A neuropsychiatric review of pediatric obsessive-compulsive disorder: etiology and efficacious treatments

Adam B Lewin
Eric A Storch
Gary R Geffken
Wayne K Goodman
Tanya K Murphy

Department of Psychiatry, University of Florida, Gainesville, FL, USA

Abstract: Pediatric obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric condition associated with broad impairments in functioning. This paper outlines current etiological theories of OCD, providing a review of neuroanatomical, neurochemical, neuroimmunological, and cognitive–behavioral explanations. Subsequently, first-line treatment modalities are discussed (serotonin reuptake inhibitors [SRIs] and cognitive–behavioral therapy [CBT] with exposure and response prevention [E/RP]) in the context of recent pharmacological, CBT, and combined trials.

Keywords: OCD, pediatric, etiology, treatment, serotonin reuptake inhibitors, cognitive behavioral therapy

Pediatric obsessive-compulsive disorder (OCD) is an impairing neurobehavioral disorder that is generally highly responsive to treatment. OCD is associated with frontal-subcortical dysfunction, specifically in the cortical-striatal-thalamo-cortical (CSTC) loops that integrate motoric and cognitive functioning. One of the most common childhood psychiatric illnesses (Stewart et al 2004), data from recent epidemiological studies suggest that lifetime prevalence rates of OCD among pediatric populations range between 1% and 4% (Flament et al 1988; Douglass et al 1995; Zohar 1999). Recent estimates suggest that 50%–80% of cases have a childhood onset (Millet et al 2004). Although OCD is less common in younger children, dramatic increases in prevalence occur during adolescence (Heyman et al 2001), with a bimodal age of onset distribution, the initial peak incidence occurring prepuberty and the second in early adulthood (Pauls et al 1995). There is a male predominance (3:2, male:female ratio; Geller 1998) and earlier age of onset for males (Swedo et al 1989a). Recent data suggest high rates of comorbid mood, anxiety, attention–disruptive behavior (eg, attention deficit hyperactivity disorder [ADHD], oppositional defiant disorder [ODD]), and tic disorders (Geller et al 2003a; POTS 2004).

OCD is characterized by the presence of obsessions (persistent and intrusive thoughts, ideas, impulses, or images that result in anxiety) and/or compulsions (repetitive or ritualistic behaviors or mental acts that reduce or prevent anxiety in response to the obsessive thought) that cause distress, are time-consuming, or interfere with age-appropriate functioning (APA 2000). Expression of OCD in youth is similar to that in adulthood, with the exception that children are not required to view their OCD symptoms as bizarre and unrealistic. Notably, children may not even view their symptoms as unpleasant (AACAP 1998; Geffken et al 2005). Obsessions and compulsions are generally linked; compulsions function as behavioral or mental actions that serve to reduce anxiety elicited by obsessions. Common obsessions and compulsions in children include worries about harm to self or others, fears of

Correspondence: Eric A Storch
Department of Psychiatry, University of Florida, Box 100234, Gainesville, FL 32610, USA
Tel +1 352 392 3611
Fax +1 352 846 1455
Email estorch@psychiatry.ufl.edu.

contamination, the need for exactness and order, and religious–moralistic concerns (Swedo et al 1989a). Common compulsions–rituals include washing–decontamination rituals (excessive hand washing, showering, or bathing), confessing, checking–reassurance-seeking, ordering–arranging, praying, and avoidance.

Etiology

Prior to discussing efficacious treatments, a review of neuroanatomical (structural and functional), biochemical, autoimmune–neuroimmunological, and cognitive–behavioral etiologies of OCD are presented to provide the correspondence of these mechanisms to the pathophysiology of OCD and treatment modalities. To date, data suggest that abnormal brain serotonin metabolism is a key factor in OCD: serotonin is believed to mediate the expression of OCD symptoms. Research also suggests that disturbance in the frontal-limbic (thalamic)-basal ganglia system, areas of the brain associated with procedural learning and implicit memory, may relate to OCD symptoms. (The basal ganglia include the striatum [which includes the caudate nucleus, putamen, and nucleus accumbens].) It is believed that overactivity in the orbito-prefrontal cortex may lead to fastidiousness, excessive concerns, and meticulousness (Rauch et al 1998). Further, disruption to the head of the caudate nucleus may impair filtering of information entering the frontal cortex (Kozak and Foa 1997). Overall, it is believed that in patients with OCD, there is disruption to the system that (1) filters information (eg, intrusive thoughts) from reaching the consciousness and (2) mediates stereotyped–automated behaviors (Rauch et al 1998). The following section provides a review in greater detail.

Neuroanatomical

The neurobiology of OCD is associated with abnormalities in components of the frontal-subcortical circuitry. These circuits are believed to link the cortex to areas of the brain involved in the initiation of behavioral responses that are implemented with minimal conscious attentiveness (Saxena et al 2001). Moreover, these corticostriatal systems filter preconscious cognitions and mediate stereotyped behaviors – dysfunction or overactivity of these systems may explain intrusive cognitions and ritualized behaviors associated with OCD (Rauch et al 1998). More specifically, feedback loops involving orbitofrontal cortex, striatum, thalamus, and the basal ganglia (ie, the CSTC circuit) may mediate intrusive thoughts and repetitive behaviors (Saxena et al 1998; Szeszko et al 2004). Disruption of this feedback system may lead to symptoms consistent with OCD. Structural imaging studies lend support for this neurobiological model. For example, data from volumetric magnetic resonance imaging (MRI) suggested that patients with OCD had smaller globus pallidus volumes than normal controls and increased anterior cingulate gyrus gray matter (Szeszko et al 2004). Rosenberg and Keshavan (1998) also found increased volume of the anterior cingulate gyrus among pediatric OCD patients. Thalamic volumes have been identified to be larger among pediatric patients with OCD relative to controls (Gilbert et al 2000). Kim et al (2001) identified increased gray matter densities in both the cortex and subcortical areas of adult patients with OCD, especially the left orbitofrontal cortex. This finding suggesting that this region's role in inhibitory motor control may be linked to patients with OCD having difficulties resisting rituals (Kim et al 2001).

Functional neuroimaging techniques have also been utilized and have implicated the cortical-striatal pathway (consisting of the orbitofrontal cortex and the caudate nucleus) in the pathogenesis of OCD (Rauch and Baxter 1998). Functional MRI (fMRI) has implicated hyperactivity in the anterior cingulate cortex with symptoms consistent with OCD (eg, overmonitoring of one's actions and behaviors; Ursa et al 2003). Further, Kim et al (2001) suggested that hyperfunctioning of these circuits may increase gray matter density observed in volumetric studies. This is consistent with functional neuroimaging studies using positron emission tomography (PET) (Swedo et al 1989b; McGuire et al 1994; Rauch et al 1994). However, increased glucose metabolism identified in the globus pallidus, caudate nucleus, and putamen may be inconsistent with volumetric studies showing reduced volume of these structures (Kim et al 2001). Giedd et al (2000) reported increased volume of the basal ganglia (eg, caudate, putamen, and globus pallidus). Overall, a recent meta-analysis of functional neuroimaging identified that differences in the left orbitogyrus and in the right head of the caudate were the most consistent markers in distinguishing patients with OCD from controls (Whiteside et al 2004).

