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Obsessive-Compulsive Disorder

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Obsessive-compulsive disorder (OCD), as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [1], is characterized by recurrent obsessions or compulsions that are distressful or interfere in one's life. Obsessions are defined as persistent thoughts, images, or impulses that are ego-dystonic, intrusive, and, for the most part, senseless. “Compulsions are repetitive, purposeful, and intentional behaviors that are performed in response to an obsession, according to certain rules, or in a stereotyped fashion.” [1]

In general, compulsions are meant to relieve (or neutralize) anxiety or to prevent a dreaded event. An adolescent or adult may recognize that the ritual is unreasonable or excessive, but that is not necessarily true for the young child. Often, children and adolescents will attempt to hide their rituals, although with more severe symptoms, this usually is not possible. To meet diagnostic criteria for the disorder, the person must experience distress, spend more than 1 hour per day in either obsessions or compulsions, or there must be significant interference in one's life [1]. This article reviews the phenomenology, causes, treatment, and outcome of children and adolescents with OCD.

Clinical presentation

Typically, there is a specific list of obsessions and compulsions. Many of the symptoms can be understood as excessive worries about danger, separation, and contamination, which result in rituals of washing, checking, and hoarding. The most common obsessions include excessive concerns about contamination (dirt, germs, and illness), harm coming to the self or others (eg, parents might be kidnapped), doing the right thing (ie, scrupulosity), reassurance, or intrusive sexual thoughts. Sometimes the need (“urge”) for evenness, order, or

exactness may be described, with an accompanying feeling of “incompleteness.” The most common rituals are washing, repeating, checking, counting, touching, arranging, and hoarding [2]. Obsessions and compulsions seen in adults are similar to those seen in children, but the obsessions are more age appropriate (eg, children worry that they may be kidnapped or that their parents may be killed). It is not unusual for the OCD symptoms to change over time, and most children will have had most of the symptoms at some time in the course of their illness [3].

For individuals with a childhood onset of OCD, boys may be more likely to have a prepubertal onset and girls a pubertal onset. The male/female ratio tends to equalize in adolescence, and there are more women with OCD in adulthood than there are men [4]. Those individuals who have early onset OCD have a higher rate of tic disorders and may have a higher rate of comorbid attention deficit hyperactivity disorder (ADHD) [5]. In the children with the OCD-ADHD-tic disorder triad, the onset of the tic disorder may precede the onset of the OCD by several years [6], [7], [8]. It is hypothesized that the early onset OCD may represent a unique subtype. Family studies suggest that the children who have an early onset of OCD (before 9 years of age) have a higher rate of first-degree relatives with OCD or a tic disorder (eg, have a higher “genetic loading”) than those with later onset [9].

Despite a specific core set of OC symptoms, systematic phenomenologic studies have found significant heterogeneity among children and adolescents with OCD; for example, the onset may be abrupt or insidious and may or may not be related to a clear precipitant. In a large phenomenologic study, one third of the children and adolescents reported that certain stimuli seemed to trigger their illness [7]. Pediatric OCD may follow a waxing and waning course, a chronic stable course, or may be characterized by dramatic exacerbations and remissions [6], [7], [10], [11], [12]. Current research is studyding whether the course of illness (chronic with some fluctuations versus abrupt severe exacerbations with remission) will prove meaningful as a means of categorizing subtypes.

Most early attempts to develop subtypes of OCD were based on the specific content of the obsessions and compulsions experienced by a patient. An important core of consistent symptom presentation appears to extend across both the life span and cultures [11], [12]. However, as with adults, 90% of children in the National Institutes of Mental Health (NIMH) study reported that their obsessions and compulsions changed in both content and severity over time [3], [7]. Thus, it appears unlikely that consideration of the content of obsessions of compulsions alone will lead to an identification of specific disorder subtypes.

Several studies have reported that compared with those subjects without tics, OCD patients with a comorbid tic disorder may have a greater incidence of symmetry, exactness, and aggressive obsessions as well as touching, rubbing, staring, and blinking rituals, whereas contamination worries and cleaning compulsions were reported to be more common in patients with non-tic related OCD [13], [14]. These two putative subtypes also may differ in other important respects; compared with OCD without tics, tic-associated OCD may be more familial and more common in boys and early onset cases.

