

Fluoxetine in Children and Adolescents with Mood Disorders: A Chart Review of Efficacy and Adverse Effects

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ABSTRACT

The charts of 31 hospitalized children and adolescents (ages 9–18 years) with major mood disorders were retrospectively reviewed to examine the efficacy and side effects of treatment with fluoxetine. After treatment for a mean duration of 35 days, clinical improvement was seen in 74% of these patients; 54% had “much” to “very much” improvement as measured by the Clinical Global Impression scale (CGI). The most common adverse effects were hypomania-like symptoms (23%), irritability (19%), gastrointestinal upset (13%), and insomnia (13%). No EKG changes, blood pressure changes, anticholinergic symptoms, sedation, weight changes, or seizures were observed. None of the patients experienced an increase in suicidal or parasuicidal behavior. Discontinuation of the fluoxetine treatment occurred in 28% of cases, most commonly because of increasing irritability and hypomania-like symptoms. The hypomania-like effects included a constant sense of silliness, increased activity, poor sleep, increased energy, an increase in the stream of thoughts (racing thoughts), or socially intrusive or obnoxious behavior. Fluoxetine triggered symptoms suggestive of hypomania in all four of the depressive bipolar patients.

INTRODUCTION

SINCE ITS INTRODUCTION IN January 1988, fluoxetine has become one of the most widely prescribed antidepressants in America. While there are comprehensive data in the adult literature on fluoxetine for the indications of major depressive (MDD) and obsessive-compulsive disorders (Fontaine and Chouinard 1986, Jenike et al. 1989, Leonard and Rapoport 1990, March et al. 1989, Murphy and Pigott 1990, Nierenberg and Amsterdam 1990, Turner et al. 1985), research in child and adolescent patients has been sparse.

Simeon et al. (1990), in a double-blind placebo-controlled study, administered fluoxetine up to 60 mg/day to 40 inpatient and outpatient adolescents with MDD (ages 13–18 years). Of the 30 patients who completed the study, there was a statistically significant difference between fluoxetine and placebo only with respect to anxiety. The most frequently reported side effects included headache (43%), tremor (29%), insomnia (24%), rhinitis (24%), vomiting (14%), and weight loss (14%). No relationship was identified between the dose of fluoxetine and the plasma level.

Riddle et al. (1990) studied 10 subjects (ages 8–16 years) with depressive or OCD symptoms who were treated with fluoxetine. Within two weeks of starting the medication, 5 of 10 (50%) had adverse effects. Recently, Riddle et al. (1990, 1991) reported on 24 patients (ages 8–16 years) who received fluoxetine; 12 (50%) developed side effects which included motor restlessness, sleep disturbances, social disinhibition or a “subjective sensation of excitation.” By lowering the fluoxetine dosage, adverse symptoms could be decreased. In their articles, Riddle and colleagues consistently noted that the side effects of fluoxetine were difficult to separate from symptoms commonly found in children with behavioral problems.

Unlike tricyclic antidepressants, which have adverse symptoms of sedation, anticholinergic and cardiotoxic effects, a lowering of seizure threshold, and the risks of overdose, fluoxetine has been found to be relatively safe and limited in major side effects (Riddle et al. 1988, Wernicke 1985). The adult literature shows that the most common difficulties have been nausea, headache, nervousness, and insomnia (Cooper 1988). Fluoxetine has anticholinergic effects, but they occur to a much lesser degree than for tricyclic antidepressants. Most of the other side effects, such as the alleged increase in self-destructive phenomena (King et al. 1991, Teicher et al. 1990), have generally been anecdotal.

This paper presents the side effect profile and efficacy of fluoxetine in a retrospective chart review study of children and adolescents. Particular interest is paid to the reasons for discontinuation and the risk/benefit ratio as reflected on the Clinical Global Impressions Scale (CGI, Guy 1987).

METHODS

The charts of 31 inpatient children and adolescents who were treated with fluoxetine between January 1989 and March 1990, on the inpatient services of Western Psychiatric Institute and Clinic, were reviewed. The retrospective chart study was done by two child and adolescent psychiatrists (B.B. and M.G.) and a senior child psychiatry fellow (U.J.), with each individual’s evaluation independent and blind to the others.

In addition to general demographic factors, information was obtained in 7 areas: (a) the indications for the use of fluoxetine; (b) how fluoxetine was prescribed; (c) the profile of the adverse symptoms; (d) measures of EKG, blood pressure, and weight; (e) previous history of psychopathology in the patient; (f) family history; and (g) the effectiveness of the medication in managing the patient’s clinical symptoms. The rationale for the use of fluoxetine was determined by the *DSM-III-R* diagnosis given on admission and reported in the discharge summary. Since the indicated reason for using fluoxetine was depression, subjects with a primary diagnosis different from MDD were not included in the analysis.

