

Obsessive-compulsive disorder in pediatrics and adolescents: Review of treatment and future directions

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ABSTRACT

Obsessive-compulsive disorder (OCD) is an anxiety disorder associated with significant morbidity, and found at a relatively high overall prevalence in the pediatric and adolescent population. This article reviews the treatment of OCD in pediatrics and adolescents.

KEYWORDS

obsessive-compulsive disorder (OCD), pediatrics, adolescents

INTRODUCTION

Obsessive-compulsive disorder (OCD) is an anxiety disorder found in the pediatric and adolescent population at a relatively high overall prevalence (reported from 1 – 4% of the general population).¹ With an estimated average age of onset at 11 years and average age of treatment initiation at 13 years, OCD may be an under recognized illness in the youth population.² It is associated with significant morbidity due to the time-consuming and potentially distressing nature of the illness's characteristic recurrent obsessions and/or compulsions which can be more heterogeneous and dynamic compared with adult presentations. Additionally, unlike adults with OCD, youth tend to present with less insight into their illness and may not identify with the perception that their obsessions or compulsions are unpleasant.³

Children and adolescents that develop OCD are faced with significant impairment in academic, familial, and social functioning that may persist through adulthood if not adequately identified and treated.⁴ Overall response rates to initial pharmacotherapy are in the order of 70%; however, other psychiatric comorbidities, which occur at rates greater than 50%, may also influence treatment response and rate of symptom relapse. The most common psychiatric comorbidities implicated in the prognosis of OCD include attention deficit hyperactivity disorder (ADHD), tic disorder, and oppositional defiant disorder.³ Therefore, it is important to assess children with psychiatric complaints thoroughly in order to appropriately identify and manage their illness.¹⁻³

NEUROBIOLOGY AND ETIOLOGY

The underlying cause of OCD is largely unknown but appears to be multifactorial. Twin studies and studies of first-degree relatives have supported the presence of a genetic component of pediatric OCD.² Modern studies of gene expression have also begun to shed light on specific genomic components that may contribute to risk of development of OCD and are the subject of continued development.

The classical model of neurobiological dysfunction is implicated through a proposed dysregulation of serotonin, norepinephrine and/or dopamine; these theories are largely derived from positive response in pharmacological treatment studies. Glutamate, however, is a more recently implicated neurotransmitter in the treatment of OCD.⁵ This theory has arisen from evidence of dysfunction in the cortical-striatal-thalamocortical (CSTC) circuitry of the brain, for which glutamate is considered the primary neurotransmitter.⁶

Furthermore, the potential role of environmental exposure in pediatric OCD is another interesting facet of the illness. Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS) is a clinical entity describing the potential link between infection with group A streptococci and symptoms of OCD, tics, or Tourette's.^{3,7} The cause of psychiatric symptoms may be related to an inflammatory process in the basal ganglia of the brain following infection; this may cause abrupt changes in mood, behavior, and motor movements. There are currently diagnostic criteria available for PANDAS, however detailed and consistent

literature about PANDAS is lacking and the difference between it and non-PANDAS related OCD appears difficult to clinically discern. Furthermore, the role of antibiotic prophylaxis and immunomodulating treatment modalities for this small subset of the population has yet to be fully elucidated.⁷

PHARMACOLOGICAL TREATMENT

Although cognitive behavioral therapy (CBT) monotherapy is considered first line treatment for mild-moderate OCD, pharmacotherapy is frequently utilized in cases of poor response, higher severity, or difficulty participating in CBT. It is important to note that CBT alone or in combination with pharmacotherapy results in improved outcomes compared with pharmacotherapy alone. Selective serotonin reuptake inhibitors (SSRIs) are considered first line for management of pediatric OCD, with clomipramine considered as an alternative first line agent due to its more significant adverse effect profile when compared with SSRIs.¹⁻⁵ An overview of dosing for pediatric and adolescent OCD can be found in Table 1.