Increasing evidence suggests that early or prepubertal onset OCD is a unique subtype of the disorder. Proposed subtypes, which are neither necessarily mutually exclusive nor distinct, include early onset OCD, tic-related OCD, and streptococcal-precipitated OCD. Patients with an onset of OCD before age 9 are more likely to have a

subtype that is familial and related to tic disorders [9]. Patients with OCD and a comorbid tic disorder may be more likely to have compulsions with more sensory phenomena and may need to perform the compulsions until they are “just right” [15]. Early onset OCD is associated with male preponderance, comorbidity with ADHD and other disorders, frequent absence of insight, and increased family loading for OCD [5]. The age at onset may help to identify developmental subtypes [16].

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

A subgroup of children with a pediatric onset of either OCD or a tic disorder has been described as having pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). These children have an abrupt onset of symptoms after a group A β-hemolytic streptococcal (GABHS) infection, and their course of illness is characterized by dramatic, acute worsening of symptoms with periods of remission. Only recently, with parallel studies of Sydenham's chorea [7], [17], [18], was this subgroup noted to have an onset of symptoms after GABHS infection [18].

The PANDAS subgroup is defined by five clinical characteristics: (1) the presence of OCD or a tic disorder; (2) a prepubertal symptom onset; (3) a dramatic onset and acute exacerbations with an episodic course of symptom severity; (4) temporal association between symptom exacerbations and GABHS infections; and (5) associated neurologic abnormalities (eg, choreiform movements) [2]. Fifty children meeting these criteria were systematically evaluated at the NIMH [2]. Identifying this subtype is important because they require a different assessment and treatment. In a child who has an acute onset of OCD or tics or has had a dramatic deterioration, medical illnesses (including seemingly benign upper respiratory infections) in the months prior should be considered carefully. Obtaining a throat culture, an antistreptolysin O titer, and anti-DNase B streptococcal titer may help to diagnose such an infection, even in the absence of clinical symptoms of pharyngitis [2], [19]. The most obvious presentation to a pediatric or primary care office may be separation anxiety, worry, or increased urinary frequency [19]. For a recent review of the PANDAS subtype, the reader is referred to a study by Snider and Swedo [20].

Associated disorders

Patients with Tourette's disorder may have OCD or associated obsessive-compulsive symptoms [21], [22], [23], [24]. In clinical practice, it is sometimes difficult to categorize a behavior as a ritual or a tic. Generally, if an action is preceded by a specific cognition, then it is considered to be a compulsive ritual; however, some complex motor tics may be preceded by a sensation or “urge.” It may be impossible to distinguish a complex motor tic from a compulsive ritual, especially in patients with both OCD and Tourette's disorder. However, it is important to attempt to make the distinction, because they are treated differently.

The assessment of comorbidity is crucial for effective treatment planning, because other diagnoses are common in children and adolescents with OCD [5], [7]. In the 70 consecutive children with OCD studied at the NIMH, comorbidity was common, with 18 children (26%) having no other psychiatric diagnosis [7], [12]. Geller and colleagues [5] studied 30 consecutively referred pediatric OCD patients and found higher rates of comorbidity, with only one patient (3%) having no other diagnosis. Diagnoses shown to commonly co-occur with OCD include major depression and other mood disorders, multiple anxiety disorders, tic disorders, and disruptive behavior

disorders, particularly attention-deficit hyperactivity disorder and oppositional defiant disorder; of these, only tic disorders are believed to have a shared genetic origin with OCD [9], [24], and the relationship with ADHD merits further study [5], [25]. Thus, comorbidity in OCD is common and frequently requires its own diagnostic and treatment interventions.

Differential diagnosis

When evaluating a child with recurrent thoughts or repetitive behaviors, it is important to consider whether the symptoms are developmentally appropriate. Developmental rituals of childhood are normal at certain ages, although they may be performed in a stereotypic or rule-bound fashion. The specific contents of developmental rituals do not typically resemble OCD rituals. Additionally, OCD rituals are associated with a later age at onset and usually are more dramatic, persistent, and distressing [26], [27].

