Obsessive-Compulsive Disorder in Children and Adolescents

Adam B. Lewin, Jennifer M. Park, and Eric A. Storch

Abstract Pediatric obsessive-compulsive disorder (OCD) is a chronic and debilitating neuropsychiatric disorder that is associated with significant psychosocial and functional impairment. This chapter reviews the literature on pediatric OCD, including clinical characteristics and etiological theories. Assessment methods, available treatment modalities (psychopharmacological and behavioral approaches), methods of treatment augmentation, and directions for future research regarding treatment dissemination are discussed.

Keywords Obsessive-compulsive disorder • OCD • Children • Adolescents • Treatment • Assessment • Phenomenology

Case Scenario

Zoe, an 11-year-old girl, was evaluated at an outpatient child psychiatric clinic specializing in obsessive-compulsive disorder (OCD) on her parents' referral. She said that following a salmonella outbreak at her aunt's farm, everything associated with the farm was now "contaminated." Because her father was at the farm at the time of the outbreak, her father and all of her father's possessions were contaminated (including pictures of her aunt's family/farm). Later, she had to wash her hands repeatedly throughout the day after touching any person or object that she believed was "contaminated." She also took 60–90-min showers each day. Zoe stated that the level of contamination could increase if two already contaminated objects (or people) were to touch. If she imagined the farm, she would say a "cleansing" prayer ten times in her head. By the time that she was seen in the clinic, she had not touched her father in 3 months and refused to enter any room in the house that he may enter, eat from dishes, or sit in furniture he may have used. Her hands and arms were raw and chapped

A.B. Lewin (✉)
Neuropsychiatry – University of South Florida, 880 6th Street South, Suite 460, Rothman Center - Box 7523, Child Rehabilitation and Development Building, St. Petersburg, FL 33701, USA
e-mail: alewinhealth@usf.edu

J.M. Park
Department of Psychology, University of South Florida, 4202 E. Fowler Avenue, PCD4118G, Tampa, FL 33620, USA

E.A. Storch
University of South Florida, 880 6th Street South, Suite 460, Rothman Center - Box 7523, Child Rehabilitation and Development Building, St. Petersburg, FL 33701, USA

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from the repeated washing. Her parents related that she was unable to maintain her friendships because of these behaviors and that her grades in school suffered due to her symptoms as well. She acknowledged that she was probably "not really going to get sick" but was too afraid to "risk it" by not ritualizing.

Description of the Disorder

OCD is a chronic and disabling neuropsychiatric disorder that is characterized by the presence of intrusive and distress-provoking thoughts or images (obsessions) and/or repetitive or ritualistic behaviors or mental acts (compulsions) [1]. Pediatric OCD is often associated with significant psychosocial and functional impairment [2–4]. Youth with OCD endorse high rates of academic difficulties, such as concentrating on and completing homework, as well as increased rates of family dysfunction [2, 3, 5]. Relative to their unaffected peers, youth with OCD are prone to increased victimization and are less likely to participate in social activities [4, 5]. These impairments, coupled with symptom severity and the presence of comorbid disorders, contribute to an all-encompassing diminished quality of life [6]. When left inadequately treated, OCD often follows a debilitating trajectory, where early OCD-related impairments contribute to later psychological difficulties, such as an increased presence of comorbid psychiatric disorders [7, 8]. Given these concerns, it is not surprising that OCD is one of the top ten leading causes of adult disability in the developed world [9].

According to the DSM-IV, an OCD diagnosis requires the presence of obsessions or compulsions that are distressing, impairing, and/or time-consuming [1]. The symptom profile of OCD is heterogeneous; symptoms appear in various themes (e.g., contamination, aggressive, sexual, religious), which can fluctuate and change over time [7, 10]. It is not uncommon for symptoms to exacerbate during times of significant stress or change, such as moving to a new location, changing schools, or having a sickness or death in the family [11, 12]. Children and adults with OCD exhibit similar symptom presentations where the most common obsessions include fear of contamination, fear of harm to self and/or others, concerns regarding symmetry, fear of offending God, preoccupation with right and wrong, need for exactness and order, and saving obsessions [13, 14]. Common compulsions include excessive or ritualized cleaning; checking, arranging, repeating, or counting rituals; hoarding or collecting behaviors; and praying, confessing, or reassurance-seeking [15]. Factor analyses of various obsessive-compulsive symptoms in both children and adults have produced four- and five-factor models comprising distinct symptom dimensions: contamination/cleaning, aggressive/checking, sexual/religious, symmetry/ordering, and hoarding [16]. Symptom dimensions can be suggestive of illness course and prognosis [17, 18]. For example, a longitudinal study examined 45 individuals with OCD and found that at the 9-year follow-up, children who initially presented with hoarding symptoms as their primary OCD symptom had remission rates of only 10 % compared to a 54 % remission rate for children with other primary OCD symptoms [10].

Although symptom manifestation in children and adults is similar, some developmental differences exist. Compared to adults, youth with OCD may present with a general discomfort, or unpleasant feeling, rather than fear/anxiety when rituals cannot be completed. For example, vague or diffuse symptoms such as the "not just right" phenomenon are common in youth. The "not just right" phenomenon as defined by the need to engage in specific behaviors/rituals until the child feels better is often described as preceded by an urge rather than a specific fear/thought/worry. That is, youth who experience the "not just right" phenomenon often report that their behavior relieves a sense of "incompleteness" and/or sensory discomfort rather than harm/fear avoidance [19, 20]. Rituals involving family members, especially parents, are highly prevalent symptoms in youth with OCD. For example, reassurance-seeking, confessing/apologizing rituals, and family accommodation, which refers to family involvement in rituals and modifications in routine and functioning due to obsessive-compulsive symptoms, are

commonplace [21, 22]. Another distinguishing feature of pediatric OCD is limited insight. Whereas an OCD diagnosis for adults requires some recognition of the excessive and unreasonable nature of the thoughts and behaviors [1], children are exempt from this requirement and commonly present with diminished insight [23, 24] and may not consider their symptoms to be distressing.

OCD is currently classified as an anxiety disorder in the *DSM-IV-TR*. However, several substantial changes have been proposed regarding the classification of OCD in the upcoming *DSM-5,* with some suggesting that OCD should be removed from the anxiety disorders category and subsumed under a new classification of obsessive-compulsive-related disorders (OCRDs), which include body-dysmorphic disorder (BDD), hypochondriasis, Tourette's syndrome (TS), trichotillomania (TTM), eating disorders, addictions, and autism [25]. Others maintain that there are marked differences between OCD and the majority of these disorders and therefore, OCD should remain categorized as an anxiety disorder [26].

Proponents of the OCRD classification base their arguments on an etiological model that cite similarities in symptom presentation, familial rates, comorbidity, brain circuitry, and pharmacotherapy treatment response as evidence for the combined classification [25]. However, these assertions may be premature. The John Hopkins OCD Family Study found amongst 80 individuals with OCD to have the following rates of anxiety disorders in their first-degree relatives: 16.3 % OCD, 25 % specific phobia, 22.6 % social phobia, 15.6 % GAD, and 12.6 % separation anxiety [27], while the rates of OCRDs were the following: 1 % TTM, 4 % "any" eating disorders, and 17 % grooming disorder [28]. In regards to comorbidity, OCD and OCRDs have comorbidity rates that occur higher than by chance, with individual studies reporting rates up to 16 % for hypochondriasis, 15 % for BDD, 13 % for tic disorders, 9 % for anorexia nervosa, 4 % for bulimia, and 5 % for TTM [28, 29]. However, considerably higher comorbidity rates for anxiety disorders, such as generalized anxiety disorder (GAD) and social phobia, are consistently found in those with OCD [27]. Due to the increased rates of familial anxiety disorders and comorbid anxiety disorder in individuals with OCD, the argument that OCD and OCRDs are related due to family history and comorbidity is difficult to uphold.

Recommendations have also been made to remove hoarding as a subtype of OCD and classify compulsive hoarding as a separate disorder in the DSM-5 [30]. Phenomenologically, hoarding appears similar to OCD, as it is characterized by persistent concern of losing items that are sentimental or may be needed in the future; the acquisition of items and avoidance of discarding items can be characterized as compulsions. However, hoarding appears to be distinct from OCD in a number of ways. Hoarding frequently occurs in the absence of other OCD symptoms and has weaker associations with OCD-related comorbid disorders, such as anxiety and depression, relative to other OCD subtypes [31–33]. Most striking, compulsive hoarders often do not respond to standard pharmacological and/or behavioral treatments that are efficacious for OCD [34–36]. Additionally, the literature has consistently found distinct differences in genetics and the neurobiology of individuals with compulsive hoarding compared to those with other OCD subtypes [37–39].