Selective serotonin reuptake inhibitors: The SSRIs have been studied in the pediatric and adolescent OCD population with largely positive results.⁸ A review of some of the recent published literature is provided below:

Citalopram: An eight week, open-label case series of citalopram at 20-30 mg per day in 15 subjects aged 6-17 years with OCD was conducted by Mukaddes et al. The primary efficacy measure was the children's version of the Yale-Brown Obsessive-Compulsive scale (CY-BOCS) at baseline, week 4, and week 8. At week 8, 12 subjects showed a >50% improvement in total CY-BOCS scores. Two subjects had moderate improvement of 20-50%, and one subject did not respond. Overall, there was a statistically significant reduction from baseline in symptoms ($p < 0.01$). Adverse effects were mild and included sedation and nausea.⁹

A comparison study of citalopram 20 mg per day versus fluoxetine 20 mg per day for 6 weeks conducted by Alaghand-Rad et al was published in 2009 and has been the only controlled trial directly comparing the effects of 2 different SSRI agents in children. Twenty-nine subjects aged 7-18 years were randomized to receive fluoxetine or citalopram therapy. The primary efficacy measure was CY-BOCS and Clinical Global Impression-Improvement (CGI) score from baseline, 3 weeks and 6 weeks. At 6 weeks, symptom severity, as evidenced by CY-BOCS, decreased in both treatment arms in a statistically significant manner. CGI scores did not significantly change from baseline, however. Five subjects

discontinued the study early; one discontinuation was due to the development of hypomania. Other adverse effects included headache for both groups, and tremor and insomnia in the fluoxetine group. These findings suggest that citalopram and fluoxetine are equally safe and effective.¹⁰

Escitalopram: The use of escitalopram in pediatric and adolescents with OCD has not been studied. Data from adult studies and the use of other SSRIs in this population would suggest similar efficacy and tolerability.¹¹

Fluoxetine: Fluoxetine is one of the most thoroughly studied SSRIs for use in pediatrics and adolescents with OCD. Initial placebo-controlled studies examining fluoxetine at doses from 20- 60 mg per day found significant efficacy and tolerability associated with the treatment.⁸

The most recent randomized, double-blind, placebo-controlled trial was conducted by Liebowitz, et al and was published in 2002.¹¹ In this study, 43 subjects aged 8-17 years were randomized to receive either placebo or fluoxetine at a fixed dose titration to 60 mg per day by week 8. At week 8, responders, defined by a CGI-I scale score citing the subject as much or very much improved, were continued for an additional 8 weeks with the option of increasing the dose to 80 mg per day for the remainder of the study period.

Subjects were evaluated at baseline and weeks 4, 8, 12, and 16. Subjects were assessed for improvement in the CY-BOCS, Clinical Global Impression of Severity (CGI-S) and CGI-I, Hamilton Rating Scale for Depression (HAM-D), and parental completion of the Child Obsessive Compulsive Impact Scale (COIS-P). Results found that at week 8, both treatment groups had a statistically significant improvement in CY-BOCS scores compared to baseline with no difference noted between groups. By week 16, however, CY-BOCS scores in addition to parental and clinician ratings were significantly improved in the fluoxetine group compared to placebo. All subjects randomized to fluoxetine and 86% of subjects randomized to placebo reported treatment-emergent adverse effects. Significant differences in reported adverse effects in the fluoxetine group include; palpitations, weight loss, somnolence, nightmares, and muscle aches. No subjects discontinued the study due to adverse effects. These results suggest that the full clinical effects of fluoxetine therapy in this patient population may occur over a period of time longer than 8 weeks.¹²

Long term data describing the use of fluoxetine 20 mg per day for up to 20 weeks with a follow up period of 24