The differential diagnosis of OCD includes a number of disorders with obsessional features and “compulsive” behaviors, including depressive and anxiety disorders, eating disorders, somatoform disorders, and tic disorders. Obsessions differ in content, from the ruminations or brooding thoughts seen in major depression or dysthymia and from worries specific to everyday or real-life problems, as seen in other anxiety disorders (eg, separation anxiety disorder and specific phobia). In anorexia and bulimia, obsessive thoughts are limited to issues of food and weight. In body dysmorphic disorder, the obsessive concern is limited to an imagined flaw in one's physical appearance [28]. If the obsessions or compulsions are particularly bizarre and seen by the patient as reasonable, a diagnosis of psychosis should be considered.

Epidemiology

Estimates of the prevalence of OCD in children and adolescents have varied greatly, and most figures are probably low owing to the secrecy manifested by patients with the disorder. The Isle of Wight study [29], the first epidemiologic study, reported “mixed obsessional/anxiety disorders” in 7 of 2199 (0.3%) in a survey of 10- and 11-year-old children. In a whole-population adolescent epidemiologic study of OCD, Flament and colleagues (1988) reported a (weighted point) prevalence rate of 0.8% and a lifetime prevalence of 1.9% [30]. These figures suggest that OCD is a relatively common psychiatric disorder in adolescents. This rate is compatible with the estimated prevalence in the general population [31] and the finding that at least one third to one half of adults with OCD experienced the onset during childhood [4].

Causes

The serotonin hypothesis of OCD was initially based primarily on the effectiveness of the serotonin reuptake inhibitors in treating this disorder [32]. It is unlikely that just one neurotransmitter system can explain the complex findings in OCD. Neurobiological causes include neuroanatomical, neurophysiologic, and neuroimmunologic associations with metabolic abnormalities [33]. Several lines of research have implicated a neuroethologic model for the underlying explanation of OCD, resulting in fixed action patterns (obsessions and compulsions) that are inappropriately released [34].

Hormonal dysregulation also has been implicated as a cause of OCD. Notably, the male/female ratio for cases with an onset before the age of 10 years is 7:1, whereas subsequently it shifted to 1:1.5 after puberty. In a large epidemiologic study, the boys with OCD were shorter and had a flatter growth curve than normal and psychiatric controls, and the authors speculated that there may be a subtle neuroendocrine dysfunction in OCD [35].

There is a clear association between OCD and several basal ganglia illnesses, specifically Tourette's Syndrome (TS), postencephalitic Parkinson's disease, and Huntington's chorea [17], [32]. Swedo and colleagues [17] have hypothesized that Sydenham's chorea, an autoimmune inflammation of the basal ganglia triggered by streptococcal infection, may represent a medical model for OCD. In the 11 children studied, nine (82%) had obsessive-compulsive symptoms, which started several days to weeks before the chorea was observed. The authors suggested that the obsessive-compulsive symptoms were accompanying manifestations of Sydenham's chorea, and those symptoms required medical care in some cases. Subsequently, several studies of patients who have Sydenham's chorea have confirmed this association [20]. Further support for basal ganglia involvement comes from anatomic observations, psychosurgery, and brain imaging studies [33], [36].

Systematic studies support a genetic transmission for many OCD patients. Lenane and colleagues [37] have reported an increased rate (20%) of OCD in the first-degree relatives of 46 OCD probands. Thirty percent of the child probands had a first-degree family member with a lifetime history of OCD. When the histories of the parent and the child were examined, the specific OCD symptoms were dissimilar, suggesting that modeling or learning models did not account for this familial transmission.

Supporting a relationship between TS and OCD is the comorbidity of the disorder in affected individuals. There is an increased rate of tics in OCD probands [9], [24], [38], [39]. Systematic family studies have led Pauls and colleagues [39] to hypothesize initially that some forms of OCD may represent alternative expressions of the genes responsible for TS. Pauls and colleagues [9], [38], [39] have reported an increased rate of OCD in the first-degree relatives of TS probands over that of the control sample of adoptee relatives, regardless of the OCD status of the TS probands. Despite large ongoing genetic studies, the gene for OCD or TS has not been identified.

