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Behavioral Side Effects of Fluoxetine in Children and Adolescents

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ABSTRACT

Twelve (50%) of 24 children, ages 8 to 16 years, treated with fluoxetine, 20 or 40 mg/day, for depressive or obsessive compulsive symptoms, developed behavioral side effects characterized by motor restlessness (n = 11), sleep disturbance (n = 11), social disinhibition (n = 6), or a subjective sensation of excitation (n = 3). No major changes in the neurological status of these children were observed. However, the three children with ADHD showed an exacerbation of symptoms on fluoxetine. Discontinuation (n = 5) or halving the dosage (n = 7) resulted in complete resolution of these unwanted symptoms within 1 to 2 weeks. In all 7 children whose doses were reduced, improvement of the depressive or obsessive compulsive symptoms was maintained on the lower dosage. Clinicians treating children with fluoxetine are cautioned to be aware of behavioral side effects which may be alleviated by dosage reduction or possibly by starting with lower doses. These side effects may be difficult to differentiate from common psychopathological symptoms such as hyperactivity, restlessness, and impulsivity.

INTRODUCTION

FLUOXETINE, A SPECIFIC SEROTONIN uptake inhibitor, is approved for use as an antidepressant in adults and may be effective in the treatment of obsessive compulsive disorder (OCD) (Fontaine and Chouinard 1986; Jenike et al. 1989; Turner et al. 1985). In adults, nervousness, anxiety, and insomnia are among the most commonly reported side effects of fluoxetine treatment. The "package insert" describes these symptoms in 9 to 15 percent of treated patients. Lipinski and colleagues (1989) have used the term akathisia to describe fluoxetine-induced symptoms of restlessness, pacing, purposeless movement of the feet and legs, and feelings of anxiety. They estimate these symptoms occur in 10 to 25 percent of adults receiving fluoxetine.

Preliminary experience indicates that fluoxetine also may be effective in the treatment of obsessions and compulsions in children and adolescents (Riddle et al. 1990). In this small series of young patients, the most common side effect was behavioral agitation.

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We now describe 12 children and adolescents who developed fluoxetine-induced behavioral side effects. Their side effects included restlessness, hyperkinetic behavior, insomnia, an internal feeling of excitation, subtle impulsive behavioral changes, and suicidal ideation (King et al. 1991).

METHODS

Subjects

The 24 children (13 boys, 11 girls; age range 8.1–16.5 years) represent a consecutive series of all patients under age 18 years who were treated with fluoxetine for obsessive-compulsive or depressive symptoms in either the Obsessive Compulsive Disorder or Tic Disorders Clinics at the Yale Child Study Center or the Children's Psychiatric Inpatient Service in Yale–New Haven Hospital between April 1, 1988 and June 1, 1990. Excluded were children with pervasive developmental disorder, psychotic disorders, mental retardation, acute major medical illnesses, or abnormalities on clinical screening laboratory studies. None of the 24 subjects were receiving concurrent medications.

All patients received an extensive medical and psychiatric evaluation (by a child and adolescent psychiatrist and a clinical nurse specialist), and met *DSM-III-R* diagnostic criteria for OCD (n = 17), major depressive disorder (MDD, n = 2), trichotillomania (n = 1), or Tourette's syndrome (TS, n = 4) as their primary diagnosis. Additional comorbid diagnoses were also given (see Table 1).

Twenty subjects initially received fluoxetine treatment as outpatients. Seven of these outpatients participated in an ongoing double-blind, placebo-controlled, crossover trial of fluoxetine. The other 13 outpatients received fluoxetine as part of their standard clinical care. Four of the children initially received fluoxetine in an open trial as inpatients as part of their clinical care.

TABLE 1. CHARACTERISTICS OF 24 CHILDREN AND ADOLESCENTS TREATED WITH FLUOXETINE

	Activated Group	*Nonactivated Group*	*Total Group*
Number of patients:			
Total	12	12	24
Male	5	8	13
Female	7	4	11
Age of subjects (years):			
Range	8.1-15.3	8.8-16.5	8.1-16.5
Mean ± SD	11.6 ± 2.6	12.1 ± 2.6	11.9 ± 2.6
Diagnoses:			
Obsessive compulsive disorder	10	8	18
Major depressive disorder	1	3	4
Tourette's syndrome	3	6	9
Attention deficit hyperactivity disorder	3	1	1
Trichotillomania	0	1	1
Anorexia nervosa	1	0	1
Oppositional defiant disorder	0	1	1
Separation/defiant disorder	0	1	1
Clinical setting:			
Outpatient double/blind	3	4	7
Outpatient routine/clinical	8	5	13
Inpatient	1	3	4
Duration of clinical treatment (weeks)	28 ± 24	32 ± 24	30 ± 27
Dosage (mean ± SD mg/day)	25.8 ± 9.0	30.0 ± 10.4	27.9 ± 9.8

Definitions

Behavioral side effects were classified into four categories: motor restlessness, sleep disturbance, social disinhibition, and subjective sensation of excitation. For each category, the duration criterion was two weeks. Sources of information were the patient and parents.

