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REVIEW ARTICLE

Selective Serotonin Reuptake Inhibitors for the Treatment of Obsessive-Compulsive Disorder in Children and Adolescents

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The introduction of the selective serotonin reuptake inhibitors (SSRIs) has been a major advance in pediatric psychiatry, while contemporary advances in the understanding of obsessive-compulsive disorder (OCD) phenomenon in children have facilitated its identification and treatment. Currently, fluvoxamine and sertraline are the only SSRIs that have received FDA approval for the treatment of childhood OCD. The purpose of this article is to review the safety and efficacy of SSRIs in the treatment of obsessive-compulsive disorder (OCD) in children and adolescents.

Key words: Selective Serotonin Reuptake Inhibitor, SSRI, Obsessive Compulsive Disorder, OCD

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Abbreviations	
CY-BOCS	Children's Yale-Brown Obsessive-Compulsive Scale
CGI-S	Clinical Global Impressions of Severity of Illness
CGI-I	Clinical Global Improvement Scales
NIMH-GOCS	National Institute of Mental Health Global Obsessive-Compulsive Scale
PGI	Patients Global Impressions

INTRODUCTION

The process of maturing into adulthood from childhood can sometimes include feelings of worry, persistent thoughts, and impulsive behavior. However, we are now aware that these feelings in children and adolescents are not necessarily transient and harmless, but may be a reflection of more serious underlying psychological disorders.[1] Most of the published clinical trials on child and adolescent depression and anxiety disorders have evaluated the efficacy of tricyclic antidepressants (TCAs). Double-blind studies suggest that TCAs may be ineffective for depression and anxiety disorders in children and adolescents. Additionally, there are data suggesting that TCA use in this population may not be safe. Studies have found that higher serum concentrations of TCA are related to more ECG abnormalities.[2] Therefore, the introduction of the selective serotonin reuptake inhibitors (SSRIs) has been a major advance in pediatric psychiatry. Since the release of the first SSRI, fluoxetine, in 1988 the use of the SSRIs has been pervasive.[3]

Clinical trials have studied the efficacy of SSRIs in the treatment of childhood anxiety disorders as well as depression. Although the newer antidepressants have generally not been shown to be more efficacious than the TCAs, they do have fewer adverse effects, lower toxicity following overdose, and a potentially broader range of clinical indications.[3,4] In this article, we will review the safety and efficacy of SSRIs in the treatment of obsessive-compulsive disorder (OCD) in children and adolescents. This paper will review the published clinical trials that have evaluated the use of SSRIs for OCD in children and will show that the SSRIs appear to be a safe choice to effectively treat child and adolescent patients with OCD.

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OBSESSIVE COMPULSIVE DISORDER

OCD frequently has a childhood onset with adolescent prevalence rates as high as 3–4%. It occurs predominately in males and has a chronic course that is associated with a very low rate of complete remission. Unfortunately, many of these children reach adulthood before the diagnosis of obsessive-compulsive disorder is made.[4] OCD is characterized by recurrent obsessions and/or compulsions that are intense enough to cause severe discomfort. Recurrent obsessions and persistent thoughts, impulses, or images are unwanted and cause marked anxiety or distress. Frequently, they are unrealistic or irrational and are not simply excessive worries about real-life problems or preoccupations. Compulsions are repetitive behaviors or rituals (e.g., hand-washing, hoarding, keeping things in order, checking something over and over) or mental acts (e.g., counting, repeating words silently, avoiding). In OCD, the obsessions and compulsions cause significant anxiety or distress, or they interfere with the child's normal routine, academic functioning, social activities, or relationships.[5]

The symptomatology of OCD in children is similar to that in adults and consist of significant and impairing obsessions (i.e., intrusive ideations, images, or impulses), compulsions (i.e., behaviors that have to be performed in a rigid or ritualistic fashion), or both.[6] These typical OCD symptoms have also been associated with other neuropsychiatric disorders (i.e., Tourette's disorder). It has been suggested that some cases of OCD may be a part of a "Tourette's disorder spectrum" that has a specific association to OCD and not other psychiatric disorders.[7]

