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REVIEW ARTICLE

Pediatric Treatment-Resistant Obsessive Compulsive Disorder: Treatment Options and Challenges

Sana Younus[1,2] · Lauren Havel[1,2] · Jordan T. Stiede[1] · Catherine E. Rast[1] · Kirti Saxena[1,2] · Wayne K. Goodman[1] · Eric A. Storch[1]

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Abstract

Pediatric obsessive-compulsive disorder (OCD) is a chronic, potentially debilitating psychiatric condition. Although effective treatments exist, at least 10% of youth do not achieve remission despite receiving first-line treatments. This article reviews the extant, albeit limited, evidence supporting treatment approaches for youth with treatment-resistant OCD. A literature search for articles addressing pediatric treatment-resistant OCD was conducted through April 11, 2024. These results were augmented by searching for treatment-resistant OCD in adults; treatment strategies discovered for the adult population were then searched in the context of children and adolescents. In general, intensive treatment programs and antipsychotic augmentation of an antidepressant had the most substantial and consistent evidence base for treatment-resistant youth with OCD, although studies were limited and of relatively poor methodological quality (i.e., open trials, naturalistic studies). Several pharmacological approaches (clomipramine, antipsychotics [e.g., aripiprazole, risperidone], riluzole, ketamine, D-cycloserine, memantine, topiramate, *N*-acetylcysteine, ondansetron), largely based on supporting data among adults, have received varying levels of investigation and support. There is nascent support for how to treat pediatric treatment-resistant OCD. Future treatment studies need to consider how to manage the significant minority of youth who fail to benefit from first-line treatment approaches.

Key Points

There is limited, empirical guidance for how to treat pediatric treatment-resistant obsessive-compulsive disorder (OCD).

Intensive treatment programs and combined antipsychotic and antidepressant treatment had the most substantial support, although methodologically rigorous studies were limited.

Future research should further investigate novel medications, non-invasive neurostimulation, and intensive forms of psychotherapy for pediatric treatment-resistant OCD.

✉ Eric A. Storch
eric.storch@bcm.edu

[1] Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, 1977 Butler Blvd, Suite 4-400, Houston, TX 77030, USA

[2] Texas Children's Hospital, Houston, TX, USA

1 Introduction

Pediatric obsessive-compulsive disorder (OCD) is a chronic, potentially debilitating psychiatric condition characterized by intrusive, distressing thoughts (obsessions) and repetitive, time-consuming behaviors (compulsions) [1–3]. It affects approximately 0.5–2% of children and adolescents with rates consistent across geographic regions [4–12]. Evidence-based interventions include a specific type of cognitive-behavioral therapy (CBT) called exposure and response prevention (ERP) and serotonin reuptake inhibitors (SRIs) [13, 14]. Fluvoxamine, fluoxetine, sertraline, and clomipramine are the SRIs approved by the US Food and Drug Association (FDA) for treatment of pediatric OCD [15]. While all these medications inhibit serotonin reuptake, clomipramine, a tricyclic antidepressant, has a broader mechanism of action and hence broader side effect profile, as it also inhibits norepinephrine reuptake, has anticholinergic, antihistaminergic properties, and blocks alpha adrenergic receptors. Fluvoxamine, fluoxetine, and sertraline selectively act on serotonin receptors and hence are categorized as selective serotonin reuptake

inhibitors (SSRI). ERP for pediatric OCD has consistently demonstrated response in 70–75% of cases [14, 16]. SSRI monotherapy has demonstrated response in 50–60% of cases [14, 17], with mixed evidence suggesting benefit of combined treatment for youth with moderately severe OCD [18, 19]. Practice guidelines suggest that youth with mild and moderate severity be treated with ERP alone, and those with more severe OCD be treated with combined ERP-SRI therapy [20]. There is evidence that youth who fail to adequately respond to ERP alone do similarly well whether they continue ERP or switch to sertraline, with approximately 50% responding to each [21].

While many children and adolescents with OCD benefit from evidence-based interventions, a small subset experience persistent clinically significant symptoms, which are resistant to usual management strategies. For example, recent data suggest that while approximately 75% of youth treated with evidence-based interventions were in remission at 3-year follow-up, about 10% experienced persistent symptoms and never achieved clinical remission [22]. Treatment resistance in pediatric OCD poses a complex challenge for clinicians, patients, and their families, as there are few well-established options, yet it can lead to severe and sustained impairment in daily functioning, academic performance, and quality of life [23, 24]. Yet, a synthesis of the state of the literature for treatment-resistant pediatric OCD has not been recently reported. In this review, we first aim to define treatment resistance in pediatric OCD and discuss related clinical predictors, followed by an examination of the existing literature for the treatment of this population. Given the limited evidence available, this review will also draw on the adult literature to highlight emerging findings or future directions in the study of treatment-resistant pediatric OCD.

A literature search was conducted using PubMed to identify articles published in English up until April 11, 2024, on management of treatment-resistant pediatric OCD. Preliminary searches focused only on child and adolescent populations and the following search terms in the title or abstract were used: ((child* OR adolescen* OR pediatr*) AND ("obsessive-compulsive disorder")) AND (“drug resistan*” OR “medication resistan*” OR "treatment resistan*" OR "treatment refractor*” OR “non respon*"). The abstracts of all identified articles were reviewed to determine their relevance and full-text articles were obtained for potentially relevant articles. The reference sections of each article were reviewed to see if further articles could be identified. Since very few articles were identified using these strategies, the focus was expanded to include management of treatment resistant OCD in adults. The search terms ("obsessive-compulsive disorder")) AND (“drug resistan*” OR "treatment resistan*" OR "treatment refractor*"), in title or abstract, were used as a next step. Treatment strategies with evidence for use in the adult population were then searched in the context of children and adolescents. Furthermore, the reference lists of these publications were also reviewed to capture additional sources, and to ensure no pertinent articles were inadvertently omitted. PubMed was chosen as the primary database given the comprehensive nature of this database and the systematic nature of this review.

2 Results of Literature Review

2.1 Defining Treatment Resistance in Pediatric Obsessive-Compulsive Disorder

Treatment resistance has been defined in several ways. Most recently, a multi-round, web-based Delphi survey provided definitions of positive treatment response, partial response, remission, recovery, and relapse in OCD (Table 1) [25].

A recent meta-analysis of 21 randomized controlled trials (RCTs) concluded that the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS [26]) scores had sufficient discriminative ability to determine response and remission. Optimal cutoff scores for both response and remission were identified, with response defined as a 35% reduction from baseline to post-treatment, and remission as a post-treatment raw score of 12 or less [27]. Logically, treatment resistance may be defined as not achieving remission, despite receiving evidence-based treatment interventions adequate in dosage and duration. Yet, the field has not yet fully operationalized how many, how much, and which interventions are required before pediatric OCD patients are characterized as treatment resistant.

In a clinical review, Bloch and Storch [20] defined treatment-resistant pediatric OCD as adequate symptom relief not being achieved despite an adequate trial of CBT and at least two adequate trials of SRIs. This is generally consistent with the definition for adults, although slightly less stringent in the number of failed SSRI trials [28]. Assessing the adequacy of trials of both psychotherapy and medications requires attention to their duration, frequency, dose or fidelity, and adherence. In CBT, for example, this includes a sufficient number of sessions focused on ERP [29], as well as meaningful involvement of family members [30]. An SRI trial is considered adequate when a patient is fully adherent to the maximum tolerated dose, above the established threshold for a therapeutic dose of that medication, for at least 12 weeks, with the patient on the maximal dose for at least 8 weeks [20, 31]. Furthermore, comorbid conditions

Table 1 Definitions of different descriptions of treatment response in pediatric obsessive-compulsive disorder

Description	Definition	Duration
Positive treatment response	35% reduction in CY-BOCS scores plus CGI-I rating of 1 ("very much improved") or 2 ("much improved")	At least 1 week
Partial response	At least a 25% but no greater than 35% reduction on the CY-BOCS plus a CGI-I rating of at least 3 ("minimally improved")	At least 1 week
Remission	Individual no longer meets the diagnostic criteria of OCD during a structured diagnostic interview. If structured diagnostic interview is not feasible, a score of 12 on the CY-BOCS plus CGI-S rating of 1 ("normal, not at all ill") or 2 ("borderline mentally ill")	At least 1 week
Recovery	Individual no longer meets the diagnostic criteria of OCD during a structured diagnostic interview. If structured diagnostic interview is not feasible, a score of 12 on the CY-BOCS plus CGI-S rating of 1 ("normal, not at all ill") or 2 ("borderline mentally ill")	At least 1 year
Relapse	For individuals who remit or recover, OCD criteria is met again based on a structured interview. The person may also no longer meet the definition of remission/recovery based on CY-BOCS scores and CGI-I ratings	At least 1 month

CGI-I clinical global impression–improvement, *CGI-S* clinical global impression–severity, *CY-BOCS* children's yale-brown obsessive-compulsive scale, *OCD* obsessive-compulsive disorder

and features of the patient's presentation may complicate either the delivery of first-line treatment or reduce the likelihood of a robust clinical response [32]. Bloch and Storch [20] provide practical guidelines to help practitioners determine the adequacy of trials. It is important to differentiate between treatment intolerance secondary to side effects and treatment resistance.