Biochemical

Neurochemical models complement neurobiological findings from imaging studies implicating serotonin in the expression of symptoms (Gilbert et al 2000). Although primary support for neurochemical models of OCD are by the efficacy of serotonin reuptake inhibitors (SRIs) (see Flament and Bisserbe 1997; Grados et al 1999; Dougherty et al 2002), they must be taken in the context of

neuroanatomical data (Rauch et al 1998). Specifically, serotonergic medications modulate serotonin neurotransmission within the frontal cortex–thalamocortical circuits in a way that could explain their therapeutic effectiveness as antiobsessional (Baxter et al 1996; Rauch et al 1998). For example, Baxter et al (1992) found (using PET) decreased thalamic glucose metabolism in adult patients with OCD after selective serotonin reuptake inhibitor (SSRI) treatment with fluoxetine. In patients with pediatric-onset OCD, PET revealed a significant decrease in orbitofrontal regional cerebral glucose metabolism following SRI therapy with either clomipramine or fluoxetine (Swedo et al 1992). The decreased orbitofrontal glucose metabolism was associated with reductions of OCD symptoms (Swedo et al 1992). Volumetric MRI studies have identified decreased thalamic volumes among pediatric patients with OCD following treatment with paroxetine (Gilbert et al 2000).

However, Zohar et al (2000) suggested that the serotonergic hypothesis is not sufficient in explaining the biochemistry of OCD. Evidence suggests that the dopaminergic system may also be involved in the pathophysiology of OCD (Goodman et al 1990). For example, differences in the dopaminergic system in the caudate and putamen have been identified in patients with OCD (Denys et al 2004; van der Wee et al 2004). These studies suggest the role of the neurotransmitter dopamine in the pathogenesis of OCD. The glutamatergic system has also been linked to OCD. Recent research in adolescents with OCD identified significantly reduced glutamate concentrations in the anterior cingulate compared with that in healthy controls (Rosenberg et al 2004).

PANDAS and neuroimmunological–autoimmune etiologies

Autoimmune factors have also been implicated in the pathogenesis of pediatric OCD. Swedo et al. (1998) coined the term Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus (PANDAS) – a malfunction in the immune system associated with the onset and progression of neuropsychiatric disorders such as OCD and Tourette's disorder. Historic and recent literature suggests that pediatric OCD is more prevalent among patients with Sydenham's chorea (SC) that occurs secondary to an autoimmune reaction to Group A β-hemolytic streptococcus (GAS). This autoimmune response to GAS cross-reacts with epitopes (sites on an antigen that interact with specific antibodies) on the basal ganglia, resulting in motor and behavioral disturbances (Bronze and Dale 1993). Moreover, Swedo (1994) reported that a subset of patients with pediatric OCD presented with several characteristics of SC but lacked choreiform movements and other central manifestations of rheumatic fever. Diagnostic criteria for PANDAS include: (1) the presence of OCD and/or a tic disorder; (2) prepubertal onset of these symptoms (age 3 years to puberty); (3) episodic–sawtooth course of symptom severity or abrupt onset; (4) an association with GAS (eg, a history of rheumatic fever, positive streptococcus throat culture); and (5) neurological abnormalities such as motoric hyperactivity or adventitious movements (Swedo et al 1998).

It is believed that the autoimmune response to GAS in PANDAS results in inflammation of the basal ganglia that is similar to the mechanism in SC (Leonard and Swedo 2001; Murphy et al 2004). Studies have found increased antineuronal antibody binding to basal ganglia tissue in SC patients that correlate with symptom severity (Husby et al 1976; Kotby et al 1998). Patients with a propensity to produce high levels of proinflammatory cytokines in response to GAS may exhibit more severe clinical manifestations (ie, more intense OCD or tic disorder symptoms) (Leckman et al 2005). Further, new research supports antibody-mediated neuronal cell signaling in the pathogenesis of SC (Kirvan et al 2003). Potential mechanisms by which autoantibodies cause clinical manifestations in PANDAS include direct stimulation or blockade of receptors in the basal ganglia, or immune complexes promoting inflammation of these brain regions; studies have found that increased antineuronal antibody binding to basal ganglia tissue in SC patients correlates well with symptom severity (Husby et al 1976; Kotby et al 1998). Overall, the acquired basal ganglia dysfunction following the GAS autoimmune reaction may result in neuropsychiatric and behavioral symptoms consistent with pediatric OCD including: chorea, tics, obsessions, compulsions, and hyperactivity (Kurlan and Kaplan 2004). In addition to PANDAS, there are other noteworthy variants of pediatric OCD. For example, OCD with a strong family aggregation of Tourette's disorder may constitute an alternative expression of the familial OCD phenotype (Grados et al 2001). Research suggests putative differences in pathophysiology between the patients with OCD and Tourette's disorder compared with patients with OCD without Tourette's (eg, in addition to the serotonergic neurotransmitter system, dopamine and endogenous opioids have been implicated in patients with OCD and Tourette's disorder (Petter et al 1998). Neuroimaging studies suggest

the role of the corticostriatal circuits in these patients (Coffey et al 1998).

Cognitive–behavioral

Behavioral accounts of the etiology of OCD are based on two stages (Mowrer 1939, 1960): (1) acquisition of fear and avoidance via classical conditioning, and (2) maintenance via operant conditioning (Dollard and Miller 1950; Franklin and Foa 2002). First, a neutral stimulus or event becomes associated with a feared or unpleasant stimulus. By virtue of this association, the neutral stimulus becomes conditioned to elicit distress. This process can include both physical stimuli (eg, specific locations, contaminated items) and mental events (eg, dangerous thoughts; Franklin and Foa 2002). Subsequently, behaviors that function to reduce distress associated with the conditioned stimulus develop. These behaviors (ie, compulsions or rituals) are operantly maintained via a negative-reinforcement paradigm, because they temporarily ameliorate the distress associated with obsessive thoughts. Over time, these behaviors persist and become excessive; the reduction in anxiety following a compulsive behavior precipitates an increase in future reliance on compulsive behaviors.

Cognitive models are also considered central to the etiology of OCD (OCCWG 1997; Salkovskis 1999). Salkovskis (1999) posits that *appraisals* of intrusive thoughts, images, and impulses, rather than their occurrences, characterize OCD. For example, obsessional patterns develop if intrusive thoughts are interpreted to indicate responsibility for causing (or failing to prevent) harm to self or others. In general, obsessions can be inductively reduced to six intrusive belief patterns commonly misappraised among patients with OCD: (1) exaggerated sense of responsibility; (2) overvalued importance of thoughts; (3) inflated concern about the importance of controlling one's thoughts; (4) overestimation of threat; (5) intolerance of ambiguity–uncertainty; and (6) perfectionism (OCCWG 1997). Salkovskis (1999) suggested a circular pattern of intrusive thoughts→ misappraisals→distress-neutralizing behaviors→increased intrusive thoughts. In other words, patients with OCD attempt to neutralize intrusive thoughts (eg, a misperceived threat or responsibility) via motor or cognitive rituals, avoidance, and reassurance-seeking behavior. This prevents the disconfirmation of the patient's fears and facilitates proliferation of the anxiety – future cognitive intrusions are more likely followed by continued misappraisal.