Contemporary advances in the understanding of the OCD phenomenon in children have facilitated its identification and treatment. Likewise, the availability of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) has enabled practitioners to systematically assess a child for symptoms of OCD.[8] The CY-BOCS is a 10-item clinician rated, semistructured instrument that can be used to determine the clinical severity of the disorder during the previous week. This instrument can be used with the parent, the child or both and allows one to codes time spent, degree of control, and interference with daily activities due to OCD symptoms.[8] A five point ordinal scale is used with the sum of the scores for all 10 items yielding the CY-BOCS total score. This score can range from as low as zero to as high as forty. A threshold score is used to categorize children as significantly clinically impaired, and to longitudinally assess response to psychotropics.

As will be seen in the upcoming discussion of published trials, the CY-BOCS has been used to implement effective psychological and pharmacological treatment strategies; and although our discussion will be limited to OCD treatment with medication (namely SSRIs), psychosocial and cognitive-behavioral interventions are also important components of treatment.[6] Many clinicians believe that a combination of cognitive behavioral therapy and pharmacotherapy is optimal, and some studies suggest that cognitive behavioral therapy may reduce relapse rates in patients withdrawn from medication.[9]

Pharmacological treatment is best guided by a thorough evaluation of the type of obsession or compulsion, the intensity and frequency of their presentation with attention to behavioral reinforcements, and psychosocial factors that affect the course of the disease. The targets of OCD treatment are the amelioration of obsessions and compulsions. Serotonin-enhancing agents such as the SSRIs are first-line pharmacological agents in the treatment of childhood OCD, with refractory cases being aided by augmentation with other agents.[6] Currently, fluvoxamine and sertraline are the only SSRIs that have received FDA approval for the treatment of childhood OCD.[4]

THE SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) have been an important class of antidepressants. Decreased adverse effects and claims of increased safety as compared to TCAs have led to their extended use in the field of psychiatry as well as by other disciplines. Currently five SSRIs are marketed in the U.S. (Table 1). The primary pharmacological action of the SSRIs is to block the presynaptic serotonin transporter receptor. Although there seems to be variability in the serotonergic effects among the SSRIs, these variations appear to have little to no impact on the efficacy or adverse effects. When comparing SSRIs to tricyclic antidepressants, it appears that

SSRIs have less of an effect on α1, α2, histaminergic, and muscarinic receptors. This pharmacologic dissimilarity accounts for the differences in adverse effects between the two drug classes.[10] Unfortunately, paroxetine does display as significant anticholinergic effects as nortriptyline and desipramine. Table 2 summarizes the incidence of the most common adverse effects reported for those SSRIs that are commercially available in the United States.

The SSRIs are well absorbed following oral administation, with the presence of food having little clinical effect on their absorption. The SSRIs are highly lipophilic, widely distributed throughout the body and are highly plasma protein bound. They are all extensively metabolized in the liver to extremely polar metabolites, which are then excreted in the urine. Although the SSRIs are similar in many ways, the few differences among them are seen due to their individual pharmacokinetic properties.[10] For example, fluoxetine is distinguished from the other SSRIs because of its long half-life and the long half-life of its active metabolite norfluoxetine.[11] Sertraline also has an active metabolite (desmethylsertaline); however, it is approximately ten times less active than sertraline and thus deemed clinically irrelevant. With the exception of fluvoxamine, all of the SSRIs can be dosed once per day.