To be most effective for OCD, CBT must be delivered with ERP. It is not uncommon for patients to receive CBT (or another form of psychotherapy) without ERP despite this recommendation. In such cases, treatment resistance should only be considered when a repeat psychotherapy trial with ERP does not lead to adequate symptom reduction [20]. When provided with an adequate dose of ERP, as a monotherapy or augmented with an antidepressant, treatment resistance occurs in approximately 10% of individuals at 3-year follow-up [22].

2.2 Predictors of Treatment Outcome

Several outcome predictors have emerged in youth with OCD, although findings are often mixed and the overall number of studies relatively small [33]. Across both CBT and pharmacotherapy (either as monotherapies or combined treatments), OCD severity, insight [34], functional impairment [35], family accommodation [35, 36], family history [35], belonging to a racial or ethnic minoritized group [37], and comorbidity have predicted treatment outcome [32, 38, 39]. There is an association between treatment-resistant pediatric OCD and tics for SRI treatment but not CBT [33, 40, 41]. Hoarding is commonly comorbid with OCD, and is associated with poorer insight, increased anxiety, aggression, and overall symptomatology [36]. In a large meta-analysis, hoarding symptoms in children with OCD was associated with attenuated treatment response [42, 43], though subsequent studies have not found this relationship, possibly due to small sample size [44].

2.3 Pharmacologic Approaches to Treatment-Resistant Pediatric Obsessive-Compulsive Disorder

The literature on pharmacologic approaches to treatment-resistant pediatric OCD is in a nascent phase. The following sections review the available pediatric literature and draw on adult studies to help inform and contextualize the limited pediatric data.

2.3.1 Higher than Usual SRI Dose

As SSRIs are the first-line treatments for pediatric OCD, with sertraline, fluoxetine, and fluvoxamine approved by the FDA for this indication [13], a practical strategy in the face of treatment resistance is further increasing the dose. This approach has not been studied empirically in youth. In adults, however, the literature does support this strategy, with a meta-analysis finding a statistically significant dose–response relationship between high doses of SSRI (e.g., fluoxetine 60–80 mg or sertraline 200 mg) and improved treatment efficacy [45]. For example, one study found that a higher than recommended sertraline dose (400 mg) yielded statistically significant but clinically modest improvements in OCD symptoms compared with the maximum recommended dose (200 mg) in adults with treatment-resistant OCD, with similar side effects and dropout rates [46]. Additional studies in the pediatric population are needed to establish safety and efficacy profiles for this potentially valuable strategy.

2.3.2 Augmenting with Clomipramine

Clomipramine is a tricyclic antidepressant that primarily inhibits the reuptake of serotonin and norepinephrine. Augmentation of an SSRI with clomipramine after two failed trials of SSRIs is an established strategy for adults with treatment-resistant OCD [47] and is included in the National Institute for Health and Care Excellence (NICE) guidelines for both adult and pediatric OCD [48]. Several trials in adults have examined the effectiveness of the combination of SSRI and clomipramine, demonstrating greater clinical improvement in the clomipramine augmentation groups [43–45]. One limitation of generalizing the adult data to pediatric patients is the impact of pharmacokinetic and pharmacodynamic properties of clomipramine and its combination with other medications. As clomipramine has anticholinergic and antihistaminic effects, side effect profile and toxicity are both of concern. The combination of SSRI, clomipramine, and their active metabolites may exert varying effects due to hepatic metabolism and related interactions [46–48]. For instance, fluoxetine and sertraline prevent metabolism of the active metabolite of clomipramine, desmethylclomipramine, which has increased adrenergic and cardiotoxic potential. On the contrary, fluvoxamine increases the serotonergic effect of clomipramine by decreasing formation of desmethylclomipramine. This potentially raises concern for serotonin syndrome, but if monitored, can increase the desired effect, and reduce treatment-limiting adrenergic side effects of clomipramine [49, 50].

Data supporting this strategy in youth are limited [50]. In children and adolescents, Leonard [51] demonstrated in a 10-week double-blind treatment trial crossover study of 49 patients that when compared with desipramine (mean dose 153 [SD 55] mg/day), clomipramine (mean dose 150 [±53] mg/day) led to a significantly greater reduction in OCD symptoms. Figueroa et al. [52] found that clomipramine augmentation of an SSRI was beneficial in seven cases of youth (ages 9–23) treated naturalistically, at doses of clomipramine in the range of 25–100 mg/day, with side effects present in five of seven cases, including two patients each who had prolongation of QTc intervals and tachycardia. In a retrospective case review of SSRI augmentation with clomipramine in six adolescents with OCD, Fung et al. highlighted pharmacokinetic properties of the combination in addition to examining its safety (efficacy data were not reported) [50]. Based on the parameters established by Szegedi et al. [49], this pediatric study aimed to maintain the combined serum concentration of clomipramine + desmethylclomipramine under 450 ng/mL and the ratio of desmethylclomipramine to clomipramine concentration less than 0.3. The findings supported the pharmacologic rationale and found the combination was well tolerated in adolescents. They also proposed an algorithm for the use of fluvoxamine in combination with clomipramine in children and adolescents. This algorithm proposes (a) monitoring clomipramine and desmethylclomipramine serum levels and QTc intervals after a minimum of 14 days after dose adjustments, and (b) using lower daily doses of fluvoxamine (100–150 mg instead of 200 mg or more) to reduce the risk of serotonin syndrome while still effectively inhibiting the metabolism of clomipramine to desmethylclomipramine [50].

2.3.3 Augmenting with Antipsychotics

Augmenting SRIs with low-dose antipsychotic medication may be an effective strategy, supported by evidence for adults with treatment-resistant OCD [53–55]. Adult trials have been conducted on various antipsychotics, including risperidone, haloperidol, quetiapine, olanzapine, paliperidone, and aripiprazole [56–66]. In a meta-analysis of nine placebo-controlled RCTs comparing antipsychotic augmentation of SRIs with placebo, antipsychotic augmentation was favorable to placebo with an absolute risk difference (ARD) of 0.22 [54]. While it is difficult to compare agents due to the small number and variability of studies, data suggest that higher-potency antipsychotics (e.g., risperidone, haloperidol) were more consistently favorable. Patients with comorbid tics had a more robust response to antipsychotic augmentation (ARD 0.43). This meta-analysis found no support for early augmentation with antipsychotic before 12 weeks of an SRI trial, or extended trials of antipsychotic augmentation beyond 4–6 weeks.