Evidence for neurobiological changes following cognitive–behavioral interventions is inconclusive. For example, studies have identified metabolic changes in the thalamus and the caudate nucleus following cognitive–behavioral therapy (CBT) in adult patients with OCD (Baxter et al 1992). Contradictory findings were reported in another study in children with OCD following a 12-week course of CBT (Benazon et al 2003).

Although further etiological research is essential, overall, the extant neuroimaging and psychopharmacological studies combine to provide compelling support for neurobiological abnormalities in patients with OCD (Flament and Bisserbe 1997). Behavioral and cognitive etiologies are not inconsistent with these findings: individuals with neurochemical, neuroimmunological, or neurostructural abnormalities may be predisposed to behavioral conditioning. Neuroimaging studies have identified changes in the cortiostriatial system associated with both symptom provocation and following effective treatment with both SRIs and CBT (Rauch and Baxter 1998). Further, the neuropsychiatric syndrome associated with PANDAS proposes acquired dysfunction of the basal ganglia – and integral structure in the CSTC circuit (implicated in neurostructural and functional assessments). These advances in neuroimaging, neurochemistry, and neuroimmunology can elucidate the mechanisms of both OCD symptom expression and behavioral–pharmacological treatments (Breiter and Rauch 1996; Grados and Riddle 2001).

Effective interventions

The two empirically supported treatment modalities for pediatric OCD are: pharmacotherapy with an SSRI or SRI and CBT with exposure and response prevention (E/RP). CBT or CBT with concurrent pharmacotherapy using an SSRI is considered the first-line treatment for pediatric OCD (AACAP 1998; March et al 2001; Dougherty et al 2002; POTS 2004).

Pharmacotherapy

The efficacy of pharmacotherapy for OCD in pediatric populations has been demonstrated in several controlled trials with SRIs and SSRIs. The most researched SRI in the treatment of pediatric OCD is the tricyclic antidepressant (TCA) clomipramine (AACAP 1998; Grados and Riddle 2001). In a double-blind, 8-week, placebo-controlled study of clomipramine, DeVeaugh-Geiss et al (1992) found that 60% of pediatric patients showed significant improvement.

Patients treated with clomipramine reported a 37% mean reduction in OCD symptoms compared with 8% for the placebo group (as assessed using the Children's Yale-Brown Obsessive-Compulsive Scale [CYBOCS, Scahill et al 1997]). In another, 10-week controlled trial, Flament et al (1985) found a significant difference between clomipramine and placebo, 75% of pediatric patients showing at least moderate improvement. Other research found that clomipramine was superior to the noradrenergic reuptake inhibiting TCA desipramine (Leonard et al 1989). This crossover trial found that 64% of patients who initially received clomipramine during their first treatment showed relapse of OCD symptoms during desipramine treatment (Leonard et al 1989). Overall, a recent meta-analysis of pharmacotherapy trials in children identified clomipramine to be significantly superior over SSRIs in reducing OCD symptoms (Geller et al 2003b). Nevertheless, the risk profile, adverse effects, and required EKG and blood-level monitoring associated with TCAs (eg, antiadrenergic, anticholinergic, and antihistaminergic adverse effects) are of concern with clomipramine (AACAP 1998; Geller 1998; Grados et al 1999).

More recently, a multitude of placebo-controlled trials has demonstrated the efficacy of SSRIs. In a 20-week, double-blind, placebo-controlled trial of the SSRI fluoxetine in children and adolescents with OCD, 44% reductions in OCD symptoms were reported (Riddle et al 1992). A 13-week controlled trial conducted by Geller et al (2001) also demonstrated the efficacy of fluoxetine, with 55% of patients treated with fluoxetine rated as much or very much improved. Another, 16-week, placebo-controlled trial of fluoxetine in children reported that 57% of patients demonstrated significant improved ratings on the CGI (Liebowitz et al 2002). Several open trials also present favorable findings for the use of fluoxetine for pediatric OCD (see Geller 1998 for a review).

Data also support the use of the SSRI sertraline for the treatment of pediatric OCD. March et al (1998) conducted a 12-week, multicenter, randomized, placebo-controlled trial in children and adolescents with OCD. Forty-two percent of patients receiving sertraline were rated as much or very much improved. Further, in a 52-week, open-label extension of the previous study, 71% of children (ages 6–12 years) and 61% of adolescents (ages 13–18 years) demonstrated 25% decreases on the CYBOCS and were rated as much/very much improved (Cook et al 2001). More recently, another multisite, randomized, controlled trial found that 21.4% of pediatric patients entered clinical remission (defined as CYBOCS $\leq$ 10) following a 12-week course of sertraline (POTS 2004).

Finally, controlled trials have found the SSRIs fluvoxamine and paroxetine to be efficacious and well-tolerated treatments for children and adolescents with OCD. Riddle et al (2001) found that 42% of patients responded to fluvoxamine (based on a 25% reduction on the CYBOCS) while participating in a 10-week, multicenter, placebo-controlled trial. A recent 10-week, placebo-controlled trial of paroxetine for pediatric patients with OCD found that 61% of patients responded to medication (based on a 25% reduction in the CYBOCS) (Geller et al 2004). In an open-label trial of paroxetine for pediatric OCD (n = 335), 71% of patients demonstrated clinical improvement (defined by a rating of much or very much improved) (Geller et al 2003a). It is noteworthy that the response rate for patients with a diagnosis of OCD (75%) was significantly greater than for patients with comorbid psychopathology, eg, ADHD (56%), tic disorder (53%), and ODD (39%). Overall, patients with any one comorbid condition had an average response rate of 68% to paroxetine; patients with any two or three co-occurring conditions averaged 63% and 59% rates of response (Geller et al 2003a).

Overall, clinically significant reductions in OCD symptomology have been documented in children and adolescents using SSRIs, including fluoxetine, sertraline, fluvoxamine, and paroxetine, with a relatively minimal side-effect profile (compared with clomipramine). Based on these findings, SSRIs are the consensus first-line medication for pediatric OCD (Grados and Riddle 2001; Liebowitz et al 2002; Geller et al 2003b; POTS 2004). Although there are no controlled comparisons between these medications in children, research suggests that the SSRIs are equally efficacious in children and the specific choice should be based on the patient's medical history, concomitant medications, and the adverse-events profile (Snider and Swedo 2000; Geller et al 2003b). Poor clinical response to one SSRI is not necessarily predictive of failure with other SSRIs, suggesting adequate trials of multiple SSRIs may be indicated before augmentation (AACAP 1998). Significant clinical response is unlikely within the first few weeks of an SSRI – generally, 10–12 weeks at adequate dosage is necessary to fully evaluate the efficacy of the medication (AACAP 1998).