Prevalence and Course

OCD has a prevalence of approximately 1–2 % among youth [40, 41]. Initial symptom presentation is bimodal, typically occurring during prepuberty (early-onset OCD) and in late adolescence/early adulthood, with a mean age onset between 6 and 11 years old for early-onset OCD [42]. Age of onset varies by gender with a male preponderance among those with prepubertal onset; by adolescence, the gender distribution becomes roughly equivalent [43, 44]. Early-onset OCD is associated with high rates of familial risk for the disorder, while adult onset OCD has shown low rates of familial risk, suggesting that genetic factors may play an important role in the manifestation and development of symptoms in early-onset OCD [45, 46].

As previously noted, OCD is a chronic disorder; 80 % of adults with OCD report a childhood onset of the disorder [43]. Moreover, in a meta-analysis of studies examining the long-term course of 521 individuals with childhood-onset OCD, 60 % remained symptomatic at follow-up points ranging between 1 and 15 years [47].

Comorbidity

Comorbid disorders are the norm rather than the exception in pediatric OCD with up to 75 % of children diagnosed with a comorbid psychiatric condition [48–50]. Across several studies, high rates of anxiety disorders (26–70 %), tic disorders, (17–59 %), depressive disorders (10–73 %), disruptive behavior disorders (10–53 %), and attention deficit hyperactivity disorder (ADHD; 10–50 %) are reported [48, 51–53]. Indeed, in a large randomized clinical trial, 80 % of those with pediatric OCD had at least one other psychiatric disorder, with 63 % endorsing at least one internalizing disorder and 27 % endorsing at least one externalizing disorder [54]. The presence of even one comorbid condition can have a significant negative impact on presentation and outcome; comorbidity is associated with increased functional and psychosocial impairment, attenuated treatment response (both behavioral and medication therapy), and increased risk of relapse posttreatment [55–57].

Differential Diagnosis

A diagnosis of pediatric OCD requires the presence of time-consuming, interfering, and/or distressing obsessions and/or compulsions. Although seemingly straightforward, OCD can be difficult to differentiate from other disorders that may present with similar symptom presentations.

GAD is highly comorbid with OCD [58]. A common symptom of GAD is excessive worry that is often described as intrusive, difficult to control, hard to resist, and extremely distressing. Additionally, individuals with GAD may compulsively engage in reassurance-seeking or checking behaviors to alleviate the anxiety caused by the intrusive thoughts. Although symptoms seem to overlap considerably, the main differentiation between GAD and OCD is the content of the worries. Worries associated with GAD are generally related to normal everyday situations (e.g., finances, making good impressions, safety of family), while thoughts associated with OCD are often senseless or irrational (e.g., if I don't do everything three times, my parents will die) [59, 60].

Tic disorders also commonly co-occur with OCD [15]. Simple tics, such as sniffing and throat clearing, can be easily distinguished from OCD due to their brief duration and involuntary nature [61]. Complex motor and phonic tics, however, can be difficult to separate from OCD-related compulsions [61, 62]. Individuals with complex tics often report experiencing premonitory urges prior to the tics [63] and as such are usually aware of when the tics are about to begin. However, tics and compulsions may be differentiated based on the function of the behaviors (tics to reduce unpleasant sensations and compulsions to reduce anxiety). In other words, tic behaviors are often provoked by physical urges or sensations while OCD-related behaviors occur in response to anxiety, distress, or fear. As a result, children with tics will often report that resisting these sensations will cause physical discomfort, whereas those with OCD may indicate that refraining from compulsions will result in increased anxiety and/or a feared consequence.

Obsessions and compulsive behaviors are also hallmark traits of individuals with anorexia nervosa. However, in anorexia nervosa, these thoughts and behaviors are constrained to content regarding food, diet, exercise, weight, and appearance [64, 65]. Individuals with anorexia have markedly poor insight, and their behaviors are driven primarily by appearance and weight-oriented goals.

On the other hand, individuals with OCD may suffer from severe weight loss due to their OCD-related symptoms, but these cases are generally due to fears of eating certain types of food (i.e., "contaminated" foods) rather than fears of weight gain or concern regarding personal appearances [66].

Perseverative thoughts, fixated interests, and repetitive behaviors are commonly seen in children diagnosed with an autism spectrum disorder (ASD) [67, 68]. To determine whether these symptoms could be attributed to ASD or OCD, gathering information regarding the function of the behaviors is essential. Obsessive-compulsive behaviors are anxiety driven; the thoughts often cause distress, and the ritualistic behaviors are performed to avoid or decrease anxiety. In contrast, in ASD, behaviors, such as preoccupations with specific objects or interests, are considered rewarding. While parents may describe these interests as "obsessive," the function of these behaviors is unlikely related to the relief of anxiety. Similarly, ASD children engage in repetitive behaviors because they find it soothing or pleasurable [69].

Etiology

Biological

Neurobiological models have primarily implicated abnormalities in the corticothalamic striatal circuitry (CTSC) in OCD [70–72]. These circuits between the frontal lobe and basal ganglia are involved in both initiation and engagement of routine behavior, as well as emotional and motivational processes. These models cite deficits in the basal ganglia's ability to filter and inhibit cortical inputs [73, 74]. As abnormalities in the PFC can cause disruption in the ability to inhibit behaviors and thoughts, deficits within the CTSC may explain the presence of obsessions and ritualized behaviors in OCD [75–77]. Neurobiological models of OCD have been studied via neuropsychological assessment, structural imaging techniques such as computerized tomography (CT) and structural magnetic resonance imaging (MRI), and functional techniques such as positron emission tomography (PET), single positron emission computerized tomography (SPECT), and functional magnetic resonance imaging (fMRI) [72, 78–81]. Additionally, translational ablation studies suggest that lesions in the prefrontal cortex (PFC) of primates, which includes regions such as the anterior cingulate, have been shown to cause perseverative interference in behavioral performance [82].

Although the CTSC model of neuropathogenesis of OCD is better researched in adults, preliminary evidence derived from volumetric studies provides support for the involvement of CSTC in pediatric OCD. Pediatric OCD patients have shown neuroanatomical differences from healthy controls, such as decreased globus pallidus volumes and increased gray matter in the anterior cingulate gyrus [72, 83]. Rosenberg and Keshavan [72] also reported elevated volume in the anterior cingulate gyrus amongst youth with OCD. Gilbert et al. [84] found that drug-naïve pediatric OCD patients have increased thalamic volume relative to healthy controls. To lend further support for this model, there is evidence that thalamic volumes decrease after treatment in those with pediatric OCD [84]. Woolley et al. [81] found that while engaging in an inhibitory control task, youth with OCD showed decreased activations in the right orbitofrontal cortex, thalamus, and basal ganglia relative to healthy controls.

It is notable that while data across these methodologies is starting to converge, the exact pathogenesis of OCD in youth is not completely understood. This is in part due to small sample sizes, lack of replication across studies, and wide variability of neuropsychological tests administered in the context of functional assessments. Further, specifics of treatment studies that examine cortical and subcortical changes vary considerably with mixed results [74, 84, 85].

The neuroanatomical literature is also supported by complementary findings regarding neurochemical function in individuals with OCD. Neurochemical abnormalities in the serotonergic system

have been cited as possible mediators of obsessive-compulsive symptom expression [74, 84, 86]. The strongest support for this theory is based on the efficacy of selective serotonin reuptake inhibitors (SSRIs) and clomipramine in OCD treatment. Amongst those with OCD, SSRIs and clomipramine have been found to modulate serotonin neurotransmission within the frontal cortex and thalamocortical circuits as well as decrease orbitofrontal glucose metabolism and thalamic volumes [84, 86]. Abnormalities within the glutamate and dopaminergic systems have also been associated with the pathophysiology of OCD [87]. Specifically, children and adolescents with OCD have shown not only reduced glutamate levels in the anterior cingulate [88], but also, glutamate antagonists, such as riluzole, have been shown to be efficacious in reducing OCD symptoms [89]. In regard to dopaminergic systems, abnormal dopamine-binding patterns in the caudate and putamen have been identified in adults with OCD [88, 90, 91]. Additionally, atypical antipsychotics have been successful in reducing OCD symptoms in treatment-resistant adults [92].

Cognitive Behavioral

Behavioral perspectives regarding the etiology and maintenance of OCD are based on a two-factor model where the fears are first acquired through classical conditioning (an aversive association is made with an otherwise neutral stimulus) [93, 94] and maintained through operant conditioning (negative reinforcement) [95]. Exposure to the feared stimuli (physical objects and/or distressful thoughts) causes an increase in anxiety or distress, and the rituals/behaviors serve to prevent or neutralize the negative emotions thus maintaining the ritual via negative reinforcement. Likewise, because the association between the neutral stimulus and the perceived feared consequence is preserved, extinction of the classically conditioned fear is not achieved. Faulty cognitions, such as intrusive thoughts, inflated sense of responsibility, distorted interpretations, and pathological doubt, are highlighted in cognitive models of OCD [96]. These faulty cognitions exacerbate the initial distressing worries and propel the compulsive and/or avoidance behaviors [96, 97]. Cognitive models may have reduced relevance in the treatment of pediatric OCD given poor insight [23, 24]; thus, behavioral (exposure-based) models are emphasized [98].

