Curr Behav Neurosci Rep (2015) 2:127–136
DOI 10.1007/s40473-015-0047-0

Evidence-Based Treatments in Treatment-Naïve and Treatment-Resistant Pediatric Obsessive-Compulsive Disorder

Gudmundur Skarphedinsson[1] · **Tord Ivarsson**[1]

Published online: 9 July 2015

Abstract Pediatric obsessive-compulsive disorder (OCD) is a chronic, disabling, and common disorder. In this paper, we describe evidence-based treatments in treatment-naïve and treatment-refractory pediatric OCD patients. We conducted a PubMed search to identify randomized controlled trials, reviews, and expert guidelines. The evidence for cognitive behavior therapy (CBT) and specific serotonin reuptake inhibitors (SSRIs) among treatment-naïve patients is substantial and shows that both treatments are effective. Head-to-head trials in pediatric OCD only show that CBT is significantly more effective than SSRI. The evidence among CBT and SSRI non-responders is limited. One trial among CBT non-responders showed that both continued CBT and switching to an SSRI are effective strategies. Likewise, one trial among SSRI non-responders showed that augmenting with CBT is necessary. Evidence of treatments for treatment-refractory pediatric OCD is lacking. We describe the treatments available and evidence from studies of adult OCD. Evidence for emerging treatments such as modifying CBT and glutamatergic drugs is also described.

Keywords Obsessive-compulsive disorder · Children and adolescents · Treatment · Cognitive behavior therapy · Selective serotonin reuptake inhibitors · Atypical antipsychotics · Treatment-resistant · Treatment-refractory

This article is part of the Topical Collection on *Child and Developmental Psychiatry*

✉ Gudmundur Skarphedinsson
gudmundur.skarphedinsson@r-bup.no

Tord Ivarsson
tord.ivarsson@r-bup.no

[1] Center for Child and Adolescent Mental Health, Eastern and Southern Norway, Gullhaugveien 1-3, 0484 Oslo, Norway

Introduction

Pediatric obsessive-compulsive disorder (OCD) is a chronic and disabling disorder and more common than previously thought [1]. Between one third and one half of adults with OCD report that the onset of their symptoms was in childhood [1]. In this paper, we describe the evidence-based treatments for treatment-naïve and treatment-resistant pediatric OCD. Agreed definitions of treatment-resistant and treatment-refractory OCD do not exist [2, 3]. As working definitions, we therefore define treatment-naïve patients as those that have not been exposed to any current first-line treatment (cognitive behavior therapy [CBT] and specific serotonin reuptake inhibitors [SSRIs]). Treatment-resistant patients are those that have failed one of the current first-line treatments [2]. Treatment-refractory patients are those that have failed both of the current first-line treatments (patients that have tried both an adequate trial of CBT and two trials of SSRIs) [2].

We conducted a PubMed search on April 1, 2015. We used the medical subject heading term "obsessive-compulsive disorder", "child", and "adolescent". We also filtered in the terms of "randomized controlled trials" and "meta-analysis". In addition, we read recent reviews and expert guidelines to find any relevant additional publications [1, 4–11].

We organize the results into the following three sections: (1) evidence-based treatments for treatment-naïve and treatment-resistant patients (CBT, SSRIs, and their combination); (2) evidence-based treatments for treatment-refractory patients; and (3) emerging treatments.

Evidence-Based Treatments in Treatment-Naïve and Treatment-Resistant Pediatric OCD

International expert guidelines diverge in terms of their recommendations for initial treatment. European "guidelines

recommend CBT as the first-line treatment for children and adolescents with OCD" regardless of the initial severity and only switching to SSRIs when children decline or are unable to engage in CBT [12, 13]. An SSRI may also be added when the CBT response is inadequate [12]. However, American guidelines recommend CBT alone as the initial treatment for mild to moderate pediatric OCD (CY-BOCS <24) and the combined treatment of CBT and an SSRI for moderate to severe OCD (CY-BOCS>15). In the following section, we present clinical evidence for these two established treatments and their combination both in treatment-naïve and treatment-resistant patients. We also describe the main results of the predictors of the treatment outcomes.

Treatment-Naïve Pediatric OCD

CBT

CBT is an action-oriented and short-term psychotherapy that focuses on teaching youth with OCD new strategies and responses to the symptoms of OCD. The main treatment components are psycho-education, cognitive training, and exposure and response prevention (E/RP). CBT has been studied extensively and shown to be superior to waitlist [14–19] (Hedge's g, g=−1.42), pill placebo [20] (g=−0.96), psychotherapy placebo (attention-control) [21–23] (g=−0.74), and SRI [20, 24, 25] (g=−0.39) as reported in recent systematic reviews/meta-analyses [4, 5]. Furthermore, CBT has shown to be an effective treatment for a wide age group down to 3 years [18]. It has also been shown to be effective in a more parent-focused form [18, 22, 26].

Approximately 25 % of children with OCD may reject CBT. In addition, up to 30 % show little or no improvement [9, 20]. Factors have been found that can predict a poor outcome of CBT, such as higher initial OCD severity [27–29], more internalizing and externalizing symptoms/disorders [28–30], and family dysfunction or high family accommodation [27, 28, 31]. Interestingly, family accommodation does not seem to be associated with the clinical outcome when CBT follows a more intensive family approach [29]. Moreover, tic disorders do not seem to be a predictor of poor outcome either [27, 29, 30].

SRIs

The first-line drugs recommended for pediatric OCD [1, 12] are SRIs. This group includes clomipramine (tricyclic antidepressant), which is a non-specific SRI and SSRIs. Clomipramine was the first SRI to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of OCD for children (age 10 years and above) [32]. It is often considered to be more effective than SSRIs (effect size g= –1.09 vs. pill placebo) [5]. However, this large effect size is derived from older studies that may have been less methodologically rigorous. In addition, because clomipramine was the only drug available in this setting, the study participants were usually SRI-naïve. Nowadays, clomipramine is rarely the first drug of choice for children due to its frequent adverse effects [5].

