Pharmacotherapy for treatment-respondent vs. refractory obsessive–compulsive disorder in children and adults: strategies, meta-analyses and clinical guidelines

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Summary
Obsessive–compulsive disorder (OCD) is a common mental health disorder that occurs at all ages, but more commonly in younger people. It affects 1–1.5% of the general population. Many pharmacological therapies have been reported to diminish OCD symptoms, as well as increase the patient’s quality of life. So far, several meta-analyses have directly compared such treatment approaches in treatment-responsive and treatment-resistant OCD. This review evaluated all treatment options for OCD in both children and adolescents, and aimed to establish whether existing pharmacological therapies work similarly well, taking into account medical comorbidities such as substance use, anxiety, metabolic disorders, and finally, an overview of issues related to safety and monitoring. Our review included data from 16 meta-analyses and 8 practical guidelines focusing on OCD patients. In adults with OCD, we found that combined therapy shows favorable outcomes versus SRI alone and produced better results. In children with OCD the greatest incremental treatment gains occur early in treatment with selective serotonin reuptake inhibitors (SSRIs). Finally, in treatment-resistant OCD augmentation of SRIs can be regarded as an evidence-based measure in pharmacological therapy. The results of this review mostly support the previous reviews on the pharmacological management of OCD. However, we noted that combination/augmentation of SSRIs significantly improved symptoms in treatment-resistant OCD compared with monotherapy. From a clinical perspective, antipsychotics combination/augmentation of SSRIs should be used in comorbid psychosis, a frequent comorbidity in OCD, especially as the presence of comorbidities is highly associated with treatment resistance in OCD.

INTRODUCTION
Obsessive–compulsive disorder (OCD) is a common mental health disorder that occurs at all ages, but is more common in younger people, with uncontrollable, repeated thoughts, urges or mental images (obsessions) and repetitive behaviors and feelings in response to an obsessive thought (compulsions) [1]. Although OCD
may initially reduce anxiety in the individual, it generally affects their lifestyle. Symptoms of OCD span a mild to severe range. Some people may have obsessive thoughts, while some may be able to control obsessive thoughts and involuntary behaviors for a short time and thus mask their symptoms when at school or at work. But in more severe cases, OCD can take over so much of a person’s life that they can no longer work or perform day-to-day activities, as they spend a lot of their time on an obsessive ritual. Obsessions include thoughts, images or impulses that occur repeatedly (such as hesitation and doubt about doing a job); the person thinks they are outside of their control and find them uncomfortable, disturbing and meaningless [2]. Compulsive obsessions are compulsory acts that a person performs repeatedly and in accordance with a series of rules and rituals to neutralize their obsessive thoughts, such as rechecking, washing, numbering, asking, preoccupation with symmetry and accuracy, and storing too many objects. But symptoms such as hate or anxiety about body secretions (urine, feces, saliva), fear of the possibility of terrible events happening (fire, death of a relative, wasting and excessive worship, belief in special properties of numbers like 13, chewing nails) may also be considered obsessive symptoms [2]. OCD is sometimes associated with depression, eating disorders (overeating or anorexia nervosa), substance abuse (addiction), personality disorder, attention deficit and hyperactivity disorder (ADHD) or other anxiety disorders, which probably occur because of universal dimensions of distress or negative affectivity, a common genetic predisposition and a shared neurobiology [3]. Combining these disorders with the desire to hide the problem makes it difficult to diagnose and treat it and so people with OCD do not receive treatment for many years after the onset of the symptoms.

DIAGNOSIS

OCD diagnosis presents diagnostic challenges due to the similarity and overlapping of symptoms with those of personality, anxiety, depression, schizophrenia or other mental health disorders [7]. Moreover, it is possible to have OCD comorbid with another mental health disorder [8]. Usually an OCD diagnosis is made by clinical interview based on DSM-IV diagnostic criteria for OCD, which include the existence of obsessions and compulsions. Adolescence, impulse, reversible mental retardation, disruptive and maladaptive disturbances leading to anxiety or discomfort could all be misdiagnosed as OCD [9]. Patients with OCD take approximately 10
years to be diagnosed correctly; thus, if it is diagnosed correctly at an early stage, OCD can be treated well and efficiently [10].