The primary uses for the SSRIs include unipolar and bipolar major depression and all of the anxiety disorders. However, controlled trials also support the use of SSRIs in the treatment of other psychiatric disorders including dysthymia, premenstrual dysphoria, obesity, borderline personality disorder, alcoholism, rheumatic pain, and migraine headache.[10]

The SSRIs are individually approved by the FDA for various conditions. Sertraline is approved for the treatment of depression, posttraumatic stress disorder (PTSD), and OCD in children 6 years and older, while fluoxetine is approved for the treatment of bulimia nervosa, adult and geriatric depression, maintenance therapy for depression, OCD in adults, and premenstrual dysphoric disorder (PMDD). Paroxetine also has many FDA approved uses,

Table 1. SSRI Medications Marketed in the United States

GENERIC (Trade)	FDA APPROVED INDICATIONS	Dosage (mg/day)	STRENGTH
Citalopram HBr (Celexa*)	Depression (NBE)		10 mg/5mL peppermint flavored solution; 10, 20, 40 mg tablets
Fluoxetine HCl† (Prozac‡ ; Sarafem§)	OCD, PMDD, bulimia nervosa, depression, (NBE)	5–60 mg/day	20 mg/5mL mint flavored solution (0.23% alcohol); 10, 20, 40 mg Pulvule; 10 mg tablet
Fluvoxamine maleate† (Luvox‖)	OCD (>8 yrs of age)	25–250 mg/day	25, 50, 100 mg tablets (sodium metabisulfite)
Paroxetine HCl† (Paxil¶)	OCD, depression, GAD, PTSD, panic disorder, social anxiety disorder (NBE)	10–30 mg/day	10 mg/5mL orange flavored suspension; 10, 20, 30, 40 mg tablet; 12.5, 25, 37.5 control release tablet
Sertraline HCl (Zoloft††)	OCD, depression, PTSD, (>6 yrs of age)	25–150 mg/day	concentrate 20 mg/mL (12% alcohol); 25, 50, 100 mg tablet

NBE= use not been established in children; OCD=obsessive compulsive disorder; PMDD= premenstrual dysphoric disorder; GAD=generalized anxiety disorder; PTSD=posttramatic stress disorder;
* *Forest Pharmaceuticals, Inc, St. Louis, MO*
† *Generic available*
‡ *Dista, Indianapolis, IN*
§ *Lilly, Indianapolis, IN*
‖ *Solay Pharmaceuticals, Marietta, GA*
¶ *GlaxoSmithKline, Research Triangle Park, NC*
†† *Pfizer Inc, NY, NY*

including depression, generalized anxiety disorder (GAD), OCD in adults, panic disorder, PTSD, and social anxiety disorder. The only FDA approved use for citalopram is depression, although it has other therapeutic uses including OCD. Fluvoxamine also has only one FDA approved indication, which is OCD in patients eight years of age and older.

Doses of the different SSRIs vary in adults with OCD. The recommended daily dose for fluoxetine is 20–80mg for OCD. Doses larger 20 mg/day do not produce an improved therapeutic response in most adult patients.[12] The dosage of fluvoxamine has ranged between 50–300 mg/day. Doses larger than 150 mg/day have not been shown to produce greater efficacy.[13] Although the minimum effective dose for paroxetine is 20 mg/day, larger doses should be reserved for patients who have failed a three to four week trial of 20 mg/day.[14] In adults with OCD, the dosage of sertraline ranges from 50–200 mg/day.[15]

To date, only two of the SSRIs have been approved by the FDA for use in children. Fluvoxamine and sertraline are approved for children older than 8 and 6 years, respectively. Because fluvoxamine had been used extensively and safely used in children in Canada and Europe prior to its availability in the United States, it was the first SSRI to receive FDA approval for use in children. Although most physicians prefer to use medications the FDA has approved specifically for use in children, other SSRIs may be prescribed for the treatment of OCD based on published data and clinical experience. The customary dosage for sertaline's in children ranges from 25–150 mg/day, while that of fluoxetine has ranged of 5–60 mg/day. Fluoxetine is preferred by some physicians because it is available in a liquid dosage form. Paroxetine has often been used in doses ranging of 10 to 30 mg per day, while 25–250 mg/day of fluvoxamine has been used in children with OCD. Although only approved for the treatment of depression, citalopram has been used for the treatment of OCD in children at doses ranging from 20 to 60mg per day.