Subsequent drugs approved by the FDA and European Medicines Agency belong to the SSRI group: sertraline [20, 33], fluvoxamine [34], fluoxetine [35, 36], and paroxetine [37]. The FDA approves fluvoxamine for age 8 years and above (dose range 50–300 mg/day), fluoxetine for age 7 years and above (dose range 10–80 mg/day), and sertraline for age 6 years and above (dose range 50–200 mg/day). However, paroxetine does not have an indication in pediatric OCD [1, 38]. The studies on which approval has been based are methodologically rigorous, with an adequate duration (10–12 weeks), an adequate time (4–6 weeks), and potentially effective doses. The mean effect size of placebo-controlled trials of SSRIs for pediatric OCD is in the moderate range (g=−0.43) with no differences between them [5].

Clinical guidelines recommend continuous 6- to 12-month treatment after stabilization [1]. SSRIs are considered to be tolerated well and with clear benefits over adverse events [39]. Long-term (up to 1 year) treatment seems to be necessary [25, 40, 41]. SSRI treatment can be accompanied by both common adverse events such as gastrointestinal distress and rarer symptoms such as an initial increase in suicidal thinking or behavior [1]. However, Bridge [39] noted that suicidality is a relatively small problem with SSRI treatment compared with the benefits, particularly in OCD and anxiety disorders. Clinicians should also be aware of agitation (behavioral activation) in younger children and demotivation [42].

In the most recent review [27] of predictors of SSRI response, comorbid tics and externalizing disorders were associated with a poorer outcome. However, there was little evidence that gender, age, or duration of OCD predicted treatment response. Studies of adults indicate that the hoarding dimension of OCD predicts poor treatment outcome [43]. The only study of a pediatric sample confirming those results was a naturalistic follow-up study of 94 children treated with an SSRI, where children with hoarding symptoms reported worse outcomes than children with contamination obsessions and washing rituals [44].

CBT or SSRIs as the First Choice

Three studies have compared these treatments directly in treatment-naïve and shown the significant pooled superiority of CBT [20, 24, 25]. However, the difference is small and perhaps not clinically significant. In considering this result, treatment providers and patients should also reflect on other factors. First, therapist factors such as expertise may be

important. In the largest head-to-head comparison of CBT and SSRIs [20], large and significant site differences were observed, showing that the site with considerable CBT expertise (Penn) had a large CBT effect, while the effect was only moderate at Duke. Second, long-term effects are important. Only one study compares the long-term stability of CBT with that of sertraline. No differences were observed between the groups after 12 weeks. At the 9-month follow-up, the CBT group showed significantly lower rates of relapse. However, the SSRI group discontinued sertraline after 12 weeks [25]. Third, one would need to take into consideration that the recommended minimum duration of SRI treatment is 1 year [41]. By contrast, CBT is usually more time-limited and has a durable effect after treatment termination [25, 45, 46].

Combined Treatment

Two studies have compared the combined treatment with CBT alone [20, 47]. Their combined effect size does not show the superiority of the combined treatment (g=−0.13) [5]. Adult OCD trials show that the combination of CBT and an SSRI generally does not confer additional benefits to CBT alone. The pooled results from a recent meta-analysis of pediatric and adult OCD trials concluded that the combined treatment does not provide an incremental benefit to CBT alone [48].

The POTS [20] trial showed that the combined treatment of CBT and SSRIs resulted in significantly lower total CY-BOCS scores compared with CBT or an SSRI alone at posttreatment. However, the site differences were large, as the CBT group showed a large effect size at one site (Penn) similar to the combined treatment, but a moderate and significantly lower effect size at Duke. Interestingly and perhaps consequently, baseline OCD severity did not turn out to be a moderator of treatment outcomes, indicating that all treatments (CBT alone, an SSRI alone, and the combined treatment) were effective regardless of OCD severity at baseline [28]. These CBT site differences may be explained by various factors such as therapist ability and experience [20], and it is important that such effects are studied. One could speculate that when CBT expertise is available, the addition of an SSRI does not confer an additional benefit, while the lack of CBT expertise requires the addition of an SSRI to obtain the same benefit as when CBT expertise is available. It is necessary to study these effects before recommendations for the combined treatment are given. In conclusion, there is little evidence supporting the additional effect of an SSRI in combination with CBT. Nevertheless, the combined treatment seems to be significantly more effective than an SSRI alone [20, 49] with a pooled effect size of g=−0.59 [5]. The pooled results from a recent meta-analysis of pediatric and adult OCD trials also showed the superiority of the combined treatment over SRI alone [48].

Treatment-Resistant Pediatric OCD

CBT non-Responders

If standard CBT is unsuccessful, the clinician may choose from three different strategies: (1) continue with CBT, (2) continue with CBT and augment with an SSRI, or (3) terminate CBT and switch to an SSRI. International guidelines recommend that SSRIs should be added to unsuccessful CBT [1, 12]. However, the sequence of treatment (i.e., start with CBT and if the patient does not respond, augment with an SSRI) is only based on expert consensus, not empirical evidence. Only one study has compared different strategies for CBT non-responders. Children and adolescents that still had moderate to severe OCD (CY-BOCS >15) after 14 weekly sessions of CBT were randomized to continue with their CBT for ten sessions or switched to an SSRI (sertraline) for 16 weeks. No significant differences between the groups were found for the primary outcomes. However, both groups seemed to benefit from the treatment [50]. Preliminarily, clinicians should thus evaluate whether switching to an SSRI could be a better choice for pediatric OCD CBT non-responders with comorbid tic disorder as shown in a post hoc analysis within the same study [51].