One of the most interesting lines of work concerns the PANDAS subgroup [2]. The cause of OCD and tics in the PANDAS subgroup is unknown but is theorized to occur as a result of post-streptococcal autoimmunity in a manner similar to that of Sydenham's chorea. The working hypothesis for the pathophysiology begins with a Group A beta-hemolytic streptococcal (GAS) infection in a susceptible host that results in the production of antibodies (to GAS), which cross-react with the cellular components of the basal ganglia. The neuropsychiatric symptoms are hypothesized to arise from an interaction of these antibodies with neurons of the basal ganglia. Studies are underway to determine the specific parts of the basal ganglia that may be involved, as well as the cellular and humoral immune responses [20].

Treatment

Psychosocial treatments: behavioral therapy

Cognitive-behavioral treatments (CBT) are used clinically with much success in children with OCD, although its efficacy had been based predominantly on adult treatment studies and open trials [40], until the large Pediatric

OCD Treatment Study (POTS) [41] combined treatment comparison was published. Authors of the expert consensus guidelines [42] and American Academy of Child and Adolescent Psychiatry (AACAP) practice parameters for OCD [43] consider CBT, specifically exposure with response prevention (ERP), an important intervention, and recommend starting with CBT or CBT plus selective serotonin reuptake inhibitors (SSRI), depending on the severity and comorbidity.

Exposure-based behavioral interventions came from the theoretical framework of instrumental condition, and the cognitive interventions are both used in OCD treatment [44]. ERP involves therapist-assisted in vivo exposure to feared situations, imaginal exposure to feared disasters, and instructions to refrain from rituals and avoidance behaviors. For the exposure exercises to be successful, the patient must have the information that corrects the distortion of the cognition (eg, that a situation is dangerous if its safety cannot be proven). Adjunctive interventions, including family involvement in treatment, anxiety management, training, cognitive restructuring, contingency management, and supportive therapy may enhance the efficacy of ERP through increasing treatment compliance and motivation [45].

A review of uncontrolled CBT treatment trials to that date report that the majority of patients were responders, with a mean Child Yale-Brown OC Scale (CY-BOCS) decrease from 50% to 67%. A consistent problem that complicates the interpretation of the findings of many of the uncontrolled studies is that some patients were receiving SSRI before and during the course of CBT, and therefore the separate effects of the CBT cannot be determined [46]. Additionally, there may have been ascertainment biases in enrolling patients and families, with those who were motivated for behavior therapy treatment.

March and colleagues [47] have reported on the manualized, structured CBT open protocol in 15 youth ages 8 to 18 years old. There were significant differences from pre- to post-treatment, with a mean reduction in symptom severity of approximately 50%. Sixty-seven of the patients showed more than 50% symptom improvement (which was maintained at follow-up). Only 20% were nonresponders. At the end of treatment, 40% of patients were rated as asymptomatic, and 60% of patients were rated as asymptomatic at follow-up. Forty percent of the sample was able to discontinue medication with booster sessions. This work led to a manual for children and adolescents with OCD (8–17 years old) [48], consisting of 14 visits over 12 weeks, spread out over five phases: psychoeducation, cognitive training, mapping OCD, exposure and response prevention, and relapse prevention and generalization training. Other investigators have applied similar models using gradual exposure, as reviewed by Piacentini [45]. The manual by March and Mulle [48] used in the POTS study [41] and those results are detailed below under combined treatments.

Pilot studies that have included a follow-up evaluation [47], [49] support the durability of CBT, with therapeutic gains maintained for up to 9 months post-treatment. The consistent impression in the field is that CBT may provide larger and more long lasting symptom improvement than that seen with medication.