Pediatric studies are smaller and less likely to be masked or controlled; however, the limited results suggest augmenting SRIs with low-dose antipsychotic medication may be an effective treatment strategy for treatment-resistant pediatric OCD. A small case series ($N = 4$) demonstrated likely benefit of low-dose risperidone in adolescents, including a statistically significant decrease in CY-BOCS scores, but no patients achieved clinical remission during the course of the 12-week open-label trial [67]. Masi and colleagues assessed aripiprazole augmentation of SRI treatment in adolescents with OCD ($N = 39$; 28 males, 11 females, age range 12–18 years) who had not responded to two trials of SRI monotherapy. This was a representative clinical sample with high rates of comorbidity, with diagnoses including depression, bipolar disorder, anxiety disorders, and ADHD, among others. A mean aripiprazole dosage of 12.2 (SD 3.4) mg/d was achieved. After 6 months, 59% ($n = 23$) of patients had a Clinical Global Impression (CGI)—Improvement score of 1 or 2 (very much or much improved) plus a CGI—Severity score of 3 or below and were considered responders to aripiprazole augmentation. A specific assessment of OCD

symptoms at endpoint was not included [68]. A retrospective chart review explored clinical data from 48 children (14 females, 34 males) diagnosed with treatment-resistant OCD. These children had not responded to at least two cycles and a minimum of 10 weeks of treatment with adequately dosed SSRIs combined with CBT. Treatment with fluoxetine ($n = 28$) or sertraline ($n = 20$) was augmented with aripiprazole at a mean dose of 2.2 (SD 1.1) mg. The dose of aripiprazole was escalated until reaching a mean of 3.4 (SD 2.2) mg at follow-ups. SSRI dose was also optimized at follow-ups. Outcomes were measured using the CY-BOCS, which demonstrated statistically significant change (33.3 [SD 7.5] to 11.7 [SD 9.3]; $p < 0.001$). A secondary sensitivity analysis of 29 patients with only aripiprazole dose optimization also showed statistically and clinically significant improvement in CY-BOCS (34.2 [SD 7.9] to 13 [SD 10]). Weight gain was noted with augmentation of SSRI with aripiprazole (body weight: mean initial body weight 49.6 ± 9.3 kg, mean at final evaluation 51.3 ± 9.7 kg; $p < 0.001$) [69].

Based on the parameters established by Szegedi et al. [49], this pediatric study aimed to maintain the combined serum concentration of clomipramine + desmethylclomipramine under 450 ng/mL and the ratio of desmethylclomipramine to clomipramine concentration less than 0.3 [66, 70, 71]. In one open trial, 120 patients (age range 6–18 years) with OCD and comorbid tic disorder were treated with an SSRI (sertraline, fluvoxamine, or fluoxetine) for at least 12 weeks. Of these, 69 patients (62 males, mean age 13.7 [SD 2.4] years) did not respond to treatment and received augmentation with either risperidone ($n = 35$, mean dose: 1.7 [SD 0.8] mg) or aripiprazole ($n = 34$, mean dose: 8.9 [SD 3.1] mg) for 12 weeks, with 56.5% showing statistically significant improvement in symptoms, rated on the CGI-I and the Children's Global Assessment Scale (CGAS), regardless of OCD subtype and presence of comorbidities and 68.1% showing improvement in tics. No difference was noted between risperidone and aripiprazole for improvement in either symptomatology. Further, patients had good medication adherence despite side effects, as risperidone was associated with weight gain and sedation, while aripiprazole was associated with mild/moderate agitation [72].

In addition to risperidone and aripiprazole, sulpiride has been recommended as a potential augmentation agent in children with treatment-resistant OCD and comorbid tic disorders [73, 74]. However, sulpiride has been studied only in adults with comorbid OCD and Tourette syndrome (TS) in a 14-week, double-blind, placebo-controlled crossover trial of fluvoxamine versus sulpiride, followed by single-blind combined therapy in 11 adults with comorbid OCD and TS [74].

The potential side effect profile of antipsychotics may make their use less appealing for youth and their parents. In the absence of compelling data for this strategy in pediatric treatment-resistant OCD, and evidence of risk with long-term use, an inadequate response to antipsychotic augmentation should be followed by discontinuation of these medications.

2.4 Emerging Treatments

2.4.1 Riluzole

Riluzole is a neuroprotective agent used for the treatment of amyotrophic lateral sclerosis. It regulates extracellular glutamate at the synapse through multiple mechanisms and is another possible option for pediatric treatment-resistant OCD. A preliminary small open-label trial of riluzole for treatment-resistant pediatric OCD showed promising results. In this trial, 6 patients (ages 8–16 years) who had received adequate symptomatic benefit following at least one trial of SSRI were treated for 12 weeks with riluzole, which was added to their existing medication regimen. Riluzole was started at a 10-mg dose and was increased every few days (average dose at 12 weeks: 101 mg), and four out of six patients had at least a 39% reduction on the CY-BOCS, with few side effects. One patient showed no improvement and another showed improvement after 12 weeks [75]. However, findings were not replicated in an RCT that included 59 children and adolescents with OCD, with 17 patients also having a comorbid diagnosis of autism [76]. As an adjunct treatment, riluzole did not demonstrate a statistically significant improvement in symptoms compared with placebo. Most patients reported side effects, with treatment discontinued for five patients due to elevations in transaminases and one patient due to the development of pancreatitis [76, 77].

2.4.2 Ketamine

Ketamine is a potent N-methyl-D-aspartate (NMDA) receptor antagonist, and an established anesthetic agent for children, adolescents, and adults. Psychiatrically, it likely exerts its effects through multiple receptor systems. Esketamine (the s-enantiomer) is FDA-approved in adults for the adjunctive treatment of major depressive disorder via intranasal delivery [78]. Since glutamatergic neurotransmission is hypothesized to be dysregulated in OCD, the potential of ketamine is of interest [79]. Studies examining ketamine in youth with OCD, however, remain scarce. The trials available in adult OCD literature have contrasting results with significant methodological heterogeneity [80], and no studies have examined the effectiveness of ketamine in youth with OCD.

2.4.3 D-Cycloserine

D-cycloserine is another agent that acts on the NMDA glutamate receptor. It is a partial agonist on that receptor and has been used in low doses to augment ERP, as it is hypothesized that increased glutamatergic transmission in the amygdala can facilitate extinction learning [81], which is the core mechanism in exposure-based therapies. Placebo-controlled trials in youth with OCD have compared ERP with and without d-cycloserine augmentation [82]. However, a subsequent, larger trial did not replicate this effect. This was a randomized, double-blinded, placebo-controlled trial comparing treatment response in 142 patients (age range 7–17 years, mean age 12.7 [SD 2.9] years) when CBT was augmented with d-cycloserine. Placebo or d-cycloserine (25–50 mg, based on weight) was taken 1 hour before CBT sessions 4 through 10. D-cycloserine augmentation of CBT was tolerated well; however, it was not found to be superior to CBT monotherapy [30]. Overall, the magnitude of effect associated with d-cycloserine augmentation of ERP is modest but positive across anxiety-based disorders, but the relative magnitude of effects may not be greater than simply doing several additional exposure-based sessions [30, 81, 83–86].

2.4.4 Memantine

Memantine is an NMDA-receptor antagonist used in the treatment of Alzheimer's disease and other neurodegenerative illnesses to slow glutamatergic excitotoxicity. Use of memantine in adults with treatment-resistant OCD has mixed evidence [85–87]. A metanalysis of eight studies, with a total of 125 adults with OCD, showed a significant overall mean reduction of 11.73 points on Y-BOCS for those receiving memantine augmentation. The study concluded that augmentation of usual treatment with 20 mg/day of memantine was a safe and effective intervention for adults with treatment-resistant OCD [87].

There are no complete pediatric trials available exploring memantine as an augmenting agent in treatment-resistant OCD; however, descriptive findings from an incomplete, randomized, double-blind, placebo-controlled trial show promising results. In this study, participants ($n = 7$, aged 6–17 years) in the treatment arm received memantine 5 mg which was titrated to a maximum of 15 mg and continued for 10 weeks. Patients receiving memantine ($n = 4$) showed a more pronounced reduction in symptoms and reported no serious side effects [88].

2.4.5 Topiramate

Topiramate is an antiepileptic drug that inhibits the AMPA/kainite glutamate receptors. It is used in the pediatric population for epilepsy and migraines; however, its use in the treatment of pediatric OCD is not established. Although the adult trials that have explored the use of topiramate augmentation of SSRIs in treatment-resistant OCD are small, they have shown promising results. In a small, double-blind, placebo-controlled trial, Mowla and colleagues [89] found that a greater percentage of patients in the topiramate versus placebo augmentation group experienced clinical response. Berlin and colleagues [90] reported decreases in compulsions, but not obsessions, in adults receiving adjunctive topiramate. Other adult trials have not showed benefits of topiramate [91]. All these studies are limited by concerns around poor tolerability of topiramate at treatment dosages, and no data in youth with treatment-resistant OCD are available.

2.4.6 N-acetylcysteine

N-acetylcysteine (NAC) is an amino acid used as an antidote to acetaminophen toxicity and an antioxidant agent. It also has glutamate modulating properties, which makes it a potential treatment agent for OCD. Some adult trials have demonstrated superiority of NAC augmentation when compared with placebo in patients with treatment-resistant OCD [92–94], although others have not demonstrated separation or effects comparable to other first-line treatments [95]. This may be due to lack of clarity on optimal therapeutic dosage and/or absence of medicinal formulations of NAC [96].