Beyond the available evidence, the clinician must consider a number of factors with CBT non-responders. For instance, partial response to CBT may indicate that continued CBT alone should be tried first. However, when patients do not comply with treatment despite the therapist's efforts to increase compliance, a natural step would be to switch to an SSRI as guidelines recommend [12]. An additional strategy for CBT or SSRI non-responders is to provide more concentrated CBT. One pediatric OCD open trial with non- or partial responders to SSRIs showed that the majority benefitted by receiving one CBT session per day for 3 weeks [52].

Switching to Another SSRI or Clomipramine

If a child does not respond to an SSRI, the next step could be to switch to another SSRI [1, 12]. However, minimal data exist that can direct the choice [1]. By analogy, switching fluvoxamine non-responders to fluoxetine was effective in the Research Unit on Pediatric Psychopharmacology Anxiety Study [53].

Another strategy recommended by expert guidelines is to add clomipramine to an SSRI [1, 12]. The rationale stated is to combine the serotonergic effects of each medication but to minimize adverse events across different drug classes. Fluvoxamine may have the greatest synergistic effect when added to clomipramine because it is able to inhibit the conversion of clomipramine to desmethylclomipramine and to increase it to a ratio that is in favor of the serotonergic parent compound. One needs to monitor the EKG indices when

clomipramine is used, but when combined with an SSRI, such as fluvoxamine, or CYP-450 2D6 inhibitors, such as fluoxetine or paroxetine, additional care must be taken because of the potentially toxic increases in serum clomipramine levels that need to be monitored. Higher dose of clomipramine and lower dose of fluvoxamine (as a metabolic blocker mainly) may work best. Additionally, the risk should be weighed against the harm to the patient from the OCD [1, 54]. The evidence for this combination is limited. Only two case series exist in pediatric OCD showing beneficial effects on OCD symptoms as well as adverse events in the form of [55, 56]. One double-blind RCT in adult OCD showed the superiority of clomipramine + fluoxetine compared to quetiapine + fluoxetine in SSRI non-responders. However, no difference was detected between clomipramine + fluoxetine and pill placebo + fluoxetine indicating that the period of SSRI alone should be extended (optimally with maximum dose) before a combination with clomipramine is applied [57].

It is also important to note that the dissemination of CBT is a large and universal problem; thus, in many areas of the world, children and adolescents with OCD are often treated exclusively with SSRIs [58]. Despite that combining CBT and SSRIs may be necessary and in fact much more effective than continuing with an SSRI alone, even for those that do not respond to SSRIs [59].

Evidence-Based Treatments for Treatment-Refractory Pediatric OCD

This section discusses evidence-based treatments for patients that still have significant and functionally impairing symptoms despite one standard CBT trial and two SSRI trials (or one SSRI trial and a clomipramine add-on) [1, 3]. Expert guidelines recommend pharmacological augmentation or more intensive CBT [1]. Augmentation is the procedure off adding drugs with different mechanisms of action compared with the first-line SSRI in order to aid the therapeutic effects. Research indicates that in addition to serotonin, other neurotransmitters may be involved in the pathophysiology of OCD such as glutamate [10] and dopamine [11]. However, the evidence-based literature—at least for pediatric OCD—is lacking. Thus, pharmacologists always find themselves in off-label settings when treating this group. When appropriate evidence is lacking, we will introduce studies of adult OCD.

Atypical Antipsychotics (Neuroleptics)

The most prominent augmentation strategy in OCD is the use of atypical antipsychotics, also called second generation antipsychotics (SGAs). These work mainly by blocking the dopamine pathways within the cortex. In adults with OCD, randomized controlled trials (RCTs) have been conducted to show the effects of risperidone (e.g., [60]), aripiprazole, quetiapine, olanzapine, and haloperidol, which is a typical or first generation antipsychotic [11, 61]. The effect seems to be greater in patients with comorbid OCD and tic disorder [61]. However, no RCT exists in pediatric OCD, and inferring that children and adolescents should benefit in the same way as adults are fraught with difficulties and depend on the presupposition that adult and pediatric OCD are equivalent, even though the transmitter systems in young people are not mature as those in adults [62]. However, naturalistic open trials using risperidone and aripiprazole as an augmentation to an SSRI in pediatric OCD indicate that the combination may be beneficial [44, 63, 64]. In a naturalistic comparative study, children with tic-related OCD that were non-responders after an SSRI trial (N=69) showed equal benefits from risperidone and aripiprazole. However, risperidone was associated with serious metabolic adverse events such as weight gain and sedation and aripiprazole to mild/moderate agitation [63]. Similarly, case studies show that risperidone might be beneficial [65–67]. However, many of the patients included were CBT-naïve before using SGAs. A study of adult OCD shows that SSRI non-responders that have not received CBT previously fare better if randomized to CBT in contrast to risperidone [68]. Thus, by taking the effects and adverse events into account, we argue that using SGAs is not a viable option unless adequate trials of CBT and SSRI have been conducted. The risk of untreated OCD should be compared with potential SGA-adverse events, and the pharmacotherapist should follow the advice of Mayan and Correll [69].

Benzodiazepines

Using benzodiazepines such as clonazepam is also off-label [1]. Only one case study exists in pediatric OCD, reporting considerable improvement after a combination treatment of fluoxetine and clonazepam [70]. Two double-blind placebo control studies in adult OCD showed no effect of clonazepam when added to an SSRI in SSRI non-responders [71, 72]. Thus, in view of the current state of knowledge, this strategy is not recommended.