PREVALENCE

Epidemiological studies have shown the prevalence of OCD ranging from 1 to 3%, ranking it the 4th most often occurring psychiatric disorder. Usually about 10% of patients are referred to neurologists, psychiatrists and psychologists. According to the World Health Organization (WHO), OCD is the fourth substance-related and major depressive disorder. Among adolescents, boys suffer from this disorder more often than girls, and the prevalence rate is the same among adults [11-13]. Onset is on average at the age of 20; in men it happens a bit earlier and in women it is at about 22.

TREATMENT APPROACHES

• Conventional treatment for OCD

Similar to adults with OCD, as well as children and adults with major depression, the highest incremental treatment gains in pediatric patients with OCD happen early in SSRI treatment [14]. Former studies have revealed that nearly 60% of the patients with OCD treated with SS-RIs showed a 25–35% reduction in symptoms according to the Yale–Brown Obsessive Compulsive Scale (Y-BOCS), which is not enough to reach an acceptable level of quality of life [15,16]. A decline of <25% in a Y-BOCS score is seen as non-response to treatment [17], while response to therapy is defined as a 35–50% Y-BOCS score decrease [18]. Even with a modest reduction in Y-BOCS scores, a response to therapy of more than 3 to 5% reduction of symptoms is usually attained with placebo [19]. The term recovery has been proposed to describe a nearly complete OCD remission or a widespread absence of symptoms, as well as a Y-BOCS score of ≤ 8 [20]. It was also proposed that treatment-resistant OCD occurs in patients who had been exposed to first-line therapies but did not achieve a satisfactory response to treatment; in this paper, refractory OCD is defined as OCD in a patient who did not respond suitably to several conventionally effective treatments [6]. A flow diagram of conventional treatment options usually considered in OCD is presented below (Figure 1).

• Treatment approaches for treatment-resistant (refractory) OCD

Treatment-resistant OCD, defined as OCD in patients who are treated with a sufficient course of SRI therapy (clomipramine or SSRI) but who do not respond or display an unsatisfactory response; it accounts for 40–50% of all cases of OCD [21,22]. When treatment resistance is present, a logical next strategy is augmentation with a pharmacological agent such as an antipsychotic; however, even augmentation with a pharmacological agent created a substantial response in only one-third of patients [23]. Studies revealed a more effective response in patients with a history of maximal SSRI monotherapy for more than 12 weeks. Further treatment approaches comprise continuing with the selected SSRI for 3 to 6 months, dose titration to the maximum tolerated dose, switching medications or augmenting treatment with another first-line agent. Switching to further treatment approaches is recommended when patients still do not respond to treatment. In one study, authors reported that the ethanol-like experience suggests that µ-agonists and glutamate antagonists might be an option during the exacerbation of symptoms; however, these treatments warrant further validation [24]. Despite significant advances in OCD diagnosis and treatment strategies, some patients either do not respond at all or show little response to treatment [25]. Some patients with OCD get slightly better, but they remain with symptoms that are associated with no improvement in performance and quality of life. OCD can also be difficult to treat with an exposure and response prevention therapy [26]. Pharmacological management of treatment-resistant OCD is summarized in Figure 2. The meta-analyses revealed the effectiveness of a combination treatment with antipsychotics and SRIs, as well as the possible consideration of risperidone as an agent of first choice, which should be preferred to quetiapine and olanzapine, especially in patients who do not respond to conventional pharmacotherapies.

• Combination therapy: old procedure, new path

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An inclusive systematic review and meta-analysis of all existing studies on psychotherapeutic and psychopharmacological treatments recommended a combination therapy, as it may be the most effective approach in OCD treatment [27]. In an open-label case series, patients with OCD were successfully treated with combination of clomipramine plus an SSRI, but some adverse effects appeared in most patients, including cardiovascular, tachycardia, manic switch, insomnia and in some cases headaches [28]. Thus, recommendations for combination therapy are to control electrocardiograms (ECG), drug blood concentrations and vital signs because SSRIs could raise the blood levels of clomipramine, whereas clomipramine may also possibly increase SSRI absorption. In this context, in a randomized trial of a new combined approach, patients with OCD who had responded to a 3-month drug therapy with venlafaxine or paroxetine received additional cognitive behavior therapy (CBT), and reported that this approach is useful; CBT was recommended to be added immediately after drug response was achieved [29]. In a case report, a patient with OCD who received combination therapy with escitalopram and fluvoxamine experienced a remarkable improvement, especially in social functioning [30]. Furthermore, combination therapy is more recommended for treatment-resistant OCD [31]. Another study reported a patient with treatment-resistant OCD who benefited from a combination therapy of buspirone and sertraline [32]. Despite this fact, combination therapy with two SSRIs is not recommended due to the risk of drug interactions. From a clinical perspective, antipsychotics combination/augmentation of SSRIs should be used if there is comorbid psychosis, as comorbidity is highly associated with treatment resistance in OCD [33].
Further treatment options

