Selective Serotonin Reuptake Inhibitors in Autism: A Review of Efficacy and Tolerability

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Background: Awareness of the impact and prevalence of autism spectrum disorders has significantly increased in recent years. Given the dearth of reliable interventions, there is great interest in demonstrating efficacy of the various treatment options. A growing body of evidence links autism spectrum disorders to abnormalities in serotonin function, and the selective serotonin reuptake inhibitors (SSRIs) have been utilized to target various symptoms of the disorders. This article reviews the available data on the efficacy and tolerability of SSRIs in individuals with autism spectrum disorders. Objectives for future research in this area will also be suggested.

Data Sources and Study Selection: The entire PubMed database including MEDLINE (1966–July 2005) was searched for English-language biomedical articles. Search terms included *autism*, *autism spectrum disorder*, *citalopram*, *escitalopram*, *fluoxetine*, *fluvoxamine*, *paroxetine*, *pervasive developmental disorder*, *selective serotonin reuptake inhibitors*, and *sertraline*. All clinical trials evaluating treatment outcomes associated with the use of SSRIs in managing symptoms of autism that were identified in the search were reviewed. All randomized controlled trials and open-label trials were included in this review. Case reports and case series were excluded.

Data Synthesis: We identified 3 randomized controlled trials and 10 open-label trials or retrospective chart reviews on the use of SSRIs in autism and autism spectrum disorders. The SSRIs that have been studied in autism spectrum disorders are citalopram, escitalopram, fluoxetine, fluvoxamine, and sertraline. Most studies demonstrate significant improvement in global functioning and in symptoms associated with anxiety and repetitive behaviors. While side effects were generally considered to be mild, increased activation and agitation occurred in some subjects.

Conclusions: Although SSRIs may demonstrate therapeutic benefit in autism spectrum disorders, methodological weaknesses of many of the clinical trials suggest the need for additional randomized controlled trials. Furthermore, given the increased awareness of the dangers associated with SSRI-induced activation and agitation, the presence of these side effects in the autistic population warrants closer attention to dosage, titration, and subject selection issues.

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Central nervous system regulation of serotonin has been implicated in a variety of roles critical to human behavior, and individuals with autism spectrum disorders may demonstrate impairment in many of the functions that serotonin mediates. Functions associated with the serotonin system may include, but are not limited to, aggression, anxiety, mood, impulsivity, sleep, ingestion behavior, reward systems, and psychosis.[1] There is also a significant body of evidence to support the notion that serotonin plays a crucial role in brain development. Specifically, serotonin has been shown to regulate cell division and differentiation, neurite growth, and synaptogenesis.[2] As a result, the impact of serotonin neurotransmission on the development and treatment of neuropsychiatric disorders has been a vital topic of ongoing research.

Work specifically examining the association between serotonergic regulation and autism dates back to 1961, when Schain and Freedman[3] first reported elevated levels of whole blood serotonin in a subgroup of autistic individuals. Since then, most investigators have found that peripheral serotonin levels are significantly higher in autistic subjects as compared with normal controls,[4–10] and approximately one third of autistic individuals are considered to have hyperserotonemia. Given that selective serotonin reuptake inhibitors (SSRIs) are known to impact levels of peripheral and central serotonin, the implications with respect to autism spectrum disorders are clear: if serotonin regulation is impaired in autism and its spectrum disorders, serotonergic medications may correct the dysregulation and ameliorate associated symptoms.

Recent neuroimaging studies are noteworthy in their ability to potentially demonstrate developmental

Table 1. Randomized Controlled Trials of SSRIs in Autism Spectrum Disorders

Authors	Design	Sample	Medication	Measure	Outcome	Side Effects
Hollander et al, 2004[22]	Placebo controlled crossover	45 children and adolescents	Fluoxetine	CGI-AD, CYBOCS	Significant decrease in repetitive behavior	No overall difference between groups
Buchsbaum et al, 2001[23]	Placebo controlled crossover	6 adults	Fluoxetine	YBOCS, HAM-A	Significant improvement in anxiety	Data unavailable
McDougle et al, 1996[24]	Double-blind placebo controlled	30 adults	Fluvoxamine	YBOCS, CGI, Vineland, Brown, Ritvo-Freeman	Significant improvements in repetitive behavior and aggression	Nausea, sedation