In pediatric cases that are unresponsive to CBT and trials with multiple SSRIs, second-line pharmacological treatments include augmentation (Dougherty et al 2002). Grados and Riddle (2001) discuss five augmentation

approaches for refractory pediatric OCD including: (1) typical neuroleptics (eg, haloperidol and pimozide); (2) atypical neuroleptics (eg, olanzapine, risperidone, and quetiapine); (3) lithium and buspirone; (4) clomipramine; and (5) benzodiazepines (eg, clonazepam). In the adult OCD treatment literature, numerous agents have been used in combination with SRIs for patients whose symptoms have not been reduced in monotherapy. For example, a limited number of controlled trials and case series in adults support the augmentation of SRI pharmacotherapy with either low doses of the dopamine antagonist haloperidol or the benzodiazepine clonazepam (for reviews, see Geller 1998; Dougherty et al 2002). Unlike the adult literature, however, there is a paucity of empirical data supporting augmentation strategies for pediatric OCD. Additionally, significant undesirable side-effects should be considered prior to prescribing neuroleptics and benzodiazepines in children. Two pediatric case-series suggest that SSRI augmentation with clomipramine resulted in marked improvement, but this combination requires diligent blood, EKG, and side-effect monitoring (Simeon et al 1990; Figueroa et al 1998). Lithium carbonate, buspirone, and clonidine have generally not been efficacious augmentation strategies for treatment-refractory OCD in adults (see Grados and Riddle 2001 for a review). There is preliminary support for SSRI augmentation with atypical antipsychotics for refractory OCD in adult patients. For example, an 8-week, double-blind, placebo-controlled trial was performed to determine the efficacy of risperidone augmentation in adults with treatment-resistant OCD (Hollander et al 2003). Forty percent of patients responded to augmentation with risperidone, although a small sample size limits the generalization of these findings. Two recent meta-analyses of off-label use of neuroleptics (haloperidol, risperidone, olanzapine, and quetiapine; Sareen et al 2004) and atypical neuroleptics (risperidone, olanzapine, and quetiapine; Fountoulakis et al 2004) in adults with OCD suggest that initial findings from open-trials, controlled trials, and case-series are promising despite a need for substantial further research. A recent open trial of mirtazapine in adults with OCD resulted in a 53.3% response rate (Koran et al 2005a). Preliminary data suggest the potential efficacy of opioids as alternative therapies for treatment-resistant OCD in adults using oral morphine (Koran et al 2005b) and tramadol hydrochloride (Goldsmith et al 1999). Finally, the OCD subtype etiologically related to Tourette's disorder (see above) may require combined therapy of serotonin-reuptake inhibitors plus neuroleptics or other augmentation strategies (see Miguel et al 2003 for a review).

Given recent concern regarding the safety of SSRIs in children, we will outline medications currently approved by the United States Food and Drug Administration (FDA) for pediatric use: sertraline (not under age 6 years), fluoxetine (not under 7), and fluvoxamine–paroxetine (not under 8). The TCA clomipramine is also FDA approved for children age 10 and older. On October 15 2005, the FDA issued a Black Box Warning for antidepressant medications to alert health care providers to an increased risk of suicidality (suicidal thinking and behavior) in children and adolescents being treated with these agents. In light of this warning, increased attention to symptoms of depression among pediatric patients being treated with antidepressant medications appears warranted. This should include formal assessment of suicidal ideation before and throughout the course of pharmacological treatment. This Black Box Warning may suggest a need for expedited research on other classes of medications (see above; eg, atypical neuroleptic). An additional implication of this warning may be to attempt an adequate trial of the cognitive-behavioral therapy (the other first-line treatment for pediatric OCD; see below) prior to pharmacological intervention.

Cognitive–behavioral therapy

The efficacy of CBT in children has been demonstrated in numerous open trials (March et al 1994; Franklin et al 1998; Thienemann et al 2001; Benazon et al 2002; Piacentini et al 2002) and three controlled trials (de Hann et al 1998; Barrett et al 2004; POTS 2004). Indeed, treatment response rates in the extant CBT trials was quite high, ranging from 57% to 88% (Bolton et al 1995; Franklin et al 1998; Benazon et al 2002; Piacentini et al 2002; Barrett et al 2004). Preliminary data also support the use of CBT for PANDAS (Storch et al 2004). Further, unlike pharmacotherapies (for which relapse is not uncommon when medication is discontinued) treatment gains from CBT commonly endure after therapy is completed (AACAP 1998). In contrast, CBT with E/RP for OCD is distinguished from other "talk-therapies" with no supported efficacy in the extant literature. Generally, no demonstrated effects for play-based, supportive, insight-oriented, relaxation, psychoanalytic, and psychodynamic therapies have been identified for the treatment of pediatric OCD (AACAP 1998; March and Mulle 1998; March et al 2001; Franklin and Foa 2002; Piacentini and Langley 2004). Aspects of CBT for OCD

are discussed below; treatment manuals are available for further detail, eg Lewin et al (2005); March and Mulle (1998).

Efficacious CBT protocols consist of exposure (placing the patient in situations that elicit anxiety related to their obsessions), response prevention (deterring the compulsive or ritualistic behaviors, which may serve to reduce or avoid anxiety, from occurring), and cognitive therapy (training the patient to identify and reframe anxiety-provoking cognitions) (Lewin et al 2005). Prior to beginning E/RP, education about OCD is provided to both the patient and family (often in context of a story for young children). It is explained to the patient and his/her family that compulsions–rituals–avoidance are (1) ineffective at reducing anxiety in the long term; (2) interfere with normal functioning; and (3) prevent the child from developing more effective strategies for coping with anxiety. Specifically, because compulsive behaviors–rituals actually function to reduce anxiety in the short term (and make the child feel better, albeit temporarily), these behaviors are more likely to be used the next time an obsessive thought occurs (Franklin and Foa 2002).

Also at this phase of treatment, a "fear-hierarchy" is developed. The hierarchy consists of situations the patient avoids or for which the patient would find it difficult to inhibit compensatory overt or mental rituals. The therapist assists the family and patient to develop a list of stimuli–situations that would elicit a range of symptoms from mild discomfort to incapacitating anxiety in the child (if compensatory compulsions–rituals are prevented). The child is then instructed to rate how anxiety provoking each situation would be, on a scale of 0 (no anxiety) to 100 (extreme anxiety). The hierarchy consists of situations the patient avoids or for which the patient finds it difficult to inhibit rituals. Subjective units of disturbance scales (SUDS) with a narrower range (eg, 0–10) may be more appropriate for younger children with OCD who might have difficulty selecting from a wide range. March and Mulle's (1998) fear thermometer can be helpful in establishing SUDS ratings with younger children.