While a variety of doses have been used, the–"best" dose of a medication for OCD must be determined on an individual, case-by-case basis. As true with most medications, the lowest effective dose is preferable. Because the hepatic clearance of medications is enhanced in children, they may larger doses in order to experience alleviation of their OCD symptoms.[16]

SERTRALINE

March and colleagues reported the results of a large, multi-center randomized controlled trial of sertraline in children and adolescents (6–17 years) who had OCD.[17] A total of 187 patients (107 children and 80 adolescents) were randomized to receive either sertraline or placebo. The starting dosage was 25 mg/day for children and 50 mg/day for adolescents. Sertraline was titrated by 50 mg/week to a maximum of 200 mg/day. The maximum tolerated dose that each patient received during the first four weeks of double-blind therapy was continued for an additional for eight weeks. Therapy was continued for a total of 12 weeks. Seventy-four out of 92 (80%) patients treated with sertraline and 82 out of 95 (86%) treated with placebo completed the 12 weeks of double-blind treatment. Mean doses at endpoint were 167 mg/day of sertraline and 180 mg/day of placebo. Outcome measures used were: the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), the National Institute of Mental Health Global Obsessive-Compulsive Scale (NIMH-GOCS), the NIMH Clinical Global Impressions of Severity of Illness (CGI-S) and Improvement (CGI-I) Scales.

In the intent-to-treat analysis, sertraline patients exhibited statistically greater improvement than those taking placebo on the CY-BOCS (P=0.005), NIMH-GOCS (P=0.02), and CGI-I scores (P=0.002). The change in CGI-S scores was not statistically significant. The results were similar in the completer analysis, where improvement was seen in the CY-BOCS (P=0.004), NIMH-GOCS (P=0.03), and CGI-I scores (P=0.002) and the change in CGI-S score was not statistically significant. Twelve of the patients in the sertraline group and three in the placebo group withdrew for the study due to adverse events (i.e., insomnia, nausea, agitation, and tremor). The authors concluded that sertraline appears to be a safer and more effective short-term treatment than placebo for children and adolescents with OCD.

Due to the concern over fluoxetine and sertraline association with vital sign changes, Wilens et al.[18] prospectively assessed the cardiovascular effects of sertraline of ≤200 mg/day in

patients enrolled in the aforementioned study by March.[17] This placebo-controlled, prospective study evaluated blood pressure, heart rate) and electrocardiograph (ECGs) parameters at baseline and throughout treatment. There were no clinically meaningful differences in baseline vs treatment supine or standing heart rates values for those receiving sertraline or placebo. Although statistically significant, a clinically unimportant elevation (3%) in pre- and post-treatment standing heart rate) was noted. There were no significant differences in systolic or diastolic blood pressures at any point. Likewise, there was no significant difference between the sertraline- or placebo-treated groups at baseline in any of the ECG indices. The investigators concluded that monitoring of vital signs and ECGs is not necessary in the routine care of otherwise healthy children who are receiving recommended doses of sertraline.

For a period of 52 weeks, Cook et al. used an open-label study design to evaluated sertraline in 72 children and 65 adolescents who had been diagnosed with OCD.[19] The patients ranged in age from 6 to 18 years. Sertraline was administered in an upward titration from 25 mg/day (children) and 50 mg/day (adolescents) to a maximum of 200 mg/day. Outcomes were measured using the change in CY-BOCS, NIMH-GOCS, CGI-S and CGI-I scores. Following titration, the mean daily sertraline dose was 120 mg in all patients, 108 mg in children 6–12 years of age, and 132 mg in those 13–18 years of age. Statistically significant improvements from baseline were demonstrated for all four outcome measurements in the 132 patients who could be evaluated. Significant improvement was shown in all parameters for the overall study population, as well as the child and adolescent groups when evaluated individually. At study endpoint, 72% of the children and 61% of the adolescents met response criteria (>25% decrease in CY-BOCS and a CGI-I score of 1 or 2).

