



Obsessive-compulsive disorder in children and adolescents: epidemiology, diagnosis and management

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Abstract: Obsessive-compulsive disorder (OCD) can be found in about 4% of the general population and is characterized by various compulsions and obsessions that interfere with the person's quality of life from a mild to severe degree. The following discussion reflects on current concepts in this condition, including its epidemiology and etiologic underpinnings (behavioral, neurological, immunological, gastroenterological, as well as genetic). The interplay of PANS and PANDAS are included in this review. In addition, the core concepts of OCD diagnosis, differential diagnosis, and co-morbidities are considered. It is stressed that the quality of life for persons with pediatric OCD as well as for family members can be quite limited and challenged. Thus, principles of management are presented as a guide to improve the quality of life for these persons as much as possible.

Keywords: Obsessions; compulsions; diagnosis; co-morbidities; quality of life; psychological therapy; selective serotonin reuptake inhibitors

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Introduction

The presence of obsessions and compulsions with or without the obsessive-compulsive disorder (OCD) has been observed and suggested in human beings for eons of time with considerable impact on human history as well as world religions ("religious scrupulosity") (1-5). Scrupulosity focusing on morality was noted in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-TR that identified it as a symptom of obsessive-compulsive personality disorder (6,7). Medical attention on obsessive-compulsive traits and disorder in children and adolescents—apart from that found in adults—gradually began in the 20th century and has continued into

the 21st century as well (8-11). This discussion considers the current understanding of pediatric OCD with special focus on its epidemiology, etiology, diagnosis, differential diagnosis, co-morbidities, and management (12-15).

Overview

OCD is currently identified by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) as a condition with obsessions (repeating urges or ideas that are irrational, intrusive) combined with compulsions (behaviors) interfering with the person's quality of life and often in association with other neurodevelopmental or psychiatric

conditions (16,17). As research on OCD continues, the question can be raised whether the core aspect is the person's compulsions that lead to various obsessions, or do the obsessions stimulate the compulsions in a way to minimize anxiety caused by irrational fears (18). Other symptomatic features which may arise include impulsivity, rage episodes, aggressive behavior, sexual obsessions, religious rituals (scrupulosity), and eating obsessions in eating disorders (19-25). Various fears may arise about hygiene, contamination, cleanliness, the need for continuous checking and establishment of constant symmetry in their lives (10-15).

OCD is a chronic condition that impacts humans from early childhood through adulthood with a continuum between obsessive-compulsive traits to overt OCD (26,27). OCD is often under-diagnosed and is often found with minimal insight in those who have OCD as well as considerable family accommodation that they enjoy from their families (28,29). Older parental age increases risks for some neurodevelopmental disorders like OCD and autism spectrum disorder (30).

Epidemiology

Studies over the past decades note that OCD is variably found in 1% to 4% of persons (children, adolescents, adults) throughout the world often with a seriously negative impact on their lives; approximately 4 in 10 with OCD develop it as a chronic condition, and many seek to conceal their OCD from others (31-38). The World Health Organization (WHO) places OCD in the top ten of the most handicapping disorders of humans (36). OCD can begin in childhood, and approximately 8 in 10 of those developing OCD initiate it by 18 years of age (37). The research seeks to find various OCD subtypes based on concepts of etiology; there is, for example, OCD in children called Early Onset OCD that reflects a neurodevelopmental perspective (39).

Etiology

Research reveals a variety of underlying etiologic factors in the development of OCD in humans of various ages. These include inter-connecting issues based on behavioral, neurological, infectious, and immunological underpinnings (11-16).

Behavioral etiology

Various psychological and neuropsychological models of etiology describe a complex process in which the OCD person learns or is driven to determine what are perceived as errors in their thinking patterns in order to cope with deep-seated anxiety (40). The role of over-protective parenting styles with rigid rules, a person's perspective that their actions are never acceptable to others and various other adverse childhood experiences continue to be debated, especially in light of 20th and 21st century methods of studying the central nervous system (41,42).

Neurological etiology

Changes leading to neurological dysfunctions are noted in various studies of the central nervous system leading to OCD and its identification as a complex, heterogeneous condition. These brain studies included brain scans, magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), whole-brain voxel-based morphometry (VBM), and diffusion tensor imaging (DTI) (43). These changes are noted in the cortico-striato-thalamocortical circuits of the brain and brain white matter (44). This frontal-striatal-thalamic model of neurological dysfunction has been a center point of brain imaging OCD research for the past several decades showing diffuse changes including frontoparietal-limbic dysfunction, orbitofrontal dysfunction, brain volume reduction, basal ganglia dysfunction, and error-related brain activity (45-59).