Abbreviations: Brown = Brown Aggression Scale, CGI = Clinical Global Impressions scale, CGI-AD = CGI adapted for global autism, CYBOCS = Children's Yale-Brown Obsessive Compulsive Scale, HAM-A = Hamilton Rating Scale for Anxiety, Ritvo-Freeman = Ritvo-Freeman Real-Life Rating Scale, Vineland = Vineland maladaptive behavior subscales, YBOCS = Yale-Brown Obsessive Compulsive Scale.

changes in brain serotonin synthesis capacity by using positron emission tomography (PET) and radiolabeled α[^{11}C]methyl-L-tryptophan. Although it is necessary to exercise caution in interpreting their results, Chugani and colleagues[11] found significant differences in serotonin synthesis capacity between autistic and nonautistic children using PET imaging. Their results may indicate a disruption in the serotonergic mechanisms that regulate synthesis capacity during early development in autism and could provide indirect support for trials of serotonergic medications in young autistic children.

Given the consistency of reports that document serotonergic abnormalities in autism, and the possibility that altered serotonin regulation may reflect an underlying genetic liability to autism,[12] much effort has focused on attempts to discover genetic explanations to clarify these findings. The serotonin transporter, for example, has been subjected to intense scrutiny because of its crucial role in serotonergic neurotransmission and also because it is the site of action of SSRIs. The serotonin transporter gene (*SCL6A4*) is located on chromosome 17 and contains a variable repeat sequence in the promoter region (5HTTLPR) that is a candidate gene in autism. There is a more common 16-repeat long allele, but the less common 14-repeat short allele form has been shown to reduce both the transcriptional efficiency of the transporter[13–15] and serotonin uptake.[16] Linkage between polymorphisms in the promoter region of the serotonin transporter gene and autism has been demonstrated, and variant alleles of the gene may be preferentially inherited in family members affected with autism.[17–20] In contrast, work by Tordjman and colleagues[21] did not demonstrate preferential inheritance of variant promoter alleles in autism but instead found that the short promoter variant was associated with a more severely affected clinical phenotype.

Understanding the mechanism of serotonergic abnormalities in autism will hopefully provide further clues to the underlying abnormality in the central nervous system, the development of more specific markers for studying the disorder, and additional approaches to treatment. In the meantime, SSRIs are known to influence both peripheral and central serotonin levels and also have the potential ability to ameliorate many related psychiatric symptoms. Irritability, aggression, and compulsive behavior, for example, are frequently present in autism and occur similarly in other disorders that are known to respond to SSRIs. Although the precise relationship between autism and the serotonergic system has yet to be elucidated, some evidence supports the use of SSRIs to improve autistic symptomatology. Given the dearth of available pharmacologic treatment in autism, and in light of the recent controversy surrounding the use of SSRIs in children and adolescents with depression, the following review will critically examine all of the clinical trials of SSRIs in the treatment of autism and its associated symptoms in order to assess the issues of efficacy and tolerability.

METHOD

Three randomized controlled trials (Table 1)[22–24] and 10 open-label trials or retrospective chart reviews (Table 2)[25–34] on the use of SSRIs in autism spectrum disorders were identified by searching the entire PubMed database for English-language biomedical articles on clinical trials with SSRIs in autism and autism spectrum disorders. PubMed is a service of the National Library of Medicine that includes over 15 million citations from Medline and additional life science journals that date back to the 1950s. The medications studied were citalopram, escitalopram, fluoxetine, fluvoxamine, and sertraline.

RESULTS

Citalopram

The only published trial of citalopram[26] was done in 2003 and retrospectively reviewed charts of 15 children and adolescents (aged 6 to 16 years) with pervasive developmental disorders (PDD) using the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I) to assess improvement. The mean ± SD dose of citalopram was 16.9 ± 12.1 mg daily with a range of 5 to 40 mg, and the mean duration of treatment was 218.8 ± 167.2 days. Eleven out of the 15 subjects (73%) were found to be "much improved" or "very much improved." No association was detected between dose and response, but duration of treatment was posi-

Table 2. Open-Label Trials and Chart Reviews of Selective Serotonin Reuptake Inhibitors in Autism Spectrum Disorders