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

Coined by Swedo et al. [99], PANDAS refers to the acute onset and progression of neuropsychiatric symptoms, including obsessions/compulsions and tics putatively resulting from an autoimmune response following exposure to the Group A β (beta)-hemolytic streptococcus (GAS). Inflammation of the basal ganglia, caused by the GAS autoimmune response, is hypothesized to mediate PANDAS-related OCD symptoms and associated neurological abnormalities [100–102] in a mechanism similar to the pathophysiology of rheumatic fever and Sydenham's chorea. Putative diagnosis of PANDAS-onset OCD requires prepubertal, abrupt onset of OCD (and/or tic) symptoms, episodic or sawtooth progression and severity of symptoms, temporal association with GAS, and neurological abnormalities (e.g., choreiform movements, hyperactivity, abnormal movements). Not uncommon are reports of emotional lability, sudden deterioration of motor functioning, neurocognitive abnormalities, stuttering, and enuresis. Like other psychiatric diagnoses, there are no laboratory tests for PANDAS, and the diagnosis is made by expert clinician review.

Notably, there has been some debate regarding the impact of infection-mediated immunoresponse on the pathogenesis of neuropsychiatric symptoms such as OCD and tics. Although more empirical studies are needed, Murphy et al. provide a comprehensive review, including debate within this emerging area [100].

Assessment

Various factors may complicate the presentation of OCD in children and adolescents. It is not uncommon for children to be secretive and unwilling to report embarrassing thoughts or compulsions [103]. Some children (particularly younger children) may be unable to verbalize their obsessions or be aware of the link between their cognitions and behaviors. Additionally, parents may be unable to properly identify OCD symptoms. For example, family members may mistake OCD-related tantrums to be acts of oppositional behavior, while clinicians can generally differentiate between the two. Given these factors, as well as the presence of reduced insight, symptom heterogeneity, and comorbidity, a multimethod and multi-informant assessment approach is necessary for an accurate diagnosis [104]. The following measures are focused on OCD-specific assessments. Broad-based assessment instruments are covered in Chap. 12.

Clinician-Rated Measures

Assessment and evaluation of obsessive-compulsive symptom severity is essential to monitor and track treatment progress. The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) [105] is a 10-item, semi-structured, clinician-administered interview. Considered the gold-standard measure for OCD severity, the interview provides a comprehensive checklist of commonly endorsed obsessions and compulsions, which are rated individually based on frequency, distress, efforts to resist, perceived control, and interference. Ratings are then combined to provide a composite severity score.

As family accommodation occurs frequently in pediatric OCD, it is important to measure the presence, frequency, and severity of the accommodating behaviors. The Family Accommodation Scale (FAS) [106] is a brief clinician-rated measure that provides a composite score that is reflective of the degree to which family members have accommodated their child's behavior over the past month.

Parent- and Self-report Measures

Parent- and self-report measures are time- and cost-efficient methods that can supplement clinician assessment. They are easy to score and interpret and can be used to obtain specific, detailed information regarding the nature of the child's obsessive-compulsive symptoms and associated impairment. For identifying *specific OCD symptom types* that the individual may display (i.e., ascertaining specific OCD obsessions and compulsions the child may have), the Obsessive Compulsive Inventory-Child Version (OCI-CV) [107] and the Children's Florida Obsessive Compulsive Inventory (CFOCI) [13] may be appropriate tools. The CFOCI also assesses OCD symptom severity. The OCI-CV total score and subscale scores have demonstrated strong internal consistency, test-retest reliability, and treatment sensitivity [107]. The CFOCI has shown good construct and discriminant validity, as well as acceptable internal consistency [13]. To measure *OCD functional impairment* (e.g., impairment in school, home, family), the Child OCD Impact Scale-Revised, Parent and Child Reports, (COIS-RP, COIS-RC) [3] can be utilized. The COIS-RP and COIS-RC have demonstrated good internal consistency, test-retest reliability, and concurrent validity. For a self-report assay of *OCD symptom severity*, the Children's Obsessional Compulsive Inventory (ChOCI) can be administered [108]. The ChOCI has shown good internal consistency and criterion and convergent validity [108]. Notably, to obtain a comprehensive OCD assessment, it is recommended to include an assessment of symptom types, severity, and impairment, which requires the administration of multiple measures.

Treatment

Currently there are two well-established treatment modalities for pediatric OCD: pharmacotherapy using SSRIs and cognitive behavioral therapy (CBT) with exposure and response prevention (E/RP). Both treatment methods, as well as their combination, have demonstrated efficacy in a number of methodically sound research trials [54, 109–119]. Studies looking at direct comparisons between SSRIs and CBT have found that CBT monotherapy and combination CBT + SSRI are superior to SSRI monotherapy [54, 116]. Indeed, practice parameters suggest that CBT alone should be used as a first-line treatment for mild to moderate cases and combination CBT + SSRI for severe cases [98].

Pharmacotherapy

There are four medications that carry Federal Drug Administration (FDA) indications for use in pediatric OCD (see Table 1). Clomipramine, a tricyclic antidepressant, is approved for those 10 years old and older (dosages from 50–200 mg). Table 1 provides the ages and dose ranges for the three SSRIs approved for use for pediatric OCD (sertraline, fluoxetine, fluvoxamine). To date, citalopram and escitalopram are not FDA approved for pediatric OCD.

All four medications have produced modest but positive results for the treatment of pediatric OCD. Clomipramine, once considered the frontline pharmacological approach for OCD, has demonstrated treatment efficacy in a number of randomized-controlled trials in adults and youth. A recent meta-analysis summarizing these studies indicated that clomipramine was superior to SSRIs in the reduction of obsessive-compulsive symptoms in children [120]; nevertheless, clomipramine is not considered a first choice pharmacotherapy due to the side effect profile and risks associated with clomipramine, such as anticholinergic, anti-adrenergic, and anti-histaminergic responses (e.g., dry mouth, constipation, dizziness, sweating) [98, 117], as well as medical monitoring of heart rate and blood pressure irregularities [109]. Recent practice parameters for the treatment of childhood OCD published by the American Academy of Child and Adolescent Psychiatry (AACAP) outline baseline evaluation (including general pediatric examination and system review and assessment of personal and family history), precautions, and contraindications associated with the use of clomipramine in children [98]. Please refer to the practice parameters for specific recommendations concerning clomipramine and other SRIs. Due to these concerns, clomipramine should be prescribed with caution. See Table 1 for randomized-controlled trials of clomipramine.

More recently, the utilization of SSRIs for pediatric OCD has received significant attention. Fluoxetine is the most studied SSRI for pediatric OCD and has been tested in three positive randomized-controlled

Table 1 Controlled pharmacotherapy trials for FDA-approved medications for pediatric obsessive-compulsive disorder

Medication	FDA-approved ages	Studies	Dose ranges	Treatment response rates[a]
Fluoxetine	7 years and up	Liebowitz et al. [114] Geller et al. [111]	20–80 mg/day	55–57 %
Fluvoxamine	8 years and up	Riddle et al. [115]	50–200 mg	42 %
Sertraline	6 years and up	POTS [54] March et al. [121]	25–200 mg	42–53 %
Clomipramine	10 years and up	DeVeaugh-Geiss et al. [118] Flament et al. [117]	50–200 mg	60–75 %

[a]Response rates based off of multiple outcomes (e.g., CY-BOCS, Clinical Global Impressions-Severity)

trials. In a 13-week, double-blind, placebo-controlled trial ($n=103$; ages 7–17 years), Geller et al. [111] found that fluoxetine demonstrated superior efficacy in reducing obsessive-compulsive symptoms relative to placebo with 49 % of the fluoxetine group and 25 % of the placebo group deemed treatment responders. Similarly, Liebowitz et al. [114] conducted a 16-week, placebo-controlled trial ($n=43$; ages 6–18 years) and found significantly reduced obsessive-compulsive symptoms for those who received fluoxetine as opposed to placebo; 57 % of the fluoxetine group was considered treatment responders relative to 27 % of the placebo group. Fluvoxamine was demonstrated superior to placebo in a 10-week randomized, placebo-controlled trial ($n=120$, ages 8–17 years), with treatment response rates of 42 % for fluvoxamine and 26 % for placebo [115].