Motor restlessness was defined as an increase in the child's level of gross motor activity that was sufficient to cause concern to the child's parents or teachers. Although the reported and observed activity may have appeared "driven" or "pressured," these qualities were not essential to the definition.

Sleep disturbance was defined as a change in the child's pattern of sleep that was sufficient to cause concern to the child's parents. The most common change in sleep pattern was difficulty falling asleep, usually accompanied by decreased total sleep. Middle of the night awakening and early morning awakening were included in the definition.

Social disinhibition was manifested by garrulousness or subtle impulsivity that was considered uncharacteristic for the child. It was the degree of this disinhibition, rather than the functional impact, that was considered important in the definition.

A child was said to have a "subjective sensation of excitation" if the child reported an internal sense of restlessness, agitation, or excessive energy that was experienced as uncomfortable or unpleasant.

Procedures

All subjects were started on fluoxetine 20 mg/day. Outpatients were seen for medication followup visits about every four weeks. Outpatients who participated in the double-blind study were asked about side effects at each monthly visit, using a review of systems format. Possible side effects were listed on a form specifically designed for this purpose. The outpatients receiving the medication in an open trial were also asked about side effects at each visit; however, a formal review of systems format was not stringently followed. Side effects were noted on an outpatient visit followup form.

Inpatients were evaluated three times each week by a child psychiatrist. Possible side effects were recorded in the medical records.

If a child was found to have behavioral side effects, after discussion with the child and parents, the fluoxetine was either discontinued or the dosage was reduced by half. The primary factors considered in the decision to discontinue the medication as opposed to reducing it included the severity of the behavioral side effects and the magnitude of therapeutic response to the medication.

Data analyses

Student's *t*-test and chi square with Yates' correction (for cell sizes < 5) were used to compare the behaviorally activated versus nonactivated subjects on several variables.

RESULTS

Characteristics of subjects

Twelve of the 24 children (50%) had two or more behavioral side effects. Characteristics of those with ("activated") and without ("nonactivated") behavioral side effects are presented in Table 1. There were no significant differences between the behaviorally activated and nonactivated groups in gender ratio, age, primary diagnoses, clinical setting, or duration or dosage of fluoxetine treatment. Although there were more girls in the activated group, the gender ratio difference did not reach statistical significance.

TABLE 2. BEHAVIORAL SIDE EFFECTS IN 24 CHILDREN AND ADOLESCENTS TREATED WITH FLUOXETINE

Motor restlessness	$n = 11$
Sleep disturbance	$n = 11$
Social disinhibition	$n = 6$
Subjective sensation of excitation	$n = 3$

Behavioral side effects

Behavioral side effects occurred as follows: motor restlessness = 11, sleep disturbance = 11, social disinhibition = 6, and subjective sensation of excitation = 3 (see Table 2). Of the 11 children who had motor restlessness, 10 had sleep disturbance. Of the 11 children with sleep disturbance, 10 had motor restlessness. Of the 6 children with social disinhibition, all 6 had motor restlessness and 5 had sleep disturbance. Of the 3 children with a subjective sensation of excitation, all had sleep disturbance and 2 had motor restlessness and social disinhibition. Overall, 2 patients had four of these behavioral side effects, 2 patients had three side effects, and 8 patients had two side effects.

These behavioral effects were neither observed nor reported in any of the 7 children who received placebo treatments. Three of the children had received a diagnosis of attention deficit hyperactivity disorder (ADHD) (see Table 1) prior to starting fluoxetine. In these three children, the ADHD symptoms appeared exacerbated by the medication.

Response to intervention

At the time that the side effects were observed, 9 patients were receiving fluoxetine 20 mg/day and 3 patients were recieving fluoxetine 40 mg/day. Fluoxetine was discontinued in five patients, four of whom were on 20 mg/day and one on 40 mg/day. In these five patients, the behavioral side effects resolved within one to two weeks after discontinuation.