Authors	Design	Sample	Medication	Measure	Outcome	Side Effects
Owley et al, 2005[25]	Prospective open label	28 Children and adolescents	Escitalopram	ABC-CV, CGI	61% Responded with significant improvement across all measures	78% With "dose-related" side effects, including hyperactivity, irritability, and aggression
Namerow et al, 2003[26]	Retrospective chart review	15 Children and adolescents	Citalopram	CGI	73% Showed improvement in severity of PDD symptoms	33% With "mild" side effects: headache, sedation, aggressiveness, agitation, lip dyskinesia
Martin et al, 2003[27]	Prospective open label	18 Children and adolescents	Fluvoxamine	CGI, CYBOCS, SCARED	No significant change on any outcome measures	50% With akathisia, behavioral activation, and sleep difficulties; also headaches, appetite changes, abdominal discomfort
DeLong et al, 2002[28]	Open label	129 Children	Fluoxetine	Nonstandardized	77% Showed an excellent, good, or fair response	Behavioral activation; data on other side effects unavailable
DeLong et al, 1998[29]	Open label	37 Children	Fluoxetine	Nonstandardized	59% With improvements in language and social interaction	Hyperactivity, aggression
McDougle et al, 1998[30]	Prospective open label	42 Adults	Sertraline	CGI, YBOCS, Vineland, Brown, Ritvo-Freeman	57% Improved in repetitive symptoms and aggression	Anorexia, tinnitus, alopecia, weight gain, sedation, anxiety, agitation
Steingard et al, 1997[31]	Open label	9 Children	Sertraline	Nonstandardized	89% With "positive response"	Worsening behavior, stomachaches
Hellings et al, 1996[32]	Open label	9 Adults	Sertraline	CGI	89% With significant improvement	1 Dropout because of agitation and worsening self-picking
Cook et al, 1992[33]	Open label	23 Children, adolescents, and adults	Fluoxetine	CGI	65% With significant improvement	Restlessness, hyperactivity, agitation, decreased appetite, insomnia, elated affect
Fatemi et al, 1988[34]	Retrospective chart review	7 Adolescents and young adults	Fluoxetine	ABC	Significant decrease on lethargy subscale	Appetite suppression, vivid dreams, hyperactivity, agitation, worsening depression

Abbreviations: ABC = Aberrant Behavior Checklist, ABC-CV = ABC-Community Version, Brown = Brown Aggression Scale, CGI = Clinical Global Impressions scale, CYBOCS = Children's Yale-Brown Obsessive Compulsive Scale, PDD = pervasive developmental disorder, Ritvo-Freeman = Ritvo-Freeman Real-Life Rating Scale, SCARED = Screen for Child Anxiety Related Emotional Disorders, Vineland = Vineland maladaptive behavior subscales, YBOCS = Yale-Brown Obsessive Compulsive Scale.

tively correlated with response to treatment. Although the charts of patients across the entire spectrum of PDD were included in the analysis, there was no significant relationship between diagnosis and response to citalopram.

Sixty-six percent of patients experienced significant improvement in symptoms of anxiety as defined by the authors, especially with respect to preoccupation with nonfunctional routines, repetitive behaviors or stereotypies, and rigid adherence to daily routines. Forty-seven percent of subjects had significant improvement in mood symptoms, particularly mood lability, aggression, and irritability. Interestingly, 9 of the 10 responders reported an inadequate response to SSRI treatment in the past, and this may imply a possible advantage for citalopram over other SSRIs in the treatment of PDD. Adverse experiences were also systematically recorded and incorporated in the review. Thirty-three percent of subjects reported side effects that included headaches, sedation, aggressiveness, agitation, and lip dyskinesia. Two subjects discontinued the medication due to side effects, but none required emergency intervention.

This study suggests that citalopram may be effective in treating mood and anxiety symptoms associated with PDD. However, caution must be exercised in interpreting these results because subjects were selected retrospectively and no control group was available for comparison. Patients were also receiving concurrent psychotropic medications in addition to psychotherapy throughout the study period, and it is therefore unclear whether therapeutic effects were due to citalopram or the combination of treatments.