Finally, research also supports the use of sertraline in the treatment of pediatric OCD. March et al. [121], in a 12-week, double-blind, placebo-controlled trial ($n=187$, ages 6–17 years), found that sertraline was significantly more efficacious in reducing obsessive-compulsive symptoms relative to placebo with treatment response rates of 42 % for sertraline and 26 % for placebo. Similarly, a multicenter, double-blind, placebo-controlled trial ($n=112$, ages 7–17 years) found that sertraline combined with CBT-enhanced treatment outcome was superior in reducing OCD symptoms relative to sertraline alone [54].

Several SSRIs that have not been FDA approved have also been shown to be efficacious treatments for pediatric OCD. Geller et al. [122] reported that paroxetine, in a 10-week, double-blind, placebo-controlled trial ($n=203$, ages 7–17 years), significantly reduced obsessive-compulsive symptoms, relative to the placebo group. Obsessive-compulsive symptoms were also significantly decreased in an 8-week open-label trial of citalopram ($n=15$, ages 6–17 years) [123]. Although paroxetine and citalopram have shown evidence for reducing symptoms in pediatric OCD, due to the stronger efficacy and safety data available for sertraline and fluoxetine, some caution use of these non-FDA-approved drugs.

Across trials, SSRIs were well-tolerated with low rates of discontinuation due to adverse events. Although generally considered safe, SSRIs have been the focus of attention regarding "behavioral activation syndrome," which is the stimulation or increase in suicidal thoughts or behaviors as a side effect of SSRI initiation or dosage increase [124]. Behavioral activation symptoms can include a worsening of symptoms, increased hyperactivity, impulsivity, talkativeness, or irritability [125–127]. These symptoms have been shown to occur in approximately 3 % of children and adolescents following initiation or change in SSRI treatment [128]. These concerns have lead to the FDA-mandated "black box" warning labels to remind physicians and patients to carefully monitor SSRI-related side effects.

Although SSRIs have been shown to be efficacious in the treatment of pediatric OCD, complete symptom remission occurs infrequently, and up to 42 % of individuals fail to respond to treatment [129]. For these children, additional pharmacotherapy interventions may be utilized such as atypical antipsychotic augmentation of SSRIs. These atypical antipsychotics are prescribed off-label and largely rely on the modest results shown in adult OCD populations. To date, no controlled pharmacological studies utilizing atypical antipsychotics in pediatric OCD have been reported; rather, the literature consists of several case studies and open-label trials. For example, Thomsen [130] conducted an open-label trial of 1–2 mg of risperidone-augmented SSRIs with medication-resistant adolescents and young adults ($n=17$, ages 15–19 years) and found significant reductions in obsessive-compulsive symptoms posttreatment. Similarly, Masi et al. [131] found in an open-label study ($n=39$, ages 12–18 years) that 5–20 mg of aripiprazole augmentation of SSRIs was successful in reducing obsessive-compulsive symptoms in medication-resistant cases, producing a treatment response rate of 59 %. Although the use of atypical antipsychotics in refractory cases seem promising, the lack of supporting efficacy data and the high frequency of associated side effects (e.g., significant weight gain) [132] suggest that further research in this area is warranted.

Cognitive Behavioral Therapy

CBT for pediatric OCD consists of three main components: psychoeducation, E/RP, and cognitive training. The first session(s) is focused on psychoeducation and rapport building. Next, a fear hierarchy is created where the child and parents list anxiety-provoking stimuli and rank them from lowest to highest degree of fear. Third is the core element of CBT for pediatric OCD, namely, E/RP. During exposure sessions, children are systematically exposed to the feared stimuli outlined in the fear hierarchy. Children gradually move from low-anxiety exposures to high-anxiety exposures, all the while refraining from engagement in compulsions or rituals. Exposure and response prevention is based on the notion that fear extinction can be facilitated through extended and repeated exposures to feared stimuli. Once a child consistently habituates (i.e., experiences elevated distress at the beginning of the exposure and eventually experiences substantial decreases in distress at the end of the exposure), the therapist moves on to the next feared stimuli on the hierarchy. Generalization is common; even stimuli initially perceived to be extremely anxiety-provoking are often manageable following mastery of E/RP with lower-level stimuli during the course of treatment.

During treatment, cognitive strategies may be employed when developmentally appropriate (usually in older children, adolescents, and sometimes bright younger children). Youth are taught to counter maladaptive cognitive thoughts via cognitive restructuring and constructive self-talk. Cognitive restructuring teaches children to challenge the validity of their obsessions by developing alternative explanations for the thoughts. By doing this, the value/importance placed on the obsessions should putatively decrease, thereby reducing the distress associated with the thoughts (i.e., shrinking the meaning associated with a given intrusive thought). For younger children, coping phrases ("I can say 'NO' to OCD!") can be helpful in competing against problematic intrusive thoughts that may emerge ("My OCD controls me and I can't do anything about it"). However, therapists should use caution when employing self-talk and other cognitive techniques, making sure the child is not substituting self-talk and phrases provided in therapy in the place of their rituals (i.e., ritual replacement).

Treatment for pediatric OCD often occurs within the context of the family, even when a specific family-based intervention is not implemented. As previously noted, children and adolescents with OCD frequently involve family members in their obsessive-compulsive symptoms; family members often aid by enabling avoidance of feared stimuli or facilitating the actual compulsions (e.g., washing contaminated clothes, providing reassurance). Additionally, children and adolescents are substantially embedded within the family unit and are therefore subjected to a number of variables outside of their control (e.g., marital dysfunction, family dynamics) and are dependent on their families for support. Because of this, individual therapy for pediatric OCD is not indicated without substantial parental support, and structured family-based interventions have been implemented in a number of CBT efficacy studies.

Although CBT with E/RP has been identified as an efficacious and advantageous method of treatment, there are a number of factors that may impede treatment response (for review, see Storch et al. [133]). Variables that are associated with poor treatment outcome include lack of insight and motivation, expectancy factors, increased family accommodation, and the presence of comorbid disorders. Clinically, limited insight poses to be problematic, as oftentimes individuals who are less aware of their symptoms do not attempt to resist or control their obsessions or behaviors. Indeed, children with poor insight have been found to have greater impairment, increased OCD symptom severity, family accommodation, and depressive symptoms [23, 57]. Similarly, treatment expectancy and motivation have been shown to be strong predictors of treatment outcome. Parent and child's expectations regarding treatment are associated with OCD symptom reduction as well as treatment adherence [134].

As previously noted, family accommodation occurs frequently in pediatric OCD [22]. Although family members participate in rituals (e.g., providing reassurance, opening doors, washing clothes) to reduce the child's anxiety or anger, family accommodation is related to increased familial stress and functional impairment [21]. The presence of comorbid disorders, particularly disruptive disorders,

Table 2 Controlled psychotherapy trials for pediatric obsessive-compulsive disorder

Randomized-controlled trials	Intervention	Duration	Treatment response rates[a]
Barrett et al. [112]	CBT with E/RP-based individual family therapy vs. group family therapy	14 weeks	Individual family = group family
Storch et al. [113]	Family-based CBT with E/RP intensive (daily) vs. weekly sessions	Intensive: daily for 3 weeks Weekly: 14 weeks	Intensive = weekly
Piacentini et al. [110]	Family-based CBT (FCBT) with E/RP vs. psychoeducation plus relaxation (PRT)	14 weeks—12 sessions	FCBT > PRT
POTS [54]	CBT with E/RP vs. SSRI vs. combination CBT + SSRI	12 weeks	Combination CBT + SSRI > CBT = SSRI > placebo
Asbahr et al. [119]	Group CBT vs. sertraline	12 weeks	Group CBT = sertraline
de Haan et al. [116]	CBT vs. clomipramine	12 weeks	CBT > clomipramine

[a]Response based upon multiple outcomes (e.g., CY-BOCS, CGI-Severity, CGI-Improvement)

can lead to attenuated treatment response [56]. Indeed, Storch et al. [57] found that the presence of comorbid externalizing disorders (ADHD, oppositional defiant disorder, etc.) was related to lower remission rates.

CBT for pediatric OCD has demonstrated robust treatment response rates with studies showing that up to 90 % of children and adolescents respond to treatment (See Table 2 for an overview of CBT efficacy trials). These studies have shown efficacy of CBT in comparison to wait lists as well as other types of psychotherapy. For example, Piacentini et al. [110] reported in a 14-week, randomized-controlled study ($n = 71$, 8–17 years) that family-based CBT was superior in decreasing obsessive-compulsive symptoms compared to individual psychoeducation/relaxation training [110]. The manual detailing this treatment is commercially available [135]. Similarly, Barrett et al. [112] compared the efficacy of individual family-based CBT and group family-based CBT in a 14-week randomized, wait-list controlled trial ($n = 77$, ages 7–17 years) and found that both groups produced significant decreases in obsessive-compulsive symptoms relative to wait-list controls with treatment response rates of 61 % (individual CBT) and 65 % (group CBT). In a 12-session pilot study of 5- to-8-year-olds with OCD ($n = 42$), family CBT was superior to family-based relaxation therapy (for the completer sample but not the intent-to-treat sample) [136]. Among completers, remission was achieved in 69 % of youth receiving CBT but only 20 % receiving relaxation therapy.