Psychosocial treatment: other psychotherapeutic modalities

Behavioral family intervention

Cognitive, developmental, and symptom differences, and most specifically the “embeddedness” in the family context play an important role in assessing and treating early onset OCD. Freeman and colleagues [50] have proposed that the family context is an important vehicle for treatment delivery, and behavioral family intervention (BFI) is an important paradigm in the treatment of childhood disorders [51]. Behavioral family intervention involves parents, teachers, and significant others as "behavior change agents” or “mediators.” By dealing with the affective and cognitive aspects of the parent-child relationship as well as the targets of intervention, BFI is likened to a “cognitive-behavioral family intervention." Freeman and colleagues [50] have developed a BFI manualized treatment for children and their families with OCD, and initial pilot results seem promising. This suggests that a different conceptual approach is needed for younger children and that treatment designed for older children cannot be just extrapolated downward. A 12-week controlled study comparing BFI to relaxation therapy is ongoing.

Family therapy

An assessment of the family usually is a necessary component of an evaluation of an adolescent with OCD [52]. By dealing with the specific family dynamic issues and their resulting obstacles to engage in treatment, the family can participate in the OCD treatment plan of the identified patient in constructive and positive ways. Although there are no systematic studies of family therapy, family therapy may be useful to address issues of family discord, marital difficulties, and inappropriate roles or boundaries, which interfere with the adolescent's ability to participate in treatment for his or her OCD [52].

Dynamically oriented individual therapy

Jenike [53] has reviewed the psychotherapeutic interventions for OCD and concluded that the “traditional psychodynamic psychotherapy is not an effective treatment for obsessions or rituals in patients meeting criteria for OCD as defined in the DSM-III-R; there are no reports in the modern psychiatric literature of patients who stopped ritualizing when treated with this method alone.” However, psychodynamic psychotherapy may play an adjunctive role in addressing both general and specific issues in the patient's life, such as how OCD affects the individual's self-esteem, personal relationships and outlook, and by encouraging compliance other therapies that focus more directly on the OCD symptoms.

Pharmacologic treatment of obsessive-compulsive disorder

The systematic efficacy studies of SSRI for the treatment of pediatric OCD form the largest body of work in the pharmacotherapy of childhood psychiatric disorders, other than that of ADHD. A review of the systematic studies supports the acute efficacy of clomipramine and SSRI in the treatment of children and adolescents with OCD.

The tricyclic antidepressant, clomipramine, a SRI (with an active metabolite with noradrenergic reuptake inhibition) was the first medication to be studied systematically in children and adolescents with OCD. Three studies have supported the efficacy of clomipramine for pediatric OCD [54], [55], [56]. Flament and colleagues [55] have reported that in 23 youths in a 10-week double blind, placebo-controlled crossover study, clomipramine (in doses of 3 mg/kg) was significantly more effective than placebo in decreasing OCD symptoms

at week 5. In an 8-week multicenter double blind parallel comparison, DeVeaugh-Geiss and colleagues [54] reported that clomipramine was superior to placebo for the treatment of OCD in youth. This study led to the first Food and Drug Administration (FDA) approval of a SRI in pediatric OCD (children aged 10 years and older). Clomipramine was found to be generally well tolerated and has an anticholinergic-adverse effects profile. Periodic EKGs are obtained during ongoing clinical care because of concerns about tachycardia and prolongation of the QTc interval.

To address whether the serotonergic specificity of clomipramine was critical, a double blind crossover comparison of clomipramine versus desipramine (a selective noradrenergic reuptake inhibitor without serotonergic activity) was completed in 48 children and adolescents with OCD [56]. In this 12-week double blind design, clomipramine (targeting 3 mg/kg/day and not exceeding 5 mg/kg/day) was significantly better than desipramine in decreasing the OCD symptoms at week 5. This study concluded that the serotonergic reuptake inhibition may be critical.

The SSRI (which include citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) has emerged as the first-line pharmacotherapeutic agent for OCD. SSRIs have the advantage over clomipramine of having a generally more tolerable side effect profile (with few anticholinergic effects), a safer profile in overdoses, and do not require EKG monitoring. The expert consensus guidelines authors [42] suggest that clomipramine be used when a patient has failed two or three adequate trials of a SSRI in combination with CBT. A meta-analysis of systematic studies in pediatric OCD has reported that clomipramine was significantly superior to each of the SSRIs but that the SSRIs were comparably effective [57].