Escitalopram

There has been 1 clinical trial using escitalopram in the treatment of PDD.[25] Twenty-eight subjects with PDD between the ages of 6 and 17 years old were enrolled in this 10-week trial that used a forced titration, open-label design. The dose of escitalopram was started at 2.5 mg/day and increased weekly to a maximum of 20 mg/day. The Abberant Behavior Checklist-Community Version (ABC-CV) and the CGI were used to assess outcome. Significant improvement was demonstrated on the CGI severity ratings and all of the ABC-CV subscale scores (irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech). Treatment response was defined as a decrease of 50% or more on the ABC-CV irritability subscale score and 17 (61%) of 28 subjects responded. Seven (25%) of 28 subjects responded to a dose of less than 10 mg/day, and 10 (36%) of 28 tolerated doses

of at least 10 mg/day. Among the 23 study completers, 5 subjects reportedly experienced no side effects and 18 subjects showed dose-related side effects that required a dose reduction. Although side effects were not reported systematically, 7 subjects were described to exhibit "primarily irritability," 6 subjects showed primarily "hyperactivity," and 5 subjects had "high levels of both hyperactivity and irritability." In addition, 1 subject was noted to manifest "extreme aggression" on a 5-mg dose. No suicidal ideation, self-injurious behavior, or sleep disturbance was recorded. Ten of 28 subjects (and 7/17 responders) were reportedly unable to tolerate a 10-mg dose of escitalopram, and the mean final dose was 11.1 mg/day (SD = 6.5 mg, range: 0–20 mg). There was no correlation between final dose and weight, although there was a significant, albeit weak, association between dose and age.

This study appears to provide support for the use of escitalopram in PDD. According to these results, this medication is both tolerable and efficacious for several of the associated symptom domains in PDD. These data also demonstrate the dose-related nature of side effects in this population and emphasize the importance of starting medications at low doses and using slow titration schedules. However, these conclusions must also be considered with respect to this study's primary limitation which is its open-label design.

Fluoxetine

A recent placebo-controlled crossover trial examined the efficacy of liquid fluoxetine in 45 children and adolescents (aged 5–16 years) with autism spectrum disorders.[22] The study included two 8-week phases separated by a 4-week washout period. The Children's Yale-Brown Obsessive Compulsive Scale (CYBOCS), the CGI adapted for global autism (CGI-AD), and a Global Autism Composite Improvement Measure were used as outcome measures. Patients were free of concurrent medications throughout the study period. Fluoxetine dosing began at 2.5 mg per day for the first week and was titrated over a 2-week period to a maximum dose of 0.8 mg/kg per day depending on symptoms and side effects. The mean ± SD final dosage for fluoxetine was 9.90 ± 4.35 mg daily. As measured by the CYBOCS, subjects showed a significant reduction in repetitive behaviors during fluoxetine treatment as compared with placebo, with a medium to large effect size (0.76). No difference was observed between fluoxetine and placebo on the CGI-AD, although both showed improvement. On a global autism composite improvement measure, which included ratings of target behaviors and other core symptoms, there was a trend toward greater improvement for fluoxetine over placebo that did not reach statistical significance.

Side effects were systematically measured by the fluoxetine side effects symptom checklist in this study, and there were no significant differences in side effect profiles between placebo and fluoxetine. Sedation, agitation, and anorexia occurred numerically but not statistically more often among subjects taking fluoxetine, whereas anxiety, insomnia, diarrhea, and weight gain occurred numerically but not statistically more often among subjects taking placebo. Sixteen percent of subjects required dose reduction due to agitation with fluoxetine, and 5% required dose reduction due to agitation with placebo. Using the suicide subscale of the Overt Aggression Scale-Modified, there was no significant risk of suicidal ideation in subjects taking fluoxetine. This study was the first controlled trial of liquid fluoxetine in children and adolescents and provides evidence to support the efficacy of this medication in autism. This study also illustrates a possible advantage for the use of lower doses in younger populations; while the generalization of these findings to a higher dose range may not be permissible, efficacy was nevertheless demonstrated without producing significant adverse events.

In 2001, Buchsbaum and colleagues[23] studied 6 adult subjects with autism spectrum disorders in a 16-week placebo-controlled crossover trial of fluoxetine. The medication was found to significantly improve anxiety symptoms as measured by the YBOCS obsessions scale and the Hamilton Rating Scale for Anxiety. In addition, using PET to measure regional cerebral glucose metabolism in these subjects revealed that those with higher baseline metabolic rates in the medial frontal region and anterior cingulate were more likely to respond favorably to fluoxetine.