The profile of adverse events was similar to those reported for adults. Events reported at an incidence of ≥10% were headache, insomnia, nausea, diarrhea, somnolence, abdominal pain, hyperkinesias, nervousness, dyspepsia, and vomiting. Most adverse events tended to occur early in treatment, were mild to moderate in severity, and their incidence decreased markedly with increasing duration of treatment. Twelve percent (16/137) of patients had their therapy discontinued due to adverse events, with hyperkinesias being the most common event leading to termination of therapy. Eight serious adverse events were noted; however, only one was considered to be study-drug related. There were no discontinuations due to changes in vital signs, lab values, or ECGs. These results suggest that sertraline's effectiveness in pediatric patients with OCD is sustained over time and enhanced with continuation of treatment. The authors also concluded that 50 to 200 mg/day sertraline was effective and generally well tolerated in the treatment of childhood and adolescent OCD for up to 52 weeks.

Alderman and colleagues evaluated the safety, efficacy and pharmacokinetics of sertraline of sertraline in children and adolescents with depression and/or OCD.[20] For the purpose of the study a child was considered between the ages of 6 and 12 years and an adolescent was defined as 13- to 17-years-old. A total of 61 patients were enrolled in the study; 44 patients were diagnosed with major depression, 16 had OCD, and one patient had both disorders. The participants received a single 50 mg dose of sertraline. One week later they received either 1) a starting dose of 25 mg/day force titrated to 200 mg/day in 25 mg increments or 2) a starting dose of 50 mg/day force titrated to 200 mg/day in 50 mg increments. These doses were continued for 35 days.

The investigators also evaluated the single- and multiple-dose pharmacokinetics of sertraline and its major metabolite, demethylsertraline. For each patient, the following pharmacokinetic parameters were determined: peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), area under the plasma concentration-time curve (AUC_{0-24}), trough plasma concentration 24 hours after drug administration (C_{min}) except on day 1, and elimination half-life ($t_{1/2}$) after the final dose. Pharmacokinetic parameters were similar in the pediatric and adolescent patients.

Efficacy was determined using CY-BOCS, NIMH-GOCS, and the CGI-S and CGI-I scales. Among the 17 patients with OCD, the mean CY-BOCS, NIMH and CGI scores decreased significantly from baseline. The safety of sertraline was assessed by means of physical examination, including vital signs and a 12-lead ECG. These tests were performed during the screening period, on day 14, and at completion of the study. Of the 61

enrolled patients, 51 (84%) reported at least one adverse event. Headache (21%), nausea (21%), insomnia (21%), somnolence (15%), dyspepsia (12%), and anorexia (12%) were the most frequently reported side effects. The majority of the adverse events were either mild or moderate. The safety and pharmacokinetic results of this study indicate that extrapolation of current adult use and dosage in the pediatric population is appropriate.

FLUOXETINE

Geller and colleagues investigated the effectiveness and tolerability of fluoxetine in the acute treatment of childhood and adolescent OCD. [21] This 13-week, placebo controlled, randomized trial involved 72 children (6–12 years) and 65 adolescents (13–18 years). The subjects were randomized to receive fluoxetine or placebo in a 2:1 ratio. The mean age of the treatment group was 11.4±3 and 11±2.8 for the placebo group. The treatment group's dosage was initiated at 10 mg fluoxetine for 2 weeks, and then increased to 20 mg daily to a maximum daily dosage of 60 mg. The mean daily dose for the fluoxetine group was 24.6mg. The primary outcome measure was the CY-BOCS. Other measures used for OCD were the CGI-S, CGI-I, NIMH-GOCS, OCD Impact Scale, and the Patients Global Impressions (PGI) scale. Compared with placebo, fluoxetine was associated with significant reduction of OCD severity as measured by total CY-BOCS score (P=0.026). Secondary outcome results improved significantly as well.