Other Possible Medications

Other potential strategies for treatment-refractory patients are stimulants, gabapentin, sumatriptan, pindolol, morphine, tramadol, anfranal, inositol, opiates, St. John's wort, N-acetylcysteine, and glutamate antagonists (e.g., memantine and riluzole) [1]. In addition, it has been suggested that switching to serotonin-norepinephrine reuptake inhibitors such as venlafaxine and duloxetine might be beneficial. However, RCTs among adult OCD do not suggest that venlafaxine is more effective than the SSRI paroxetine [73]. In a subsequent study of the non-responders of these drugs, switching from venlafaxine to paroxetine was found to be

significantly more effective than vice versa [74]. However, serotonin-related genes may predict which patients respond to SSRIs and which patients respond to serotonin-norepinephrine reuptake inhibitors [75]. Furthermore, increasing SSRI doses have been suggested to be an effective strategy in adults with OCD. One RCT in SSRI non-responders showed the benefits of 400 mg of sertraline compared to 200 mg daily [76]. Indeed, as stated in the most recent expert guidelines, these strategies are off-label, and with the exception of riluzole, they are at most based on a limited number of case reports [1]. The other strategy is augmenting an SSRI with a serotonin 5-HT_3 receptor antagonist [77]. One double-blind RCT has shown the benefits of augmenting an SSRI with granisetron in adult OCD [78], and two double-blind RCTs have shown the benefits of ondansetron in adult OCD [79, 80]. These treatments are clearly to be used by experts in true treatment-refractory OCD.

Somatic Treatments

Among somatic treatments is ablative neurosurgery, which has been used for many decades for treatment-refractory adult OCD only [81]. In addition, the emerging treatment of deep brain stimulation involves the surgical implantation of electrodes and targeted electrical stimulations. The advantage compared with neurosurgery is that this procedure is reversible. A review of 90 cases of treatment-refractory adult OCD shows some indications of benefits [82]. Another treatment option is repetitive transcranial magnetic stimulation, which is noninvasive. Here, one uses the magnetic field to apply electrical activity within the cortex. Currently, no evidence supports the use of repetitive transcranial magnetic stimulation in OCD [83].

Emerging Treatments

In this section, we describe novel and experimental treatments. Some of these treatments can be considered for treatment-naïve and treatment-refractory patients alike, while others should be reserved for treatment-refractory patients due to cost or adverse events.

CBT Combination

D-cycloserine and CBT

D-cycloserine is believed to enhance the extinction of learned fear [84]. The theoretical mechanism is that the *N*-methyl-D-aspartate (NMDA) receptor is involved in fear extinction and that D-cycloserine as an NMDA partial agonist is able to enhance this extinction. As the mechanism of CBT for OCD is to extinguish the relationship between an anxiety-producing stimulus and obsessive fear by exposing patients to these stimuli, one could potentially enhance this extinction by taking D-cycloserine approximately 1 h before CBT sessions. Two RCTs have confirmed that D-cycloserine has an additive effect when combined with CBT, as it was proven to be superior to CBT+pill placebo [85, 86]. In line with this synthesized theory, D-cycloserine does not seem to work when administered after E/RP sessions [87]. Pending further studies, the augmentation of D-cycloserine may become a viable and safe option in the future to reduce OCD symptoms quickly and effectively.

CBT with other Combinations

CBT is ineffective for some patients as they engage poorly with E/RP or other components of the treatment. Adding motivational interviewing may thus be helpful. One preliminary RCT showed that adding motivational interviewing to intensive CBT for 3 weeks was more effective than adding extra psycho-education sessions [88].

Attention modification programs (AMPs) have also been suggested as an add-on to CBT/SSRI. AMPs are used to disengage attention from cues that are considered to be threatening. One preliminary RCT with severe or complicated cases of anxiety disorders exists (the majority of children had OCD as their primary diagnosis). The participants added either AMPs or attention control conditions to their CBT, and the results showed clear benefits to the AMP group [89].

Modified CBT

Modifying CBT may enhance response or reduce cost and thus the availability of CBT. By comparing these with established standard CBT, one can examine whether they outperform CBT in terms of mean effect, the effect of a subset of patients, or cost reduction. International expert guidelines recommend intensive CBT as a strategy for treatment-resistant or treatment-refractory patients [1, 12]. However, research on the effectiveness of intensive CBT is limited. One RCT shows that daily CBT for 3 weeks is as effective as weekly sessions over 14 weeks. Additional well-powered studies are thus needed. Two open trials exist in treatment-resistant patients showing the benefits of intensive CBT [52, 90].

Group-based CBT seems to be equally effective as individual CBT [14, 45]. Group CBT has been studied more extensively in adults with OCD, and the results from well-designed studies consistently show no differences between CBT and group CBT [91–93]. However, group CBT is dependent on a steady flow of patients [94], meaning that it may be more feasible in large rather than small clinics. Such a group setting also provides less therapist contact than an individual setting.

However, some therapeutic benefits might be unique to group CBT such as the modeling of CBT exercises, support

from peers, reinforcement of homework exercises, normalization and de-stigmatization of the symptoms of OCD, and acquisition of knowledge on other OCD symptoms [94]. Hence, there might be an added benefit to combine a group setting with one-to-one contact between a therapist and a patient. One RCT in adults with OCD shows the benefits of an individually delivered intensive E/RP in a group setting [95].

Another cost-effective approach might be to minimize the initial therapeutic resources while maximizing the effects as much as possible (e.g., by providing bibliotherapy as the first step [96]). While no studies of the benefits of bibliotherapy in pediatric OCD exist, one open trial showed the effects of computerized bibliotherapy with minimal therapeutic contact [97]. Optimally, this treatment form should be compared with standard CBT in a stepped care study in order to evaluate both effects and cost [96].

Another treatment form is to reduce the number of sessions. One brief format of CBT that consisted of five sessions was compared with standard CBT (12 sessions) and waitlist. While both CBT forms showed superiority over waitlist, there was no difference between the two [15].

Remote CBT is another viable option where CBT is delivered through telephone or videoconferencing. One RCT showed that CBT delivered through Skype was superior to waitlist [16]. At least one uncontrolled feasibility study also exists [98]. A non-inferiority RCT comparing telephone-delivered CBT with standard in-office CBT showed that CBT could be effectively delivered over the telephone [99].

