiatry Res. 2019;282:112602.
90 Afshar H, Roohafza H, Mohammad-Beigi H, Haghighi M, Jahangard L, Shokouh P, et al. N-acetylcysteine add-on treatment in refractory obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. J Clin Psychopharmacol. 2012;32:797-803.
91 Sarris J, Oliver G, Camfield DA, Dean OM, Dowling N, Smith DJ, et al. N-Acetyl Cysteine (NAC) in the treatment of obsessive-compulsive disorder: a 16-week, double-blind, randomised, placebo-controlled study. CNS Drugs. 2015;29:801-9.
92 Paydary K, Akamaloo A, Ahmadipour A, Pishgar F, Emamzadehfard S, Akhondzadeh S. N-acetylcysteine augmentation therapy for moderate-to-severe obsessive-compulsive disorder: randomized, double-blind, placebo-controlled trial. J Clin Pharm Ther. 2016; 41:214-9.
93 Costa DLC, Diniz JB, Requena G, Joaquim MA, Pittenger C, Bloch MH, et al. Randomized, double-blind, placebo-controlled trial of N-acetylcysteine augmentation for treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2017;78:e766-3.
94 Mowla A, Ghaedsharaf M. Pregabalin augmentation for resistant obsessive-compulsive disorder: a double-blind placebo-controlled clinical trial. CNS Spectr. 2020;25:552-6.
95 Pittenger C, Bloch MH, Wasylink S, Billingslea E, Simpson R, Jakubovski E, et al. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a pilot randomized placebo-controlled trial. J Clin Psychiatry. 2015;76:1075-84.
96 Emamzadehfard S, Kamaloo A, Paydary K, Ahmadipour A, Zeinoddini A, Ghaleiha A, et al. Riluzole in augmentation of fluvoxamine for moderate to severe obsessive-compulsive disorder: Randomized, double-blind, placebo-controlled study. Psychiatry Clin Neurosci. 2016;70:332-41.
97 Afshar H, Akuchekian S, Mahaky B, Zarean E. Topiramate augmentation in refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled trial. J Res Med Sci. 2014; 19:976-81.
98 Foa EB, Liebowitz MR, Kozak MJ, Davies S, Campeas R, Franklin ME, et al. Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. Am J Psychiatry. 2005; 162:151-61.
99 Del Casale A, Sorice S, Padovano A, Simmaco M, Ferracuti S, Lamis DA, et al. Psychopharmacological treatment of obsessive-compulsive disorder (OCD). Curr Neuropharmacol. 2019;17: 710-36.
100 Shapiro DA, Cavanagh K, Lomas H. Geographic inequity in the availability of cognitive behavioural therapy in England and Wales. Behav Cogn Psychother. 2003;31:185-92.
101 Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. 2010;15:53-63.
102 Andrade C. Augmenting selective serotonin reuptake inhibitors with clomipramine in obsessive-compulsive disorder: benefits and risks. J Clin Psychiatry. 2013;74:e1128-33.
103 Diniz JB, Shavitt RG, Pereira CA, Hounie AG, Pimentel I, Koran LM, et al. Quetiapine versus clomipramine in the augmentation of selective serotonin reuptake inhibitors for the treatment of obsessive-compulsive disorder: a randomized, open-label trial. J Psychopharmacol. 2010;24:297-307.
104 Crapanzano C, Francesco Laurenzi P, Casolaro I, Politano A, Amendola C. Antipsychotic monotherapy in obsessive-compulsive disorder. Psychiatr Danub. 2022;34:106.
105 Matsunaga H, Nagata T, Hayashida K, Ohya K, Kiriike N, Stein DJ. A long-term trial of the effectiveness and safety of atypical antipsychotic agents in augmenting SSRI-refractory obsessive-compulsive disorder. J Clin Psychiatry. 2009;70:863-8.
106 Schmidt H, Hagen M, Kriston L, Soares-Weiser K, Maayan N, Berner M. Management of sexual dysfunction due to antipsychotic drug therapy. Cochrane Database Syst Rev. 2012;11:CD003546.
107 Mataix-Cols D, Cruz LF, Nordsletten AE, Lenhard F, Isomura K, Simpson HB. Towards an international expert consensus for defining treatment response, remission, recovery and relapse in obsessive-compulsive disorder. World Psychiatry. 2016;15:80-1.