Although current pharmacotherapy strategies may be useful, as they increase the effectiveness of treatment, pharmacotherapy may not be applicable to all patients. Therefore, other therapeutic interventions are needed to target poor prognosis and resistance to therapies. New interventions should target the limitations of current therapeutic interventions. Given the importance of the route of drug administration in OCD, intravenous route (IV) could be superior to oral administration. A 3-week open-label trial of intravenous citalopram for OCD patients unresponsive to at least two orally administered SSRIs indicated a response rate of 59% [34]. In a double-blind controlled trial of IV compared with orally administered clomipramine over a 12-week treatment, pulse-loaded IV did not induce a greater Y-BOCS score reduction in treatment-resistant OCD [35]. Another open-label trial was performed to assess the efficacy of IV administered clomipramine in treatment-resistant OCD, and reported that IV route could be beneficial for patients with severe OCD that is unresponsive to several therapies, including orally administered clomipramine [36]. Other non-pharmacological treatment options are currently under evaluation, including deep brain stimulation (DBS). DBS is a neurosurgical procedure involving modulation of the brain circuits that are thought to be patient does not respond to the treatment

Meta-analyses result proposed the effectiveness of a combination treatment of antipsychotics and SSRIs

Recommendation 1: The first step in treating the patient with treatment-resistant OCD should be to examine the dose the patient is given.

Patient respond to the treatment

High-dose escitalopram (50 mg/day) and of high-dose sertraline (400 mg/day)

Patient respond to the treatment

Maximum doses: 120 mg/day for citalopram, 300 mg/day for clomipramine, 60 mg/day for escitalopram, 120 mg/day for fluoxetine, 450 mg/day for fluvoxamine, 100 mg/day for paroxetine and 400 mg/day for sertraline.

Recommendation 2: only after SSRI failure (with an adequate dose and for an adequate duration) should the physician consider changing the medication, or augmentation

Attempt to increase the dose, for at least 12 weeks, while monitoring the adverse effects

Patient responds to the treatment

No advantages of clomipramine over an SSRI. Clomipramine has more adverse effects and is generally less safe, so there are no reasons to switch to clomipramine over an SSRI

Should switch from an SSRI to clomipramine or to another SSRI?

Fig. 2. Pharmacological management of treatment-resistant OCD
implicated in OCD. This non-pharmacological treatment is a conventional approach for severe, treatment-resistant neurological disorders such as Parkinson’s disease, dystonia and essential tremor [37], as well as being currently evaluated for a number of psychiatric disorders [38]. Balderrmann et al., in a meta-analysis of 57 studies evaluated the efficacy of DBS for Tourette syndrome using the pooled Yale Global Tic Severity Scale (YGTSS) as the primary outcome. Even with small patient numbers (156 cases), they concluded that DBS can be considered as a valid option for medically intractable patients with Tourette syndrome [39]. Alonso et al. studied the existence of clinical predictors of response to DBS in OCD alongside its efficacy and tolerability in a meta-analysis of 31 studies involving 116 subjects. They confirmed that DBS is a valid alternative to lesion surgery for patients with severe, treatment-resistant OCD [40].