Fluoxetine dosages and schedules were carefully documented. When a side effect occurred, information was gathered regarding the time of its onset following the initiation of fluoxetine, its duration, and the use of any other medication to alleviate these symptoms. Adverse effects were recorded in the progress notes of the medical chart on a daily basis by both nurses and physicians. If a patient had been on a concurrent medication, any changes were scrutinized to determine if there had been a drug interaction. Blood pressure, weight, screening EKG, and blood indices [complete blood count (CBC), differential, blood urea nitrogen (BUN), creatinine, and liver function tests] were reviewed to establish the safety of fluoxetine in these patients.

The past history of the patient identified whether there had been previous antidepressant trials or prior psychiatric hospitalizations. In addition, a past medical history was obtained. This information was helpful in determining if a patient was being managed with fluoxetine because of treatment resistance in the past. The family history was reviewed for psychopathology, particularly loading for mood disorders.

The overall effectiveness as well as the therapeutic benefit of fluoxetine were recorded on the Clinical Global Impression Scale (CGI). This scale has three subscales: (1) “the severity of the illness” is scored from 1 (normal, not ill) to 7 (among the most extremely ill patients) and was determined from the patient’s initial presentation at admission; (2) the “global improvement scale” is a measure of how the patient did during the course of therapy on the drug, and it is scored from 1 (very much improved) to 7 (very much worse); (3) the “efficacy index” is a 4 × 4 matrix table which assesses the therapeutic effect of the medication (on the y axis) on side effects (on the x axis). Sixteen potential outcomes are possible, with each number between 1 and 16 designating a specific side-effect-to-benefit ratio (though not in consensual order). The therapeutic effect is ranked from “marked improvement” to “unchanged,” while the side effects run from “none” to “outweighs any positive effect.”

Sample characteristics

The total sample consisted of 24 females and 17 males, in the age range 9–18 years old. For this study, the subgroup of 31 patients with mood disorder (4 depressive bipolar, 27 with MDD) was examined. The 17 females were significantly older (mean 15.1 ± 2.3 years) than the 14 males (12.6 ± 2.7 years) (Mann Whitney, $p < 0.02$). Of the 4 depressive bipolar patients, 3 had been diagnosed with bipolar disorder on previous admissions; the other had cycles consistent with bipolar illness on the initial intake history.

The initial schedule of delivery in all the patients was one 20 mg tablet in the morning. Nineteen patients (64%) remained at 20 mg. The maximum doses for the remainder of the subjects included 8 (25%) who had been given 40 mg, 3 (9%) had been given 60 mg, and one (2%) had been given 80 mg. Only 14% of the total population had a schedule other than one tablet in the morning; i.e., twice daily, three times daily, or alternate-day delivery. There was no difference in the dose of the medication if the patient had MDD or a depressive bipolar disorder.

The mean trial length of fluoxetine was 35 ± 21 days, with a range of 7–89 days. The duration for depressive bipolar patients was 45 ± 26 days and for MDD patients was 34 ± 20 days (the difference was not significant). Females were treated significantly longer (45 ± 22 days) than males (26 ± 16 days) ($t = 2.45$, $df = 29$, $p < 0.03$). There were 11 patients in the 9–12-year-old group and 20 patients in the 13–18-year-old age group. The older subjects received higher doses of fluoxetine ($r = 0.44$, $p < 0.02$, $n = 31$) and were treated longer ($r = 0.41$, $p < 0.03$, $n = 31$).

Past history revealed that 55% of the cases had been previously treated with tricyclic antidepressants and that 52% of the patients had a family history of a mood disorder.

Data analysis

Fischer exact tests, Chi-square, and t tests were used to determine statistical significance between groups. Reliability among raters for all three subscales of the CGI was measured by the intraclass correlation coefficient. The correlation among raters was approximately 0.83 on the “efficacy index,” approximately 0.49 for the “severity of the illness,” and approximately 0.85 for the “global improvement scale” (0.83, 0.79, and 0.89 between raters 1-2, 1-3, and 2-3, respectively).

RESULTS*Efficacy*

Most (74%) of the sample showed some improvement; 54% had “much” to “very much” improvement, 43% had “minimal” improvement or no change, and 3% had worsening.

After treatment with fluoxetine, the results of the CGI showed several significant findings. The mean “global improvement score” was 2.7 ± 1.1 (median score 2.3, with a range of 1.3–6.0), which suggests that there was “minimal” to “much” improvement (see Fig. 1). Females (3.1 ± 1.3) tended to show more improvements than males (2.4 ± 0.9) (Mann-Whitney, $p < 0.09$). The mean “efficacy index” was 7.2 ± 3.6 (median rating of 6, with a range of 1.3–15). This corresponds to a risk/benefit ratio that suggests that the side effects of fluoxetine “do not significantly interfere with the patients’ functioning”. The mean “severity index” was 4.8 ± 0.7 (median of 5, with a range of 2–6), suggesting that most patients were “markedly ill.” There were no effects of age on any of the three rating scales previously mentioned.