Studies also reveal alterations in the hippocampus (60), and serotonergic-dopaminergic pathways as well as the glutamatergic system (61,62). Brain changes (i.e., asymmetry or thickness of subcortical structures, parietal cortex thickness, others) can be influenced by various factors such as genetics, age, anti-OCD medication effects and others (63,64). Obsessive-compulsive behavior has been anecdotally reported in some taking the anti-epileptic drug, levetiracetam, possibly because of effects on the glutamatergic system (65).

Immunological etiology

Immunological mechanisms are postulated as being involved in pediatric OCD as noted by research linking this

condition with pro-inflammatory cytokines such as TNF-alpha and IL-12 (66). Inflammatory damage to monocytes can be noted in persons with OCD and modified by effects of OCD-medication as seen with measurements of pro-inflammatory cytokines (67). The role of the immune system and infection continues to be studied as seen with a report of a pediatric person developing OCD after developing acute disseminated encephalomyelitis (ADEM) which targeted the cerebral white matter (68).

PANDAS/PANS

Further intriguing links of pediatric OCD with immuno-infectious underpinnings is found in the association of OCD symptomatology (1–10%) with the proposed [1998] PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) with positive antistreptolysin O as well as anti-DNase B antibody titers and PANS (pediatric acute-onset neuropsychiatric syndrome) (67,69–76). Though PANDAS remained a proposed syndrome and was not listed as a distinct entity in the 2013 DSM-V, proposed links with OCD remain an on-going research efforts (77).

Gastrointestinal (GI) microbiome etiology

Another intriguing area of research in the etio-pathogenesis of psychiatric disease is the microbiome-gut-brain axis in which gastrointestinal (GI) microbes influence the brain to affect human behavior via GI inflammation and immunological effects (77). The presence of various GI microbes, as influenced by various internal and external factors (stressors), can induce or influence such conditions as depression, OCD, PANS, PANDAS and others (77–79). Bacteria under study include group A beta-hemolytic streptococcus, and Bacteroidetes (i.e., Bacteroides, Odoribacter, and Oscillospira) (80–82).

Genetic etiology

If a person has OCD, this condition is increased two-times in first-degree relatives; this is increased ten-times if the OCD has a childhood-onset (15). The concordance rate noted for monozygotic twins is 0.57 versus 0.22 described in dizygotic twins (15). The genetic contribution to OCD is part of the overall research looking at genetic correlations with a wide variety of psychiatric and immunological disorders (83). Various genes are under study for OCD and

one example is the SLC6A4 gene (serotonin transporter gene) that has been noted to influence OCD transmission via both genetic and epigenetic effects; epigenetic influences include DNA methylation (84). Other serotonin system genes under study for their role in OCD, in addition to SLC6A4, include HTR2A, HTR1B, and HTR2C (85).

Links with OCD have been found, for example, with serotonin transporter polymorphism 5-HTTLPR and HTR2A polymorphism rs6311 (or rs6313) (85). Serotonin system gene variants have been linked with changes in brain volumes in pediatric persons with OCD (86). Research is occurring on SLC1A1 that encodes the glutamate transporter (epithelial and neuronal) and potential association with OCD (87). Research on genetic links in OCD also looks at finding copy number variations (CNVs), suggesting that CNVs can be part of the underlying etiologic mechanism for OCD (88).

The complexities of genetic contributions to OCD and other neuropsychiatric/ neurodevelopmental disorders continue to be unraveled by research. One report noted deletions at two chromosomes (18q22.1 and 13q12.3–q13.1) in a person with OCD along with Tourette syndrome and dysmorphism (89). Given the enormous entanglements of genetic influence on OCD and the difficulties of OCD itself, genetic counseling is recommended for families (i.e., parents, others) to help them deal with OCD in a family member (i.e., a child or others) (90).