Systematic efficacy studies have shown that fluoxetine, fluvoxamine, and sertraline were each superior to placebo for children and adolescents with OCD [16], [41], [58], [59], [60]. Open studies support the use of citalopram and paroxetine. [61], [62]. Sertraline has FDA-approved indication for the treatment of OCD in children ages 6 years and older; fluvoxamine is approved for children ages 8 years and older; and fluoxetine is approved for children 8 years and older.

March and colleagues [59] have reported on 187 children and adolescents (ages 6 to 17 years of age) with OCD studied in a randomized double blind placebo-controlled 8-week trial of sertraline (forced titration to 200 mg/day) versus placebo. Patients receiving sertraline compared with those receiving placebo showed significantly greater improvement on the CY-BOCS, the NIMH Obsessive Compulsive Scale, and the Clinical Global Improvement (CGI) scale. Significant differences (with intent-to-treat analyses) between the two groups were seen as early as week 3 and continued for the entire study. Similarly, in the POTS [41] four-arm 12-week combined treatment study, sertraline was superior to placebo.

Riddle and colleagues [60] have reported the safety and efficacy of fluvoxamine for 120 youth (ages 8 to 17 years old) with OCD in a randomized, controlled study in which they received either fluvoxamine (50–200 mg/day) or placebo for 10 weeks. Patients in the fluvoxamine group showed a significant improvement (on CY-BOCS) in comparison with the placebo group. In the fluvoxamine group, 42% of patients were responders (defined as a 25% decrease in CY-BOCS) in comparison with 26% in the placebo group, and this was significantly different.

Geller and colleagues [16] randomized 103 youth with OCD to either fluoxetine (starting at 10 mg/day) or placebo for 8 weeks. Intent-to-treat analyses reported that those in the fluoxetine group had significantly better improvement on CY-BOCs than did the placebo group. Fluoxetine (20–60 mg/day) was effective and well tolerated in the pediatric group. In the other systematic study of fluoxetine, Liebowitz and colleagues [58] randomized 43 patients to either fluoxetine or placebo for 8 weeks. Responders then went into an 8-week maintenance phase. The fluoxetine dosage was fixed at 60 mg/day for 6 weeks and then could be increased to 80 mg/day. At week 8, fluoxetine was not significantly better than placebo on the CY-BOCs or CGI-I scale; authors attributed this to either low power or short duration of treatment. The fluoxetine group continued to improve during the maintenance phase such that at week 16, 57% of the fluoxetine patients compared with 27% of the placebo patients (using data at week 8) were much or very much improved. The authors conclude that fluoxetine's effect took more than 8 weeks to develop.

A review of adverse effects of the SSRIs suggests that dropouts from blinded active medication assignment usually are less than 13%, and in many studies, there are no significant differences between the number of dropouts in the active and placebo arm [46]. Generally, the most common side effects seen with the SSRIs include sedation, nausea, diarrhea, insomnia, anorexia, tremor, sexual dysfunction, and hyperstimulation [46], [60]. Rare adverse reactions include apathy syndrome, serotonin syndrome, extrapyramidal symptoms, and hypomania. Children and adolescents may be more vulnerable to agitation or activation while receiving SSRIs than adults are, but this reaction has only recently received study. The FDA concluded that children and adolescents on antidepressants may potentially develop suicidality, worsening of symptoms, anxiety, agitation, panic, insomnia, irritability, hostility, impulsivity, akathisia, and hypomania. In late 2004, the FDA added a “black box” warning to describe the potential increased risk of suicidality in children and adolescents who are given antidepressants. The FDA has recommended that children and adolescents be assessed frequently while receiving SSRI, to watch for an emerging worsening of symptoms or “activation.”

How much do pediatric patients improve with pharmacotherapy alone? In general, a 30% to 40% reduction in OCD symptoms, which corresponds to an average six-point decrease on the CY-BOCS, is reported in the medication treatment group in the SSRI controlled studies [46]. A meta-analysis (of 12 studies with 1044 subjects) has reported the pooled standardized mean difference for results of all medication studies was 0.46 and showed a significant difference between drug and placebo treatment. Although significant, the overall effect sizes for medication were modest [57]. This, coupled with increasing scrutiny of the safety of the SSRIs, has led to further interest in CBT for the treatment of OCD.