Fluoxetine has also been studied in several open-label trials or retrospective chart reviews. In 1988, Fatemi and colleagues[34] examined the effect of the medication in 7 adolescents and young adults (aged 9–20 years) with autism using a retrospective chart review design. Subjects were treated for 1.3 to 32 months at a mean dosage of 37.1 ± 21.0 mg/day. One subject was started on a dose of 10 mg/day and the rest were started on a dose of 20 mg/day. Symptoms were monitored using the Abberant Behavior Checklist (ABC). The subscales of the ABC assess irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech. The results demonstrate a reduction in all behaviors measured by the ABC except hyperactivity, although only the decrease in lethargy was of statistical significance. The ABC lethargy subscale encompasses symptoms of social behavior and psychomotor activity, and the authors suggest that a reduction on this subscale may reflect improvement in underlying mood symptoms beyond the activating effects of the medication. There was no significant relationship between length of treatment and response.

Side effects reported were transient appetite suppression (N = 2), chronic vivid dreams (N = 1), and an increase in hyperactivity (N = 4). Two patients discontinued treatment due to worsening depression and agitation, re-

spectively. The dose magnitude may explain why 57% of subjects reportedly experienced agitation. It is important to note that this study included subjects with medical and psychiatric comorbidities as well as subjects who were receiving concurrent psychotropic medications. Study limitations also include its retrospective design, small sample size, and lack of blinding.

Also in 1998, DeLong and colleagues[29] performed an open-label study of fluoxetine in 37 children (aged 2 to 7 years) using nonstandardized outcome measures, which included "various instruments covering a wide range of functions." Assessments were made by several independent evaluators including parents and teachers. Twenty-two (59%) were described as having a positive result from the medication. Eleven showed an "excellent" response where only "vestiges of their condition remained" and 11 had a "good" response, showing significant improvement, but still "identifiably autistic." The authors concluded, on the basis of individual case descriptions, that improvement was evident in the behavioral, language, cognitive, affective, and social domains. Fifteen subjects showed no long-term improvement, and fluoxetine was discontinued. Side effects included hyperactivity, agitation, and lethargy, and 1 child developed a rash and diarrhea. The main reason for stopping treatment was hyperactivity, agitation, and/or aggressiveness.

The findings from this study support the use of fluoxetine in treating children with autism spectrum disorders, but design limitations must be considered. This was an open trial that did not employ blinding, placebo controls, or standardized outcome measures. Most of the children were also receiving concomitant treatment, including psychotropic medication, throughout the study period.

DeLong and colleagues[28] also published a follow-up of their work in treating autistic symptoms with fluoxetine but expanded the sample to include 129 children (aged 2 to 8 years) and followed them longitudinally for between 5 and 76 months (mean = 32 to 36 months). Outcome was described according to criteria defined by the authors as excellent, good, fair, or poor response, depending on the degree of improvement across the communication, social, and behavior domains of autism. However, specific outcome measures were not clearly described. The authors report that, of 129 children treated with fluoxetine who could be evaluated, 22 (17%) showed an excellent response, 67 (52%) had a good response, 10 (8%) had a fair response, and 30 (23%) had a poor response. They note that patients who were highest functioning at baseline showed the greatest improvement in general and observe that these changes may reflect not only medication effects, but possibly a natural tendency toward improvement in this subgroup.

Treatment response was also positively correlated with a family history of affective disorder. The optimal dosage of fluoxetine was also closely examined in this study and subjects separated into 2 groups: those who tolerated no more than 8 mg daily, and those who tolerated doses greater than 20 mg daily. Even among those defined as excellent/good responders, 60% had optimal doses less than 12 mg daily, and 40% tolerated higher doses ranging up to 40 mg daily. The limiting factor for tolerance was noted to be behavioral activation. Other side effects were not described in this article. Although the evidence to support the use of fluoxetine was expanded in this extension study, the design remained plagued by methodological weaknesses that preclude generalization of the findings.