The percentage of patients who completed the study was similar for both groups. Likewise, there was no significant difference between the placebo and fluoxetine groups in the percentage of patients who discontinued treatment because of a lack of efficacy or adverse events. The primary reasons for fluoxetine-treated patients to discontinue medication was headache, hyperkinesias, abnormal liver function tests, manic reaction, nervousness, and somnolence, compared to hyperkinesias or nervousness in the placebo-treated group. Fluoxetine was associated with significantly greater reduction of OCD symptom severity compared with placebo, and was well tolerated in both children and adolescents.

In order to examine the efficacy and safety of fluoxetine for short- and long-term treatment, Semerci et al. conducted an open trial and discontinuation study in children and adolescents with OCD. Twenty-three children and adolescents 7–17 years of age (mean age 12) with OCD were treated with a fixed dose of fluoxetine (20 mg/day) for 20 weeks. Symptom severity of OCD was measured with the Maudsley OCD Scale[22] and the CGI scale. The safety of the treatment was assessed through monthly monitoring of vital signs, laboratory tests, and ECG. At the end of the 20 weeks, fluoxetine administration was discontinued. The patients were then longitudinally followed for a period of 24 months.

The results showed that fluoxetine was well tolerated and side effects were relatively mild. At the end of the treatment phase (20 weeks), 21 patients (91.3%) responded well to fluoxetine with a CGI score of 1. However, 10 patients (43.5%) relapsed in the first 8 to 16 weeks after the discontinuation of therapy (mean=13±4.1 weeks). Reported side effects included dyspepsia and nausea in 13% of the patients and skin rash in one patient (4.3%). There were no significant changes in ECG, laboratory values, blood pressure or weight. The results of this study indicate that fluoxetine is effective and safe for short-term treatment of OCD. It also suggest the possibility of long-term efficacy in children and adolescents with OCD.[23]

Fluoxetine-induced mania has been reported in adolescents with attention-deficit/hyperactivity disorder, mood disorders, and/or in adolescents with depression.[24] Go and colleagues described the first reports of fluoxetine-induced mania in three adolescents with OCD.[25] The first subject, a 17-year-old male, developed uncharacteristic behaviors that included more severe irritability, heated arguments with his classmates, grandiosity, increased rate of speech, and social gregariousness. This behavior arose after 3 weeks of 10 mg/day fluoxetine for the treatment of his OCD. The second case involved a 12-year old girl with OCD who was started on fluoxetine 10 mg/day. Over a two-week period her dose was titrated up to 40 mg/day. Following administration of 40 mg/day for one week her mother noticed a marked increase in irritability, fluctuations in her mood (ranging from silly to angry to uncontrollable crying), increased impulsivity, overactivity, increasing disruptivity in class with plummeting work performance, inability to con-

centrate, and pressured speech. She also exhibited increased aggressiveness that was manifested by her holding a knife to her brother and blurting out that she wanted to kill her stepfather.

The last individual was a 17-year-old girl with a diagnosis of OCD. She had received 20 mg/day of fluoxetine for four weeks without problems. About two weeks after the dosage of was increased to 30 mg/day she suddenly developed manic behaviors. She became impulsive and exercised poor judgment, poor insight, increased energy, and increased psychomotor agitation. These symptoms had occurred for approximately one week before the physicians was notified and the fluoxetine was discontinued. Although this series of patients is small, treated openly, and not diagnosed or monitored with standardized instruments, it is still interesting to note the appearance of these type behaviors after administration of fluoxetine to three adolescents with OCD. As the use of fluoxetine increases in children and adolescents with OCD, these findings warrant heightened clinical vigilance and further study.[25]

