The Use of Selective Serotonin Reuptake Inhibitors in Young Children with Pervasive Developmental Disorders: Some Clinical Observations

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Objective: To study the effects of a new group of psychotropic medications, the selective serotonin reuptake inhibitors (SSRIs), on some symptoms of young children (under 7 years old) with pervasive developmental disorders (PDD).

Method: Open clinical trial.

Results: Medications produced positive results in half the children, particularly those with obsessional, repetitive, and anxiety symptoms. The medication was discontinued in half the children: one-quarter for worsening of symptoms and the other quarter for doubtful side effects.

Conclusions: SSRIs may have a role to play in ameliorating some symptoms of PDD. Further studies with standardized measurements, however, are needed to elucidate which children and what symptoms could benefit from which medication.

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Key Words: autism, pervasive developmental disorders, selective serotonin reuptake inhibitors

Several groups of medications have been used for the amelioration of some of the symptoms of PDD such as aggression, hyperactivity, insomnia, temper tantrums, withdrawal, stereotypies, self-injurious behaviour, depression, and obsessive-compulsive behaviour (1–4).

Neuroleptics. The efficacy of neuroleptics, especially haloperidol, but also several phenothiazines in terms of safety, short-term, and long-term effects has been investigated by a number of double-blind, placebo-controlled studies. Haloperidol reduces symptoms associated with autism, such as autism and speech deviance factors, as well as associated symptoms, such as anger, noncompliance, and hyperactivity. The serious side effects of haloperidol, particularly tardive dyskinesia, extrapyramidal symptoms, and lowering of seizure thresholds, however, have limited its use.

Psychostimulants. Although amphetamines decrease hyperactivity, the side effects on cognition and stereotypies have limited the use of these as well.

Fenfluramine. Serotonin levels in the blood are increased in 30% of children with PDD. This finding has resulted in studies about the use of fenfluramine to lower the serotonin level. Well-controlled studies have not demonstrated its efficacy, however, and its use was associated with retardation of learning in the laboratory. In addition, its possible neurotoxic effects may have limited fenfluramine’s use.

Opiate antagonists. Because some symptoms of PDD were similar to those of opiate addicts, naltrexone, an opiate antagonist, has been tried with children. The efficacy and safety of the drug, however, are still debatable (5).

Nutritional supplements and food additives. High doses of vitamin B₆ and magnesium have been reported to provide some improvement in children with PDD; however, their efficacy has not been established. In addition, dimethylglycine (a food additive sold in health-food stores) has been tried on an individual basis.
Use of SSRIs in PDD

Trying SSRIs in young children with PDD is justified for several reasons. First, none of the other medications has established itself as the medication of choice, and most of these medications are known to have serious side effects. Second, even though clomipramine (Anafranil) showed promising results in one study, it has a serious drawback in that electrocardiogram (ECG) and blood tests have to be done to monitor the children. With many of these young children, getting an ECG and drawing blood can be extremely difficult, if not impossible. Third, fluoxetine (Prozac), the most commonly used SSRI, has already been used with young children suffering from anxiety (7), depression (8), and obsessive-compulsive disorder (OCD) (9) without serious side effects. Even though its use for children has not been approved by the Food and Drug Administration (FDA), its experimental use may be justified. By contrast, paroxetine and sertraline have not been used in children, and their safety has not been established. This has to be acknowledged to the parents before they can make an informed consent. Finally, there are tentative findings that SSRIs may be effective with a variety of symptoms including aggression, hyperactivity, and OCD—the spectrum of symptoms often seen in children with PDD.