Few studies have compared efficacy rates between CBT and pharmacotherapy treatment. A recent meta-analysis of randomized-controlled trials for pediatric OCD identified an effect size of 1.45 for CBT and 0.48 for pharmacotherapy [137]. The POTS trial (Pediatric OCD Treatment Study) [54], the largest study of its kind, compared sertraline alone, CBT alone, and combination sertraline and CBT. Although all three groups showed significant decreases in obsessive-compulsive symptoms relative to the placebo group, those who received CBT alone and combination CBT and sertraline showed the greatest reductions in symptoms with effect sizes of 0.96 and 1.4, respectively (note: reductions in CY-BOCS symptoms did not differ statistically between the CBT alone and sertraline alone groups). Remission rates were fair with 39 % for CBT alone, 21 % for sertraline alone, and 56.3 % for combination CBT and sertraline. Notably, there was a group by site interaction, with youth receiving CBT at the site directing CBT for the trial doing better than youth receiving CBT at the site directing pharmacotherapy. The POTS II trial followed up the initial study in a sample of SSRI treatment-refractory patients by comparing SSRI management alone, SSRI management with CBT instructions provided by a physician, and SSRI management with CBT [138]. When compared to SSRI management alone, SSRI management with CBT had greater decreases in symptoms than SSRI management with CBT instructions (effect size of 0.85 and 0.16, respectively). It is important to note, however, that the CBT instructions condition did not include contact with a therapist trained in CBT for OCD. A limitation of the POTS II trial is that youth who did not respond to community SSRI treatment were recruited as

opposed to prospectively examining SSRI partial-responders/nonresponders following a study-initiated course of medication. Consequently, there is likely marked heterogeneity in subjects prior to randomization, obfuscating interpretation of the results. In an older study, DeHaan et al. [116] reported a statistically significant advantage for CBT with an effect size of 1.58 (66 % response rate) for intensive CBT and 1.45 (50 % response rate) for clomipramine in a 12-week trial with 22 youth ages 8–18. Based on these few comparative efficacy trials, CBT has emerged as the most-often recommended initial first-line treatment for youth with mild to moderate OCD [139, 140].

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus

Prophylactics, such as penicillin and azithromycin, have been examined as novel treatment methods for PANDAS subtype of OCD and/or tic disorder [102, 141, 142]. Garvey et al. [142] found in an 8-month, double-blind, placebo-controlled, crossover study of penicillin that penicillin was not significantly better at decreasing neuropsychiatric symptom exacerbation relative to the placebo group. In contrast, Snider et al. [141] reported that in a double-blind, randomized, controlled study of penicillin and azithromycin ($n=23$, ages 5–9), neuropsychiatric symptom exacerbations decreased significantly for both prophylactics. It is important to note that the use of antibiotic prophylactics for the treatment of PANDAS-subtype OCD and/or immunoglobulin therapy (IVIG) is an experimental treatment that should be discussed in consultation with an expert in pediatric psychoneuroimmunology. No data suggest the benefit of surgical approaches to abate or prevent symptoms (e.g., tonsillectomy/adenoidectomy). Behavioral treatment for PANDAS-subtype OCD is the same for non-PANDAS OCD and is the only recommended intervention without specialty consultation [143].

Novel Treatments

To target the sizable minority that remain either unresponsive or relapse following treatment, research has begun to focus on novel treatment methods. D-Cycloserine (DCS) is an *N*-methyl-D-aspartate (NMDA) partial agonist that has been shown to enhance learning and facilitate fear extinction [144–146] and has been examined as an adjunctive agent to CBT. Storch et al. [147] conducted a double-blind, placebo-controlled treatment trial ($n=30$; ages 8–17 years) in youth with a primary diagnosis with OCD. Results showed that those who received DCS + CBT had greater improvements at posttreatment relative to those who received placebo + CBT, suggesting that DCS + CBT may enhance fear extinction in children with OCD. Riluzole, a glutamate antagonist, has been examined as a possible treatment method for treatment-resistant youth [89]. In a 12-week open-label trial ($n=6$; ages 8–16 years), Grant et al. [89] found that 4 out of 6 youth experienced substantial reductions in OCD symptoms. Notably, no practice decisions should be based on a six-subject open trial.

Storch et al. [113] examined the efficacy of intensive (daily sessions for 3 weeks) vs. weekly (once per week for 14 weeks) family sessions for the treatment of pediatric OCD ($n=40$, ages 7–17 years) and found no differences between the two groups at posttreatment. Treatment response rates were robust for both intensive and weekly sessions: 90 % and 65 %, respectively. Unfortunately, limited access to highly trained providers makes E/RP inaccessible for many youth. Web-camera-based CBT methods have been investigated as a means for treatment dissemination. In a preliminary study, Storch et al. [148] found in a randomized, wait-list controlled study ($n=31$; ages 7–17 years) that web-camera-based CBT was superior in decreasing OCD symptoms relative to the wait-list group.

Case Follow-up

Zoe and her family participated in 12 weekly sessions of CBT with E/RP, focusing exposure on her contamination fears and prevention of her washing rituals. In session, exposures began with Zoe holding contaminated objects that she rated as producing distress levels of a 4 (on a scale of 0–10). Once she habituated to these items (provided a distress rating of 0 or 1), increasingly more difficult exposures were practiced. For example, contaminated items that she habituated to previously were now placed together to increase the level of contamination. She held these items in her hands and rubbed them along her arms and legs to enhance her anxiety and increase the difficulty level of the exposure. During these sessions she was instructed to refrain from washing her hands for the rest of the day. Between sessions, she was to practice E/RP by going into rooms that her father frequented (his bedroom, office) and to sit in the rooms until she habituated to her anxiety. After five sessions of E/RP, Zoe reported that she was ready for exposures that would cause her higher levels of distress (ratings of 8–10). In session, she practiced exposures by tossing a contaminated ball back and forth with her father. Once she habituated to the anxiety, she moved on to touching her father's arm for several minutes. By the following session, Zoe was able to hug her father with limited distress and anxiety. By the 12th session, Zoe reported an improved ability to manage her contamination fears and washing, as well as an overall decrease in anxiety. Her parents reported an increased understanding on how to react to Zoe's obsessive-compulsive symptoms and how to refrain from accommodating her symptoms. Both Zoe and her parents noted understanding on how to intervene in the future should the obsessive-compulsive symptoms reemerge.

Conclusions

OCD in children and adolescents is an impairing neuropsychiatric syndrome that, if untreated, can persist into adulthood and contribute to marked disability. Fortunately, efficacious treatments are available. Exposure and response prevention has emerged as the leading empirically supported behavioral treatment for pediatric OCD. Studies emphasizing these behavioral approaches within a family-based context appear to have more robust outcomes. Although pharmacotherapy is a more readily available efficacious treatment method than CBT, remission rates for SSRIs are lower than for CBT with E/RP, and the potential for adverse events is higher. Additionally, a substantial minority do not respond to CBT and/or pharmacotherapy. Consequently, current research seeks to better understand factors that facilitate and expedite treatment, so that increasingly individually targeted and cost-effective CBT can be disseminated. The field has already begun to examine innovative methods of treatment dissemination in children and adolescents, such as computer-administered (via web camera) E/RP [148]. However, further investigation into these novel treatment delivery options is warranted.

References

1. APA. Diagnostic and statistical manual of mental disorders (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
2. Piacentini J, Bergman RL, Keller M, McCracken J. Functional impairment in children and adolescents with obsessive-compulsive disorder. J Child Adolesc Psychopharmacol. 2003;13 Suppl 1:S61–9.
3. Piacentini J, Peris TS, Bergman RL, Chang S, Jaffer M. Functional impairment in childhood OCD: development and psychometrics properties of the Child Obsessive-Compulsive Impact Scale-Revised (COIS-R). J Clin Child Adolesc Psychol. 2007;36(4):645–53.