Diagnosis

A diagnosis of OCD is based on a thorough medical history (including family history) along with a physical examination and diagnostic interviews with psychological assessments; these include such measures as the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the Children's Yale-Brown Obsessive-Compulsive Scale, Second Edition (CY-BOCS-II), the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), the Y-BOCS self-report instrument (Y-BOCS-SR), the Yale-Brown Obsessive-Compulsive Scale Check List (Y-BOCS CL), the Anxiety Disorders Interview Schedule for DSM-IV, the Family Accommodation Scale for Obsessive-Compulsive Disorder-Patient Version (FAS-PV), Short Mood and Feelings Questionnaire, the Screen for Child Anxiety-Related Emotional Disorders, the Child Behavior Checklist-Obsessive-Compulsive Subscale (CBCL-OCS), the Child Obsessive-Compulsive Externalizing/Internalizing Scale (COCEIS) and other screening measures (91–103).

Clinicians should inquire about such symptoms as

rituals or behaviors that are repeated over and over, things or situations (locations) that are carefully evaded, and acknowledgment of invasive thoughts or ideas (92). The use of transcranial sonography as a diagnostic modality revealing subcortical echogenicity in OCD and other psychiatric disorders remains in research (104). Studies on eye-tracking measurement have not proven diagnostic in OCD (105).

Testing for the neurocognitive deficits can be useful for the identification of trait markers in those with OCD (106). Also, potentially valuable are the use of computer vision tools to find behavioral markers in those with pediatric OCD (46). Research is not definitive but continues in identifying potential subtypes of pediatric OCD based on executive functioning, aggressive traits, social reciprocity, and other features (107-110).

Differential diagnosis

An essential aspect of the OCD patient assessment is to separate the OCD diagnosis from other disorders that may be the cause of the patient's symptomatology instead of OCD. A careful assessment including, thorough medical and psychological evaluations, is critical in this regard. For example, this person may have other anxiety disorders including generalized anxiety disorder, panic disorder, and different phobias. Other disorders to consider, depending on the presentation and history include depressive disorder, anorexia nervosa, bulimia nervosa, bipolar disorder, psychosis, tic disorders, substance use disorder, hoarding disorder, body dysmorphic disorder, trichotillomania, paraphilia, gambling disorder, and personality disorder (i.e., obsessive-compulsive personality disorder).

Comorbidity

Another aspect of the evaluation is to know that OCD is well-known to co-exist with a wide variety of other disorders and an understanding of the full patient picture is critical to developing effective management strategies. Research notes that those with a pediatric-onset OCD have increased co-morbidities and, the comorbidities are similar, to some extent, with the differential diagnosis list (99).

As indicated above, a number of psychiatric disorders can co-exist with OCD including Tourette's disorder, eating disorders (i.e., anorexia nervosa, bulimia nervosa, others), major depressive disorder (lifetime co-existence in 75% of OCD persons), bipolar disorder, social phobia, panic disorder, impulse control disorders, personality disorders

(i.e., obsessive-compulsive personality disorder [OCPD]), oppositional defiant disorder (ODD) and others (111-118). Suicidality can be a worrisome co-morbidity from the viewpoint of the patient, family and healthcare givers (119).

OCD is commonly co-morbid with autism spectrum disorder (ASD) and, attention-deficit/hyperactivity disorder (ADHD) (120-126). Clinicians should also be cognizant of and observant for potential OCD co-morbidity with enuresis (non-monosymptomatic primary nocturnal enuresis), self-induced dermatoses, immunoglobulin A dysgammaglobulinemia, and sleep dysfunction [insomnia, disorders of sleep initiation and maintenance (DIMS), delayed sleep phase disorder (DSPD)] (120-130). Also complicating management plans can be other complex psychiatric comorbid disorders as hoarding, psychosis, and obsessive-compulsive personality disorder (OCPD). Issues of PANS and PANDAS have been considered before (vida supra).

Quality of life in OCD

The quality of life for those with OCD can be compromised to a considerable extent depending on various factors including the age of onset, severity of the OCD symptomatology, complications of family accommodation, failure for the OCD diagnosis (often under-diagnosed), co-morbidities, and others (131,132). In light of such factors, effective management plans for pediatric OCD is considered at this time.

Management

This section reviews the current evidence for the treatments of OCD in children and adolescents, including psychotherapy and medications, with a focus on randomized controlled trials in the pediatric population. As discussed below substantial evidence supports the use of Serotonin Reuptake Inhibitors (SSRIs) and Cognitive-Behavioral Therapy (CBT) in the treatment of OCD in children and adolescents and are often used together in clinical practice.