In youth, NAC has been found to be tolerable in trials of patients with autism, trichotillomania, and cannabis dependence [97, 98]. In a small pilot study, NAC demonstrated significant symptom reductions in children and adolescents with OCD [99]; however, these patients were not resistant to treatment. This was a double-blind, placebo-controlled clinical trial in which 11 participants (ages 8–17 years) were randomized to receive either NAC (up to 2700 mg per day) or placebo for 12 weeks. Treatment with NAC showed a statistically significant reduction in symptoms on the CY-BOCS when compared with the placebo group [99]. A double-blind, placebo-controlled add-on study that used NAC as an augmenting agent for trichotillomania in child and adolescent participants ($n = 39$, age range 8–17 years) did not demonstrate any difference in symptom improvement when compared with placebo [100]. Another double-blind, randomized, placebo-controlled trial, which included children, adolescents, and adults with OCD ($n = 34$, age range 10–21 years), examined citalopram administered concurrently with either NAC or placebo. Statistically significant reductions in CY-BOCS scores were observed in the citalopram + NAC group but not the citalopram + placebo group [101]. A review of the aforementioned trials reported mild side effects, including nausea, blurred vision, fatigue, tremors, and sweats when NAC was administered in divided

doses and titrated to 2400–2700 mg/day [102]. A broad review of trials including all patients with OCD, regardless of age, which included a range of study methodologies, indicated that compared with placebo, NAC showed a trend towards benefit, and recommended its consideration on a case-by-case basis [92].

2.4.7 Ondansetron

Ondansetron is a selective 5-HT3 receptor antagonist that acts both centrally and peripherally to reduce nausea and emesis in both adult and pediatric patients. Some clinical studies have evaluated the use of ondansetron as an augmenting strategy for adults with treatment-resistant OCD. A preliminary, single-blind, prospective study indicated improvement in OCD symptoms with ondansetron treatment and reported worsening in symptoms following its discontinuation [103]. A randomized, double-blind, placebo-controlled trial comparing the efficacy of ondansetron and granisetron showed a significant reduction in OCD symptoms for those receiving ondansetron as compared with those receiving granisetron or a placebo [104]. These studies were conducted in adults and no evidence is reported for use of ondansetron in pediatric treatment-resistant OCD.

2.5 Behavioral Approaches to Treatment-Resistant Pediatric Obsessive-Compulsive Disorder

For youth with OCD who do not respond to an initial course of CBT, Skarphedinsson and colleagues [21] demonstrated that continued CBT or beginning a course of sertraline are viable treatment options. They randomized 54 children and adolescents with OCD who did not respond to an initial 14-week course of CBT to receive sertraline or continued CBT for 16 weeks. Forty-five percent of youth in the sertraline group and 50% of youth in the CBT group responded to treatment, with no differences between groups. However, youth with a comorbid tic disorder benefited more from sertraline than continued CBT [105]. For youth with treatment-resistant OCD who do not respond to initial CBT or medication, intensive CBT programs are another potential treatment option.

The National Institute for Health and Care Excellence and the American Psychological Association have recommended intensive CBT for individuals who do not respond to traditional CBT, with these programs being especially beneficial for patients with high emotional reactivity, poor insight, and difficulty comprehending treatment rationale [106, 107]. There are different levels of intensive treatment, including intensive outpatient (i.e., 5 days/week for 1–3 hours/day), partial hospitalization/day treatment (i.e., 5 days/week for 6 hours/day), and residential day programs (i.e., 7 days/week with considerable time engaging in treatment each day). A key component of these programs is that they include a significant 'dose' of effective interventions specifically tailored to the presenting disorder (i.e., OCD).

Building on findings of a small open trial that found benefits of CBT augmentation of an SSRI [108], Storch et al. [109] administered 14 daily sessions of intensive family-based CBT to 30 youth who were partial- or non-responders to two or more medication trials. After treatment, 80% of participants had at least a 30% reduction on the CY-BOCS and 57% of participants were deemed in remission. At 3-month follow up, 53% of youth were classified as being in remission and symptom severity was reduced by 54% on the CY-BOCS. Similar effects were demonstrated in a small cohort of youth ($n = 7$) with OCD related to pediatric autoimmune neuropsychiatric disorders associated with Streptococcus who had not responded sufficiently to past SSRI and/or autoimmune focused interventions [110]. Additionally, Leonard et al. [111] examined the effectiveness of intensive ERP (i.e., approximately 26.5 hours/week) and medication management in a residential treatment facility for 172 adolescents with severe, treatment-resistant OCD. Approximately 81% of youth demonstrated a reliable change and 64% showed clinically significant change, with follow-up data indicating that treatment gains were maintained at 1.5 years post-treatment. Kay et al. [112] replicated these results in 72 youth attending residential treatment with similar treatment components, while Garcia et al. [37] replicated these findings in 185 youth with severe and/or treatment-resistant OCD treated in a partial hospitalization program, with 77.3% responding to multimodal treatment. Björgvinsson et al. [113] reported the findings of an intensive inpatient program, in which 23 adolescents that did not respond to outpatient treatment received intensive ERP and multidisciplinary support (i.e., nursing and medication management). After an average of approximately 10 weeks of treatment, 70% of patients demonstrated clinically significant improvement.

These studies indicate that intensive CBT programs are a viable option for youth who have not responded to traditional CBT and SRIs; however, controlled trials with additional follow-up data are needed. Intensive treatment allows for increased flexibility, as therapists can assign exposures across multiple contexts and go through the patient's treatment hierarchy at a faster rate [114, 115]. There are also fewer distractions that may interfere with treatment, and patients may experience increased motivation as therapy becomes their primary life task [116]. Further, Gregory et al. [117] examined the cost effectiveness of treatments for youth with treatment-resistant OCD. They found that OCD-specific intensive outpatient programs are the most cost-effective approach, followed by partial hospitalization programs, and outpatient CBT with antidepressant pharmacotherapy.

2.6 Novel Directions

2.6.1 Deep Brain Stimulation

In 1999, deep brain stimulation (DBS) for OCD targeted the anterior limb of the internal capsule in four adults with treatment-refractory OCD, with three patients demonstrating beneficial effects [118, 119]. Targeting the ventral capsule/ventral striatum (VC/VS) [120] and anteriomedial subthalamic nucleus has also led to significant improvement [121]. A recent meta-analysis showed that 66% of patients with refractory OCD were full responders to DBS [122]. There are no reports of DBS used as a treatment for youth with OCD. DBS targeting the VC/VS is approved by the FDA under a Humanitarian Device Exemption (HDE) for individuals 18 years or older with severe and intractable OCD. Of note, parents generally have favorable attitudes towards DBS for pediatric neuropsychiatric conditions including OCD [123]. This highlights the need for further understanding of this intervention as it may apply to youth [106].

2.6.2 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS), which includes repetitive TMS (rTMS) and deep TMS (dTMS), has been studied as a treatment modality for treatment-resistant adults with OCD. Although TMS has demonstrated efficacy in reducing OCD symptoms for these individuals, it has not been compared with other intensive treatment models [124]. Additionally, few studies have examined the use of TMS for youth with treatment-resistant OCD. A case report of an adolescent with TS and comorbid treatment-resistant OCD who received 10 × 1-Hz rTMS treatments (5 treatments per week) showed minimal improvement in OCD symptoms after 2 weeks of daily treatment [125]. A contrasting case report for an 18-year-old patient with TS and comorbid treatment-resistant OCD demonstrated improvements in obsessive compulsive symptoms after 1 week of 1-Hz rTMS, with the participant's Y-BOCS score being a 26 at baseline, 16 after 20 sessions of rTMS, and 18 at 3-month follow up [126]. Pedapati et al. used rTMS and fMRI to explore neural correlations of OCD symptoms in a small group of adolescents with OCD. Participants either received active rTMS to the right dorsolateral prefrontal cortex (rDLPFC) or sham rTMS. Researchers anticipated a lower subjective report of OCD-related anxiety following active rTMS; however, no statistically significant change in anxiety ratings was noted in the treatment or sham group after the stimulation [128].

A recent case report of an adolescent with OCD showed promising results with the use of dTMS. Twenty high-frequency, daily dTMS sessions were provided over the medial prefrontal cortex and anterior cingulate gyrus, with no side effects reported. Rapid improvement in symptoms was noted after 10 sessions, with continued improvement throughout treatment and a maintenance of gains at 1-month follow up [127].