In 1992, Cook and colleagues[33] examined the efficacy of fluoxetine using an open-label design in 39 children, adolescents, and adults (aged 7 to 52 years) with autism (N = 23) or mental retardation without autism (N = 16). The CGI was used to assess improvement in the overall severity of illness and repetitive behaviors. Fluoxetine dosing ranged from 20 mg every other day to 80 mg daily and was administered in an open titration. Fifteen (65%) of the 23 subjects with autism and 10 (63%) of the 16 mentally retarded subjects showed improvement in overall clinical severity. Severity ratings of perseverative and compulsive behavior also revealed a similar therapeutic response to fluoxetine in autistic and mentally retarded subjects. Side effects significant enough to "interfere with function or outweigh therapeutic effects" were reported in 6 of the 23 subjects with autism and 3 of the 16 subjects with mental retardation. Side effects were found to be more common in nonresponders than responders and to remit after dose reduction or discontinuation. The most common side effects in the autistic group were hyperactivity/restlessness/agitation (N = 5), insomnia (N = 4), elated affect (N = 4), decreased appetite (N = 4), increased rate of screaming (N = 2), crying spells (N = 1), yawning (N = 1), and maculopapular rash (N = 1). Although this study again supports the use of an SSRI in treating symptoms associated with autism, the limits of an open trial without placebo control or blind raters must be noted. The subjects in this trial also received concurrent psychotropic medication during the study period.

Fluvoxamine

A 12-week, double-blind, placebo-controlled trial of fluvoxamine[24] was completed in 30 adults (aged 18 to 53 years) with autistic disorder. Eight (53%) of the 15 subjects who received fluvoxamine versus none of the 15 subjects who received placebo were categorized as much improved or very much improved on the CGI. As measured by the YBOCS, Vineland maladaptive behavior subscales, and the Brown Aggression Scale, subjects who received fluvoxamine showed significantly greater improvement in repetitive thoughts and behavior, maladaptive behaviors, and aggression, respectively. In addition, using the Ritvo-Freeman Real-Life Rating Scale, fluvoxamine was superior to placebo in improving behavioral

symptoms according to the overall score and in improving language usage according to one of the subscales. These results were not significantly correlated with age or full-scale IQ. Side effects were reported as mild and included nausea (N = 3) and sedation (N = 2), which resolved with continued treatment.

In contrast, according to unpublished data cited by McDougle and colleagues,[35] another 12-week, double-blind, placebo-controlled trial of fluvoxamine done with children and adolescents with PDD showed the medication to be poorly tolerated and "with limited efficacy at best." In this study, 34 subjects (aged 5–18 years) were randomly assigned to receive either fluvoxamine or placebo. The medication was started at 25 mg every other day and increased by 25 mg every 3 to 7 days as tolerated with a mean final dose of 106.9 mg daily. Only 1 of the fluvoxamine-treated subjects demonstrated significant clinical improvement, and none of those in the placebo group showed improvement. Fourteen of the 18 subjects who received medication experienced adverse events, which included insomnia (N = 9), motor hyperactivity (N = 5), agitation (N = 5), aggression (N = 5), increased rituals (N = 2), anxiety (N = 3), anorexia (N = 3), increased appetite (N = 1), irritability (N = 1), decreased concentration (N = 1), and increased impulsivity (N = 1). However, 7 of the 16 subjects randomly assigned to placebo experienced adverse events (motor hyperactivity [N = 2], insomnia [N = 2], dizziness/vertigo [N = 1], agitation [N = 1), and diarrhea, decreased concentration, and increased self-stimulation [N = 1]).

Fluvoxamine has also been studied using a 10-week, prospective, open-label design in 18 children and adolescents (aged 7–18 years) with PDD.[27] In this study, the authors were especially concerned with whether a reduced dose would improve tolerability; subjects were started on either 12.5 or 25 mg daily and titrated to a maximum of 1.5 mg/kg/day in the absence of significant side effects. Assessments were made using the CGI-S, the CYBOCS, and the Screen for Child Anxiety Related Emotional Disorders. No significant changes from baseline were found on any of the measures, yet 8 subjects (44%) were determined to be either full or partial responders according to criteria defined by the authors.