Next, the therapist and child begin hierarchy-based E/RP according to stimuli identified on the patient's fear-hierarchy (typically starting at the least-distressing situation and progressing up the hierarchy during subsequent sessions). E/RP involves gradual exposure to anxiety-provoking stimuli while refraining from rituals (Meyer 1966); the procedure is based on the assumption that compulsions are performed to reduce and/or avoid anxiety associated with obsessions (ie, obsessions and compulsions are functionally related; Franklin and Foa 2002). The E/RP exercise provides the patient with objective experiences to contradict the inaccurate expectations that motivate rituals (Foa and Kozak 1996). During E/RP exercises, the *exposure* component relies on the gradual attenuation of anxiety after sufficient duration or contact with a feared stimulus (March et al 2001). Successive exposures with the feared stimulus result in both decreased elevations in anxiety and more rapid attenuation of distress. The *response-prevention* component is based on the assumption that rituals–compulsions function to reduce anxiety in the short term. However, the short-term escape–avoidance of anxiety actually maintains–increases the likelihood of compulsive behavior as well as continued distress via negative reinforcement. Therefore, individuals with OCD rely on rituals–avoidance to mitigate distress and never habituate to anxiety. Therefore, the function of E/RP is for the individual to terminate the negative reinforcement paradigm (ie, ending the compulsive behavior–avoidance) so that anxiety can be reduced via habituation instead of by rituals. In sum, treatment should include concurrent E/RP. Taken together, these treatment components teach youth with OCD that (1) the anxiety they experience in response to OCD-triggers will come down on its own without having to resort to rituals and (2) that even without rituals, the occurrence of the dreaded outcome is highly unlikely.

In addition to E/RP, adjunctive cognitive strategies are utilized with pediatric patients. Salkovskis (1999) outlined an OCD-specific form of cognitive therapy with adults, which may be applied to children. However, younger children, and those with impaired cognitive functioning, receive fewer and less sophisticated cognitive components to treatment due to developmental and cognitive limitations. A child's age, cognitive functioning, and insight into the nature of his/her OCD is paramount in determining the direction of treatment, as introduction of cognitive components of therapy depends on the child's developmental level and insight. Cognitive techniques include *cognitive restructuring* (eg, teaching the patient to challenge anxiety-provoking thoughts and/or the necessity of performing compulsive behaviors). In other words, the patient should construct and validate alternative, less threatening explanations for intrusive thoughts–images–doubts rather than focusing on disconfirming negative beliefs (Salkovskis 1999). If intrusive thoughts are not negatively interpreted, they are less likely to be viewed as significant. Despite the

utility of cognitive restructuring for children with OCD along with E/RP, clinicians must be ever-alert to the possibility that a "re-framed" thought can become a ritual for a child with OCD. For example, during therapy a child is taught to restructure fears about using a public toilet, such as, "It's okay to sit on the toilet – I won't get sick." However, it is not uncommon for children to replace a ritual with a mental ritual (eg, needing to repeat the aforementioned statement) in order to reduce anxiety, thus maintaining OCD. Teaching children coping phrases and self-talk (eg, "I can beat my OCD!" or "It may be hard, but I can do it") can assist children to mange obsessions but may be less likely to become replacement rituals. March and Mulle (1998) outline examples of self-talk strategies.

Although CBT for OCD is typically conducted via weekly 1-hour sessions (eg, March et al 1994; Benazon et al 2002; Barrett et al 2004; POTS 2004), an alternative CBT format has been utilized for the treatment of refractory pediatric OCD. Intensive cognitive behavioral therapy (I-CBT) for OCD involves techniques similar to traditional CBT with E/RP (Lewin et al 2005). However, the frequency and duration of the sessions are increased from weekly 50-minute sessions to daily 90-minute sessions. Research suggests that prolonged, continuous exposures are superior to shorter, intermittent exposures (Rabavilas et al 1976). Preliminary research supports the use of I-CBT in cases of difficult-to-treat pediatric OCD. In one open trial of I-CBT for refractory pediatric OCD, all five children who participated were treatment responders and showed significant decreases in OCD symptomatology (Storch and Geffken 2004). A noncontrolled trial by Franklin et al (1998) and several case reports (Franklin et al 2001; Storch et al 2004; Storch et al 2005; Fernandez et al in press) also found support for I-CBT. Although a randomized controlled study of I-CBT in adults produced promising results (Abramowitz et al 2003), there has yet to be a controlled trial of I-CBT versus weekly CBT for OCD in children and adolescents.

There are several prognostic indicators of a positive response to CBT for pediatric OCD. First, family involvement is central to the success of CBT for pediatric OCD (Knox et al 1996; Barrett et al 2004). In addition to extinction and differential reinforcement procedures (see Francis 1988; Fernandez et al in press), parents and families can provide substantial emotional and instrumental support with treatment. Other positive indicators include the child's willingness to cooperate with treatment, the presence of overt rituals, motivation to eliminate rituals–symptoms, developmental level, and the ability to monitor and report symptoms (March et al 2001). Conversely, several putative factors are associated with a poor response to CBT. These include extensive co-occurring psychiatric conditions (see Geller et al 2003a), impaired cognitive development (eg, developmental delay, mental retardation, and very young children; AACAP 1998); and individuals with poor insight into the senselessness of their obsessions and compulsions (Franklin and Foa 2002). Certain family factors may negatively influence CBT for OCD. For example, parents pushing their children too hard during E/RP (eg, moving up the hierarchy too quickly prior to assignment by the therapist), parents sabotaging exposures and/or being overly punitive (eg, throwing an item the child believes to be contaminated at the child without warning), or parents with OCD or other anxiety disorders themselves. Further research in the area of family factors and treatment outcomes appears warranted. Although children with OCD and Tourette's disorder are considered to be less responsive to treatment, CBT is considered the first-line treatment for these patients (Miguel et al 2003).

Conclusions

CBT alone or CBT with concurrent SSRI therapy are considered the first-line treatments (POTS 2004). Although there are few controlled comparisons between CBT, medication, and concomitant CBT and SRI in pediatric samples with OCD, CBT was found to be superior to medication alone (clomipramine, de Hann et al 1998; sertraline, POTS 2004). In addition, supplemental CBT has been demonstrated to be effective following unsuccessful fluoxetine treatment for adults with OCD (Kampman et al 2002).

Despite the efficacy of CBT with E/RP, the lack of professionals trained in CBT for OCD is among the greatest barriers to successful treatment (AACAP 1998). This limited access to specialists familiar with empirically supported treatments (eg, CBT with E/RP) may result in the prescription of pharmacotherapy alone and/or other psychotherapies that have not been demonstrated as efficacious (eg, play therapy, psychoanalytical therapy, insight-oriented therapy). For example, in a national survey of 79 clinicians treating pediatric OCD, less than 33% reported using exposure–response prevention (or similar techniques), despite rating CBT as a favorable approach to treatment (Valderhaug et al 2004). Additionally, Heyman et al (2001) found that only 36% of the families of children with OCD had consulted a healthcare practitioner; only 12% of those children were referred for specialized mental health

services. Similarly, Flament et al (1988) found that only 20% of children with OCD were receiving mental health services.

Overall, despite recent advances, considerable further research is needed to bolster etiological and interventional understanding of pediatric OCD. As evidenced by the studies presented in this review, clinical research trials and neurobiological investigations are convergent, not parallel, courses of research. That is, advances in neurochemistry guide pharmacotherapy while the efficacy of CBT might suggest brain structures for more detailed neuroimaging studies.

References

Abramowitz JS, Foa EB, Franklin ME. 2003. Exposure and ritual prevention for obsessive-compulsive disorder: Effects of intensive versus twice-weekly sessions. *J Consult Clin Psych*, 71:394–8.

[AACAP] American Academy of Child and Adolescent Psychiatry. 1998. Practice parameters for the assessment and treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*, 37: S27–45.