3 Discussion

Treatment approaches for youth with treatment-resistant OCD were reviewed in this paper, with findings demonstrating that the state of the literature is relatively nascent. With the exception of intensive CBT (i.e., several hours or more of treatment per day) [37, 108–112], few studies were controlled in nature and/or had a sufficient evidence base. This stands in relatively stark contrast to the adult literature regarding treatment-resistant OCD [107, 122, 129, 130]. While effective first-line interventions with good safety and tolerability profiles exist for pediatric OCD [14, 22], additional research is needed to identify options for youth who do not sufficiently respond to or cannot tolerate the first-line recommendations.

Intensive interventions consisting of a substantial dose of ERP with active and flexible psychopharmacological intervention demonstrated effectiveness in real-world settings with treatment-resistant youth. Although controlled investigations were scarce, the complex presentation of the children treated in these reports increases confidence in the stability of these findings. Furthermore, intensive interventions demonstrated cost effectiveness relative to outpatient psychotherapy and pharmacological therapy. It remains perplexing that the standard model for higher levels of care tends to be non-disorder-specific, in that children with a variety of presenting problems are grouped together and provided non-disorder-specific psychotherapy. The field would be well advised to consider a more specialized model of care for those youth with OCD who are treatment-resistant.

Augmentation with atypical antipsychotics also demonstrated promise, although studies were likewise of limited methodological quality (i.e., unblinded open trials). Nonetheless, placebo response in OCD tends to be extremely low [131], which provides some additional confidence in effects found. However, given the side-effect profile associated with antipsychotics in youth who are not psychotic [132, 133], and that effects may be conflated at times with comorbid tic presentation, well-designed clinical trials are needed.

There are several emerging treatments that show promise as detailed in this review and would benefit from additional investigation in children and adolescents. One theme that emerges from some of the pharmacologic agents of note is their mechanism of glutamate receptor modulation. Dysregulation of glutamatergic neurotransmission has been hypothesized to contribute to the pathophysiology of OCD [134]. This model has been valuable in the investigation of agents for treatment-resistant OCD in adults [135] and may

be a useful framework to guide future studies planned in children and adolescents.

Regardless of mechanism, the potential benefits of all treatments that may be promising for youth must be balanced against the potential risks. For instance, although DBS may be an appropriate intervention for an adult with refractory OCD, the same intervention may not be safe or acceptable in the context of ongoing growth and development. On the other hand, prescribing pharmacologic interventions that are known to be safe and well tolerated in youth, such as NAC, may be a very tolerable risk to take, in the hope that they may prove beneficial for a child with treatment-resistant OCD. In addition to establishing efficacy of these emerging treatments, future studies may also consider examining family and youth treatment preferences to further guide clinical decision making.

4 Conclusion

Despite the availability of effective treatments, a significant number of youths with OCD do not respond to conventional interventions. Intensive treatment programs and antipsychotic augmentation of an antidepressant both have substantial albeit uncontrolled naturalistic data in youth with treatment-resistant OCD. Among adults with OCD who are treatment-resistant, varied approaches have been evaluated including maximizing dosages, adding clomipramine, and augmenting with an antipsychotic or novel agent; however, few rigorous data have been published examining these strategies among treatment-resistant youth. Should clinical circumstances indicate extrapolating from adult data, careful monitoring for side effects, keeping individual and cumulative pharmacokinetic properties under consideration, and monitoring serum drug levels when available is recommended when these strategies are used [49]. Invasive and non-invasive neurostimulation for adults with treatment-resistant OCD have also shown promise. Almost all of these approaches have few reported data to support their use in youth with treatment-resistant OCD, but non-invasive approaches may hold promise for adolescents with treatment-resistant OCD. Continued high-quality research is crucial to identify additional treatment approaches for youth with treatment-resistant OCD.

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References

1. Geller DA. Obsessive-compulsive and spectrum disorders in children and adolescents. Psychiatr Clin North Am. 2006;29(2):353–70.
2. Piacentini J, Bergman RL, Keller M, McCracken J. Functional impairment in children and adolescents with obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2003;13(supplement 1):61–9.
3. Stewart SE, Geller DA, Jenike M, Pauls D, Shaw D, Mullin B, et al. Long-term outcome of pediatric obsessive–compulsive disorder: a meta-analysis and qualitative review of the literature. Acta Psychiatr Scand. 2004;110(1):4–13.
4. Rapoport JL, Inoff-Germain G, Weissman MM, Greenwald S, Narrow WE, Jensen PS, et al. Childhood obsessive-compulsive disorder in the NIMH MECA study. J Anxiety Disord. 2000;14(6):535–48.
5. Valleni-Basile LA, Garrison CZ, Jackson KL, Waller JL, Mckeown RE, Addy CL, et al. Frequency of obsessive-compulsive disorder in a community sample of young adolescents. J Am Acad Child Adolesc Psychiatry. 1994;33(6):782–91.
6. Canals J, Hernández-Martínez C, Cosi S, Voltas N. The epidemiology of obsessive–compulsive disorder in Spanish school children. J Anxiety Disord. 2012;26(7):746–52.
7. Flament MF, Whitaker A, Rapoport JL, Davies M, Berg CZ, Kalikow K, et al. Obsessive compulsive disorder in adolescence: an epidemiological study. J Am Acad Child Adolesc Psychiatry. 1988;27(6):764–71.
8. Heyman I, Fombonne E, Simmons H, Ford T, Meltzer H, Goodman R. Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. Int Rev Psychiatry. 2003;15(1–2):178–84.
9. Zohar AH. The epidemiology of obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am. 1999;8(3):445–60.