The limited durability of pharmacotherapy, which often is seen clinically, has not been well studied. A double blind study of desipramine substitution in adolescents receiving long-term clomipramine maintenance reported that eight of nine patients relapsed when they were switched to desipramine, compared with two of 11 who continued taking clomipramine [63]. It is likely that medications have less durability than CBT, but until follow-up data are analyzed (for example from the POTS [41]), this is not well delineated. Interestingly, Cook and colleagues [64] have reported that in a long-term open treatment with sertraline (52-week extension study after a 12-week double blind trial) was effective and that improvement continued to be seen in the long term, although concomitant psychotherapy was allowed.

Although the number of studies on medication augmentation for partial responders to SSRIs are few, at this point, CBT would be the first choice for an "augmenting agent." There is a three-site systematic trial studying partial responders to SSRIs who are randomized to different doses of CBT [65], but in the absence of such data, the general clinical consensus is that CBT should be considered. Unfortunately, the availability of trained therapists is sometimes limited, and some children are too sick or not motivated to participate. In considering medication augmentation, the adult studies support the trial of neuroleptic augmentation in SRI nonresponders or partial responders [66]. In a controlled risperidone versus placebo SRI augmentation study, risperidone addition was superior in reducing OCD symptoms. With increasing concerns about weight gain and increased risk of a metabolic syndrome, the atypical neuroleptics are being used more judiciously.

Combined treatments

The expert consensus guidelines [42] and the AACAP practice parameters for children who have OCD [43] recommend starting treatment with CBT or CBT plus an SSRI, depending on severity and comorbidity. Both guidelines recommend that patients started on SSRI monotherapy, who are partial responders, should have a trial of CBT.

The relative efficacy of medication, of CBT, and the combination have just been studied in a large randomized controlled trial [41]. One hundred and twelve patients, aged 7 through 17 years with a primary diagnosis of OCD were randomized to sertraline alone, pill placebo, CBT alone, or combined CBT and sertraline. Ninety-seven (87%) of the patients completed the full 12-week study. Predetermined primary outcome variables included change in CY-BOCS over 12 weeks (continuous) and remission status (dichotomous) (the responder being defined as a CY-BOCS of 10 or less). All three active treatments were each superior to placebo. Combined treatment (P=.001), CBT alone (P=.003), and sertraline alone (P=.007) proved statistically superior to placebo. Importantly, combined treatment proved superior to CBT alone (P=.008) and to sertraline alone (P=.006). Of note, CBT alone and sertraline alone did not differ significantly from one another. The remission rate (dichotomous variable) for combined treatment did not differ from that for CBT alone, but it did differ from sertraline alone and from placebo. The effect size for combined treatment, CBT alone, and sertraline alone were 1.4, 0.97, and 0.67, respectively. Sertraline was generally well tolerated, with adverse effects in at least 5% of patients treated and with an incidence at least two times that seen in patients treated with placebo. Two patients treated with sertraline experienced behavioral activation, but no patient became suicidal or attempted suicide. Patients treated with CBT, either alone or in combination with medication, showed a substantially higher probability of improvement, with the edge going to combination treatment over CBT alone at one site but not in the other. The authors conclude that children with OCD should begin treatment with the combination of CBT plus a SSRI or CBT alone.

Investigational treatments

Hypotheses concerning whether Sydenham's Chorea (SC) and PANDAS might share similarities in their pathophysiology led to the question whether penicillin prophylaxis would reduce neuropsychiatric symptom exacerbation in children with PANDAS by preventing streptococcal infection. An 8-month double blind placebo-controlled crossover trial comparing oral penicillin V (250-mg, twice daily) and placebo was conducted in 37

children [67]. There was no significant between-phase difference in either the OCD or tic symptom severity; however, penicillin administration failed to provide adequate prophylaxis against GABHS (as evidenced by the fact that 14 of 35 GABHS infections occurred during the penicillin phase). A number of children received antibiotic treatment multiple times during the placebo phase. The authors concluded that because of the failure to achieve an acceptable level of streptococcal prophylaxis, no conclusions could be drawn regarding the efficacy of penicillin prophylaxis in preventing tic or OCD symptom exacerbation.