[APA] American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders (4th ed, text revision). Washington, DC: APA.

Barrett P, Healy-Farrell L, March JS. 2004. Cognitive behavioral family treatment of childhood obsessive-compulsive disorder: A controlled trial. *J Am Acad Child Adolesc Psychiatry*, 43: 46–62.

Baxter LR, Saxena S, Brody AL, et al. 1996. Brain mediation of obsessive-compulsive disorder symptoms: evidence from functional brain imaging studies in the human and nonhuman primate. *Semin Clin Neuropsychiatry*, 1: 32–47.

Baxter LR, Schwartz JM, Bergman KS, et al. 1992. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive-compulsive disorder. *Arch Gen Psychiatry*, 49: 681–9.

Benazon NR, Ager J, Rosenberg DR. 2002. Cognitive behavior therapy in treatment-naïve children and adolescents with obsessive-compulsive disorder: An open trial. *Behav Res Ther*, 40:529–39.

Benazon NR, Moore GJ, Rosenberg DR. 2003. Neurochemical analysis in pediatric obsessive-compulsive disorder in patients treated with cognitive-behavioral therapy. *J Am Acad Child Adolesc Psychiatry*, 42:1279–85.

Bolton D, Luckie M, Steinberg D. 1995. Long-term course of Obsessive-Compulsive Disorder treated in adolescence. *J Am Acad Child Adolesc Psychiatry*, *34:*1441–50.

Breiter HC, Rauch SL. 1996. Functional MRI and the study of OCD; From symptom provocation to cognitive-behavioral probes of cortico-striatal systems and the amygdale. *Neuroimage*, 4: S127–38.

Bronze MS, Dale JB. 1993. Epitopes of streptococcal M proteins that evoke antibodies that cross-react with the human brain. *J Immunol*, 151: 2820–8.

Coffey BJ, Jones J, Shapiro S. 1998. Tourette's disorder and obsessive-compulsive disorder: clinical similarities and differences. In Jenike MA, Baer L, Minichiello WE (eds). Obsessive-compulsive disorders: practical management. 3rd ed. St Louis, MO: Mosby. p 143–61.

Cook EH, Wagner KD, March J S, et al. 2001. Long-term sertraline treatment of children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*, 40: 1175–89.

de Haan E, Hoogduin KAL, Buitelaar, JK, et al. 1998. Behavior therapy versus clomipramine for the treatment of obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*, 37:1022–29.

Denys D, van der Wee N, Janssen J, et al. 2004. Low level of dopaminergic D_2 receptor binding in obsessive-compulsive disorder. *Biol Psychiatry*, 55:1041–5.

DeVeaugh-Geiss J, Moroz G, Biederman J, et al. 1992. Clomipramine hydrochloride in childhood and adolescent obsessive-compulsive disorder: A multicenter trial. *J Am Acad Child Adolesc Psychiatry*, 31:45–9.

Dollard J, Miller NE. 1950. Personality and psychotherapy: an analysis in terms of learning, thinking and culture. New York: McGraw Hill.

Dougherty DD, Rauch SL, Jenike MA. 2002. Pharmacological treatments for Obsessive Compulsive Disorder. In Nathan PE, Gorman JM (eds). A guide to treatments that work. 2nd ed. New York: Oxford University Pr. p 387–410.

Douglass HM, Moffitt TE, Dar R, et al. 1995. Obsessive-compulsive disorder in a birth cohort of 18-year-olds: Prevalence and predictors. *J Am Acad Child Adolesc Psychiatry*, 34:1424–31.

Fernandez MA, Storch EA**,** Lewin AB et al. The principles of extinction and differential reinforcement of other behaviors in the intensive cognitive behavioral treatment of primarily obsessional pediatric OCD. *Clin Case Studies*. in press.

Figueroa Y, Rosenberg D, Birmaher B, et al. 1998. Combination treatment with clomipramine and selective serotonin reuptake inhibitors for obsessive-compulsive disorder in children and adolescents. *J Child Adolesc Psychopharmacol*, 8:61–7.

Flament MF, Bisserbe JC. 1997. Pharmacologic treatment of obsessive-compulsive disorder: comparative studies. *J Clin Psychiatry*, 58(Suppl):18–22.

Flament MF, Rapoport JL, Berg CJ, et al. 1985. Clomipramine treatment of childhood obsessive-compulsive disorder. A double-blind controlled study. *Arch Gen Psychiatry*, 42:977–83.

Flament MF, Whitaker A, Rapoport JL, et al. 1988. Obsessive compulsive disorder in adolescence: An epidemiological study. *J Am Acad Child Adolesc Psychiatry*, 27: 764-71.

Foa EB, Kozak M J. 1996. Psychological treatments for obsessive-compulsive disorder. Mavissakalian MR, Prein RF (eds). Long-term treatments for anxiety disorders. Washington: American Psychiatric Pr. p 265–309.

Fountoulakis KN, Nimatoudis I, Iacovides A, et al. 2004. Off-label indications for atypical antipsychotics: A systematic review. *Ann Gen Hosp Psychiatry*, 18:4.

Francis G. 1988. Childhood obsessive-compulsive disorder: Extinction of compulsive reassurance seeking. *J Anxiety Disord*, *2:*361–8.

Franklin ME, Foa EB. 2002. Cognitive behavioral treatments for obsessive compulsive disorder. In Nathan PE, Gorman JM (eds). A guide to treatments that work. 2nd ed. New York: Oxford University Pr. p 367–86.

Franklin ME, Kozak MJ, Cashman LA, et al. 1998. Cognitive-behavioral treatment of pediatric obsessive-compulsive disorder: An open clinical trial. *J Am Acad Child Adolesc Psychiatry*, 37:412–9.

Franklin ME, Tolin DF, March JS, et al. 2001. Treatment of pediatric obsessive-compulsive disorder: A case example of intensive cognitive-behavioral therapy involving exposure and ritual prevention. *Cog Behav Pract*, 8:297–304.

Geffken GR, Storch EA, Lewin AB, et al. 2005. The early development of a scale designed to measure ego-syntonic and ego-dystonic pediatric obsessive-compulsive disorder. In Storch EA (chair). Contemporary issues in pediatric obsessive-compulsive disorder. Symposium conducted at the annual meeting of the Anxiety Disorders Association of America. 2005 March; Seattle, WA, USA.

Geller DA. 1998. Juvenile obsessive-compulsive disorder. In Jenike MA, Baer L, Minichiello WE (eds). Obsessive-compulsive disorders: practical management. 3rd ed. St Louis, MO: Mosby. p 44–64.

Geller DA, Biederman J, Stewart SE, et al. 2003a. 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*, 13(Suppl 1):S19–29.

Geller DA, Biederman J, Stewart SE, et al. 2003b. Which SSRI? A meta-analysis of pharmacotherapy trials in pediatric obsessive compulsive disorder. *Am J Psychiatry*, 160:1919–28.

Geller DA, Hoog SL, Heiligenstein JH, et al. 2001. Fluoxetine treatment for Obsessive Compulsive Disorder in children and adolescents: A placebo-controlled clinical trial *J Am Acad Child Adolesc Psychiatry*, 40:773–9.