10. Zohar AH, Ratzoni G, Pauls DL, Apter A, Bleich A, Kron S, et al. An epidemiological study of obsessive-compulsive disorder and related disorders in Israeli adolescents. J Am Acad Child Adolesc Psychiatry. 1992;31(6):1057–61.
11. Teixeira AL, Hansen RM, Wozny JS, Schaefer CM, Machado-Vieira R, Shahani L, et al. Incidence rate of psychiatric disorders in 2020: the pivotal role played by SARS-CoV-2 infection. PLoS ONE. 2022;17(9): e0274330.
12. Dalsgaard S, Thorsteinsson E, Trabjerg BB, Schullehner J, Plana-Ripoll O, Brikell I, et al. Incidence rates and cumulative incidences of the full spectrum of diagnosed mental disorders in childhood and adolescence. JAMA Psychiat. 2020;77(2):155.
13. McGuire JF, Piacentini J, Lewin AB, Brennan EA, Murphy TK, Storch EA. A meta-analysis of cognitive behavior therapy and medication for child obsessive-compulsive disorder: moderators of treatment efficacy, response and remission. Depress Anxiety. 2015;32(8):580–93.
14. Cervin M, McGuire JF, D'Souza JM, De Nadai AS, Aspvall K, Goodman WK, et al. Efficacy and acceptability of cognitive-behavioral therapy and serotonin reuptake inhibitors for pediatric obsessive-compulsive disorder: a network meta-analysis. J Child Psychol Psychiatry. 2024;2:2.
15. Center for Drug Evaluation and Research. FDA.gov. 2022. Drug Approvals and Databases.
16. McGuire JF, Piacentini J, Lewin AB, Brennan EA, Murphy TK, Storch EA. A meta-analysis of cognitive behavior therapy and medication for child obsessive-compulsive disorder: Moderators of treatment efficacy, response, and remission. Depress Anxiety. 2015;32(8):580–93.
17. Kotapati VP, Khan AM, Dar S, Begum G, Bachu R, Adnan M, et al. The effectiveness of selective serotonin reuptake inhibitors for treatment of obsessive-compulsive disorder in adolescents and children: a systematic review and meta-analysis. Front Psychiatry. 2019;6:10.
18. The Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder. JAMA. 2004;292(16):1969.
19. Storch EA, Bussing R, Small BJ, Geffken GR, McNamara JP, Rahman O, et al. Randomized, placebo-controlled trial of cognitive-behavioral therapy alone or combined with sertraline in the treatment of pediatric obsessive–compulsive disorder. Behav Res Ther. 2013;51(12):823–9.
20. Bloch MH, Storch EA. Assessment and management of treatment-refractory obsessive-compulsive disorder in children. J Am Acad Child Adolesc Psychiatry. 2015;54(4):251–62.
21. Skarphedinsson G, Weidle B, Thomsen PH, Dahl K, Torp NC, Nissen JB, et al. Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial. Eur Child Adolesc Psychiatry. 2015;24(5):591–602.
22. Ivarsson T, Jensen S, Højgaard DRMA, Hybel KA, Torp NC, Melin K, et al. Remission and relapse across three years in pediatric obsessive-compulsive disorder following evidence-based treatments. J Am Acad Child Adolesc Psychiatry. 2023;2:2.
23. Piacentini J, Peris TS, Bergman RL, Chang S, Jaffer M. BRIEF REPORT: functional impairment in childhood OCD: development and psychometrics properties of the child obsessive-compulsive impact scale-revised (COIS-R). J Clin Child Adolesc Psychol. 2007;36(4):645–53.
24. Lack CW, Storch EA, Keeley ML, Geffken GR, Ricketts ED, Murphy TK, et al. Quality of life in children and adolescents with obsessive-compulsive disorder: base rates, parent–child agreement, and clinical correlates. Soc Psychiatry Psychiatr Epidemiol. 2009;44(11):935–42.
25. Mataix-Cols D, de la 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(1):80–1.
26. Scahill L, Riddle MA, Mcswiggin-Hardin M, Ort SI, King RA, Goodman WK, et al. Children's yale-brown obsessive compulsive scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. 1997;36(6):844–52.
27. Farhat LC, Vattimo EFQ, Ramakrishnan D, Levine JLS, Johnson JA, Artukoglu BB, et al. Systematic review and meta-analysis: an empirical approach to defining treatment response and remission in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2022;61(4):495–507.
28. Swierkosz-Lenart K, Dos Santos JFA, Elowe J, Clair AH, Bally JF, Riquier F, et al. Therapies for obsessive-compulsive disorder: current state of the art and perspectives for approaching treatment-resistant patients. Front Psychiatry. 2023;16:14.
29. Ale CM, McCarthy DM, Rothschild LM, Whiteside SPH. Components of cognitive behavioral therapy related to outcome in childhood anxiety disorders. Clin Child Fam Psychol Rev. 2015;18(3):240–51.
30. Storch EA, Wilhelm S, Sprich S, Henin A, Micco J, Small BJ, et al. Efficacy of augmentation of cognitive behavior therapy with weight-adjusted <scp>d</scp> -cycloserine vs placebo in pediatric obsessive-compulsive disorder. JAMA Psychiat. 2016;73(8):779.
31. Geller DA, March J. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2012;51(1):98–113.
32. Storch EA, Merlo LJ, Larson MJ, Geffken GR, Lehmkuhl HD, Jacob ML, et al. Impact of comorbidity on cognitive-behavioral therapy response in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2008;47(5):583–92.
33. Turner C, O'Gorman B, Nair A, O'Kearney R. Moderators and predictors of response to cognitive behaviour therapy for pediatric obsessive-compulsive disorder: a systematic review. Psychiatry Res. 2018;261:50–60.
34. Selles RR, Højgaard DRMA, Ivarsson T, Thomsen PH, McBride NM, Storch EA, et al. Avoidance, insight, impairment recognition concordance, and cognitive-behavioral therapy outcomes in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2020;59(5):650-659.e2.
35. Garcia AM, Sapyta JJ, Moore PS, Freeman JB, Franklin ME, March JS, et al. Predictors and moderators of treatment outcome in the pediatric obsessive compulsive treatment study (POTS I). J Am Acad Child Adolesc Psychiatry. 2010;49(10):1024–33.
36. Merlo LJ, Lehmkuhl HD, Geffken GR, Storch EA. Decreased family accommodation associated with improved therapy outcome in pediatric obsessive–compulsive disorder. J Consult Clin Psychol. 2009;77(2):355–60.
37. Garcia AM, Case B, Freeman JB, Walther M, Righi G, O'Connor E, et al. Predictors of treatment outcome and length of stay in a partial hospital program for pediatric obsessive-compulsive disorder. Evid Based Pract Child Adolesc Ment Health. 2023;19:1–14.
38. Geller DA, Biederman J, Stewart SE, Mullin B, Farrell C, Wagner KD, et al. Impact of comorbidity on treatment response to paroxetine in pediatric obsessive-compulsive disorder: is the use of exclusion criteria empirically supported in randomized clinical trials? J Child Adolesc Psychopharmacol. 2003;13(supplement 1):19–29.
39. Rosa-Alcázar Á, Rosa-Alcázar AI, Parada-Navas JL, Olivares-Olivares PJ, Rosa-Alcázar E. Predictors of parental

accommodation and response treatment in young children with obsessive-compulsive disorder. Front Psychiatry. 2021;16:12.
40. Storch EA, Merlo LJ, Larson MJ, Marien WE, Geffken GR, Jacob ML, et al. Clinical features associated with treatment-resistant pediatric obsessive-compulsive disorder. Compr Psychiatry. 2008;49(1):35–42.
41. Dèttore D, Pozza A, Coradeschi D. Does time-intensive ERP attenuate the negative impact of comorbid personality disorders on the outcome of treatment-resistant OCD? J Behav Ther Exp Psychiatry. 2013;44(4):411–7.
42. Storch EA, Lack CW, Merlo LJ, Geffken GR, Jacob ML, Murphy TK, et al. Clinical features of children and adolescents with obsessive-compulsive disorder and hoarding symptoms. Compr Psychiatry. 2007;48(4):313–8.
43. Bloch MH, Bartley CA, Zipperer L, Jakubovski E, Landeros-Weisenberger A, Pittenger C, et al. Meta-analysis: hoarding symptoms associated with poor treatment outcome in obsessive–compulsive disorder. Mol Psychiatry. 2014;19(9):1025–30.
44. Højgaard DRMA, Skarphedinsson G, Ivarsson T, Weidle B, Nissen JB, Hybel KA, et al. Hoarding in children and adolescents with obsessive–compulsive disorder: prevalence, clinical correlates, and cognitive behavioral therapy outcome. Eur Child Adolesc Psychiatry. 2019;28(8):1097–106.
45. 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(8):850–5.
46. Ninan PT, Koran LM, Kiev A, Davidson JRT, Rasmussen SA, Zajecka JM, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder. J Clin Psychiatry. 2006;67(01):15–22.
47. Arumugham SS, Reddy JY. Augmentation strategies in obsessive–compulsive disorder. Expert Rev Neurother. 2013;13(2):187–203.
48. 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 (UK); 2006.
49. Szegedi A, Wetzel H, Leal M, Härtter S, Hiemke C. Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety, and tolerability data. J Clin Psychiatry. 1996;57(6):257–64.
50. Fung R, Elbe D, Stewart SE. Retrospective review of fluvoxamine-clomipramine combination therapy in obsessive-compulsive disorder in children and adolescents. J Can Acad Child Adolesc Psychiatry. 2021;30(3):150–5.
51. Leonard HL. Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents. Arch Gen Psychiatry. 1989;46(12):1088.
52. Figueroa Y, Rosenberg DR, Birmaher B, Keshavan MS. Combination treatment with clomipramine and selective serotonin reuptake inhibitors for obsessive-compulsive disorder in children and adolescents. J Child Adolesc Psychopharmacol. 1998;8(1):61–7.
53. Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry. 2006;11(7):622–32.
54. Albert U, Marazziti D, Di Salvo G, Solia F, Rosso G, Maina G. A systematic review of evidence-based treatment strategies for obsessive-compulsive disorder resistant to first-line pharmacotherapy. Curr Med Chem. 2019;25(41):5647–61.
55. McDougle CJ, Goodman WK, Price LH, Delgado PL, Krystal JH, Charney DS, et al. Neuroleptic addition in fluvoxamine-refractory obsessive-compulsive disorder. Am J Psychiatry. 1990;147(5):652–4.
56. Shapira NA, Ward HE, Mandoki M, Murphy TK, Yang MCK, Blier P, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. Biol Psychiatry. 2004;55(5):553–5.
57. 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(10):850–4.
58. McDougle CJ. Haloperidol addition in fluvoxamine-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 1994;51(4):302.
59. Denys D, de Geus F, van Megen HJGM, Westenberg HGM. A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. J Clin Psychiatry. 2004;65(8):1040.
60. Carey PD, Vythilingum B, Seedat S, Muller JE, van Ameringen M, Stein DJ. Quetiapine augmentation of SRIs in treatment refractory obsessive-compulsive disorder: a double-blind, randomised, placebo-controlled study [ISRCTN83050762]. BMC Psychiatry. 2005;5(1):5.
61. Erzegovesi S, Guglielmo E, Siliprandi F, Bellodi L. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. Eur Neuropsychopharmacol. 2005;15(1):69–74.
62. Fineberg NA, Sivakumaran T, Roberts A, Gale T. Adding quetiapine to SRI in treatment-resistant obsessive-compulsive disorder: a randomized controlled treatment study. Int Clin Psychopharmacol. 2005;20(4):223–6.
63. 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. J Clin Psychiatry. 2005;66(06):736–43.
64. Maina G, Pessina E, Albert U, Bogetto F. 8-week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive–compulsive disorder. Eur Neuropsychopharmacol. 2008;18(5):364–72.
65. 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(1):47–53.
66. McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. Arch Gen Psychiatry. 2000;57(8):794.
67. Thomsen PH. Risperidone augmentation in the treatment of severe adolescent OCD in SSRI-refractory cases: a case-series. Ann Clin Psychiatry. 2004;16(4):201–7.
68. Masi G, Pfanner C, Millepiedi S, Berloffa S. Aripiprazole augmentation in 39 adolescents with medication-resistant obsessive-compulsive disorder. J Clin Psychopharmacol. 2010;30(6):688–93.
69. Akyol Ardic U, Ercan ES, Kutlu A, Yuce D, Ipci M, Inci SB. Successful treatment response with aripiprazole augmentation of SSRIs in refractory obsessive-compulsive disorder in childhood. Child Psychiatry Hum Dev. 2017;48(5):699–704.
70. Fitzgerald KD, Stewart CM, Tawile V, Rosenberg DR. Risperidone augmentation of serotonin reuptake inhibitor treatment of pediatric obsessive compulsive disorder. J Child Adolesc Psychopharmacol. 1999;9(2):115–23.
71. Selles RR, Storch EA, Lewin AB. Variations in symptom prevalence and clinical correlates in younger versus older youth with obsessive-compulsive disorder. Child Psychiatry Hum Dev. 2014;45(6):666–74.