4. Storch EA, Ledley DR, Lewin AB, et al. Peer victimization in children with obsessive-compulsive disorder: relations with symptoms of psychopathology. J Clin Child Adolesc Psychol. 2006;35(3):446–55.
5. Valderhaug R, Ivarsson T. Functional impairment in clinical samples of Norwegian and Swedish children and adolescents with obsessive-compulsive disorder. Eur Child Adolesc Psychiatry. May 2005;14(3):164–73.
6. Lack CW, Storch EA, Keeley ML, et al. Quality of life in children and adolescents with obsessive-compulsive disorder: base rates, parent–child agreement, and clinical correlates. Soc Psychiatry Psychiatr Epidemiol. Nov 2009;44(11):935–42.
7. Flament MF, Koby E, Rapoport JL, et al. Childhood obsessive-compulsive disorder: a prospective follow-up study. J Child Psychol Psychiatry. Mar 1990;31(3):363–80.
8. Thomsen PH, Mikkelsen HU. Course of obsessive-compulsive disorder in children and adolescents: a prospective follow-up study of 23 Danish cases. J Am Acad Child Adolesc Psychiatry. 1995;34(11):1432–40.
9. Murray CJ, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected in 2020. Cambridge: Harvard University Press; 1996.
10. Bloch MH, Craiglow BG, Landeros-Weisenberger A, et al. Predictors of early adult outcomes in pediatric-onset obsessive-compulsive disorder. Pediatrics. Oct 2009;124(4):1085–93.
11. Lin H, Katsovich L, Ghebremichael M, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. J Child Psychol Psychiatry. Feb 2007;48(2):157–66.
12. Lafleur DL, Petty C, Mancuso E, et al. Traumatic events and obsessive compulsive disorder in children and adolescents: is there a link? J Anxiety Disord. 2011;25(4):513–9.
13. Storch EA, Khanna M, Merlo LJ, et al. Children's Florida Obsessive Compulsive Inventory: psychometric properties and feasibility of a self-report measure of obsessive-compulsive symptoms in youth. Child Psychiatry Hum Dev. Sep 2009;40(3):467–83.
14. Storch EA, Lack C, Merlo LJ, et al. Associations between miscellaneous symptoms and symptom dimensions: an examination of pediatric obsessive-compulsive disorder. Behav Res Ther. Nov 2007;45(11):2593–603.
15. Swedo SE, Rapoport JL, Leonard H, Lenane M, Cheslow D. Obsessive-compulsive disorder in children and adolescents. Clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry. 1989;46(4):335–41.
16. Mataix-Cols D, Marks IM, Greist JH, Kobak KA, Baer L. Obsessive-compulsive symptom dimensions as predictors of compliance with and response to behaviour therapy: results from a controlled trial. Psychother Psychosom. 2002;71(5):255–62.
17. McKay D, Piacentini J, Greisberg S, Graae F, Jaffer M, Miller J. The structure of childhood obsessions and compulsions: dimensions in an outpatient sample. Behav Res Ther. Jan 2006;44(1):137–46.
18. Storch EA, Merlo LJ, Larson MJ, et al. Symptom dimensions and cognitive-behavioural therapy outcome for pediatric obsessive-compulsive disorder. Acta Psychiatr Scand. Jan 2008;117(1):67–75.
19. Coles ME, Heimberg RG, Frost RO, Steketee G. Not just right experiences and obsessive-compulsive features: experimental and self-monitoring perspectives. Behav Res Ther. Feb 2005;43(2):153–67.
20. Leckman JF, Walker DE, Goodman WK, Pauls DL, Cohen DJ. "Just right" perceptions associated with compulsive behavior in Tourette's syndrome. Am J Psychiatry. May 1994;151(5):675–80.
21. Storch EA, Geffken GR, Merlo LJ, et al. Family accommodation in pediatric obsessive-compulsive disorder. J Clin Child Adolesc Psychol. 2007;36(2):207–16.
22. Peris TS, Bergman RL, Langley A, Chang S, McCracken JT, Piacentini J. Correlates of accommodation of pediatric obsessive-compulsive disorder: parent, child, and family characteristics. J Am Acad Child Adolesc Psychiatry. 2008;47(10):1173.
23. Lewin AB, Bergman RL, Peris TS, Chang S, McCracken JT, Piacentini J. Correlates of insight among youth with obsessive-compulsive disorder. J Child Psychol Psychiatry. 2010;51(5):603–11.
24. Storch EA, Milsom VA, Merlo LJ, et al. Insight in pediatric obsessive-compulsive disorder: associations with clinical presentation. Psychiatry Res. 2008;160(2):212–20.
25. Hollander E, Braun A, Simeon D. Should OCD leave the anxiety disorders in DSM-V? The case for obsessive compulsive-related disorders. Depress Anxiety. 2008;25(4):317–29.
26. Storch EA, Abramowitz J, Goodman WK. Where does obsessive-compulsive disorder belong in DSM-IV? Depress Anxiety. 2008;25:336–47.
27. Nestadt G, Samuels J, Riddle MA, et al. The relationship between obsessive-compulsive disorder and anxiety and affective disorders: results from the Johns Hopkins OCD Family Study. Psychol Med. Apr 2001;31(3):481–7.
28. Bienvenu OJ, Samuels JF, Riddle MA, et al. The relationship of obsessive-compulsive disorder to possible spectrum disorders: results from a family study. Biol Psychiatry. 2000;48(4):287–93.
29. Richter MA, Summerfeldt LJ, Antony MM, Swinson RP. Obsessive-compulsive spectrum conditions in obsessive-compulsive disorder and other anxiety disorders. Depress Anxiety. 2003;18(3):118–27.
30. Mataix-Cols D, Frost RO, Pertusa A, et al. Hoarding disorder: a new diagnosis for DSM-V? Depress Anxiety. Jun 2010;27(6):556–72.

31. Samuels JF, Bienvenu OJ, Grados MA, et al. Prevalence and correlates of hoarding behavior in a community-based sample. Behav Res Ther. Jul 2008;46(7):836–44.
32. Olatunji BO, Williams BJ, Haslam N, Abramowitz JS, Tolin DF. The latent structure of obsessive-compulsive symptoms: a taxometric study. Depress Anxiety. 2008;25(11):956–68.
33. Abramowitz JS, Wheaton MG, Storch EA. The status of hoarding as a symptom of obsessive-compulsive disorder. Behav Res Ther. Sep 2008;46(9):1026–33.
34. Pertusa A, Frost RO, Fullana MA, et al. Refining the diagnostic boundaries of compulsive hoarding: a critical review. Clin Psychol Rev. Jun 2010;30(4):371–86.
35. Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L. Use of factor-analyzed symptom dimensions to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive-compulsive disorder. Am J Psychiatry. Sep 1999;156(9):1409–16.
36. Winsberg ME, Cassic KS, Koran LM. Hoarding in obsessive-compulsive disorder: a report of 20 cases. J Clin Psychiatry. Sep 1999;60(9):591–7.
37. Lochner C, Kinnear CJ, Hemmings SM, et al. Hoarding in obsessive-compulsive disorder: clinical and genetic correlates. J Clin Psychiatry. Sep 2005;66(9):1155–60.
38. Saxena S, Brody AL, Maidment KM, et al. Cerebral glucose metabolism in obsessive-compulsive hoarding. Am J Psychiatry. Jun 2004;161(6):1038–48.
39. Saxena S. Neurobiology and treatment of compulsive hoarding. CNS Spectr. Sep 2008;13(9 Suppl 14):29–36.
40. Rapoport JL, Inoff-Germain G, Weissman MM, et al. Childhood obsessive-compulsive disorder in the NIMH MECA study: parent versus child identification of cases. Methods for the epidemiology of child and adolescent mental disorders. J Anxiety Disord. 2000;14(6):535–48.
41. Zohar AH. The epidemiology of obsessive-compulsive disorder in children and adolescents. Child Adolesc Psychiatr Clin N Am. Jul 1999;8(3):445–60.
42. Delorme R, Golmard JL, Chabane N, et al. Admixture analysis of age at onset in obsessive-compulsive disorder. Psychol Med. Feb 2005;35(2):237–43.
43. Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. Mol Psychiatry. Jan 2010;15(1):53–63.
44. Castle DJ, Deale A, Marks IM. Gender differences in obsessive compulsive disorder. Aust N Z J Psychiatry. Mar 1995;29(1):114–7.
45. Chabane N, Delorme R, Millet B, Mouren MC, Leboyer M, Pauls D. Early-onset obsessive-compulsive disorder: a subgroup with a specific clinical and familial pattern? J Child Psychol Psychiatry. Aug 2005;46(8):881–7.
46. Nestadt G, Samuels J, Riddle M, et al. A family study of obsessive-compulsive disorder. Arch Gen Psychiatry. 2000;57(4):358–63.
47. Stewart SE, Geller DA, Jenike M, et al. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and qualitative review of the literature. Acta Psychiatr Scand. 2004;110(1):4–13.
48. Geller DA, Biederman J, Griffin S, Jones J, Lefkowitz TR. Comorbidity of juvenile obsessive-compulsive disorder with disruptive behavior disorders. J Am Acad Child Adolesc Psychiatry. 1996;35(12):1637–46.
49. Riddle MA, Scahill L, King R, et al. Obsessive compulsive disorder in children and adolescents: phenomenology and family history. J Am Acad Child Adolesc Psychiatry. 1990;29(5):766–72.
50. Hanna GL, Yuwiler A, Coates JK. Whole blood serotonin and disruptive behaviors in juvenile obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 1995;34(1):28–35.
51. Storch EA, Larson MJ, Keely ML, Geffken GR, Murphy TK, Goodman W. Comorbidity of pediatric obsessive-compulsive disorder and anxiety disorders: Impact on symptom severity and impairment. J Psychopathol Behav Assess. 2008;30(2):111–20.
52. Geller DA, Biederman J, Faraone SV, et al. Clinical correlates of obsessive compulsive disorder in children and adolescents referred to specialized and non-specialized clinical settings. Depress Anxiety. 2000;11(4):163–8.
53. Masi G, Perugi G, Millepiedi S, et al. Bipolar co-morbidity in pediatric obsessive-compulsive disorder: clinical and treatment implications. J Child Adolesc Psychopharmacol. Aug 2007;17(4):475–86.
54. POTS. 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(16):1969–76.
55. March JS, Franklin ME, Leonard H, et al. Tics moderate treatment outcome with sertraline but not cognitive-behavior therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. 2007;61(3):344–7.
56. Geller DA, Biederman J, Stewart SE, et al. Impact of comorbidity on treatment response to paroxetine in pediatric obsessive-compulsive disorder: is the use of exclusion criteria empirically supported in randomized clinical trials? J Child Adolesc Psychopharmacol. 2003;13 Suppl 1:S19–29.
57. Storch EA, Merlo LJ, Larson MJ, et al. Impact of comorbidity on cognitive-behavioral therapy response in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2008;47(5):583–92.
58. Abramowitz JS, Foa EB. Worries and obsessions in individuals with obsessive-compulsive disorder with and without comorbid generalized anxiety disorder. Behav Res Ther. 1998;36(7–8):695–700.