Geller DA, Wagner KD, Emslie G, et al. 2004. Paroxetine treatment in children and adolescents with obsessive-compulsive disorder: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry*, 43:1387–96.

Giedd JN, Rapoport JL, Garvey MA, et al. 2000. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. *Am J Psychiatry*, 157:281–3.

Gilbert AR, Moore GJ, Keshavan MS, et al. 2000. Decrease in thalamic volumes of pediatric patients with obsessive-compulsive disorder who are taking paroxetine. *Arch Gen Psychiatry*, 57:449–56.

Goldsmith TB, Shapira NA, Keck PE. 1999. Rapid remission of OCD with tramadol hydrochloride. *Am J Psychiatry*, 156:600–1.

Goodman WK, McDougle CJ, Price LH. 1990. Beyond the serotonin hypothesis: A role for dopamine in some forms of obsessive compulsive disorder? *J Clin Psychiatry*, 51(Suppl):36–43.

Grados MA, Riddle MA. 2001. Pharmacological treatment of childhood obsessive-compulsive disorder: From theory to practice. *J Clin Child Psychol*, 30:67–79.

Grados MA, Riddle MA, Samuels JF et al. 2001. The familial phenotype of obsessive-compulsive disorder in relation to tic disorders: the Hopkins OCD family study. *Biol Psychiatry*, 50:559–65.

Grados M, Scahill L, Riddle MA. 1999. Pharmacotherapy in children and adolescents with obsessive-compulsive disorder. *Child Adolesc Psychiatr Clin N Am*, 8:617–34.

Heyman I, Fombonne E, Simmons H, et al. 2001. Prevalence of obsessive-compulsive disorder in the British nationwide survey of child mental health. *Br J Psychiatry*, 179:324–9.

Hollander E, Baldini Rossi N, Sood E, et al. 2003. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*, 6:397–401.

Husby G, van de Rijn I, Zabriskie JB, et al. 1976. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. *J Exp Med*, 144:1094–110.

Kampman M, Keijsers GPJ, Hoogduin, CAL, et al. 2002. Addition of cognitive-behavioral therapy for obsessive-compulsive disorder patients non-responding to fluoxetine. *Acta Psychiatr Scand*, 106: 314–9.

Kim J, Chul Lee M, Kim J, et al. 2001. Grey-matter abnormalities in obsessive-compulsive disorder. *Br J Psychiatry*, 179:330–4.

Kirvan CA, Swedo SE, Heuser JS, et al. 2003. Mimicry and autoantibody-mediated neuronal cell signaling in Sydenham chorea. *Nat Med*, 9: 914–20.

Knox LS, Albano AM, Barlow DH. 1996. Parental involvement in the treatment of childhood obsessive compulsive disorder: a multiple baseline examination incorporating parents. *Behav Ther*, 27:93–115.

Koran LM, Aboujaoude E, Bullock KD, et al. 2005a. Double-blind treatment with oral morphine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*, 66:353–9.

Koran LM, Gamel NN, Choung HW, et al. 2005b. Mirtazapine for obsessive-compulsive disorder: an open trial followed by double-blind discontinuation. *Am J Psychiatry*, 66: 515–20.

Kotby AA, El Badawy N, El Sokkary S, et al. 1998. Antineuronal antibodies in rheumatic chorea. *Clin Diagn Lab Immunol*, 5:836–9.

Kozak MJ, Foa EB. 1997. Mastery of obsessive compulsive disorder: A cognitive-behavioral approach. Therapist guide. San Antonio, TX: The Psychological Corporation.

Kurlan R, Kaplan EL. 2004. The pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics*, 113:883–6.

Leckman JF, Katsovich L, Kawikova I, et al. 2005. Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in tourette's syndrome. *Biol Psychiatry*, 57:667–73.

Leonard HL, Swedo SE. 2001. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). *Int J Neuropsychopharmacol*, 4:191–8.

Leonard HL, Swedo SE, Rapoport JL, et al. 1989. Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents. A double-blind crossover comparison. *Arch Gen Psychiatry*, 46:1088–92.

Lewin AB, Storch EA, Atkins J. et al. 2005. Current directions in pediatric obsessive-compulsive disorder. *Pediatr Ann*, 34:128–34.

Lewin AB, Storch EA, Merlo LJ, et al. (2005). Intensive cognitive behavioral therapy for pediatric obsessive compulsive disorder: A treatment protocol for mental health providers. *Psychol Serv*, 2: 91–104.

Liebowitz MR, Turner SM, Piacentini J, et al. 2002. Fluoxetine in children and adolescents with Obsessive-Compulsive Disorder: A placebo controlled trial. *J Am Acad Child Adolesc Psychiatry*, 41:1431–8.

March JS, Franklin M, Nelson A, et al. 2001. Cognitive-behavioral psychotherapy for pediatric obsessive-compulsive disorder. *J Clin Child Psychol*, 30:8–18.

March JS, Mulle K. 1998. OCD in children and adolescents: A cognitive-behavioral treatment manual. New York: Guilford Press.

March JS, Biederman J, Wolkow R, et al.1998. Sertraline in children and adolescents with obsessive-compulsive disorder: A multicenter randomized controlled trial. *JAMA*, 280:1752–6.

March JS, Mulle K, Herbel B. 1994. Behavioral psychotherapy for children and adolescents with Obsessive-Compulsive Disorder: An open trial of a new protocol driven treatment package. *J Am Acad Child Adolesc Psychiatry*, 33:333–41.

McGuire PK, Bench CJ, Frith CD, et al. 1994. Functional anatomy of obsessive-compulsive phenomena. *Br J Psychiatry*, 164:459–68.

Meyer V. 1966. Modification of expectations in cases with obsessive rituals. *Behav Res Ther*, 4:270–80.

Miguel EC, Shavitt RG, Ferrao YA et al. 2003. How to treat OCD in patients with Tourette syndrome. *J Psychosom Res*, 55:49–57.

Millet B, Kochman F, Gallarda T, et al. 2004. Phenomenological and comorbid features associated in obsessive-compulsive disorder: influence of age of onset. *J Affect Disord*, 79:241–6.

Mowrer OH. 1939. A stimulus-response analysis of anxiety and its role as a reinforcing agent. *Psycholo Rev*, 46: 553–65.

Mowrer OH. 1960. Learning theory and behavior. New York: John Wiley.

Murphy TK, Sajid M, Soto O, et al. 2004. Detecting pediatric autoimmune neuropsychiatric disorders associated with streptococcus in children with obsessive-compulsive disorder and tics. *Biol Psychiatry*, 55: 61–8.

[OCCWG] Obsessive Compulsive Cognitions Working Group. 1997. Cognitive assessment of obsessive-compulsive disorder. *Behav Res Ther*, 35:667–81.

Pauls DL, Alsobrook JP, Phil M, et al. 1995. A family study of obsessive-compulsive disorder. *Am J Psychiatry*, 152:76–84.

[POTS] Pediatric OCD Treatment Study (POTS) Team. 2004. Cognitive-behavioral therapy, sertaline, and their combination for children and adolescents with obsessive-compulsive disorder: the Pediatric OCD treatment study (POTS) randomized controlled trial. *JAMA*, 292: 1969–76.