Side effects

The mean onset of side effects was within 12 ± 11 days. The most common side effects were hypomania-like symptoms (23%), irritability (19%), insomnia (13%), and gastrointestinal upset (13%) (see Table 1). There were no reported anticholinergic side effects, seizures, or problems of sedation. Twenty-six percent of the patients had multiple side effects. Significantly more depressive bipolar patients than those with major depression developed hypomania-like symptoms (4 vs. 3, Fisher Exact Test, $p < 0.0001$). The

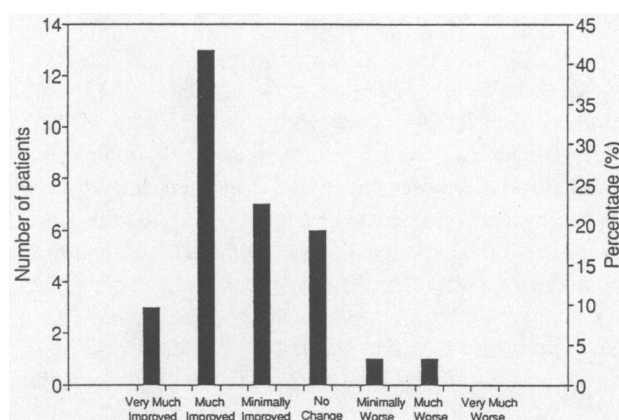


FIG. 1. Mean global improvement. This figure presents the number and percentage of subjects treated with fluoxetine who received scores on the Clinical Global Improvement Scale. Scores on the CGI range from 1 (very much improved) to 7 (very much worse).

hypomania-like features lasted 4–14 days. The duration of treatment for the depressive bipolar group (44 ± 26 days) and the major depressed group (34 ± 20 days) was not a factor which accounted for the difference in side effects ($t = 0.89$, $df = 29$, $p = 0.3$).

Twenty-eight percent of the patients on fluoxetine had the medication discontinued. The three most common reasons for discontinuation were irritability (12%), hypomania-like symptoms (7%), and lack of improvement (7%). In the latter group, the duration of the trials were 27, 29, and 49 days.

There were no EKG changes after the initiation of the medication. The mean systolic and diastolic blood pressure prior to starting fluoxetine was 108 ± 11 and 65 ± 9 mmHg, respectively. The mean systolic and diastolic pressure while on fluoxetine was 104 ± 12 mmHg and 62 ± 9 mmHg, respectively. The changes in both systolic and diastolic pressures were not significant. While posttreatment weight recordings were only obtained in 18 of the patients, there were no significant changes in weight prior to starting the medication and at the time of discharge. CBC with differential and chemistry panels were found to be within the normal range. None of the patients had increased suicidal or parasuicidal ideation.

Concurrent medications and comorbid diagnoses

Twelve (35%) of the depressed patients required the concurrent use of another drug started after fluoxetine. Eight (25%) patients were treated with lithium (5 with MDD, 3 with depressive bipolar disorder), 3 (10%) patients with MDD received neuroleptics, and 1 (2%) patient with depressive bipolar disorder was taking methylphenidate. There were no significant differences in the therapeutic response and side effects between those taking fluoxetine alone or in combination with other medications.

TABLE 1. FLUOXETINE SIDE EFFECTS IN CHILDREN AND ADOLESCENTS WITH MOOD DISORDERS

Side effects	Depressed (%) ($n = 27$)	Bipolar (%) ($n = 4$)	Total (%) ($n = 31$)	Test statistic	P-value
Hypomania-like features	3 (11.1)	4 (100)	7 (22.6)	F.E.T. ^a	0.0011
Irritability	6 (22)	0 (0)	6 (19.4)	F.E.T.	0.56
Insomnia	3 (11.1)	1 (25)	4 (12.9)	F.E.T.	0.44
GI upset	4 (14.8)	0 (0)	4 (12.9)	F.E.T.	1.00
Fatigue	3 (11.1)	0 (0)	3 (9.7)	F.E.T.	1.00
Headache	1 (3.7)	0 (0)	1 (3.2)	F.E.T.	1.00

^a Fisher's Exact Test.