Interestingly, all of the female subjects were considered responders, and although this finding cannot be generalized, it highlights the importance of specifically considering gender in clinical trials with this population. Thirteen subjects (72%) reported at least 1 adverse event: the most frequently reported side effects were akathisia/behavioral activation/agitation (50%), sleep difficulties (50%), headaches (33%), appetite changes (22%), abdominal discomfort (17%), and rhinitis (11%). Four subjects (22%) experienced severe behavioral activation that required a dose reduction in 1 subject and discontinuation of the medication in the other 3. The results of this study do not provide compelling evidence for the use of fluvoxamine in children and adolescents with PDD and, taken together with unpublished data, may imply that fluvoxamine should not be the first choice SSRI for treatment in these youth. However, several shortcomings warrant caution in interpreting the results: the use of a small sample size, the absence of a control group, and unblinded ratings all prohibit concluding that fluvoxamine is of no benefit in PDD.

Sertraline

A 12-week, prospective, open-label study in 42 adults (aged 18–39 years) with PDD[30] examined the efficacy of sertraline for reducing repetitive thoughts, repetitive behavior, and aggression and for improving social functioning. The outcome measures used were the YBOCS for repetitive thoughts and behavior, the Self-Injurious Behavior Questionnaire for aggression, and the Ritvo-Freeman Real-Life Rating Scale for general symptoms of PDD including sensory motor behavior, social relatedness, affect regulation, sensory responses, and language. Doses ranged from 50 to 200 mg as tolerated. Maximum dose was reached within 3 weeks and maintained for 9 weeks. Patients were free of any medications for at least 4 weeks prior to commencement of the study, and no concurrent medications were administered throughout the study. Twenty-four (57%) of the 42 subjects were treatment responders, defined as either "much improved" or "improved" on the CGI. Improvement was evident primarily in the aggressive and repetitive behavior symptoms. It is interesting to note that subjects with autism and PDD not otherwise specified showed significantly greater improvement than subjects with Asperger's disorder. Sertraline was generally well tolerated by most subjects. Among the 37 subjects who completed the study, the following side effects were reported: anorexia (N = 1), headache (N = 1), tinnitus (N = 1), alopecia (N = 1), weight gain (N = 3), sedation (N = 1), and anxiety/agitation (N = 2). However, 3 subjects dropped out of the study because of persistent agitation and were classified as nonresponders. The results of this open-label trial support the use of sertraline in adults with PDD; yet, the efficacy and tolerability of this medication in children and adolescents cannot be generalized from these results.

In a second open-label study,[31] sertraline was administered for the treatment of transition-associated anxiety and agitation in children with autism. Nine subjects with autism (aged 6–12 years old) were started on sertraline 25 to 50 mg daily for transition-associated behavioral impairment. According to a series of case descriptions, 8 of 9 subjects (89%) showed "some degree of response to sertraline treatment." In 3 patients, an initial response was attenuated after 3 to 7 months of treatment and resulted in discontinuation of the medication.

Adverse effects were described as minimal, with 1 subject reporting "stomachaches." However, 2 patients

showed significant worsening of their behavior when their doses were raised to 75 mg daily. The authors note that small doses of sertraline may be effective and may reduce the emergence of adverse effects and that some children may benefit from divided doses as a result. Both subjects who experienced dose-related worsening of their behavior subsequently improved when the dose was decreased. Although this open-label trial provides support for the use of sertraline in children and adolescents with transition-associated anxiety and agitation, the results must be considered in light of the absence of an adequate sample size, comparison group, or standardized outcome measures.

A third open-label trial[32] examined the efficacy of sertraline for the treatment of self-injury and aggression in 9 adults with mental retardation, 5 of whom had comorbid autism. Doses ranged from 25 to 150 mg/day. Behavior severity was measured using the CGI at baseline and after 28 days of treatment. Eight (89%) of 9 subjects showed improvement on the CGI. Side effects were generally not reported, but 1 subject was noted to have discontinued the study due to an increase in agitation and worsening of "self-picking" behavior. However, the presence or absence of autism among the responders was not included in the analysis. This study was also limited by its small sample size, the use of concomitant medications including neuroleptics, the lack of rater blinding, and the inclusion of patients with multiple psychiatric and medical comorbidities.