Information about the use of SSRIs in PDD in general, and especially in children and adolescents, is rare. Our knowledge consists mainly of case reports (10–12), with only one open study (13) of a group of patients. McDougle and others (10) reported a good response to fluvoxamine (Luvox) in a 30-year-old man with a dual diagnosis of autistic disorder (AD) and OCD. Mehlinger and others (11) reported on a 26-year-old autistic woman who showed temper outbursts and aggressive behaviour and was treated with low doses of fluoxetine (20 mg every 2 days). In addition to decreasing her anxiety, fluoxetine improved her social interactions and compulsive behaviours, and her use of language became more appropriate. Todd (12) briefly reported on 4 autistic cases (a 13-year-old female and 8-, 11-, and 19-year-old males) treated with fluoxetine. Three showed a reduction in ritualistic behaviour and greater tolerance for changes in routine, but none showed a change in language or in cognitive or social functions.

Recently, there have been studies using fluoxetine and clomipramine involving larger numbers of patients. The first, using fluoxetine (13), was an open study involving 23 subjects with AD (average age, 15.9 ± 6.2 years) and 16 subjects with mental retardation (MR; average age, 21.0 ± 11.5 years). Significant improvement was found in the Clinical Global Impression (CGI) ratings of clinical severity in 15 (65%) AD subjects and 10 (63%) MR subjects. In 9 of the 39 subjects all together, side effects of restlessness, hyperactivity, agitation, decreased appetite, and insomnia led to discontinuation of the drugs. Results included improvement in clinical severity and preservative compulsive behaviours on CGI ratings. A review of the individual cases also showed an improvement in mood, impulsivity, eating disorders, and activity levels. In the second study (6), Gordon and others used a double-blind comparison of clomipramine, desipramine, and a placebo on 24 subjects with AD (mean age, 10.4 ± 4.1 years). Clomipramine was superior both to the placebo and desipramine on ratings of autistic symptoms, anger and compliance, and ritualized behaviour, with no difference between desipramine and the placebo. In addition, for amelioration of hyperactivity, clomipramine equalled desipramine, and both tricyclics exceeded the placebo.

Since information on SSRI effectiveness in younger patients is scant, I have reported on the medications used to treat 8 children with PDD at The Hospital for Sick Children from 1994 to 1995.

Method

Eight children under the age of 7 years (6 boys and 2 girls) with a diagnosis of PDD (5 AD, 2 pervasive developmental disorder not otherwise specified [PDDNOS], and 1 Asperger’s syndrome) were treated, 6 with fluoxetine, 2 with paroxetine (Paxil), and 2 with sertraline (Zoloft). (Two children were tried on 2 medications.) Four of the 8 children were diagnosed by the author using the DSM-III-R criteria almost 3 years ago, when they were 2 to 3 years old and were involved in a treatment program for young PDD children, which did not include medication for behavioural symptoms. The other 4 cases were all diagnosed previously, at ages 2 to 3, by other physicians also using DSM-III-R criteria. They were seen by the author for their behavioural difficulties at the age reported in the study. In every case, the diagnosis was confirmed.

Medication was considered for a variety of disruptive symptoms. All the children were observed by their parents and the clinician without medication (for varying periods of time) to establish a baseline of observations. The parents chose and listed the 3 most disruptive symptoms and (approximately monthly) evaluated the progress of each symptom on a scale from 1 to 5, ranging from no change to mild, moderate, good, and extremely good changes, respectively. Narrative comments about the parents’ observations were also elicited, recorded, and followed up. In addition, the parents were given a list of the most common side effects of the medications, and these and any other observable side effects were noted and followed up.

Fluoxetine was used with most children because of its availability in liquid form, which makes it easier to administer and titrate. Paroxetine and sertraline were each used with 4 children who could swallow a pill because of their shorter action and excretion time.
The medications were given in an open clinical trial. All the children were started on 10 mg of either fluoxetine or paroxetine or 25 mg of sertraline; after a period of approximately one month, they were evaluated by the parents and the clinician. The dose was then increased by 50% every 2 or 3 weeks, with a further evaluation before another increase was given. The ultimate dose was determined either by the clinical response or by the side effects.