59. Turner SM, Beidel DC, Stanley MA. Are obsessional thoughts and worry different cognitive phenomena? Clin Psychol Rev. 1992;12:257–70.
60. Taylor S, Thoardarson DS, Sochting I. Obsessive-compulsive disorder. In: Antony MM, Barlow DH, editors. Handbook of assessment and treatment planning for psychological disorders. New York: Guildford Press; 2002. p. 182–214.
61. Mansueto CS, Keuler DJ. Tic or compulsion?: It's Tourettic OCD. Behav Modif. Sep 2005;29(5):784–99.
62. Castellanos FX. Tic disorders and obsessive-compulsive disorder. In: Cohen DJ, Bruun RD, Leckman JF, editors. Child psychopharmacology. New York: Wiley; 1998.
63. Leckman JF, Walker DE, Cohen DJ. Premonitory urges in Tourette's syndrome. Am J Psychiatry. Jan 1993;150(1):98–102.
64. Jimenez-Murcia S, Fernandez-Aranda F, Raich RM, et al. Obsessive-compulsive and eating disorders: comparison of clinical and personality features. Psychiatry Clin Neurosci. Aug 2007;61(4):385–91.
65. Strober M, Freeman R, Lampert C, Diamond J. The association of anxiety disorders and obsessive compulsive personality disorder with anorexia nervosa: evidence from a family study with discussion of nosological and neurodevelopmental implications. Int J Eat Disord. 2007;40 Suppl 3:S46–51.
66. Lewin AB, Menzel J, Strober M. Assessment and treatment of comorbid anorexia nervosa and obsessive compulsive disorder. In: Storch EA, Mckay D, editors. Handbook of treating variants and complications in anxiety disorders; 2013 (in press).
67. Lewin AB, Wood JJ, Gunderson S, Murphy TK, Storch EA. Obsessive compulsive symptoms in youth with high functioning autism spectrum disorders. J Dev Phys Disabil. 2011;23:543–53.
68. Ivarsson T, Melin K. Autism spectrum traits in children and adolescents with obsessive-compulsive disorder (OCD). J Anxiety Disord. Aug 2008;22(6):969–78.
69. Rapp JT, Vollmer TR. Stereotypy I: a review of behavioral assessment and treatment. Res Dev Disabil. 2005;26(6):527–47.
70. Saxena S, Brody AL, Schwartz JM, Baxter LR. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. Br J Psychiatry Suppl. 1998;35:26–37.
71. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 1986;9:357–81.
72. Rosenberg DR, Keshavan MS. A.E. Bennett Research Award. Toward a neurodevelopmental model of obsessive–compulsive disorder. Biol Psychiatry. 1998;43(9):623–40.
73. Rapoport JL, Wise SP. Obsessive-compulsive disorder: evidence for basal ganglia dysfunction. Psychopharmacol Bull. 1988;24(3):380–4.
74. Baxter Jr LR, Schwartz JM, Bergman KS, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. Arch Gen Psychiatry. Sep 1992;49(9):681–9.
75. Rauch SL, Baxter LR. Neuroimaging in obsessive-compulsive disorder and related disorders. In: Jenike MA, Baer L, Minichiello WE, editors. Obsessive-compulsive disorders: practical management, vol. 3. St. Louis, MO: Mosby; 1998. p. 289–317.
76. Saxena S, Bota RG, Brody AL. Brain-behavior relationships in obsessive-compulsive disorder. Semin Clin Neuropsychiatry. 2001;6(2):82–101.
77. Kim JJ, Lee MC, Kim J, et al. Grey matter abnormalities in obsessive-compulsive disorder: statistical parametric mapping of segmented magnetic resonance images. Br J Psychiatry. Oct 2001;179:330–4.
78. MacMaster FP, O'Neill J, Rosenberg DR. Brain imaging in pediatric obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. Nov 2008;47(11):1262–72.
79. Arnold PD, Macmaster FP, Richter MA, et al. Glutamate receptor gene (GRIN2B) associated with reduced anterior cingulate glutamatergic concentration in pediatric obsessive-compulsive disorder. Psychiatry Res. 2009;172(2):136–9.
80. Friedlander L, Desrocher M. Neuroimaging studies of obsessive-compulsive disorder in adults and children. Clin Psychol Rev. 2006;26:32–49.
81. Woolley J, Heyman I, Brammer M, Frampton I, McGuire PK, Rubia K. Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. Br J Psychiatry. 2008;192:25–31.
82. Iversen SD, Mishkin M. Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. Exp Brain Res. 1970;11(4):376–86.
83. Szeszko PR, MacMillan S, McMeniman M, et al. Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. Am J Psychiatry. 2004;161(6):1049–56.
84. Gilbert AR, Moore GJ, Keshavan MS, et al. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. Arch Gen Psychiatry. 2000;57(5):449–56.
85. Szeszko PR, MacMillan S, McMeniman M, et al. Amygdala volume reductions in pediatric patients with obsessive-compulsive disorder treated with paroxetine: preliminary findings. Neuropsychopharmacology. 2004;29(4):826–32.