Table 1: Overview of dosing for pediatric and adolescent OCD

| Agent | Dosing Guidelines | Monotherapy vs. Augmentation | Type of evidence |
|--------------------------------|---|------------------------------|------------------|
| Citalopram | 10 – 40 mg per day, average 20 mg per day | Monotherapy | Open label |
| Fluoxetine* | 10 – 60 mg per day, average 20 – 30 mg per day | Monotherapy | RCTs |
| Fluvoxamine Immediate Release* | Initial 25 mg, up to 200 mg (8-12 yrs) or 300 mg (12-17 yrs) per day | Monotherapy | RCTs |
| Paroxetine | 10 – 60 mg per day, average 30 mg per day | Monotherapy | RCTs |
| Sertraline* | Initial 25 mg (6-12 yrs) or 50 mg (13-17 yrs) per day, up to 200 mg daily | Monotherapy | RCTs |
| Clomipramine* | Initial 25 mg per day, up to 3 mg/kg per day (max 200 mg) | Monotherapy, augmentation | RCTs |
| Aripiprazole | 5 – 20 mg per day | Augmentation | Case series |
| Risperidone | 1 – 2 mg per day | Augmentation | Case series |
| D-cycloserine | 25 – 50 mg prior to CBT | Augmentation | RCT |
| Riluzole | 100 – 200 mg per day | Augmentation† | Open label |

*FDA approval for pediatric OCD: fluoxetine ages 7+, fluvoxamine IR ages 8+, sertraline ages 6+, clomipramine ages 10+. RCT= Randomized controlled trial. † 2 of 6 subjects were taking no other therapy during trial.^{3, 8-19}

months after discontinuation are available. Data suggest continued safety and efficacy of therapy and reveal a 43.5% relapse rate after responders to therapy discontinued treatment.¹³

Fluvoxamine: The efficacy and tolerability of fluvoxamine treatment in OCD of children and adolescents was most recently described by Riddle, et al in 2001 in a randomized, multi-center, placebo-controlled study.¹⁴ One hundred twenty subjects aged 8-17 were randomized to receive placebo or flexible dose fluvoxamine at 50-200 mg per day for up to 10 weeks. Efficacy was measured using the CY-BOCS scale primarily with CGI-I, CGI-S, and CGI-P (parent) scales as well as adverse effects as secondary measures. Subjects were evaluated at baseline and weeks 1, 2, 3, 4, 6, 8, and 10. Fluvoxamine was found to have significantly greater improvement in the CY-BOCS score at all visits except week 8, with a mean reduction of 6.0 points compared with 3.3 in the placebo group. This difference in score may not reflect a clinically significant improvement. However, improvement was also significant based on the CGI scores provided. Subjects in the fluvoxamine group were more likely to experience insomnia and asthenia compared with placebo.

Paroxetine: The safety and efficacy of paroxetine in doses of 10- 50 mg per day in children and adolescents with OCD was suggested by Geller et al in 2004 after conducting a randomized, multicenter, double-blind, placebo-controlled trial.¹⁵ A total of 207 subjects aged 7-17 years were randomized to receive up to 10 weeks of flexible-dose paroxetine or matching placebo. The primary outcome of efficacy was measured utilizing the CY-BOCS scores, CGI-I, CGI-S, and the Global Assessment

of Functioning (GAF) scores. At mean doses of approximately 30 mg per day, the adjusted mean difference in CY-BOCS scores with paroxetine versus placebo was -8.78 and -5.34 points respectively, which was considered statistically significant. Change in CGI-I, CGI-S, and GAF scores showed no statistically significant difference between groups. The most frequently reported adverse effects with paroxetine included headache, abdominal pain, nausea, respiratory infections, somnolence, and hyperkinesia.