Psychotherapeutic management

Cognitive behavioral therapy (CBT) is widely regarded as the first-line treatment of OCD for mild-moderate cases in children and adolescents. CBT has shown comparable and, at times, superior results to medication management for treatment of OCD (133-136). These studies are summarized in *Table 1*. There is minimal evidence for the

Table 1 Evidence for psychotherapy treatments for pediatric OCD

Authors, country, year	N	Outcome measures	Subjects	Study design, duration	Outcomes
Therapy vs. waitlist/placebo control					
March, USA, 1998, (135)	112	CY-BOCS	Male and female patients ages 7–17 with DSM-IV diagnosis of OCD and CY-BOCS >16	Randomized to pill placebo, CBT, sertraline, or CBT and sertraline combination for 12 weeks	The CBT, sertraline, and combination group had a statistically significant response over placebo group. Combination treatment was more efficacious than either only CBT or only sertraline. Results of CBT alone group did not differ significantly from sertraline alone group
Williams, UK, 2010, (137)	21	CY-BOCS	Male and female outpatients ages 9–18 with DSM-IV diagnosis of OCD	10 sessions of manualized cognitive behavioral treatment with a 12-week waiting list. Assessments completed at baseline, 3 months, and 6 months	The group who received treatment improved more than the comparison group who waited for 3 months. The original waitlist group subsequently received the same treatment and made similar gains
Frequency/duration					
Storch, USA, 2007, (138)	40	CYBOCS, remission status, CGI-S, CGI-I	Male and female outpatients ages 7–17 with DSM-IV diagnosis of OCD and CY-BOCS >16	Randomized to 14 sessions of either weekly or daily family-based CBT. Symptoms were evaluated before treatment, immediately after treatment, and at 3 months post-treatment	Daily and weekly CBT were equally effective with no statistical differences seen during follow-up and improvements in symptoms maintained over time
Bolton, UK, 2011, (139)	96	CY-BOCS	Male and female patients ages 8–17 with DSM-IV diagnosis of OCD	Randomized to full CBT course (12 sessions with therapist), brief CBT course (5 sessions with therapist, use of a therapist-guided workbook), or waitlist control group for 12 weeks	Compared to the waitlist group, both treatment groups experienced a statistically significant improvement in symptoms. Between the two treatment groups, there were no significant differences. At 14-week follow-up, improvement in symptoms was maintained
Torp, Norway, 2015, (136)	50	CYBOCS, remission status	Male and female outpatients ages 7–17, DSM-IV diagnosis of OCD who did not respond to initial 14-week course of individual CBT	Randomized to sertraline or ongoing CBT for an additional 16 weeks	No significant difference between the treatments ($P=0.351$). In CBT group, 50.0% response rate. In sertraline group, 45.4% response rate

Table 1 (continued)

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Authors, country, year	N	Outcome measures	Subjects	Study design, duration	Outcomes
Family involvement					
Piacentini, USA, 2011, (140)	71	CY-BOCS, CGI-I, Child Obsessive Compulsive Impact Scale-Revised (COIS-R)	Male and female outpatients ages 8–17 at pediatric OCD specialty clinic; primary DSM-IV diagnosis of OCD with CY-BOCS >15, on no medication	Randomized to 12 sessions of family CBT (FCBT) or PRT (psychoeducation + relaxation training) for 14 weeks	FCBT group had remission rate of 43%, while PRT remission rate was 18%
Peris, USA, 2013, (141)	21	CGI-I	Male and female patients ages 8–17 with DSM-IV diagnosis of OCD with CY-BOCS >15 and “high levels of family distress” defined by scales of measure for level of family cohesion, conflict, and blame	Randomized to individual child CBT (with weekly parent check-ins) or Positive Family Interaction Therapy (PFIT), which was structured as individual child CBT with six additional family sessions focused on family dynamics. Both treatments delivered for 12 weeks	Both treatment groups reported high level of satisfaction. 95% of the PFIT family sessions were attended by both parents. Patients in individual CBT only experienced a 40% response rate on their CGI-I, while those in PFIT arm experienced a 79% response rate. Improvement in symptoms was maintained at 3-month follow-up for both groups
Reynolds, UK, 2013, (142)	50	CYBOCS	Male and female patients ages 12–17 with DSM-IV diagnosis of OCD	Randomized to individual CBT (with parental involvement in three sessions) or “parent-enhanced CBT” with parental involvement at all sessions. Treatments were delivered for 14 sessions	Both groups demonstrated improvement in OCD symptoms
Group format					
Barrett, Australia, 2004, (143)	77	The Anxiety Disorders Interview Schedule for Children-Parent version (ADIS-P), The National Institute of Mental Health Global Obsessive-Compulsive Scale (NIMH GOCS), CY-BOCS	Male and female patients ages 7–17, with DSM-IV diagnosis of OCD, on stable medication regimen or no medications	Randomized to individual CBFT, group CBFT, or a 4- to 6-week waitlist control condition. Assessments completed pre- and post-treatment, 3-month follow-up, and 6-month follow-up	Individual CBFT demonstrated 88% response rate vs. 76% in group CBFT vs. 0% in waitlist group. There were no significant differences in symptom improvement between the two groups receiving treatment