72. Masi G, Pfanner C, Brovedani P. Antipsychotic augmentation of selective serotonin reuptake inhibitors in resistant tic-related obsessive-compulsive disorder in children and adolescents: a naturalistic comparative study. J Psychiatr Res. 2013;47(8):1007–12.
73. Rothenberger A, Roessner V. Psychopharmacotherapy of obsessive-compulsive symptoms within the framework of tourette syndrome. Curr Neuropharmacol. 2019;17(8):703–9.
74. George MS, Trimble MR, Robertson MM. Fluvoxamine and sulpiride in comorbid obsessive–compulsive disorder and gilles de la tourette syndrome. Hum Psychopharmacol Clin Exp. 1993;8(5):327–34.
75. Grant P, Lougee L, Hirschtritt M, Swedo SE. An open-label trial of riluzole, a glutamate antagonist, in children with treatment-resistant obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2007;17(6):761–7.
76. Grant PJ, Joseph LA, Farmer CA, Luckenbaugh DA, Lougee LC, Zarate CA, et al. 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. Neuropsychopharmacology. 2014;39(6):1453–9.
77. Grant P, Song JY, Swedo SE. Review of the use of the glutamate antagonist riluzole in psychiatric disorders and a description of recent use in childhood obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2010;20(4):309–15.
78. Office of the Commissioner. FDA.gov. 2020. FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic.
79. Martinotti G, Chiappini S, Pettorruso M, Mosca A, Miuli A, Di Carlo F, et al. Therapeutic potentials of ketamine and esketamine in obsessive-compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. Brain Sci. 2021;11(7):856.
80. Bandeira ID, Lins-Silva DH, Cavenaghi VB, Dorea-Bandeira I, Faria-Guimarães D, Barouh JL, et al. Ketamine in the treatment of obsessive-compulsive disorder: a systematic review. Harv Rev Psychiatry. 2022;30(2):135–45.
81. Mataix-Cols D, Fernández Cruz L, Monzani B, Rosenfield D, Andersson E, Pérez-Vigil A, et al. D-cycloserine augmentation of exposure-based cognitive behavior therapy for anxiety, obsessive-compulsive, and posttraumatic stress disorders. JAMA Psychiat. 2017;74(5):501.
82. Storch EA, Murphy TK, Goodman WK, Geffken GR, Lewin AB, Henin A, et al. A preliminary study of d-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. 2010;68(11):1073–6.
83. Farrell LJ, Waters AM, Boschen MJ, Hattingh L, McConnell H, Milliner EL, et al. Difficult-to-treat pediatric obsessive-compulsive disorder: feasibility and preliminary results of a randomized pilot trial of d-cycloserine-augmented behavior therapy. Depress Anxiety. 2013;30(8):723–31.
84. Wilhelm S, Berman N, Small BJ, Porth R, Storch EA, Geller D. D-Cycloserine augmentation of cognitive behavior therapy for pediatric OCD: Predictors and moderators of outcome. J Affect Disord. 2018;241:454–60.
85. Park JM, Small BJ, Geller DA, Murphy TK, Lewin AB, Storch EA. Does d-cycloserine augmentation of CBT improve therapeutic homework compliance for pediatric obsessive-compulsive disorder? J Child Fam Stud. 2014;23(5):863–71.
86. Farrell LJ, Waters AM, Tiralongo E, Mathieu S, McKenzie M, Garbharran V, et al. Efficacy of D-cycloserine augmented brief intensive cognitive-behavioural therapy for paediatric obsessive-compulsive disorder: a randomised clinical trial. Depress Anxiety. 2022;39(6):461–73.
87. 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.
88. Niemeyer L, Mechler K, Dittmann RW, Banaschewski T, Buitelaar J, Durston S, et al. Memantine as treatment for compulsivity in child and adolescent psychiatry: descriptive findings from an incompleted randomized, double-blind, placebo-controlled trial. Contemp Clin Trials Commun. 2022;29: 100982.
89. Mowla A, Khajeian AM, Sahraian A, Chohedri AH, Kashkoli F. Topiramate augmentation in resistant OCD: a double-blind placebo-controlled clinical trial. CNS Spectr. 2010;15(11):613–7.
90. Berlin HA, Koran LM, Jenike MA, Shapira NA, Chaplin W, Pallanti S, et al. Double-blind, placebo-controlled trial of topiramate augmentation in treatment-resistant obsessive-compulsive disorder. J Clin Psychiatry. 2011;72(05):716–21.
91. 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(10):976–81.
92. Couto JP, Moreira R. Oral *N*-acetylcysteine in the treatment of obsessive-compulsive disorder: a systematic review of the clinical evidence. Prog Neuropsychopharmacol Biol Psychiatry. 2018;86:245–54.
93. Gautam M. Clinical recommendations for augmentation agents in obsessive-compulsive disorder partially responsive to serotonin reuptake inhibitors. J Clin Psychopharmacol. 2023;43(4):369–77.
94. 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(6):797–803.
95. 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(7):e766–73.
96. Carollo M, Carollo N, Montan G. The promise of N-acetylcysteine in the treatment of obsessive-compulsive disorder. CNS Neurosci Ther. 2024;30:2.
97. Gray KM, Carpenter MJ, Baker NL, DeSantis SM, Kryway E, Hartwell KJ, et al. A double-blind randomized controlled trial of *N*-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry. 2012;169(8):805–12.
98. Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzenberg LA, et al. A randomized controlled pilot trial of oral *N*-acetylcysteine in children with autism. Biol Psychiatry. 2012;71(11):956–61.
99. Li F, Welling MC, Johnson JA, Coughlin C, Mulqueen J, Jakubovski E, et al. *N*-acetylcysteine for pediatric obsessive-compulsive disorder: a small pilot study. J Child Adolesc Psychopharmacol. 2020;30(1):32–7.
100. Bloch MH, Panza KE, Grant JE, Pittenger C, Leckman JF. *N*-acetylcysteine in the treatment of pediatric trichotillomania: a randomized, double-blind, placebo-controlled add-on trial. J Am Acad Child Adolesc Psychiatry. 2013;52(3):231–40.
101. Ghanizadeh A, Mohammadi MR, Bahraini S, Keshavarzi Z, Firoozabadi A, Alavi SA. Efficacy of *N*-acetylcysteine augmentation on obsessive compulsive disorder: a multicenter randomized double blind placebo controlled clinical trial. Iran J Psychiatry. 2017;12(2):134–41.
102. Parli GM, Gales MA, Gales BJ. N-acetylcysteine for obsessive-compulsive and related disorders in children and adolescents: a review. Ann Pharmacother. 2023;57(7):847–54.
103. Pallanti S, Bernardi S, Antonini S, Singh N, Hollander E. Ondansetron augmentation in treatment-resistant obsessive-compulsive disorder: a preliminary, single-blind, prospective study. CNS Drugs. 2009;23(12):1047–55.
104. Sharafkhah M, Aghakarim Alamdar M, Massoudifar A, Abdolrazaghnejad A, Ebrahimi-Monfared M, Saber R, et al. Comparing