Sertraline: Similar to fluoxetine, sertraline is considered one of the more thoroughly studied of the SSRIs for this population. Studies include a comparison of sertraline up to 200 mg per day compared with CBT in 40 subjects showing positive results in both groups.¹⁶ A large study of 187 subjects comparing sertraline up to 200 mg per day with placebo confirmed the positive outcomes associated with its use as evidenced by improvement in CGI and CY-BOCS scores.¹⁷ Additionally, an open-label extension study of 52 weeks supported continued efficacy of sertraline at a dose of 50- 200 mg per day; however 16 subjects (>10%) discontinued therapy due to treatment-emergent adverse effects.¹⁸

One of the most well known studies was conducted by The Pediatric OCD Treatment Study (POTS) Team. This study, funded by the National Institute of Mental Health (NIMH), examined the effects of 12 weeks of CBT, sertraline monotherapy up to 200 mg per day, combination therapy, or placebo on 112 outpatients aged 7 – 17 years with a clinical diagnosis of OCD. Efficacy outcomes included CY-BOCS scores and the NIMH Global Severity score in addition to the CGI-S. Based on these measures, both sertraline and CBT monotherapy were

found to be significantly more effective than placebo, while combination CBT/sertraline was found to be superior to CBT monotherapy, sertraline monotherapy, and placebo.¹⁹

Other serotonergic agents:

Clomipramine: Clomipramine is a tertiary amine tricyclic antidepressant which was the first agent FDA approved for treatment of OCD in the pediatric population. The positive outcomes associated with clomipramine use in children and adolescents with OCD have been clearly established through multiple controlled trials in the late 1980s and early 1990s.⁸ Its considerable adverse effect profile, including arrhythmogenic potential, has diminished its use in modern day therapy and led to the naming of the more serotonin-selective antidepressants as first line pharmacotherapy.³

Venlafaxine: Although not formally studied in pediatrics and adolescents for OCD, venlafaxine has been studied in other youth anxiety disorders as well as treatment-resistant OCD in adults.^{20,21}

Comparison of agents: There are few data available to directly compare different agents in terms of superiority, so there is little convincing guidance to lead a clinician to choose one agent over the others.

A meta-analysis from 2003 compared fluoxetine, fluvoxamine, paroxetine, and sertraline with clomipramine for treatment of pediatric obsessive-compulsive disorder. The authors of the analysis found a statistically significant but moderate effect size of 0.46 for all therapy compared to placebo. Additionally, the multivariate analysis suggested superiority of clomipramine to SSRIs, with comparable efficacy between all SSRI agents.²²

A Cochrane Review published in 2010 evaluated the efficacy and tolerability of medication for treatment of anxiety disorders in children and adolescents. The review found a favorable and statistically significant treatment response to medications compared with placebo, translating into an average decrease in the CY-BOCS scale of -4.5 with a response rate to therapy of 58.1% compared with 31.5% in the placebo groups. Across agents, SSRIs were found to be similar in efficacy outcome measures; however, fluoxetine and paroxetine may have an additional improvement in short-term functioning that was not fully elucidated in this Cochrane Review. Tolerability comparing venlafaxine to SSRIs in non-OCD pediatric anxiety disorders was also found to be

similar. Larger effect size associated with clomipramine use was also duplicated in this analysis.²¹

AUGMENTATION AND FUTURE DIRECTIONS

There is currently a paucity of encouraging data to assist in guiding the clinician to effective pharmacological augmentation strategies in the event of a partial responder to therapy. Below summarizes some of the available literature and newer treatment modalities for the management of refractory OCD.

Clomipramine: The combination of SSRI augmented by clomipramine has been studied in the late 1990s as a potential method to obtain the suggested higher efficacy of clomipramine with an improved safety and tolerability profile. The combination proves potentially useful, but one must exercise caution with these two agents together. Concomitant use of CYP2D6 inhibitors such as fluoxetine and paroxetine may reduce clomipramine metabolism to desmethylclomipramine and increase exposure to clomipramine which could potentially become toxic even at low doses. Electrocardiograms and serum drug levels of clomipramine should continue to be monitored if a combination of clomipramine and SSRI is utilized.^{3,23}

Antipsychotics: There are some data that support the use of atypical antipsychotics in adult OCD. Small studies of haloperidol, risperidone, olanzapine, and quetiapine in adults with OCD have been promising and have gained acceptance as an augmenting strategy for adults, but require further research to better establish efficacy.²⁴ Data for the pediatric and adolescent population, however, are even more scarce. Published data for use of antipsychotics in this specific population are listed below.