Table 1 (continued)

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Authors, country, year	N	Outcome measures	Subjects	Study design, duration	Outcomes
Asbahr, Brazil, 2005, (133)	40	CY-BOCS	Male and female patients ages 9–17 years old with DSM-IV diagnosis of OCD with NIMH GOCS >7	Randomized to receive group CBT or sertraline. Group CBT was manual-based program lasting 12 weeks. Assessments completed pre-treatment, during treatment, and post-treatment (1, 3, 6, and 9 months following treatment)	Both Group CBT and sertraline conditions had significant improvement CY-BOCS total scores (both groups: $P < 0.001$) at conclusion of treatment. Those in group CBT experienced a significantly lower rate of symptom relapse at the 9-month follow-up compared to those in sertraline group
Telephone and web-based format					
Storch, USA, 2011, (144)	31	CY-BOCS, CGI-I, remission status	Male and female patients ages 7–16 with DSM-IV diagnosis of OCD and CY-BOCS >16	Randomized to family-based CBT provided through web-camera (W-CBT) or waitlist control. Assessments performed before treatment, after treatment, and at 3-month follow-up	Those receiving W-CBT had statistically significant improvements in all outcome measures over those in waitlist control group. 56% of W-CBT vs. 13% of waitlist showed remission response, maintained at 3-month follow-up
Turner, UK, 2014, (145)	72	CYBOCS	Male and female outpatients ages 11–17 with DSM-IV diagnosis of OCD	Randomized to telephone-based or in-person CBT with exposure and response prevention for 14 sessions	There was no significant difference in response rate between the two groups at post-treatment (90.6% for in-person vs. 87.5% for TCBT) or at follow-ups (3-, 6-, 12-month)
Age of participants					
Freeman, USA, 2012, (146)	127	CGI-I, CY-BOCS.	Male and female outpatients ages 5–8, with DSM-IV diagnosis of OCD with CY-BOCS >16	Randomized to FB-RT (family-based relaxation training) or FB-CBT (family-based CBT) with exposure and response prevention for 14 weeks	At 14 weeks, 72% of FB-CBT participants and 41% of FB-RT participants were scored as much improved or very much improved based on CGI-I
Variations on CBT format					
Merlo, USA, 2010, (147)	16	CY-BOCS	Male and female patients ages 6–17 with DSM-IV diagnosis of OCD with CY-BOCS >16 who were already participating in intensive family-based CBT for OCD	Randomized to CBT plus motivational interviewing (MI) or CBT plus extra psychoeducation (PE) sessions	Average CY-BOCS score for the CBT + MI group was significantly lower than the CBT + PE group at 4 weeks, but at post-treatment, these scores were not significantly different

CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; CGI-S, Clinical Global Impression-Severity scale; CGI-I, Clinical Global Impression -Improvement scale; NIMH GOCS: The National Institute of Mental Health Global Obsessive-Compulsive Scale; CBFT, cognitive-behavioral family therapy.

use of other forms of psychotherapies for pediatric OCD.