Medications

Recent evidence from a number of directions (genetic, neuroimaging, animal models, and treatment studies) implies that an abnormal concentration of glutamate, the main neurotransmitter within cortico-striatal-thalamic circuits, may be associated with OCD [10, 100]. Thus, researchers have shown increasing interest in the potential efficacy of glutamate-targeting agents for OCD treatment. One of these is riluzole, which has been approved by the FDA for treating amyotrophic lateral sclerosis. Although uncontrolled studies had previously shown effects in children [101] and adults [102, 103], the first RCT trial conducted among (S)SRI non-responders did not show any effect over pill placebo. However, 28 % of participants had concomitant autism disorder [104].

Other glutamatergic drugs are ketamine, memantine, topiramate, and lamotrigine [10]. No studies in the pediatric OCD population exist [6]. *N*-acetylcysteine, a naturally occurring amino acid, is also a glutamate-modulating drug with a beneficial safety profile that may be a good alternative to children that have failed both CBT and two SSRI trials.

Conclusion

What are the implications of the results of current studies for clinical guidelines? First, when CBT expertise is available, one can successfully treat pediatric OCD patients with CBT and continue even when the patient does not respond after a standard duration of treatment. Second, when CBT expertise is absent, treatment-naïve patients can confidently be treated with an SSRI. However, if they do not respond, previous studies indicate that the addition of full CBT may be necessary to obtain a response [59].

Moreover, American clinical guidelines recommend the combined treatment of CBT and SSRIs for patients with moderate to severe OCD [1]. The pooled results of the combined treatment of CBT and SSRIs were not found to be superior to CBT alone [20, 47] with no evidence of different effects based on symptom severity [28]. Thus, the data support the European guidelines [12]. One could hypothesize that CBT alone is as good as the combined treatment when delivered by experts [20, 47]. When the results of CBT are attenuated for some reason, the addition of medication may be important [20]. However, continuing CBT beyond a standard trial of 14 sessions seems to be a viable option [50].

The evidence beyond first-line treatments for pediatric OCD is limited. More studies are needed in CBT non- or partial responders. Moreover, we need new compounds that have higher efficacy than the (S)SRI class of drugs, based on the improved understanding of OCD neurobiology and neurochemistry that is emerging. Some forms of augmentation such as SGAs have limited evidence for their effects and may be dangerous with regard to adverse events; hence, they should only be used by experts. Long-term follow-up studies of patients recruited to RCTs are also needed to increase our understanding of the duration and robustness of the treatment effects.

Acknowledgments The Center for Child and Adolescent Mental Health, Eastern and Southern Norway gave the main authors the support to perform this work.

Compliance with Ethics Guidelines

Conflicts of interest Dr. Ivarsson is consultant and Speaker's bureau for Shire, Sweden. Dr. Skarphedinsson has no declaration of interest to report.