Aripiprazole: The use of aripiprazole in augmentation of SSRI therapy in 39 children aged 12-18 years was studied through a case series at a single center. Patients were required to have a lack of response to at least 2 trials of SSRIs for treatment of OCD. Aripiprazole at a mean dose of 12.2 mg per day resulted in response (significant reduction in CGI-I or CGI-S) in 59% of subjects at 6 months. Adverse effects reported included agitation, sedation, sleep disorders, and weight gain between 2 and 5 kg.²⁵

Risperidone: The efficacy of risperidone as an augmenting agent in treatment resistant OCD has been described through a case series at a single center. Seventeen subjects aged 15-19 years received 12 weeks of open-label risperidone from 1-2 mg per day. Ten subjects experienced a 10-25% reduction in total Y-BOCS score while 4 patients experienced a greater than 25%

reduction in score. No subjects reported worsening of symptoms. The most common adverse effects were weight gain and sedation.²⁶

Glutamate modulators: The alteration of fear pathways by pharmacological modulation of glutamate is a potentially promising target for newer therapy in OCD of both adults and pediatrics. To date, a number of studies suggest potential efficacy of memantine, riluzole, n-acetylcysteine, and d-cycloserine in the treatment of OCD in adults.²⁷ Specific data pertaining to the pediatric population is summarized below and includes d-cycloserine and riluzole.

D-cycloserine: D-cycloserine (DCS) is a partial agonist of N-methyl-D-aspart (NMDA) in the amygdala. A population of 30 subjects aged 8-17 years were included in a randomized, double-blind, placebo-controlled augmentation trial in of DCS 25- 50 mg based on weight or placebo, dosed prior to weekly CBT sessions from weeks 4-10 of CBT. At the end of the study period, CY-BOCS reduction was 72% for the combination treatment arm compared with 58% in the CBT monotherapy arm. Other scales including the CGI-S had a non-statistically significant trend of further benefit with combination therapy. No adverse effects were reported.²⁸

Riluzole: Riluzole is considered a glutamate inhibitor. It is FDA-approved for the treatment of amyotrophic lateral sclerosis (ALS), but its potential use in the psychiatric population has gained attention in recent years. A 12 week, open-label trial of riluzole in 6 children ages 8-16 years with treatment-resistant OCD resulted in 4 subjects experiencing a >46% improvement on the CY-BOCS and much or very much improved on the CGI-I scale.²⁹ This led to the initiation of a double blind, placebo-controlled 12 week study funded by the NIMH studying the agent's effects alone or in combination for the treatment of OCD

with or without autism spectrum disorders. Data from this study has yet to be reported.³⁰

CONCLUSION

Early-onset OCD is a frequently debilitating anxiety disorder that is oftentimes associated with significant comorbidities and clinical challenges. Approximately 50-80% of adults with OCD have reported symptom onset during childhood which indicates a potential for a chronic illness to develop.²⁴ CBT is an important facet of treatment in all levels of severity of OCD; however, most patients with moderate to severe symptoms will require pharmacological management.³ Serotonin modulators, specifically SSRIs are first line pharmacological agents for the management of OCD in children and adolescents due

to their modest efficacy and favorable adverse effect profiles. Clinicians should, however, closely monitor young patients exposed to SSRI therapy due to the FDA-issued black box warning for suicidality.

Potential augmenting agents for individuals who do not respond to first line therapy have been described through small controlled trials and case studies. Despite recent advancement in gene studies and newer treatment modalities, further research and large, controlled clinical trials are necessary to better describe the etiology and management of this multifactorial disorder as well as identify new potential drug targets.

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