Petter T, Richter MA, Sandor P. 1998. Clinical features distinguishing patients with Tourette's syndrome and obsessive-compulsive disorder from patients with obsessive-compulsive disorder without tics. *J Clin Psychiatry*, 59:456–9.

Piacentini J, Bergman RL, Jacobs C, et al. 2002. Open trial of cognitive behavior therapy for childhood obsessive-compulsive disorder. *J Anxiety Disord*, 16:207–19.

Piacentini J, Langley AK. 2004. Cognitive-behavioral therapy for children who have obsessive-compulsive disorder. *J Clin Psychol*, 60: 1181–94.

Rabavilas AD, Boulougouris JC, Stefanis C. 1976. Duration of flooding sessions in the treatment of obsessive-compulsive patients. *Behav Res Ther*, 12:239–43.

Rauch SL, Baxter LR. 1998. Neuroimaging in obsessive-compulsive disorder and related disorders. In Jenike MA, Baer L, Minichiello WE (eds). Obsessive-compulsive disorders: practical management. 3rd ed. St Louis, MO: Mosby. p 289–317.

Rauch SL, Jenike MA, Alpert NM, et al. 1994. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry*, 51:62–70.

Rauch SL, Whalen PJ, Dougherty D, et al. 1998. Neurobiological models of obsessive-compulsive disorder. In Jenike MA, Baer L, Minichiello WE (eds). Obsessive-compulsive disorders: practical management. 3rd ed. St Louis, MO: Mosby. p 222–53.

Riddle MA, Reeve EA, Yaryura-Tobias JA, et al. 2001. Fluvoxamine for children and adolescents with Obsessive-Compulsive Disorder: A randomized, controlled, multicenter trial. *J Am Acad Child Adolesc Psychiatry*, 40:222–9.

Riddle M, Scahill L, King R, et al. 1992. Double-blind, crossover trial of fluoxetine and placebo in children and adolescents with obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*, 31: 1062–9.

Rosenberg DR, Keshavan MS. 1998. Towards a neurodevelopmental model of obsessive-compulsive disorder. *Biol Psychiatry*, 43:623–40.

Rosenberg DR, Mirza Y, Russell A, et al. 2004. Reduced anterior cingulate glutamatergic concentrations in childhood OCD and major depression versus healthy controls. *J Am Acad Child Adolesc Psychiatry*, 43: 1146–53.

Salkovskis PM. 1999. Understanding and treating obsessive-compulsive disorder. *Behav Res Ther*, 37:S29–52.

Sareen J, Kirshner A, Lander M, et al. 2004. Do antipsychotics ameliorate or exacerbate obsessive compulsive disorder symptoms? A systematic review. *J Affect Disord*, 82:167–74.

Saxena S, Bota RG, Brody AL. 2001. Brain-behavior relationships in obsessive-compulsive disorder. *Semin Clin Neuropsy*, 6:82–101.

Saxena S, Brody AL, Schwartz JM, et al. 1998. Neuroimaging and frontal-subcortical circuitry in obsessive-compulsive disorder. *Br J Psychiatry*, 173(Suppl 35):26–37.

Scahill L, Riddle MA, McSwiggin-Hardin M, et al. 1997. Children's Yale-Brown Obsessive Compulsive Scale: Reliability and validity. *J Am Acad Child Adolesc Psychiatry*, 36:844–52.

Simeon JG, Thatte S, Wiggins D. 1990. Treatment of adolescent obsessive-compulsive disorder with a clomipramine-fluoxetine combination. *Psychopharmacol Bull*, 26:285–90.

Snider LA, Swedo SE. 2000. Pediatric obsessive-compulsive disorder. *JAMA*, 284:3104–6.

Stewart SE, Geller DA, Jenike M, et al. 2004. Long-term outcome of pediatric obsessive-compulsive disorder: a meta-analysis and quantitative review of the literature. *Acta Psychiatr Scand*, 110:4–13.

Storch EA, Geffken GR. 2004. Intensive cognitive behavior therapy for pediatric obsessive-compulsive disorder. In Geffken GR (chair). Update on pediatric Obsessive-Compulsive Disorder. Symposium presented at the annual meeting of the Anxiety Disorders Association of America. 2005 March; Miami, FL, USA.

Storch EA, Gerdes A, Atkins J, et al. 2004. Behavioral treatment of child with pediatric autoimmune neuropsychiatric disorder associated with Group A streptococcal Infection. *J Am Acad Child Adolesc Psychiatry*, 43:510–1.

Storch EA, Heidgerken A, Adkins J, et al. 2005. Peer victimization and the development of obsessive-compulsive disorder in adolescence: A case report. *Depress Anxiety*, 21:41–4.

Swedo, SE. 1994. Sydenham's chorea. A model for childhood autoimmune neuropsychiatric disoders. *JAMA*, 272:1788–91.

Swedo SE, Leonard HL, Garvey M, et al. 1998. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: Clinical description of the first 50 cases. *Am J Psychiatry*, 155: 264–71.

Swedo SE, Pietrini P, Leonard HL, et al. 1992. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. Revisualization during pharmacotherapy. *Arch Gen Psychiatry*, 49:690–4.

Swedo SE, Rapoport JL, Leonard H, et al. 1989a. Obsessive-compulsive disorder in children and adolescents: Clinical phenomenology of 70 consecutive cases. *Arch Gen Psychiatry*, 46:335–41.

Swedo SE, Schapiro MB, Grady CL, et al. 1989b. Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Arch Gen Psychiatry*, 46:518–23.

Szeszko PR, MacMillan S, McMeniman M, et al. 2004. Brain structural abnormalities in psychotropic drug-naive pediatric patients with obsessive-compulsive disorder. *Am J Psychiatry*, 161:1049–56.

Thienemann M, Martin J, Cregger B, et al. 2001. Manual-driven group cognitive-behavioral therapy of adolescents with obsessive-compulsive disorder: A pilot study. *J Am Acad Child Adolesc Psychiatry*, 40: 1254–60.

Ursu S, Stenger VA, Shear MK, et al. 2003. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol Sci*, 14:347–53.

Whiteside SP, Port JD, Abramowitz JS. 2004. A meta-analysis of functional neuroimaging in obsessive compulsive disorder. *Psychiat Res: Neuroim*, 132:69–79.

Valderhaug R, Gunnar Gotestam K, Larsson B. 2004. Clinicians' views on management of obsessive-compulsive disorders in children and adolescents. *Nord J Psychiatry*, 58:125–32.

van der Wee NJ, Stevens H, Hardeman JA, et al. 2004. Enhanced dopamine transporter density in psychotropic-naïve patients with obsessive-compulsive disorder shown by [^{123}I]β-CIT SPECT. *Am J Psychiatry*, 161:2201–6.

Zohar AH. 1999. The epidemiology of obsessive-compulsive disorder in children and adolescents. *Child Adolesc Psychiatr Clin N Am*, 8: 445–60.

Zohar J, Chopra M, Sasson Y, et al. 2000. Obsessive compulsive disorder: serotonin and beyond. *World J Biol Psychiatry*, 1:92–100.