Studies demonstrating positive benefit from CBT for OCD in children typically include components of psychoeducation, cognitive retraining, and exposure response prevention. Other specific components for successful CBT for use in pediatric OCD have also been evaluated. A program as short as five weeks in duration has shown to lead to significant improvements in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) score and functional improvement (139). Weekly CBT sessions were found to be as effective as daily sessions (138). Parental involvement is often heavily incorporated into the CBT model. The Positive Family Interaction Therapy model involves both individual CBT with the child or adolescent patient as well as additional family sessions demonstrated a 70% response rate compared to the more traditional model of individual CBT with parent check-ins and psychoeducation (141). Given the concerns about accessibility of high-quality CBT in the community, research into the telephone- and web-based programs have yielded positive results (144,145). The modalities have found to be superior to placebo and equivalent to traditional office-based CBT. CBT can also be administered in group format without compromising its effectiveness (133,143). In the Pediatric Obsessive-Compulsive Disorder Treatment Study for Young Children (146), investigators reviewed the relative efficacy of family-based CBT, involving exposure and response prevention (ERP), to family-based relaxation treatment in children 5 to 8 years old and demonstrated improvement in clinical symptoms and functional impairment.

Pharmacotherapy of OCD

Pharmacological treatment of OCD in children and adolescents has grown over the past thirty years. Clomipramine was the first medication to be studied that showed clinical efficacy in treating pediatric OCD (148), followed shortly by fluoxetine (149), but subsequent trials have also demonstrated the efficacy of fluvoxamine (150,151), sertraline (135), and paroxetine (152). Serotonergic medications are generally well-tolerated often with higher rates of mild side effects, most commonly nausea, but rarely serious adverse effects. Response rates, however, vary between 40–60% leaving a substantial number of non-responders. Study design often excludes children and adolescents with comorbid psychiatric conditions, including tic disorders, other primary mood disorders, and autism spectrum disorders. The studies are

summarized in *Table 2*.

Combination treatment

Published in 2004, the Pediatric OCD Treatment Study (POTS) was a randomized placebo-controlled trial of 112 patients, ages 7–17 years, and was designed to evaluate the efficacy of an SSRI (sertraline), CBT, and the combination across 12 weeks. Outcomes were based on the change in CY-BOCS score over the 12 weeks with remission defined as a CY-BOCS score of <10 (155). Significant improvements were noticed in all three groups in the CY-BOCS score compared to the placebo group, with the greatest improvement in the combination group (53.6% remission compared to 39.3% for CBT alone, 21.4% for sertraline alone, and 3.6% for placebo). Outcomes with CBT alone did not differ significantly from SSRI alone ($P=0.24$) but did separate from placebo ($P=0.002$). Sertraline alone did not differ significantly from placebo ($P=0.10$). No serious adverse effects were noted, but minor side effects, including nausea and diarrhea, were significantly higher in treatment groups.

POTS II, a follow-up study completed in 2011 was a randomized controlled trial of 124 pediatric patients, ages 7–17, with OCD as their primary diagnosis (156). Participants were randomized to 12 weeks of medication (SSRI) only, medication and CBT “instruction”, and medication management with CBT. “Instruction” in CBT was described as extended sessions with the psychiatrist providing medication management during which CBT principles including psychoeducation, reviewing stimulus hierarchy and identifying ERP targets were introduced, and subjects were instructed to implement these skills between sessions with assigned homework. CBT instruction did not include the therapist-assisted exposure and imaginal exposure. Didactic parent sessions were included in the third treatment group. This group had 14 visits, each being 1-hour long, over 12 weeks with a participating psychologist in addition to the medication provider. Outcomes were based on improvement in CY-BOCS score with response defined >30% change from baseline to week 12. Medication management with CBT yielded a significantly greater proportion of participants who responded to treatment (68.6% for medications + CBT, 34.0% for medications + instruction in CBT, and 30.0% for medication alone).