EVIDENCE

At the time of our study, 16 meta-analyses were available on the effectiveness of pharmacotherapy for patients with OCD (Table 1); 4 have examined the efficacy in treatment-resistant OCD. In 2011, Dold et al. conducted a meta-analysis of 11 double-blind, randomized, placebo-controlled trials with a total of 356 subjects on the efficacy of a combination therapy of SRIs and antipsychotics in treatment-resistant OCD. They showed significant differences regarding the antipsychotic dosage and SRI treatment duration before the augmentation [41]. They updated this systematic review in 2013 [42] and again in 2015 [43], and concluded that risperidone can be considered as the agent of first choice and more trials including higher antipsychotic doses are required to improve pharmacological treatment for treatment-resistant OCD; and that antipsychotic augmentation of SRIs can be regarded as an evidence-based measure in these cases. Recently, Soleimani et al. published a protocol for a systematic review and meta-analysis of all randomized clinical trials evaluating lithium, anticonvulsive or antipsychotic medication for patients with treatment-resistant OCD, but no results have been reported so far [44]. The remaining 14 meta-analyses included patients with treatment-respondent OCD. Of these 14 studies, 6 were about double-blind, randomized, placebo-controlled trials on pediatric patients with OCD that showed superiority of SRIs for the treatment of OCD with a moderate effect size and a non-significant risk of suicidality, as well as that combined therapy was no more effective irrespective of the initial severity of the samples [14, 45-49]. All meta-analyses found that high doses of SSRIs were more effective as first-line therapy for patients with OCD; however, combined therapy was more effective than monotherapy. Though the treatment effect of pharmacotherapy has been estimated by various statistical measures, all meta-analyses reported a significant improvement with SRIs, as well as SSRIs in combination with other treatment approaches.

Table 1. Summary of the data obtained in previous meta-analyses on OCD treatment

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Target study design</th>
<th>Comparison groups</th>
<th>No. of paper included</th>
<th>Patient group</th>
<th>Number of cases</th>
<th>Estimated value</th>
<th>Final finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dold et al.,</td>
<td>DB-RPCT</td>
<td>SRI plus anti-psychotic</td>
<td>11 studies</td>
<td>TR-OCD</td>
<td>356 patients</td>
<td>RR (95%CI) : (1.36-3.43) PMC-Y-BOCS SMD(95%CI): 0.69 (0.38 - 1.00)</td>
<td>Effectiveness a combination treatment of antipsychotics and SRIs</td>
</tr>
<tr>
<td>2011[33]</td>
<td></td>
<td>SRI plus placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dold et al.,</td>
<td>DB-RPCT</td>
<td>SRI plus anti-psychotic</td>
<td>12 studies</td>
<td>TR-OCD</td>
<td>394 patients</td>
<td>RR (95%CI) : (2.10 (1.16-3.80) PMC-Y-BOCS SMD(95%CI): 0.54 (0.15–0.93)</td>
<td>risperidone can be considered as the agent of first choice and should be preferred to quetiapine and olanzapine</td>
</tr>
<tr>
<td>2013[34]</td>
<td></td>
<td>SRI plus placebo</td>
<td></td>
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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment 1</th>
<th>Treatment 2</th>
<th>Number of Studies</th>
<th>Patients</th>
<th>Effect Size</th>
<th>Effect Size (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sánchez-Meca et al., 2014[35]</td>
<td>DB-RPCT</td>
<td>PT CBT CMB</td>
<td>Placebo</td>
<td>18</td>
<td>1223</td>
<td>d+ (95%CI)</td>
<td>PT: 0.74 (0.36-1.13) CBT: 1.74 (1.33-2.14) CMB: 1.71 (1.0 – 2.42)</td>
<td>Clomipramine was more efficacious than SSRIs, but its adverse effects were more severe.</td>
</tr>
<tr>
<td>Romanelli et al., 2014[36]</td>
<td>HTH-RCT</td>
<td>PT CBT CMB</td>
<td>Placebo</td>
<td>13</td>
<td>959</td>
<td>PMC-Y-BOCS PT, SMD(95%CI): 0.22 (-0.02 – 0.47) CBT, SMD(95%CI): 0.37 (0.10 – 0.64)</td>
<td>BT is more effective than SSRIs, overall, but not selective SRIs. The combination of behavioral therapy plus an SRI is more effective than an SRI alone.</td>
<td></td>
</tr>
<tr>
<td>Ducasse et al., 2014 [37]</td>
<td>DB-RPCT</td>
<td>SRI plus anti-psychotic SRI plus placebo</td>
<td>Placebo</td>
<td>13</td>
<td>431</td>
<td>————</td>
<td>risperidone proved its effectiveness; aripiprazole, haloperidol, and amisulpride showed good preliminary data</td>
<td></td>
</tr>
<tr>
<td>Skarphedinsson et al., 2015[38]</td>
<td>DB-RPCT</td>
<td>SI-CBT Placebo</td>
<td>13</td>
<td>757</td>
<td>PMC-Y-BOCS SMD(95%CI): -0.2 (-2.32 – 1.9)</td>
<td>The effects of SI-CBT and active treatments were not significantly different</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strawn et al., 2015[39]</td>
<td>DB-RPCT</td>
<td>SSRIs SSNRIs Placebo</td>
<td>9</td>
<td>1,673</td>
<td>d+ (95%CI) 0.64 (0.34 – 0.96)</td>
<td>Superiority to placebo for the treatment of pediatric anxiety disorders with a moderate effect size and a non-significant risk of suicidality</td>
<td></td>
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</tr>
<tr>
<td>Ivarsson et al., 2015[40]</td>
<td>DB-RPCT</td>
<td>SSRIs Placebo CBT</td>
<td>14</td>
<td>1136</td>
<td>PMC-Y-BOCS SMD(95%CI): -3.5 (-4.6 – -2.3)</td>
<td>CBT has the superior efficacy. CMB versus CBT shows that SRI treatment adds little to concomitant CBT, while CMB shows favorable outcome versus SRI alone</td>
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</tbody>
</table>
### Pharmacotherapy for treatment-respondent vs. refractory obsessive–compulsive disorder in children