PAROXETINE

Rosenberg and colleagues published the first report of the use of paroxetine in children and adolescents with OCD in 1999.[26] They investigated the safety and efficacy of paroxetine using an open-label study that was performed over a 2-week period. This trial was unique in that it examined the effectiveness of paroxetine in patients with other co-morbid illness. In this trial, 9 males and 11 females ranging from 8 to 17 years received daily doses ranging from 10 to 60 mg of paroxetine. All of the patients were started on paroxetine 10 mg/day, and dosages were increased by ≤10mg every two weeks to a maximum of 60 mg/day. The mean dose at the end of the study was 41.11 mg/day. Response to paroxetine was defined as ≥30% reduction in OCD symptom severity, as assessed with the CY-BOCS. Severity of anxiety was measured with the Hamilton Anxiety Rating Scale and severity of tics was rated with the Yale Global Tic Severity Scale. Overall improvement was assessed by the Children's Global Impression Scale, and the Adverse Experience Scale was used to rate adverse events and side effects. Patients with OCD showed a significant decrease in OCD symptom severity as measured by their CY-BOCS scores (P=0.0001). The participants also demonstrated increased in CGAS (P=0.0001) and a decrease in CGI scores (P=0.0001). It is important to note that the two patients presenting with tic-related OCD did not improve while receiving paroxetine. One of these patients with a co-morbid Tourette's disorder demonstrated an increase in CY-BOCS score and a doubling of tic severity during treatment. Patients with OCD also showed a significant decrease in severity of anxiety (P=0.008).

Mild side effects reported to the treating psychiatrist that were not present at baseline included: hyperactivity/behavioral disinhibition (30%), headache (25%), insomnia (15%), gastrointestinal distress (15%), increased anxiety (10%), drowsiness (5%), and dry mouth (5%). Severe side effects included suicidal ideation (5%) and increased frequency of tics (5%). The authors concluded that paroxetine may be an efficacious and safe for the treatment of pediatric outpatients with OCD, although paroxetine alone may not be useful for Tourette disorder and other tic-related conditions.

CITALOPRAM

A study conducted in Denmark examined the adverse effects and potential clinical value of citalopram in 23 children and adolescents (11 males and 12 females) aged 9 to 18 years with OCD.[27] In this open-label trial, 10 to 40 mg of citalopram was administered daily for 10 weeks. All of the patients received individual cognitive-behavioral therapy (including exposure prevention), supportive family therapy, and pharmacotherapy. Outcome measures included the Y-BOCS and the CY-BOCS. The presence of obsessive-compulsive and co-morbid symptoms was rated with the Children's Assessment Schedule (CAS) and social functioning was rated with the CGAS. The side effects were elicited by following a checklist of expectable and possible side effects. Most of the patients (20/23) were treated with 40 mg of citalopram.

The mean total Y-BOCS/CY-BOCS scores were significantly reduced over the 10 weeks of treatment. Inpatients did not differ significantly from outpatients on the Y-BOCS/CY-BOCS (in: 31.2±3.4, out: 29.7±3.7). Mild side effects were re-

Table 2. Incidence of SSRIs Adverse Effects (%)

Adverse Effect	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Nausea	21	21.1	40	25.7	26
Headache	---	20.3	22	17.6	20
Sedation	18	11.6	22	23.3	13
Dry Mouth	20	9.5	14	18.1	16
Diarrhea	8	12.3	11	11.6	18
Sexual Dysfunction	6	1.9	8	12.9	16
Anorexia	4	8.7	6	6.4	2.8
Weakness/ Fatigue	5	4.2	14	15	11
Insomnia	15	13.8	21	13.3	16

Adapted from reference 11

ported by 13 of the 23 patients, but most adverse drug effects vanished after a few weeks of treatment. The most commonly reported side effects were dry mouth, headache, and tremor. Although the results seem encouraging, it is important to note that only 6 patients (26%) appeared to have changed sufficiently to no longer fulfill DSM-III-R criteria for OCD, and even these patients retained obsessive-compulsive symptoms at endpoint. The findings suggest that citalopram is effective and well tolerated in children and adolescents with severe OCD. This study also suggests that concomitant administration of behavioral and cognitive treatment may work synergistically with citalopram in relieving obsessive-compulsive disorder.