86. Barr LC, Goodman WK, Price LH, McDougle CJ, Charney DS. The serotonin hypothesis of obsessive compulsive disorder: implications of pharmacologic challenge studies. J Clin Psychiatry. Apr 1992;53(Suppl):17–28.
87. Goodman WK, McDougle CJ, Price LH, Riddle MA, Pauls DL, Leckman JF. Beyond the serotonin hypothesis: a role for dopamine in some forms of obsessive compulsive disorder? J Clin Psychiatry. 1990;51(Suppl):36–43. discussion 55–38.
88. Rosenberg DR, Mirza Y, Russell A, et al. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. J Am Acad Child Adolesc Psychiatry. Sep 2004;43(9):1146–53.
89. 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. Dec 2007;17(6):761–7.
90. Denys D, van der Wee N, Janssen J, De Geus F, Westenberg HG. Low level of dopaminergic D2 receptor binding in obsessive-compulsive disorder. Biol Psychiatry. 2004;55(10):1041–5.
91. van der Wee NJ, Stevens H, Hardeman JA, et al. Enhanced dopamine transporter density in psychotropic-naive patients with obsessive-compulsive disorder shown by [123I]{beta}-CIT SPECT. Am J Psychiatry. Dec 2004;161(12):2201–6.
92. Denys D, de Geus F, van Megen HJ, Westenberg HG. A double-blind, randomized, placebo-controlled trial of quetiapine addition in patients with obsessive-compulsive disorder refractory to serotonin reuptake inhibitors. J Clin Psychiatry. 2004;65(8):1040–8.
93. Mowrer OH. A stimulus–response analysis of anxiety and its role as a reinforcing agent. Psychol Rev. 1939;46:553–65.
94. Mowrer OH. Learning theory and behavior. New York: John Wiley; 1960.
95. Franklin ME, Foa EB. Cognitive behavioral treatments for obsessive compulsive disorder. In: Nathan PE, Gorman JM, editors. A guide to treatments that work, vol. 2. 386: Oxford University Press; 2002. p. 367.
96. Salkovskis PM. Understanding and treating obsessive-compulsive disorder. Behav Res Ther. 1999;37 Suppl 1:S29–52.
97. Salkovskis PM. Obsessional-compulsive problems: a cognitive-behavioural analysis. Behav Res Ther. 1985;23(5):571–83.
98. AACAP. Practice parameter for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. 2012;51(1):98–113.
99. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry. Feb 1998;155(2):264–71.
100. Murphy TK, Kurlan R, Leckman J. The immunobiology of Tourette's disorder, pediatric autoimmune neuropsychiatric disorders associated with Streptococcus, and related disorders: a way forward. J Child Adolesc Psychopharmacol. Aug 2010;20(4):317–31.
101. Murphy TK, Sajid M, Soto O, et al. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. Biol Psychiatry. 2004;55(1):61–8.
102. Leonard HL, Swedo SE. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Int J Neuropsychopharmacol. 2001;4(2):191–8.
103. Jenike MA. Obsessive-compulsive and related disorders: a hidden epidemic. N Eng J Med. 1989;321(8):539–41.
104. Lewin AB, Piacentini J. Evidence-based assessment of child Obsessive Compulsive Disorder: recommendations for clinical practice and treatment research. Child Youth Care Forum. Apr 2010;39(2):73–89.
105. Scahill L, Riddle MA, McSwiggin-Hardin M, et al. Children's Yale-Brown Obsessive Compulsive Scale: reliability and validity. J Am Acad Child Adolesc Psychiatry. Jun 1997;36(6):844–52.
106. Calvocoressi L, Mazure CM, Kasl SV, et al. Family accommodation of obsessive-compulsive symptoms: instrument development and assessment of family behavior. J Nerv Ment Dis. 1999;187(10):636–42.
107. Foa EB, Coles M, Huppert JD, Pasupuleti RV, Franklin ME, March J. Development and validation of a child version of the obsessive compulsive inventory. Behav Ther. Mar 2010;41(1):121–32.
108. Shafran R, Frampton I, Heyman I, Reynolds M, Teachman B, Rachman S. The preliminary development of a new self-report measure for OCD in young people. J Adolesc. Feb 2003;26(1):137–42.
109. Biederman J. Sudden death in children treated with a tricyclic antidepressant. J Am Acad Child Adolesc Psychiatry. May 1991;30(3):495–8.
110. Piacentini J, Bergman RL, Chang S, et al. Controlled comparison of family cognitive behavioral therapy and psychoeducation/relaxation training for child obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry. Nov 2011;50(11):1149–61.
111. Geller DA, Hoog SL, Heiligenstein JH, et al. Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. J Am Acad Child Adolesc Psychiatry. 2001;40(7):773–9.
112. 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(1):46–62.

113. Storch EA, Geffken GR, Merlo LJ, et al. Family-based cognitive-behavioral therapy for pediatric obsessive-compulsive disorder: comparison of intensive and weekly approaches. J Am Acad Child Adolesc Psychiatry. 2007;46(4):469–78.
114. Liebowitz MR, Turner SM, Piacentini J, et al. Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2002;41(12):1431–8.
115. Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. Fluvoxamine for children and adolescents with obsessive-compulsive disorder: a randomized, controlled, multicenter trial. J Am Acad Child Adolesc Psychiatry. Feb 2001;40(2):222–9.
116. 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(10):1022–9.
117. Flament MF, Rapoport JL, Berg CJ, et al. Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind controlled study. Arch Gen Psychiatry. 1985;42(10):977–83.
118. DeVeaugh-Geiss J, Moroz G, Biederman J, et al. Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder—a multicenter trial. J Am Acad Child Adolesc Psychiatry. Jan 1992;31(1):45–9.
119. Asbahr FR, Castillo AR, Ito LM, Latorre MR, 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. Nov 2005;44(11):1128–36.
120. Geller DA, Biederman J, Stewart SE, et al. Which SSRI? A meta-analysis of pharmacotherapy trials in pediatric obsessive-compulsive disorder. Am J Psychiatry. Nov 2003;160(11):1919–28.
121. March JS, Biederman J, Wolkow R, et al. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA. 1998;280(20):1752–6.
122. Geller DA, Wagner KD, Emslie G, 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(11):1387–96.
123. Mukaddes NM, Abali O, Kaynak N. Citalopram treatment of children and adolescents with obsessive-compulsive disorder: a preliminary report. Psychiatry Clin Neurosci. Aug 2003;57(4):405–8.
124. Goodman WK, Murphy TK, Storch EA. Risk of adverse behavioral effects with pediatric use of antidepressants. Psychopharmacology (Berl). Mar 2007;191(1):87–96.
125. Carlson GA. Early onset bipolar disorder: clinical and research considerations. J Clin Child Adolesc Psychol. Jun 2005;34(2):333–43.
126. Guile JM. Sertraline-induced behavioral activation during the treatment of an adolescent with major depression. J Child Adolesc Psychopharmacol. Winter 1996;6(4):281–5.
127. Riddle MA, King RA, Hardin MT, Scahill L, Ort SI, Leckman JF. Behavioral side effects of fluoxetine in children and adolescents. J Child Adolesc Psychopharmacol. 1991;1:193–8.
128. Safer DJ, Zito JM. Treatment-emergent adverse events from selective serotonin reuptake inhibitors by age group: children versus adolescents. J Child Adolesc Psychopharmacol. 2006;16(1–2):159–69.
129. Bridge JA, Iyengar S, Salary CB, 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(15):1683–96.
130. 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.
131. Masi G, Pfanner C, Millepiedi S, Berloffa S. Aripiprazole augmentation in 39 adolescents with medication-resistant obsessive-compulsive disorder. J Clin Psychopharmacol. Dec 2010;30(6):688–93.
132. Lewin AB, Storch EA, Storch HD. Risks from antipsychotic medications in children and adolescents. JAMA. 2010;303(8):729–30.
133. Storch EA, Bjorgvinsson T, Riemann B, Lewin AB, Morales MJ, Murphy TK. Factors associated with poor response in cognitive-behavioral therapy for pediatric obsessive-compulsive disorder. Bull Menninger Clin. Spring 2010;74(2):167–85.
134. Lewin AB, Peris TS, Lindsey Bergman R, McCracken JT, Piacentini J. The role of treatment expectancy in youth receiving exposure-based CBT for obsessive compulsive disorder. Behav Res Ther. Sep 2011;49(9):536–43.
135. Piacentini J, Langley A, Roblek T. Overcoming childhood OCD: a therapist's guide. New York: Oxford University Press; 2007.
136. Freeman JB, Garcia AM, Coyne L, et al. Early childhood OCD: preliminary findings from a family-based cognitive-behavioral approach. J Am Acad Child Adolesc Psychiatry. May 2008;47(5):593–602.
137. Watson HJ, Rees CS. Meta-analysis of randomized, controlled treatment trials for pediatric obsessive-compulsive disorder. J Child Psychol Psychiatry. May 2008;49(5):489–98.
138. Franklin ME, Sapyta J, Freeman JB, et al. Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder: the Pediatric OCD Treatment Study II (POTS II) randomized controlled trial. JAMA. 2011;306(11):1224–32.

139. Lewin AB, Piacentini J. Obsessive-compulsive disorder in children. In: Sadock BJ, Sadock VA, Ruiz P, editors. Kaplan & Sadock's comprehensive textbook of psychiatry, vol. 2. 9th ed. Philadelphia: Lippincott, Williams & Wilkins; 2009. p. 3671–8.
140. Barrett PM, Farrell L, Pina AA, Peris TS, Piacentini J. Evidence-based psychosocial treatments for child and adolescent obsessive-compulsive disorder. J Clin Child Adolesc Psychol. 2008;37(1):131–55.
141. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Biol Psychiatry. 2005;57(7):788–92.
142. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Biol Psychiatry. 1999;45(12):1564–71.
143. Storch EA, Murphy TK, Geffken GR, et al. Cognitive-behavioral therapy for PANDAS-related obsessive-compulsive disorder: findings from a preliminary waitlist controlled open trial. J Am Acad Child Adolesc Psychiatry. Oct 2006;45(10):1171–8.
144. Walker DL, Ressler KJ, Lu KT, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. J Neurosci. 2002;22(6):2343–51.
145. Ledgerwood L, Richardson R, Cranney J. D-Cycloserine and the facilitation of extinction of conditioned fear: consequences for reinstatement. Behav Neurosci. Jun 2004;118(3):505–13.
146. Ledgerwood L, Richardson R, Cranney J. Effects of D-cycloserine on extinction of conditioned freezing. Behav Neurosci. Apr 2003;117(2):341–9.
147. Storch EA, Murphy TK, Goodman WK, et al. A preliminary study of D-cycloserine augmentation of cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. Biol Psychiatry. 2010;68(11):1073–6.
148. Storch EA, Caporino NE, Morgan JR, et al. Preliminary investigation of web-camera delivered cognitive-behavioral therapy for youth with obsessive-compulsive disorder. Psychiatry Res. 2011;189(3):407–12.