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Design</th>
<th>Intervention/Comparator</th>
<th>N</th>
<th>Outcome</th>
<th>Effect Size</th>
</tr>
</thead>
</table>
| Dold et al., 2015[41] | DB-RPCT | SRI plus antipsychotic vs. SRI plus placebo | 14 studies | TR-OCD | Hg: SMD(95%CI): -0.64 (-4.6 – -2.3)  
MH: RR (95%CI) : 1.98 (1.34-2.92)  
Antipsychotic augmentation of SRIs can be regarded as an evidence-based measure in TR-OCD |
| McGuire et al., 2015[42] | DB-RPCT | PT vs. CBT vs. CMB vs. placebo | 20 studies | P-OCD | PT, RR(95%CI): 0.50 0.37 – 0.63  
CBT, RR(95%CI): 1.21 (0.83 – 0.1.59)  
The treatment effects for CBT and SRIs across three important outcome metrics, and provide evidence for moderators of CBT across trials. |
| Brakoulias et al., 2015[43] | ALL* | PT vs. CBT | 7 studies | OCD | ER (95%CI): 0.58 (0.37–0.76)  
Study encourages us to consider the use of SRIs in patients with hoarding disorder |
| Issari et al., 2016[44] | DB-RPCT | PT vs. placebo | 17 studies | OCD | SMD (95%CI): -0.91 (-0.54 – -1.28)  
The greatest incremental treatment gains in OCD are seen early on in SSRI treatment |
| Skapinakis et al., 2016[45] | DB-RPCT | PT vs. CBT vs. CMB vs. placebo | 86 studies | OCD | SMD (95%CI): -3.49 (-5.12 – -1.81)  
In adults, psychological interventions, clomipramine, SSRIs or combinations of these are all effective, whereas in children and adolescents, psychological interventions, either as monotherapy or combined with specific SSRIs, were more likely to be effective. |
| Öst et al., 2016[46] | DB-RPCT | PT vs. CBT vs. CMB | 42 studies | P-OCD | g-value(95%CI)  
PT: 0.48 (0.26-0.70)  
CBT: 0.53 (0.25-0.80)  
CMB: 0.80 (0.48 – 1.11)  
CMB was not more effective than CBT alone irrespective of initial severity of the samples. RCTs have a number of methodological problems |
Selective serotonin reuptake inhibitors (SSRIs); Selective serotonin-norepinephrine reuptake inhibitors (SSNRIs); Treatment-resistant obsessive-compulsive disorder (TR-OCD); Relative risk (RR); Double-blind, randomized, placebo-controlled trials (DB-RPCT); pooled mean change in the Yale-Brown obsessive compulsive scale (PMC-Y-BOCS); Pharmacological therapy (PT); Combined therapy (CMB); Pediatric-OCD (P-OCD); d+, mean effect size; head-to-head-RCTs (HTH-RCT); Children-Adult-OCD (C-A-OCD); standard individual cognitive behavior therapy (SI-CBT); Hedges’s g (Hg); Mantel-Haenszel risk ratios (MH); *, randomized controlled trial (RCT), open-label trial (OLT) or case series (CS); ER, Event Rate showing responded to pharmacotherapy; SMD, weighted mean difference on the Y-BOCS of SSRI treatment compared to placebo [50-54]. The most recent clinical practice guidelines on the pharmacotherapy of patients with OCD have been published by the British Association for Psychopharmacology. These guidelines address various features of facility provision, pharmacological methods for individuals with OCD from different age groups. While the evidence base is quickly growing, a number of major gaps and forthcoming revisions of these guidelines will integrate new scientific evidence as it develops. These guideline offer a number of recommendations to address these gaps in evidence-based practice. Moreover, as well as introducing new pharmacotherapies for individuals with OCD, the influence of many psychiatric and medical comorbidities, such as substance use, anxiety, metabolic disorders, and finally, an overview of issues related to safety and monitoring, will be addressed by these guidelines.