In this situation, an open clinical trial is justified because of the chronicity of the disorder, the variety of doses needed, and the length of time needed to reach the required dose of the medication. Geller and others (7) suggested that the efficacy of fluoxetine on OCD in children has been established in their open study, whereas a previous double-blind, placebo-controlled study failed to show its efficacy because standardized and lower dosages were used. Ultimately, however, only double-blind, placebo-controlled studies that allow physicians to alter the dose will establish the efficacy of the medication.

**Results**

The medication had to be discontinued in 4 (50%) of the children. It was stopped in 2 subjects because of worsening symptoms; in 2 others, their parents elected to discontinue the treatment (Table I). Of the remaining subjects, 3 children showed positive results, and one child showed mixed results.

**Discontinued Because of Worsening of Symptoms**

Patient A was a 7-year-old boy diagnosed with AD. His parents were concerned about his hyperactivity, agitation, and stereotypical movements. He was started on 10 mg of fluoxetine for one month, which increased his hyperactivity and agitation until it was of concern to his parents and teachers. Discontinuation of the medication resulted in a decrease of both symptoms. Approximately a year later, he was tried on 25 mg of sertraline for one month. The same increase in symptoms necessitated the discontinuation of the medication.

Patient B was a 7-year-old boy with a diagnosis of AD. His parents were concerned about his aggressive temper tantrums, self-injurious behaviour, impulsivity, and hyperactivity. He was put on 10 mg of paroxetine. Within 2 days he developed an acute, severe state of agitation and aggression that lasted for a few days and disappeared within a week of discontinuation of the medication.

**Discontinued for Doubtful Reasons**

Patient C was a 5-year-old boy who was diagnosed at age 3 as having PDDNOS; when examined during the study, however, he fit the diagnosis of AD. His parents were concerned about his repetitive behaviour, his lack of respect for other peoples’ boundaries, and his low tolerance for frustration. He was started on fluoxetine, which was gradually increased to 25 mg. An initial increase in hyperactivity subsequently subsided. His parents rated the amelioration of his repetitiveness at +4 (good), but saw no improvement in the other 2 symptoms. In addition, they reported increased language skills and communication, imaginative play, and concentration. He was described as being more cuddly and showed more concern for others. It was also stated that his teacher “can’t get over the changes in him.” The improvements in his behaviour permitted him to stay overnight with his grandmother and to take a 3-day car and ferry trip with his family, both for the first time, without difficulty. Four months later, however, he developed a severe diarrhea that was attributed by his parents to fluoxetine. The diarrhea, which

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*Worsened by medication.*
continued for several weeks after the discontinuation of fluoxetine, was later thought to be caused by a virus. Some of the described improvement, however, continued for several months after the discontinuation of fluoxetine.

Patient D was a 6-year-old boy diagnosed with AD. He was previously diagnosed as having PDDNOS at age 3. His parents were concerned about his hyperactivity, lack of concentration, and repetitive behaviour. After D spent a month on 10 mg of fluoxetine, they reported a moderate (+3) improvement in his 3 symptoms. In addition, they reported that he became more verbal, thought things through, and increased his eye contact with others. On a visit to a lumberyard, however, he became excited and pulled some of the lumber down. His mother attributed the behaviour to fluoxetine and discontinued its use.

Approximately a year later, he was started on 25 mg of sertraline. His parents were pleased with his improvement, but school staff who knew him to be taking medication thought that he was more hyperactive and insisted that it be discontinued.

Positive Responses

Patient E was a 6-year-old girl who was diagnosed as having PDDNOS at age 3. She showed an avoidance of eye contact, lack of interest in peer relationships, language delay, and obsessive interest in objects such as toys. She was involved in a treatment program that focused on increasing her interactions. Attempts to evaluate her speech or provide her with speech therapy failed because of her refusal to cooperate. She showed slow progress in all her symptoms. When a medication was considered, her parents’ main concerns were obsessive behaviour (“getting stuck”), lack of compliance with parental rules, and hyperactivity. She was started and kept on 10 mg of fluoxetine. She had a number of side effects: fatigue, sporadic hyperactivity, nonstop talking, loss of appetite, and a 7-pound weight loss. Fortunately, all of the side effects improved or disappeared in a short time; the weight loss persisted longer, although eventually she regained the lost weight.