The 23 adolescents previously described,[26] along with an additional 7 patients, were included in another study conducted by Thomsen et al.[27] This trial evaluated the tolerability and effectiveness of citalopram in the treatment of OCD in the 30 adolescents ranging from 13 to 18 years of age. The study was a prospective, open-label study in a flexible-dose fashion (dose ranging from 20–70 mg; mean dose 46.5 mg), with follow-up continuing for up to 2 years. Efficacy was tested using the Yale-Brown Obsessive Compulsive Scale (child or adult version) as well as the Children's Global Assessment Scale (CGAS). As for efficacy, the mean Y-BOCS score significantly decreased after six months, and again at 12 months. However, from year one to two of treatment, no further significant reduction in score was noted. Therefore, efficacy was demonstrated in treatment up to one year. It is noteworthy that patients in this study were also undergoing concurrent cognitive behavioral therapy throughout the study, which is a recommended combination in OCD patients. Safety was assessed using personal reports of adverse effects. These included dry mouth, nausea, headache, sedation, sexual dysfunction, insomnia, tremor, weight increase, and aggressive behavior. Although it was reported that none of the patients experienced serious adverse effects, 16 patients dropped out before the study's completion for various reasons. The clinical efficacy and side effects of citalopram are comparable with observations of other SSRIs in childhood and adolescent OCD.

FLUVOXAMINE

Riddle and colleagues studied the safety and efficacy of fluvoxamine in children and adolescents diagnosed with OCD.[29] One hundred and twenty subjects aged 8 to 17 years (mean age=13.4) were randomly assigned to either fluvoxamine 50 to 200 mg/day or placebo for 10 weeks. The response of OCD to therapy was evaluated using the CY-BOCS, NIMH-OC and CGI scales. The fluvoxamine group showed significantly greater improvement than the placebo group in CY-BOCS score in weeks 1, 2, 3, 4, 6, and 10. NIMH-OC and CGI scores were also significantly improvement. As for safety, adverse events were generally mild and well tolerated. Adverse events occurring in more than 10% of the fluvoxamine group included headache, insomnia, infection, asthenia, abdominal pain, nausea, diarrhea, dyspepsia, pharyngitis, agitation, hyperkinesias, rhinitis, and somnolence. Fluvoxamine was found to be significantly better than placebo in reducing the severity of OCD in children and adolescents aged 8 to 17 years. Although five subjects from the fluvoxamine group withdrew from the study due to adverse events experienced, occurrences were similar in both groups. Fluvoxamine was found to have a rapid onset of action and was well tolerated and effective for the short-term treatment of OCD in children and adolescents.

Neziroglu and colleagues explored the addition of behavior therapy to fluvoxamine treatment in a randomized 10-week trial.[30] Ten children and adolescents aged 10 to 17 years who had been diagnosed with OCD were randomly assigned to receive either fluvoxamine alone or fluvoxamine with behavior therapy. Outcome measures used were the NIMH-GOCS, the CGI-S, CGI-I, and the CY-BOCS. For both groups, fluvoxamine was administered at 50 mg/day and increased at increments of 50mg weekly over the first month to a maximal dose of 200 mg/day. No patients does was reduced as the result of an intolerable side effect. Although the focus of this trial was the addition of behavioral therapy to fluvoxamine treatment, it was noted that fluvoxamine alone was efficacious in most of the patients. Although the study showed that the addition of behavioral therapy to fluvoxamine resulted in greater improvement in CY-BOCS scores than fluvoxamine alone, significant improvement was observed even when medication was administered alone.

SUMMARY

Most of the studies of SSRIs for the treatment of pediatric OCD were open-label trials that used control groups. Although they did not employ ideal study designs they were able to show positive clinical effects with minimal adverse effects. The results of the studies suggest that SSRIs are viable options for pediatric patients with OCD due to their low side-effect profile and lack of need for serum concentration monitoring. Compared to the TCAs, the SSRIs have a good safety profile in overdose, which is especially important given the critical consequences of pediatric psychological problems. Since the FDA has only approved two of the five currently available SSRIs for the treatment of childhood and adolescents with OCD, additional controlled studies are needed in this population. Our review shows that the SSRIs do appear to be a safe choice to effectively treat children and adolescents with OCD.

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