Gudmundur Skarphedinsson has no disclosures relevant to this work. Tord Ivarsson received payment for an educational presentation/speaking engagement.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Geller D, March J. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:98–113.
2. Jenike MA, Rauch SL. Managing the patient with treatment-resistant obsessive compulsive disorder: current strategies. J Clin Psychiatry. 1994;55(Suppl):11–7.
3. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, Marazziti D, et al. Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol. 2002;5:181–91.
4. Skarphedinsson G, Hanssen-Bauer K, Kornor H, Heiervang ER, Landro NI, Axelsdottir B, et al. Standard individual cognitive behaviour therapy for paediatric obsessive-compulsive disorder: a systematic review of effect estimates across comparisons. Nordic J Psychiatry. 2015;69:81–92.
5. Ivarsson T, Skarphedinsson G, Kornor H, Axelsdottir B, Biedilae S, Heyman I, et al. The place of and evidence for serotonin reuptake inhibitors (SRIs) for obsessive compulsive disorder (OCD) in children and adolescents: views based on a systematic review and meta-analysis. Psychiatry Res. 2015;227:93–103.
6. Bloch MH, Storch EA. Assessment and Management of Treatment-Refractory Obsessive-Compulsive Disorder in Children. J Am Acad Child Adolesc Psychiatry. 2015;54:251–62.
7. Sánchez-Meca J, Rosa-Alcázar AI, Iniesta-Sepúlveda M, Rosa-Alcázar Á. Differential efficacy of cognitive-behavioral therapy and pharmacological treatments for pediatric obsessive-compulsive disorder: a meta-analysis. J Anxiety Disord. 2014;28:31–44.
8. Pittenger C, Bloch MH. Pharmacological treatment of obsessive-compulsive disorder. Psychiatr Clin N Am. 2014;37:375–91.
9. Freeman J, Garcia A, Frank H, Benito K, Conelea C, Walther M, et al. Evidence base update for psychosocial treatments for pediatric obsessive-compulsive disorder. J Clin Child Adolesc Psychol. 2014;43:7–26.
10. Grados MA, Specht MW, Sung HM, Fortune D. Glutamate drugs and pharmacogenetics of OCD: a pathway-based exploratory approach. Expert Opin Drug Discov. 2013;8:1515–27.
11. Dold M, Aigner M, Lanzenberger R, Kasper S. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. Int J Neuropsychopharmacol. 2013;16:557–74.
12. National Institute for Heath and Clinical Excellence (2005) Obsessive compulsive disorder (OCD) and body dysmorphic disorder (BDD). In: Excellence NIfHaC (ed)National Institute for Health and Clinical Excellence, London, p National Institute for Health and Clinical Excellence
13. Socialstyrelsen. Nationella riktlinjer för vård vid depression och ångestsyndrom 2010 – stöd för styrning och ledning [Swedish National Guidelines for the Treatment of Depression and Anxiety Disorders 2010]. Stockholm: Socialstyrelsen; 2010.
14. Barrett P, Healy-Farrell L, March JS. Cognitive-behavioral family treatment of childhood obsessive-compulsive disorder: a controlled trial. J Am Acad Child Adolesc Psychiatry. 2004;43:46–62.
15. Bolton D, Williams T, Perrin S, Atkinson L, Gallop C, Waite P, et al. Randomized controlled trial of full and brief cognitive-behaviour therapy and wait-list for paediatric obsessive-compulsive disorder. J Child Psychol Psychiatry. 2011;52:1269–78.
16. Storch EA, Caporino NE, Morgan JR, Lewin AB, Rojas A, Brauer L, et al. Preliminary investigation of web-camera delivered cognitive-behavioral therapy for youth with obsessive-compulsive disorder. Psychiatry Res. 2011;189:407–12.
17. Williams TI, Salkovskis PM, Forrester L, Turner S, White H, Allsopp MA. A randomised controlled trial of cognitive behavioural treatment for obsessive compulsive disorder in children and adolescents. Eur Child Adolesc Psychiatry. 2010;19:449–56.
18. Lewin AB, Park JM, Jones AM, Crawford EA, De Nadai AS, Menzel J, et al. Family-based exposure and response prevention therapy for preschool-aged children with obsessive-compulsive disorder: a pilot randomized controlled trial. Behav Res Ther. 2014;56:30–8.
19. Bolton D, Perrin S. Evaluation of exposure with response-prevention for obsessive compulsive disorder in childhood and adolescence. J Behav Ther Exp Psychiatry. 2008;39:11–22.
20. POTS Study Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. JAMA. 2004;292:1969–76.
21. Freeman JB, Garcia AM, Coyne L, Ale C, Przeworski A, Himle M, et al. Early childhood OCD: preliminary findings from a family-based cognitive-behavioral approach. J Am Acad Child Adolesc Psychiatry. 2008;47:593–602.
22. Piacentini J, Bergman RL, Chang S, Langley A, Peris T, Wood JJ, et al. Controlled comparison of family cognitive behavioral therapy and psychoeducation/relaxation training for child obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:1149–61.
23. Freeman J, Sapyta J, Garcia A, Compton S, Khanna M, Flessner C, et al. Family-based treatment of early childhood obsessive-compulsive disorder: the Pediatric Obsessive-Compulsive Disorder Treatment Study for Young Children (POTS Jr)—a randomized clinical trial. JAMA Psychiatry. 2014;71:689–98.
24. de Haan E, Hoogduin KA, Buitelaar JK, Keijsers GP. Behavior therapy versus clomipramine for the treatment of obsessive-compulsive disorder in children and adolescents. J Am Acad Child Adolesc Psychiatry. 1998;37:1022–9.
25. Asbahr FR, Castillo AR, Ito LM, Latorre MRDDO, Moreira MN, Lotufo-Neto F. Group cognitive-behavioral therapy versus sertraline for the treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2005;44:1128–36.
26. Torp NC, Dahl K, Skarphedinsson G, Thomsen P, Valderhaug R, Weidle B, et al. Effectiveness of cognitive behavior treatment for pediatric obsessive-compulsive disorder: Acute outcomes from The Nordic Long-term OCD Treatment Study (NordLOTS). Behav Res Ther. 2015;64:15–23.
27. Ginsburg GS, Kingery JN, Drake KL, Grados MA. Predictors of treatment response in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2008;47:868–78.
28. 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;49:1024–33. quiz 1086.
29. Torp NC, Dahl K, Skarphedinsson G, Thomsen PH, Valderhaug R, Weidle B, et al. Predictors associated with improved cognitive-behavioral therapy outcome in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2015;54:200–7.
30. 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;47:583–92.
31. 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;77:355–60.
32. DeVeaugh-Geiss J, Moroz G, Biederman J, Cantwell D, Fontaine R, Greist JH, et al. Clomipramine hydrochloride in childhood and