Her parents reported an improvement of +4 to +5 in her 3 symptoms. In addition, they reported better language and communication skills, as well as a major improvement in her school performance. A speech therapist who had been trying to test her for 2 years was finally able to do so and found her to be 2.5 years behind in her language skills. A year later her language skills had improved by one year.

Subsequently, her compliance with rules at home and school decreased, and the fluoxetine was increased to 15 mg. This resulted in increased agitation, hyperactivity, and defiant behaviour. All of these symptoms disappeared 3 to 4 days after fluoxetine was stopped briefly; it was resumed at 10 mg. Although E continues to show some behavioural difficulties, particularly with her mother, her mother was ecstatic about the changes in her language and sociability and said, “I feel I have a new lease on life. I feel that finally I have a daughter.”

Patient F was a 7-year-old boy previously diagnosed with Asperger’s syndrome. His assessment during the current study confirmed that diagnosis. His parents were concerned about his rigidity, “arm tics” (namely, hand flapping), and obsessive and socially inappropriate talking about dinosaurs, cows, and archeology. He was started on fluoxetine, which was gradually increased to 30 mg per day. His parents reported improvements in these 3 symptoms of +2, +2 to +3, and +4, respectively. In addition, they reported that their son showed increased concern for others, displayed improved study habits, and had developed an increased ability to tolerate groups, to negotiate, and to plan. Four to five months later, he became rigid again and started to get into arguments and fights with other children. When his dose was increased to 40 mg, his regression disappeared. He still has difficulties with his social relationships and study habits, but is responding to tutoring.

Patient G was a 6-year-old boy diagnosed with PDDNOS 2 years ago. A psychosocial treatment program that included speech and occupational therapy had been initiated, and he showed some progress in his language and social relationships. After a year, however, the parents were concerned about his obsessive mannerisms, his slow language development, and his inability to concentrate.

Following a trial of 20 mg of fluoxetine, his obsessive symptoms completely disappeared; his concentration improved (+3) to the point that he was able to read and write better, and his speech both improved in content and became more comprehensible (+3). The child’s parents also noticed increased sensitivity on his part, in that he now could get hurt when he was called names (in the past, he had been oblivious to insults), and better-developed life skills such as brushing his teeth and dressing himself. An increase in his hyperactivity was found to be manageable by his family and school. Approximately a year later, fluoxetine was discontinued to test his status. He showed no recurrence of his obsessional behaviour or his inability to concentrate, but continued to show mild language delay, which was treated by a speech therapist, and mild difficulties in social interactions.

Mixed Results

Patient H was a nonverbal 7-year-old girl with AD and a history of major abuse and neglect. At the time of the referral, she was living with foster parents who were becoming overwhelmed by her aggressiveness, lack of concentration, lack of sleep, and activity level. She was put on 10 mg of paroxetine, which did not improve her destructiveness (breaking objects, throwing things). She did, however, show major improvement in her sleep (+5), in that she was able to stay asleep for 8 to 10 hours, which afforded the foster parents
a respite. Her concentration improved somewhat (+3) after the initiation of paroxetine. Support for the “mixed results” nature of her improvement came from staff at her school, who sent me an unsolicited report of the pros (calmer, limited screaming, more attentive, follows directions, increased babbling, and less aggressive) and cons (little or no social interactions with peers, increased attention-seeking behaviour, deterioration in her eating habits) of her new state.

An increase of her dosage to 15 mg resulted in an increase in her hyperactivity and unmanageableness, but she improved when the dose was decreased again to 10 mg. Subsequently, the addition of buspirone, 10 mg tid, resulted in an improvement of her aggressiveness and hyperactivity (both +3).