Augmentation strategies

Despite adequate treatment trials, 40% of patients with

Table 2 Evidence for pharmacological treatments for pediatric OCD

Authors, country, year	N	Outcome measures	Gender, ages	Study design, duration	Outcomes
Clomipramine					
DeVeough-Geiss, USA, 1992, (148)	60	CY-BOCS	Male and female patients ages 10–17 with DSM-III diagnosis of OCD with CY-BOCS >16	Randomized to 8-week trial of clomipramine vs. placebo	Average decrease in CY-BOCS of 37% of clomipramine vs. 8% in the placebo group
de Haan, Holland, 1998, (134)	22	CY-BOCS and Leyton Obsessional Inventory-Child Version (LOI-CV)	Male and female patients ages 8–18 with DSM-III diagnosis of OCD	Randomized to behavior therapy or clomipramine (mean dose of 2.5 mg/kg) for 12 weeks. Behavior therapy involved weekly sessions of exposure and response prevention	Participants in behavior therapy arm had 59.9% mean improvement from baseline CY-BOCS total compared to 33.4% in clomipramine group. No significant difference on the LOI-CV between the two treatments
Fluoxetine					
Riddle, USA, 1992, (149)	14	CY-BOCS	Male and female patients ages 8–15 with DSM-III diagnosis of OCD and CGI-S >4	Randomized to fixed dose of fluoxetine (20 mg daily) or placebo. Study lasted 20 weeks with crossover at 8 weeks	At 8 weeks, fluoxetine treatment group had an average decrease in CY-BOCS total score of 44% compared to 27% in placebo group
Geller, USA, 2001, (153)	103	CY-BOCS	Male and female patients ages 7–17 with DSM-IV diagnosis of OCD and CY-BOCS >16	Randomized to fluoxetine (10 mg daily x 2 weeks, then 20 mg daily) or placebo. At 4 weeks and at 7 weeks, fluoxetine dose was increased by 20 mg daily for non-responders	Fluoxetine group had a significant reduction in OCD severity over the placebo group. Fluoxetine and placebo groups had a similar rate of discontinuation due to adverse effects
Liebowitz, USA, 2002, (154)	43	CY-BOCS, CGI-I	Male and female patients ages 6–18 with DSM-IV diagnosis of OCD and CY-BOCS >16	Randomized to fluoxetine or placebo for 8 weeks. Responders continued treatment for an additional 8-week maintenance period	No statistical difference in CY-BOCS at 8 weeks, but by 16 weeks, fluoxetine group had significantly lower CY-BOCS compared to placebo. At 16 weeks, 57% of fluoxetine and 27% of placebo patients were much or very much improved per CGI-I scale. No patients withdrew from the study due to adverse effects
Fluvoxamine					
Neziroglu, USA, 2000, (150)	10	CY-BOCS	Male and female patients ages 10–17 with DSM-IV diagnosis of OCD	All patients started on fluvoxamine for 10 weeks. After initial 10 weeks, patients randomized to continue on fluvoxamine alone or continue on fluvoxamine and receive 20 sessions of behavioral therapy. Both groups received treatment for 1 year	By week 10, 80% patients had significant improvement on CY-BOCS. Patients in combination treatment demonstrated significantly more improvement vs. patients on fluvoxamine alone

Table 2 (continued)

Table 2 (continued)

Authors, country, year	N	Outcome measures	Gender, ages	Study design, duration	Outcomes
Riddle, USA, 2001, (151)	14	CY-BOCS	Male and female patients ages 8–17 with DSM-III diagnosis of OCD and CY-BOCS >16	Randomized to fluvoxamine (50–200 mg/day) or placebo for 10 weeks. At 6 weeks, non-responders could choose to withdraw from double-blind phase and enter open-label trial of fluvoxamine	Significant difference in percentage of responders (defined as 25% or greater reduction in CY-BOCS)—42% of fluvoxamine group vs. 26% of placebo group
Paroxetine					
Geller, USA, 2004, (152)	203	CY-BOCS	Male and female patients aged 7–17 with DSM-IV diagnosis of OCD	Randomized to Paroxetine (10–50 mg/day) vs. placebo for 10 weeks	–8.78 vs. –5.34 points on CY-BOCS at week 10 ($P=0.002$)
Sertraline					
March, USA, 1998, (135)	187	CY-BOCS. NIMH GOCS. CGI-S. CGI-I	Male and female patients ages 6–17 with DSM-III diagnosis of OCD and GOCS >7	Randomized to sertraline (up to 200 mg daily) or placebo. Sertraline dose was titrated during the first 4 weeks of treatment, then sertraline recipients were maintained on the same dose for an additional 8 weeks	Sertraline patients had significantly greater improvement compared to placebo patients on all measures—on CY-BOCS (adjusted mean, –6.8 vs. –3.4, $P=0.005$), on NIMH GOCS (–2.2 vs. –1.3, $P=0.02$), and on CGI-I (2.7 vs. 3.3, $P=0.002$)
March, USA, 2006, (155)	112	CY-BOCS	Male and female patients ages 7–17 with DSM-IV diagnosis of OCD and CY-BOCS >16	Randomized to pill placebo, CBT, sertraline, or combined CBT and sertraline for 12 weeks	The CBT, sertraline, and combination group had a significantly significant response over the placebo group. Combination treatment was more efficacious than either only CBT or only sertraline. Results of CBT alone group did not differ significantly from sertraline alone group

CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; CGI-S, Clinical Global Impression-Severity scale; CGI-I, Clinical Global Impression-Improvement scale; NIMH GOCS, The National Institute of Mental Health Global Obsessive-Compulsive Scale.