**PUBLISHED GUIDELINES**

To date, only five guidelines for the management of OCD have been published (Table 2)

### Table 2. Published guidelines on treatment strategies in OCD

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Organization</th>
<th>Basis of the guideline</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Baldwin et al., 2014[53] | British Association for Psychopharmacology | based on available evidence, were constructed after extensive feedback from participants | Despite the availability of many evidence-based pharmacological and psychological treatments, a substantial proportion of patients will not respond fully to initial treatments, provided in primary medical care.  
  The criteria for referral to secondary care mental health services should be sufficiently flexible to ensure that patients with disabling and treatment-resistant anxiety disorders can have equitable access to mental health specialists. |
PHARMACOLOGICAL THERAPY OF TREATMENT-RESISTANT OCD

Although CBT is considered first-line treatment for patients with OCD, pharmacological therapy is often used when poor response, greater severity, or difficulty with taking part in CBT is present. Medical experts dealing with treatment-resistant with OCD should take into account all phenomenological risk factors [55], which could lead to different interpretations and treatment choices, and be responsible poor response to conventional treatment (Figure 3). These phenomenological aspects of OCD are considered risk factors for poor response to treatment and can be divided into two categories, intrinsic and extrinsic aspects. Intrinsic aspects related to OCD that may lead to poor response to conventional treatment are listed in Figure 2. Some evidence shows that OCD patients with early onset OCD have a poor prognosis, and consequently poor response to conventional treatments [56, 57].

The alternative treatment approaches (non-conventional pharmacological approaches) to treatment-resistant OCD include greater doses of standard drugs used in conventional therapy considered with caution, intravenous monotherapy with clomipramine and citalopram, combined/augmented pharmacotherapy, and other biological interventions, such as fatty acids.

LIMITATIONS

Numerous clinical and methodological limitations possibly restraining the findings of meta-analyses, including no examination of some available drugs in double-blind studies; consequently, the efficacy of such drugs in treatment-resistant OCD patient remains unknown. A further limitation arises from the differences in the included meta-analyses in terms of their samples, therapeutic modalities, trials’ duration, comorbidities, and the administered pharmacologic agents’ doses.
CONCLUSIONS

SSRIs have been largely studied in both pediatric and adolescent patients with OCD reporting widely positive results. Based on the results of meta-analyses and practical guidelines for treatment-resistant OCD patients, SSRIs combined with antipsychotic drugs could be considered as evidence-based treatment choice in treatment-resistant OCD. Moreover, we are presently aware of a meta-analysis of head-to-head trials that directly compare antipsychotic and SSRI drugs in treatment-resistant OCD. Despite the aforementioned limitations, the methodological quality of the included meta-analyses was acceptable, and we could confirm that combination/augmentation of SSRIs significantly improved symptoms in treatment-resistant OCD patients compared with monotherapy. From a clinical perspective, antipsychotics combination/augmentation of SSRIs should be particularly beneficial if there are comorbidities such as psychosis.

REFERENCES