adolescent obsessive-compulsive disorder—a multicenter trial. In: Journal of the American Academy of Child and Adolescent Psychiatry; 1992. p. 45–9.
33. March JS, Biederman J, Wolkow R, Safferman A, Mardekian J, Cook EH, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA. 1998;280:1752–6.
34. Riddle MA, Reeve EA, Yaryura-Tobias JA, Yang HM, Claghorn JL, Gaffney G, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. J Am Acad Child Adolesc Psychiatry. 2001;40: 222–9.
35. Riddle MA, Scahill L, King RA, Hardin MT, Anderson GM, Ort SI, et al. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 1992;31:1062–9.
36. Geller DA, Hoog SL, Heiligenstein JH, Ricardi RK, Tamura R, Kluszynski S, et al. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. In: Journal of the American Academy of Child and Adolescent Psychiatry; 2001. p. 773–9.
37. Geller DA, Wagner KD, Emslie G, Murphy T, Carpenter DJ, Wetherhold E, et al. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2004;43:1387–96.
38. Walsh KH, McDougle CJ. Psychotherapy and medication management strategies for obsessive-compulsive disorder. Neuropsychiatr Dis Treat. 2011;7:485–94.
39. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007;297: 1683–96.
40. Leonard HL, Swedo SE, Lenane MC, Rettew DC, Cheslow DL, Hamburger SD, et al. A double-blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive-compulsive disorder. Arch Gen Psychiatry. 1991;48:922–7.
41. Cook EH, Wagner KD, March JS, Biederman J, Landau P, Wolkow R, et al. Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2001;40:1175–81.
42. Offidani E, Fava GA, Tomba E, Baldessarini RJ. Excessive mood elevation and behavioral activation with antidepressant treatment of juvenile depressive and anxiety disorders: a systematic review. Psychother Psychosom. 2013;82:132–41.
43. Saxena S, Maidment KM, Vapnik T, Golden G, Rishwain T, Rosen RM, et al. Obsessive-compulsive hoarding: symptom severity and response to multimodal treatment. J Clin Psychiatry. 2002;63:21–7.
44. Masi G, Millepiedi S, Mucci M, Bertini N, Milantoni L, Arcangeli F. A naturalistic study of referred children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2005;44:673–81.
45. Barrett P, Farrell L, Dadds M, Boulter N. Cognitive-behavioral family treatment of childhood obsessive-compulsive disorder: long-term follow-up and predictors of outcome. J Am Acad Child Adolesc Psychiatry. 2005;44:1005–14.
46. O'Leary EMM, Barrett P, Fjermestad KW. Cognitive-behavioral family treatment for childhood obsessive-compulsive disorder: a 7-year follow-up study. J Anxiety Disord. 2009;23:973–8.
47. 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;51:823–9.
48. Romanelli RJ, Wu FM, Gamba R, Mojtabai R, Segal JB. Behavioral therapy and serotonin reuptake inhibitor pharmacotherapy in the treatment of obsessive-compulsive disorder: a systematic review and meta-analysis of head-to-head randomized controlled trials. Depression Anxiety. 2014;31:641–52.
49. Neziroglu F, Yaryura-Tobias JA, Walz J, McKay D. The effect of fluvoxamine and behavior therapy on children and adolescents with obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2000;10:295–306.
50. 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;24:591–602.
51. Skarphedinsson G, Compton S, Thomsen PH, Weidle B, Dahl K, Nissen JB, et al. Tics moderate sertraline-, but not cognitive-behavior therapy (CBT), in CBT non-responding pediatric obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2015;25:432–9.
52. 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;39:260–8.
53. Walkup J, Labellarte M, Riddle MA, Pine DS, Greenhill L, Fairbanks J, et al. Treatment of pediatric anxiety disorders: an open-label extension of the research units on pediatric psychopharmacology anxiety study. J Child Adolesc Psychopharmacol. 2002;12:175–88.
54. Arumugham SS, Reddy JY. Augmentation strategies in obsessive-compulsive disorder. Expert Rev Neurother. 2013;13:187–202. quiz 203.
55. Simeon JG, Thatte S, Wiggins D. Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. Psychopharmacol Bull. 1990;26:285–90.
56. 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: 61–7.
57. Diniz JB, Shavitt RG, Fossaluza V, Koran L, Pereira CADB, Miguel EC. A double-blind, randomized, controlled trial of fluoxetine plus quetiapine or clomipramine versus fluoxetine plus placebo for obsessive-compulsive disorder. J Clin Psychopharmacol. 2011;31:763–8.
58. Franklin ME, Dingfelder HE, Coogan CG, Garcia AM, Sapyta JJ, Freeman JL. Cognitive behavioral therapy for pediatric obsessive-compulsive disorder: development of expert-level competence and implications for dissemination. J Anxiety Disord. 2013;27: 745–53.
59. Franklin ME, Sapyta J, Freeman JB, Khanna M, Compton S, Almirall D, Moore P, Choate-Summers M, Garcia A, Edson AL, Foa EB, March JS (2011) Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder: the Pediatric OCD Treatment Study II (POTS II) randomized controlled trial. In: JAMA : the journal of the American Medical Association. p 1224–1232
60. 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;57:794–801.
61. 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;11:622–32.
62. Bylund DB, Reed AL. Childhood and adolescent depression: Why do children and adults respond differently to antidepressant drugs? Neurochem Int. 2007;51:246–53.
63. 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;47:1007–12.
64. Masi G, Millepiedi S, Perugi G, Pfanner C, Berloffa S, Pari C, et al. Pharmacotherapy in paediatric obsessive-compulsive disorder: a naturalistic, retrospective study. CNS Drugs. 2009;23:241–52.
65. Thomsen PH. Risperidone augmentation in the treatment of severe adolescent OCD in SSRI-refractory cases: a case-series. Ann Clin Psychiatry. 2004;16:201–7.
66. 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;9:115–23.
67. Lombroso PJ, Scahill L, King RA, Lynch KA, Chappell PB, Peterson BS, et al. Risperidone treatment of children and adolescents with chronic tic disorders: a preliminary report. J Am Acad Child Adolesc Psychiatry. 1995;34:1147–52.
68. Simpson HB, Foa EB, Liebowitz MR, Huppert JD, Cahill S, Maher MJ, et al. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. JAMA Psychiatry. 2013;70:1190–9.
69. Maayan L, Correll CU. Management of antipsychotic-related weight gain. Expert Rev Neurother. 2010;10:1175–200.
70. Leonard HL, Topol D, Bukstein O, Hindmarsh D, Allen AJ, Swedo SE. Clonazepam as an augmenting agent in the treatment of childhood-onset obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 1994;33:792–4.
71. Hollander E, Kaplan A, Stahl SM. A double-blind, placebo-controlled trial of clonazepam in obsessive-compulsive disorder. World J Biol Psychiatry. 2003;4:30–4.
72. Crockett BA, Churchill E, Davidson JR. A double-blind combination study of clonazepam with sertraline in obsessive-compulsive disorder. Ann Clin Psychiatry. 2004;16:127–32.
73. Denys D, van der Wee N, van Megen HJ, Westenberg HG. A double blind comparison of venlafaxine and paroxetine in obsessive-compulsive disorder. J Clin Psychopharmacol. 2003;23:568–75.
74. Denys D, van Megen HJ, van der Wee N, Westenberg HG. A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. J Clin Psychiatry. 2004;65:37–43.
75. Denys D, Van Nieuwerburgh F, Deforce D, Westenberg HGM. Prediction of response to paroxetine and venlafaxine by serotonin-related genes in obsessive-compulsive disorder in a randomized, double-blind trial. J Clin Psychiatry. 2007;68:747–53.
76. Ninan PT, Koran LM, Kiev A, Davidson JR, Rasmussen SA, Zajecka JM, et al. High-dose sertraline strategy for nonresponders to acute treatment for obsessive-compulsive disorder: a multicenter double-blind trial. J Clin Psychiatry. 2006;67:15–22.
77. Serata D, Kotzalidis GD, Rapinesi C, Janiri D, Di Pietro S, Callovini G, et al. Are 5-HT3 antagonists effective in obsessive-compulsive disorder? A systematic review of literature. Hum Psychopharmacol. 2015;30:70–84.
78. Askari N, Moin M, Sanati M, Tajdini M, Hosseini S-M-R, Modabbernia A, et al. Granisetron adjunct to fluvoxamine for moderate to severe obsessive-compulsive disorder: a randomized, double-blind, placebo-controlled trial. CNS Drugs. 2012;26:883–92.
79. Soltani F, Sayyah M, Feizy F, Malayeri A, Siahpoosh A, Motlagh I. A double-blind, placebo-controlled pilot study of ondansetron for patients with obsessive-compulsive disorder. Hum Psychopharmacol. 2010;25:509–13.
80. Heidari M, Zarei M, Hosseini SM, Taghvaei R, Maleki H, Tabrizi M, et al. Ondansetron or placebo in the augmentation of fluvoxamine response over 8 weeks in obsessive-compulsive disorder. Int Clin Psychopharmacol. 2014;29:344–50.
81. Greenberg BD, Rauch SL, Haber SN. Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. Neuropsychopharmacology. 2010;35:317–36.
82. Blomstedt P, Sjoberg RL, Hansson M, Bodlund O, Hariz MI. Deep brain stimulation in the treatment of obsessive-compulsive disorder. World Neurosurg. 2013;80:e245–53.
83. Slotema CW, Blom JD, Hoek HW, Sommer IE. Should we expand the toolbox of psychiatric treatment methods to include Repetitive Transcranial Magnetic Stimulation (rTMS)? A meta-analysis of the efficacy of rTMS in psychiatric disorders. J Clin Psychiatry. 2010;71:873–84.
84. Norberg MM, Krystal JH, Tolin DF. A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. Biol Psychiatry. 2008;63:1118–26.
85. Storch EA, Murphy TK, Goodman WK, Geffken GR, Lewin AB, Henin A, Micco JA, Sprich S, Wilhelm S, Bengtson M, Geller DA (2010) A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. In: Biological psychiatry. p 1073–1076
86. 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. Depression Anxiety. 2013;30:723–31.
87. Mataix-Cols D, Turner C, Monzani B, Isomura K, Murphy C, Krebs G, et al. Cognitive-behavioural therapy with post-session D-cycloserine augmentation for paediatric obsessive-compulsive disorder: pilot randomised controlled trial. Br J Psychiatry. 2014;204:77–8.
88. Merlo LJ, Storch EA, Lehmkuhl HD, Jacob ML, Murphy TK, Goodman WK, et al. Cognitive behavioral therapy plus motivational interviewing improves outcome for pediatric obsessive-compulsive disorder: a preliminary study. Cogn Behav Ther. 2010;39:24–7.
89. Riemann BC, Kuckertz JM, Rozenman M, Weersing VR, Amir N. Augmentation of youth cognitive behavioral and pharmacological interventions with attention modification: a preliminary investigation. Depression Anxiety. 2013;30:822–8.
90. Bjorgvinsson 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;14:137–45.
91. Fals-Stewart W, Marks AP, Schafer J. A comparison of behavioral group therapy and individual behavior therapy in treating obsessive-compulsive disorder. J Nerv Ment Dis. 1993;181:189–93.
92. Anderson RA, Rees CS. Group versus individual cognitive-behavioural treatment for obsessive-compulsive disorder: a controlled trial. Behav Res Ther. 2007;45:123–37.
93. Jonsson H, Hougaard E, Bennedsen BE. Randomized comparative study of group versus individual cognitive behavioural therapy for obsessive compulsive disorder. Acta Psychiatr Scand. 2011;123:387–97.
94. Himle JA, Van Etten M, Fischer DJ. Group cognitive behavioral therapy for obsessive-compulsive disorder: a review. Brief Treat Crisis Interv. 2003;3:217–29.