OCD continue to have impairing symptoms. Augmentation strategies should be considered for patients who fail to respond to two or more trials of SSRIs or clomipramine of adequate dose and duration, in addition to failure to respond to CBT.

Atypical antipsychotics

Augmentation of serotonergic agents with antipsychotics is the most commonly used strategy in clinical practice. Antipsychotic augmentation can effectively treat

approximately 30% of treatment-refractory adults without significant differences in efficacy between typical or atypical medications (157). While efficacy has been demonstrated in adults (158,159), this has not been evaluated systematically in the pediatric population aside from case series and open trials.

Other augmentation approaches

Other augmentation strategies, for example, novel medications and neuro-modulatory approaches, including

Repetitive Transcranial Magnetic Stimulation (rTMS) and more invasive Deep Brain Stimulation (DBS) have also been studied. A body of evidence shows that the efficacy of DBS exists in adults (160). Non-surgical techniques e.g., rTMS has a limited body of evidence and questionable efficacy for OCD in adults (161). No randomized controlled trials exist for these approaches in children and adolescents.

Novel medications that have been studied in children and adolescents are discussed below. None have shown a statistically significant benefit.

D-cycloserine (DCS)

DCS is a partial NMDA receptor agonist, which has been used in adult trials to enhance the efficacy of exposure therapy with an anxiety disorder. In one study of 30 children and adolescents ages 8–17 (162), participants were randomized to either CBT and placebo or CBT and DCS (weighted doses of either 25 or 50 mg). CBT consisted of seven ERP sessions. DCS or the placebo was administered one hour before each session. While no adverse effects were documented, there was no significant difference between the placebo and the DCS group. In 2016, a larger RCT of 142 children and adolescents ages 7–17 with a primary diagnosis of OCD were randomized to receive CBT and DCS or CBT and placebo; however, there was once again no significant additional benefit to the addition of DCS (163).

Riluzole

The glutamate pathway has also been considered as a target for modulation in the treatment of OCD. Riluzole is an anti-glutamatergic agent that has been studied. In an open-label trial of riluzole (164) in six children ages 8–16 years old who had failed previous pharmacotherapy for OCD, four children had a significant reduction (of greater than 46%) of their baseline CY-BOCS score and a CGI-I score of “much improved” or “very much improved.” Riluzole was well-tolerated. This study was followed up by a 12-week placebo-controlled trial of 60 treatment-resistant children and adolescents with moderate to severe OCD (165). Seventeen of these participants have a diagnosis of autism spectrum disorder. Subjects were randomized to receive riluzole (titrated to 100 mg/day) or placebo in addition to their existing treatment regimen. This study failed to demonstrate a significant difference between placebo and riluzole and also resulted in more drop-outs related to adverse side effects (one case of pancreatitis, five patients

with elevated transaminases).

N-acetylcysteine (NAC)

NAC has also been considered as an adjuvant treatment to SRIs for OCD in children and adolescents. In a 10-week placebo-controlled randomized double-blind trial, 34 patients were randomized, to receive either citalopram and NAC or citalopram and placebo (166). The CYBOCS and Pediatric Quality of Life Inventory were used as primary outcomes. The YBOCS of NAC group significantly decreased from 21.0 to 11.3 during the study, but no statistically significant decrease of YBOCS was found in the placebo group. In the Quality of Life inventory, a similar pattern was found. There were no serious adverse effects in either group.

Conclusions

Pediatric OCD is a chronic remitting relapsing condition that often persists into adulthood. The field has advanced significantly during the last decade and we have a better understanding of neurological and genetic underpinnings of this disease. Despite the fact that medications have a significant role in the treatment, current literature continues to converge in support of CBT as a first line treatment, which has long-term positive outcomes for pediatric OCD.

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Footnote

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