Among the remaining 7 patients, fluoxetine dosage was reduced from 20 mg/day to 20 mg every other day in five cases, and from 40 mg/day to 20 mg/day in two cases. In all 7 patients, the behavioral side effects also resolved within one to two weeks. All 7 patients continued on the reduced dosage, which was perceived by the clinician and parents as having a beneficial effect on the obsessive, compulsive, or depressive symptoms.

DISCUSSION

The fluoxetine-induced behavioral side effects observed in these 12 children and adolescents included restlessness, hyperkinetic behavior, insomnia, an internal sense of increased excitation, and subtle impulsive behavioral changes. Aside from the temporal relationship between the initiation of fluoxetine and their appearance, these side effects were often difficult to distinguish from symptoms commonly observed in children with behavioral disturbances.

Similar side effect profiles have been observed in adults treated with fluoxetine. Lipinski and colleagues (1989) have noted that, in adults, some of these symptoms, for example, restlessness and an internal feeling of hyperexcitability, are indistinguishable from neuroleptic-induced akathisia. Gorman and colleagues (1987) observed "increased agitation, restlessness, jitteriness, diarrhea, and insomnia" (p. 331) in adults being treated with fluoxetine for panic attacks.

The frequency and time course of fluoxetine-induced behavioral side effects are not known. In the patients reported in this study, the onset of the side effects generally occurred within a few days of initiation of the medication. However, because the younger children were frequently unaware of the side effects, and because most of the parental reports were retrospective, interpretation of the onset data remains uncertain. Also, the side effects remained relatively stable for two to eight weeks until the fluoxetine was either reduced or discontinued. Whether or not tolerance to the side effects would have developed, as is common with the

activating side effects of tricyclic antidepressants, is also unknown. Lipinski et al. (1989) reported that restlessness and anxiety persisted for one year in one patient in their series.

The psychopharmacological mechanisms underlying the behavioral side effects are open to speculation. Based on a review of preclinical studies, Lipinski and colleagues (1989) and Bouchard and colleagues (1990) suggest that fluoxetine treatment enhances serotonin-mediated inhibition of dopaminergic cells in the midbrain ventral tegmental area (VTA) or other dopaminergic projections in the nigrostriatal system. Lending support to this hypothesis are case reports of: (1) extrapyramidal symptoms in a 39-year-old woman taking haloperidol and fluoxetine (Tate 1989), and (2) extrapyramidal symptoms in a 45-year-old woman and a 47-year-old woman taking only fluoxetine (Bouchard et al. 1990). Furthermore, Baldessarini and Marsh (1990) have shown that in rat brain, "a relatively large dose of fluoxetine moderately but significantly inhibited the synthesis of catecholamines acutely in several dopamine-rich areas of the mammalian forebrain and that, while this short-term effect may diminish with repeated treatment elsewhere, it appeared to persist or even to increase in the hippocampus and the extrapyramidal region (striatum)" (p. 192).

Lowering the dosage of fluoxetine was an effective intervention in most of the children and adolescents in whom fluoxetine was not discontinued. In these cases, dosage reduction led to resolution of the side effects while some degree of therapeutic efficacy was maintained. In our subsequent experience with fluoxetine, some children have benefited from doses as low as 5 or 10 mg/day. Such low dosing requires alternate-day administration, or dissolving the contents of the capsule in liquid. A low-dose formulation would clearly be beneficial to clinicians working with children.

An alternative approach might have been to treat the side effects with another medication. In addition to dosage reduction, Lipinski (1989) found that propranolol, a beta-adrenergic antagonist, reduced the severity of fluoxetine-induced behavioral side effects. Perhaps a higher dosage of fluoxetine and a greater level of therapeutic efficacy could be maintained by using propranolol. On the other hand, the use of multiple medications, especially in children with complex clinical presentations, may further complicate an already confusing situation.

With heightened interest in the use of fluoxetine for depression as well as obsessive-compulsive disorder spectrum conditions, fluoxetine is now being administered to a growing number of children and adolescents. The 50% rate of behavioral side effects reported here may be an overestimate because of the dose regimen and the lack of adjustment for placebo-induced side effects. However, physicians and mental health professionals must remain vigilant for possible behavioral side effects which may require adjustment or discontinuation of the medication. A better understanding of the pathogenesis of these side effects awaits further advances in our understanding of the underlying mechanisms of action of fluoxetine in the developing brain.

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