95. Havnen A, Hansen B, Öst L-G, Kvale G. Concentrated ERP delivered in a group setting: an effectiveness study. J Obsessive-Compulsive Relat Disord. 2014;3:319–24.
96. Tolin DF, Diefenbach GJ, Gilliam CM. Stepped care versus standard cognitive-behavioral therapy for obsessive-compulsive disorder: a preliminary study of efficacy and costs. Depression Anxiety. 2011;28:314–23.
97. Lenhard F, Vigerland S, Andersson E, Ruck C, Mataix-Cols D, Thulin U, et al. Internet-delivered cognitive behavior therapy for adolescents with obsessive-compulsive disorder: an open trial. PLoS ONE. 2014;9, e100773.
98. Comer JS, Furr JM, Cooper-Vince CE, Kerns CE, Chan PT, Edson AL, et al. Internet-delivered, family-based treatment for early-onset OCD: a preliminary case series. J Clin Child Adolesc Psychol. 2014;43:74–87.
99. Turner CM, Mataix-Cols D, Lovell K, Krebs G, Lang K, Byford S, et al. Telephone cognitive-behavioral therapy for adolescents with obsessive-compulsive disorder: a randomized controlled Non-inferiority trial. J Am Acad Child Adolesc Psychiatry. 2014;53:1298–1307.e1292.
100. Wu K, Hanna GL, Rosenberg DR, Arnold PD. The role of glutamate signaling in the pathogenesis and treatment of obsessive-compulsive disorder. Pharmacol Biochem Behav. 2012;100:726–35.
101. 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;17:761–7.
102. Pittenger C, Kelmendi B, Wasylink S, Bloch MH, Coric V. Riluzole augmentation in treatment-refractory obsessive-compulsive disorder: a series of 13 cases, with long-term follow-up. J Clin Psychopharmacol. 2008;28:363–7.
103. Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G, et al. Riluzole augmentation in treatment-resistant obsessive-compulsive disorder: an open-label trial. Biol Psychiatry. 2005;58:424–8.
104. Grant PJ, Joseph LA, Farmer CA, Luckenbaugh DA, Lougee LC, Zarate Jr CA, et al. 12-week, placebo-controlled trial of add-on riluzole in the treatment of childhood-onset obsessive-compulsive disorder. Neuropsychopharmacology. 2014;39:1453–9.