the efficacy of ondansetron and granisetron augmentation in treatment-resistant obsessive-compulsive disorder: a randomized double-blind placebo-controlled study. Int Clin Psychopharmacol. 2019;34(5):222–33.
105. Skarphedinsson G, Compton S, Thomsen PH, Weidle B, Dahl K, Nissen JB, et al. Tics moderate sertraline, but not cognitive-behavior therapy response in pediatric obsessive-compulsive disorder patients who do not respond to cognitive-behavior therapy. J Child Adolesc Psychopharmacol. 2015;25(5):432–9.
106. Ben-Arush O, Wexler JB, Zohar J. Intensive outpatient treatment for obsessive-compulsive spectrum disorders. Isr J Psychiatry Relat Sci. 2008;45(3):193–200.
107. Giridharan N, Smárason O, Provenza NR, Banks GP, Shofty B, Goodman WK, et al. Psychotherapy for treatment-resistant obsessive-compulsive disorder. Adv Psychiatry Behav Health. 2023;3(1):1–10.
108. Storch EA, Bagner DM, Geffken GR, Adkins JW, Murphy TK, Goodman WK. Sequential cognitive-behavioral therapy for children with obsessive–compulsive disorder with an inadequate medication response: a case series of five patients. Depress Anxiety. 2007;24(6):375–81.
109. Storch EA, Lehmkuhl HD, Ricketts E, Geffken GR, Marien W, Murphy TK. An open trial of intensive family based cognitive-behavioral therapy in youth with obsessive-compulsive disorder who are medication partial responders or nonresponders. J Clin Child Adolesc Psychol. 2010;39(2):260–8.
110. Storch EA, Murphy TK, Geffken GR, Mann G, Adkins JJ, Merlo L, et al. Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary wait-list controlled open trial. J Am Acad Child Adolesc Psychiatry. 2006;45(10):1171–8.
111. Leonard RC, Franklin ME, Wetterneck CT, Riemann BC, Simpson HB, Kinnear K, et al. Residential treatment outcomes for adolescents with obsessive-compulsive disorder. Psychother Res. 2016;26(6):727–36.
112. Kay B, Eken S, Jacobi D, Riemann B, Storch EA. Outcome of multidisciplinary, CBT-focused treatment for pediatric OCD. Gen Hosp Psychiatry. 2016;42:7–8.
113. Björgvinsson T, Wetterneck CT, Powell DM, Chasson GS, Webb SA, Hart J, et al. Treatment outcome for adolescent obsessive-compulsive disorder in a specialized hospital setting. J Psychiatr Pract. 2008;14(3):137–45.
114. Riise EN, Kvale G, Öst LG, Skjold SH, Hansen B. Concentrated exposure and response prevention for adolescents with obsessive-compulsive disorder: a replication study. J Obsessive Compuls Relat Disord. 2018;19:15–22.
115. Wolters LH, Ball J, Brezinka V, Bus M, Huyser C, Utens E. Brief intensive cognitive behavioral therapy for children and adolescents with OCD: Two international pilot studies. J Obsessive Compuls Relat Disord. 2021;29: 100645.
116. Foa EB, Steketee G. Behavioral treatment of phobics and obsessive-compulsives. In: Psychotherapists in clinical practice: cognitive and behavioral perspectives. Guilford: Guilford Press; 1987. p. 78–120.
117. Gregory ST, Kay B, Riemann BC, Goodman WK, Storch EA. Cost-effectiveness of treatment alternatives for treatment-refractory pediatric obsessive-compulsive disorder. J Anxiety Disord. 2020;69: 102151.
118. Nuttin B, Cosyns P, Demeulemeester H, Gybels J, Meyerson B. Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. Lancet. 1999;354(9189):1526.
119. Alonso P, Cuadras D, Gabriëls L, Denys D, Goodman W, Greenberg BD, et al. Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. PLoS ONE. 2015;10(7): e0133591.
120. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, et al. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. Neuropsychopharmacology. 2006;31(11):2384–93.
121. Mallet L, Polosan M, Jaafari N, Baup N, Welter ML, Fontaine D, et al. Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. N Engl J Med. 2008;359(20):2121–34.
122. Gadot R, Najera R, Hirani S, Anand A, Storch E, Goodman WK, et al. Efficacy of deep brain stimulation for treatment-resistant obsessive-compulsive disorder: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2022;93(11):1166–73.
123. Storch EA, Cepeda SL, Lee E, Goodman SLV, Robinson AD, De Nadai AS, et al. Parental attitudes toward deep brain stimulation in adolescents with treatment-resistant conditions. J Child Adolesc Psychopharmacol. 2020;30(2):97–103.
124. Suhas S, Malo PK, Kumar V, Issac TG, Chithra NK, Bhaskarapillai B, et al. Treatment strategies for serotonin reuptake inhibitor-resistant obsessive-compulsive disorder: a network meta-analysis of randomised controlled trials. World J Biol Psychiatry. 2023;24(2):162–77.
125. Mantovani A, Leckman JF, Grantz H, King RA, Sporn AL, Lisanby SH. Repetitive transcranial magnetic stimulation of the supplementary motor area in the treatment of tourette syndrome: report of two cases. Clin Neurophysiol. 2007;118(10):2314–5.
126. Singh S, Kumar S, Kumar N, Verma R. Low-frequency repetitive transcranial magnetic stimulation for treatment of tourette syndrome: a naturalistic study with 3 months of follow-up. Indian J Psychol Med. 2018;40(5):482–6.
127. Das R, Sharma P, Sundas A, Goyal N, Kumar G, Shukla D, et al. Safety and efficacy of H7 deep transcranial magnetic stimulation in adolescent obsessive-compulsive disorder: a case report. Asian J Psychiatr. 2023;83: 103510.
128. Pedapati E, DiFrancesco M, Wu S, Giovanetti C, Nash T, Mantovani A, et al. Neural correlates associated with symptom provocation in pediatric obsessive compulsive disorder after a single session of sham-controlled repetitive transcranial magnetic stimulation. Psychiatry Res Neuroimaging. 2015;233(3):466–73.
129. Gershkovich M, Wheaton MG, Simpson HB. Management of treatment-resistant obsessive-compulsive disorder. Curr Treat Options Psychiatry. 2017;4(4):357–70.
130. Sijercic I, Whitfield KM, Cassin SE, Antony MM. A systematic review of cognitive-behavioral therapy for pharmacotherapy treatment-resistant obsessive-compulsive disorder. J Obsessive Compuls Relat Disord. 2020;26: 100532.
131. Nasir M, Li F, Courley S, Olten B, Bloch MH. Meta-analysis: pediatric placebo response in depression trials does not replicate in anxiety and obsessive-compulsive disorder trials. J Child Adolesc Psychopharmacol. 2021;31(10):670–84.
132. Zuddas A, Zanni R, Usala T. Second generation antipsychotics (SGAs) for non-psychotic disorders in children and adolescents: A review of the randomized controlled studies. Eur Neuropsychopharmacol. 2011;21(8):600–20.
133. Daviss WB, Barnett E, Neubacher K, Drake RE. Use of antipsychotic medications for nonpsychotic children: risks and implications for mental health services. Psychiatr Serv. 2016;67(3):339–41.
134. Pittenger C, Bloch MH, Williams K. Glutamate abnormalities in obsessive compulsive disorder: neurobiology, pathophysiology, and treatment. Pharmacol Ther. 2011;132(3):314–32.
135. Marinova Z, Chuang DM, Fineberg N. Glutamate-modulating drugs as a potential therapeutic strategy in obsessive-compulsive disorder. Curr Neuropharmacol. 2017;15:7.