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Twelve children had a second diagnosis (2 had attention-deficit hyperactivity disorder, 5 had oppositional-defiant disorder, and 5 had conduct disorder), but there were no consistent comorbidity findings with regard to side effects. Patients with only MDD showed a trend toward more global improvement (2.3 ± 0.7) when compared to those patients with MDD and a second diagnosis (3.3 ± 1.4) ($t = 2.43$, $df = 29$, $p = 0.02$), but the sample sizes were small. There were no statistical differences in side effects between males and females.

DISCUSSION

Interest in fluoxetine has increased, partially because its therapeutic efficacy in adults has been shown to rival that of conventional tricyclic antidepressants (Jenike et al. 1990, Stark and Hardison 1985) and partially because fluoxetine does not have the same overdose potential and great number of side effects. The risk of a lethal intake has always been a major detractor when tricyclic antidepressants are used in adolescents. The confidence in prescribing fluoxetine has led to its increased use in younger children.

The use of fluoxetine, in our sample, led to 74% of patients having some improvement, of which 52% had much to very much improvement (see Fig. 1). The response rate is consistent with other placebo response rates in other studies of depression in children and adolescents. In this study, 59% of the patients had one adverse effect, and half of these had multiple symptoms. However, in the majority of cases, the side effects did not interfere with the patients' functioning, as reflected in the efficacy index subscale of the CGI.

Irritability was the most common reason for discontinuation of fluoxetine. In two of the cases, a dose relationship was noted: irritability worsened as the dose was increased, and then decreased as the dose was dropped. The irritability had a quality of a grinding anger with short temper and increasing oppositionalism. Other symptoms that were commonly cited in the charts included a constant sense of silliness, increased activity, poor sleep, increased energy, an increase in the stream of thoughts (racing thoughts), and socially intrusive and obnoxious behavior. These hypomania-like effects may have been more prevalent had the duration of the trials been longer. Some of the patients with major depression who had this symptom may, in fact, turn out to be bipolar.

The hypomania-like symptoms in our study were similar to the "behavioral activation" as described by Riddle et al. (1990). In the studies done by Riddle's group, the parents and teachers described the children as "revved up," "hyper," and "super energized." Jerome (1991) described a single case of fluoxetine-induced "reactive hypomania" which had the added quality of "grandiosity." Achamallah and Decker (1991) reported a single case of mania induced by fluoxetine in a 15-year-old boy five days after medication was started. Since the structure of fluoxetine is very similar to an amphetamine (Schmidt et al. 1988), it may be that the "activation" triggered by fluoxetine is a mild stimulant-like euphoria aroused by the medication (Rapoport et al. 1980).

In this study, fluoxetine was found to be a safe drug. While this study does not have data on overdoses, the adult literature suggests that risks are minimal even with large overdoses (Wernicke 1985). Riddle et al. (1988) reported a patient, after ingesting 1.88 grams of fluoxetine, who experienced a grand mal seizure, nausea, dizziness, headache, and EKG changes. In our study, EKG findings (both before the medication was begun and after peak dosing) did not change, even when the dose was at 80 mg per day. Also blood pressure and weight did not change.

Teicher et al. (1990) reported the emergence of intense suicidal preoccupation 2–7 weeks after fluoxetine treatment in 6 patients who had all been previously treated with MAOIs. King et al. (1991) described the emergence of self-destructive behavior in 6 obsessive-compulsive patients, aged 10–17. However, as both above studies noted, it was difficult to separate the course of an illness, which may manifest suicidal ideation, from an iatrogenic effect of a medication. None of the patients in our study had increased suicidal ideation. It may be, however, that the length of time the patients were treated with medication did not allow for this effect to be exposed (Schweizer et al. 1990), and the small number in the sample may have been insufficient to uncover the symptom. Hersh et al. (1991) reported a case of transient psychosis but recognized that the history of head trauma and abnormal EEG may have been mitigating factors that contributed to the emergence of this symptom. Other side effects that were noted included insomnia (13%), fatigue (10%), headache (2%), nausea (2%), and tremor (2%).

Increased maximum doses and larger samples may have uncovered greater problems, but the four patients who received doses larger than 40 mg showed no increased benefit or side effects. The present dosing schedule

is the same as the regimen used in adults (Altamura et al. 1988, Wernicke et al. 1989). More study is required to determine the pharmacokinetics in children and adolescents, and better dosing schedules could evolve from such work.

This study was undertaken as a preamble to further investigations into fluoxetine in children and adolescents. The greatest limitation of this study was that it was a retrospective analysis. The study could be enhanced by having standardized lists of side effects, formal treatment outcome measures, and a placebo-controlled, double-blind, prospective design. This would be the more objective way to determine the effectiveness of this drug as well as to establish clear guidelines to assess the severity of the illness process and the adverse symptoms. It is highly conceivable that the use of fluoxetine will continue to spread, which will increase the urgency to do these tasks.

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