Discussion

The use of SSRIs in the treatment of some symptoms of PDD clearly shows mixed results. An improvement rate of 50% is not great, but is still acceptable. I suggest that SSRIs should be tried, for some symptoms of PDD, for the following reasons:

- The side effects of the medications most commonly used with PDD children, namely haloperidol and other neuroleptics, are serious, while the side effects for the 50% who improve seem negligible.
- SSRIs have been given to children for extended periods of time (up to 2 years) without serious adverse effects. The long-term consequences of these medications when used with children, however, are still unknown.
- SSRIs are easier to administer than clomipramine, which requires ECG and blood monitoring.
- Fluoxetine is currently the easiest SSRI to administer because it comes in a liquid form. It is known, however, that the efficacy of all the SSRIs is equivalent and that some patients may have side effects with one of them but not with another (14). Thus, if a child is able to take pills or if the others are made in liquid form in the future, a trial with more than one SSRI may be useful. Two children in the study sample, however, reacted in the same negative way when they tried fluoxetine and sertraline.

The limitations of this clinical study include a small sample size, a heterogeneous group of patients, and ratings based on the clinical observations of parents, rather than objective rating scales. In addition, the improvement of the symptoms was rated by the parents, but they could only report that the symptoms worsened enough to warrant discontinuation. I suggest the following tentative observations, however.

First, the children diagnosed with the less severe forms of PDD, namely with PDDNOS and Asperger’s syndrome, responded better than those with more disturbed varieties (AD). This could reflect the possibility that PDDNOS is more closely related to OCD and anxiety disorders (the symptoms of which are known to be responsive to SSRIs) than to AD.

Second, it is clear that each child has a specific dose for efficacy, above which serious side effects can occur (for example, patients E and H). By contrast, some wearing-off of the effects of the medication occurs, requiring an increase in dosage (patient G). Only by trying can we know whether increasing the dosage will precipitate serious side effects or improve the clinical conditions. This makes the open trial, with a specific dosage for each child, the more practical way to use SSRIs.

These tentative observations should be followed by further studies. Many drugs that showed initial improvements in open clinical trials were not found to be effective when submitted to double-blind, placebo-controlled clinical trials. In the meantime, more objective measurements of the children’s status through behavioural checklists, administered before and during the trial of medication and during a period of discontinuation of the medication, may give us a better measure of the effectiveness of the medications. In addition, it would be important to follow the children for a long period of time (at least 2 years), not only to measure the continuous effectiveness and safety of the medication but also to see the effect of the change in symptoms upon the psychosocial treatment process and perhaps upon the course of the disorder itself when the medications are given at a young age.

Clinical Implications

- SSRIs may be tried with children with PDD.
- More than one SSRI may be tried.
- Dosage is specific for each individual.

Limitations

- Too few patients.
- Wide range of diagnoses.
- Better measurements of the patient’s status are needed.

References


Résumé

Objectifs : Étudier les effets d’un nouveau groupe de médicaments psychotropes, les inhibiteurs sélectifs du recaptage de la sérotonine (ISRS), sur certains symptômes des jeunes enfants (de moins de 7 ans) atteints de troubles de développement profonds (TDP).

Méthode : Essai clinique ouvert.

Résultats : Les médicaments ont donné des résultats positifs chez la moitié des enfants, en particulier ceux qui présentaient des symptômes d’anxiété, d’obsession et de répétition. On a mis un terme au traitement chez la moitié des enfants : chez un quart d’entre eux en raison d’une aggravation des symptômes et chez l’autre quart des enfants en raison d’effets secondaires inquiétants.

Conclusion : Les ISRS peuvent jouer un rôle dans l’atténuation de certains symptômes des TDP. Il faudra toutefois mener d’autres études au moyen de mesures normalisées afin d’élucider quels médicaments conviennent à des enfants ou à des symptômes en particulier.