In a subsequent study, the NIMH group compared antibiotic prophylaxis with azithromycin (250 mg, twice daily, once per week, with placebo administered twice daily on the other 6 days) or penicillin V-K (250 mg, twice daily) for 12 months [68]. Twenty three children with PANDAS were enrolled in this double blind randomized, controlled trial. Rates of streptococcal infections and neuropsychiatric symptom exacerbations were compared between the study year and the baseline year before entry (collected retrospectively). Significant decreases in streptococcal infections during the study year were found, with a mean of 0.1 infections per subject compared with the baseline year, with 1.9 infections in the penicillin group and 2.4 infections in the azithromycin group ($P \leq .01$). Significant decreases in neuropsychiatric exacerbations during the study year were also found, with a mean of 0.5 exacerbations per subject in the penicillin group and 0.8 exacerbations in the azithromycin group, compared with the baseline year, with 2.0 exacerbations in the penicillin group and 1.8 exacerbations in the azithromycin group ($P \leq .01$). The authors concluded that penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbation in the PANDAS subgroup. The authors caution that there was a small sample size and lack of placebo control and that other evidence suggests that azithromycin prophylaxis should not be routinely recommended for PANDAS children (eg, macrolide-resistant *Streptococci*). Penicillin prophylaxis may be considered for children who meet all criteria for PANDAS criteria and who have an ongoing risk of streptococcal exposure.

If post-streptococcal autoimmunity is the cause of the exacerbations in this subgroup, then children with PANDAS may benefit from immunomodulatory therapies that have been shown in preliminary findings to treat symptoms of SC. Children with severe infection-triggered exacerbations of OCD or tic disorders were randomly assigned to plasma exchange (five single-volume exchanges over 2 weeks), intravenous immunoglobulin (IVIG) (1 g/kg, daily on 2 consecutive days), or placebo (saline solution given in the same manner as IVIG) [69]. Plasma exchange and IVIG were both effective in lessening of symptom severity for this group of children. Ratings were completed at 1 month, and symptom gains were maintained at 1 year. It should be noted that these children were much more significantly impaired than the average child with OCD or tics was, and therefore, these invasive interventions were considered. These interventions are investigational and should be considered in the context of research approved by a Human Investigations Committee and not in the context of routine clinical care.

Prognosis

Long-term outcome data have been limited by a few large systematic studies. A meta-analysis of sixteen samples followed for 1 to 15 years have reported that long-term persistence of pediatric OCD may be lower than reported previously [70]. Pooled mean persistence rates were 41% for full OCD and 60% for full or subthreshold OCD. Earlier age of onset, increased OCD duration, and inpatient (versus outpatient) status predicted greater persistence. Comorbid psychiatric illness and poor initial treatment response were poor prognostic factors.

The long-term medication studies, which are confounded by intercurrent treatment and by dropouts, suggest modest incremental improvement but not normalization over 52 weeks of SRI treatment [64]. The relapse rate after SSRI discontinuation has not been reported systematically but is suspected to be high. One assumes that with the development of new treatments (SSRIs and CBT) that more children will be able to access treatment earlier and are more likely to improve. As to whether this will improve long-term outcome remains to be studied.

Research questions

The PANDAS subtype remains one of the most interesting areas of research study. If children with this subtype could be identified early in their illness, would they have a different course or outcome? Genetic vulnerabilities as well as the identification of immune processes remain open and important areas of study.

One of the critical, unanswered questions is the long-term relative efficacy and durability of a SSRI, CBT, and their use in combination. The POTS [41] has provided important relative efficacy for the short-term treatment. What are the predictors for response for each of the different modalities? It has been reported that the availability of these two treatment modalities will improve the long-term prognosis, but a long-term comparison is required.