CONCLUSIONS

From the studies reviewed, SSRIs appear to demonstrate therapeutic benefit in the treatment of autism spectrum disorders. Most open-label and controlled studies show significant improvements in overall global functioning and in a wide range of symptoms, including anxiety, aggression, and repetitive behavior. Fluoxetine in particular has 2 placebo-controlled trials with positive results to support the use of this medication. Fluvoxamine also has a controlled trial, albeit in adults, to provide evidence of its efficacy, yet results from open-label trials do not support its use in children. On the basis of most of the available data, SSRIs do not seem to directly improve communication and social deficits; yet, it is possible to suggest that improved behavioral control may indirectly result in prosocial behavior and subsequent progress in communication. Unfortunately, most studies did not specifically measure the core domains of communication and social impairment characteristic of PDD. Incorporating a more comprehensive battery of outcome measures to assess these domains in long-term clinical trials is an appropriate direction for future research.

Selective serotonin reuptake inhibitors may be well tolerated in many patients with autism spectrum disorders, but differences exist between adult and child/adolescent populations. The majority of reported side effects may be characterized as mild, although agitation appeared in a significant number of subjects and was severe enough to warrant medication discontinuation or reduction in several of the trials. The presence of agitation was reported across many, but not all, of the studies, which emphasizes the need to exercise caution and careful monitoring of the use of SSRIs in this patient population, to initiate treatment with low starting dosages and gradual titration schedules, and to select subjects who do not have high levels of agitation or mood cycling at baseline.

As with other medications, benefits (both short-term and long-term) must be weighed against risks, and future research with larger samples and controlled designs will aid in that calculation. Further, future studies, controlled or otherwise, would benefit from systematic assessment of side effects in order to help differentiate which of the SSRIs may be more likely to cause specific side effects. Likewise, improving our understanding of the nature and likelihood of SSRI-associated side effects in autistic populations may help identify risk factors to predict in advance which individuals are most vulnerable.

The marked difference in efficacy and tolerability of SSRIs in children and adolescents as compared with adults, particularly in the case of fluvoxamine, highlights the importance of considering developmental factors when prescribing these medications. It is possible that developmental changes in brain capacity of serotonergic neurotransmission play a role in determining the efficacy and tolerability of the SSRIs. These differences also emphasize the need to adjust doses and monitor children and adolescents closely. This is despite findings from one study that used magnetic resonance spectroscopy to determine that, in children with PDD, brain concentrations of fluoxetine and fluvoxamine do not differ from adult levels when adjusted for dose and mass.[36] Nevertheless, future trials in preschool-aged children may help clarify the developmental trajectory of the effect of SSRIs and possibly serve to mitigate the course of serotonergic dysregulation in autistic individuals. Pharmacogenetic differences among individuals with autism may also affect the efficacy and tolerability of SSRIs and warrant further investigation.

Several challenges to designing valuable clinical trials exist and need to be overcome before sufficient evidence mounts to incorporate SSRIs as the standard of care in autism spectrum disorders. Hollander and colleagues[37] emphasize the importance of identifying target symptoms that reflect core features of the disorder and the need to develop better outcome measures to gauge improvement. They also highlight the value of incorporating inclusion criteria that are realistic and can be generalized to clinical practice. Finally, an important direction for the future is to design studies that evaluate the efficacy of these medications over both the short and long term.

Another general consideration is the need to increase sample sizes in order to improve the power to detect medication effects, and demographic variables, such as age, IQ, language function, and comorbidity should also be controlled for. Most of the available data has been gathered using study designs that lack blinding, placebo control groups, and standardized outcome measures. Furthermore, current literature on the use of SSRIs in autism is likely to be biased given that clinical trials with negative findings do not get published as frequently as those with positive findings. The health care community at large would benefit greatly from access to both positive and negative clinical trials in the future.

Research efforts in the future may conceivably be enhanced by incorporating biochemical measures to further characterize the autistic phenotype and potentially predict treatment response. If the relationship between serotonin levels and the repetitive behavior domain could be clarified, for example, it may be possible to identify a subgroup of individuals with autism who respond to treatment with serotonergic medications. Genetic predictors of treatment response and side effects would also significantly advance the field, and the identification of putative predictors, such as the serotonin transporter genotype, should be a goal of future research.

Drug names: citalopram (Celexa and others), escitalopram (Lexapro), fluoxetine (Prozac and others), sertraline (Zoloft).

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