An open trial and discontinuation study of fluoxetine in children and adolescents with obsessive-compulsive disorder

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The purpose of this study was to examine the efficacy and safety of fluoxetine for short-term and long-term treatment in children and adolescents with obsessive-compulsive disorder (OCD). Twenty-three children and adolescents (mean age 12.0, SD = 2.3) treated with fluoxetine for OCD with or without Gilles de la Tourette's syndrome were the subjects of this study. The design was an open-label trial for 20 weeks of fixed-dose fluoxetine (20 mg/day). OCD symptom severity was measured with the Maudsley OCD scale and with Clinical Global Impression Scale (CGI). All of the patients were followed-up after discontinuation of the drug for 24 months. Patients with OCD showed a significant decrease in the severity of their OCD symptoms according to Maudsley OCD scores ($p < 0.001$) and CGI scores ($p < 0.001$). Fluoxetine was generally well tolerated, and side effects were relatively mild. Ten patients (43.5%) with OCD who responded to fluoxetine relapsed in the follow-up period, but responded well to fluoxetine. These results indicate that fluoxetine is effective and safe for short-term and long-term treatment of OCD in children and adolescents.

Key words: obsessive-compulsive disorder, children, adolescents, follow-up, fluoxetine.

Recent epidemiological data shows that obsessive-compulsive disorder (OCD) occurs in children and adolescents as in adults. The point and life-time prevalence of OCD in children and adolescents are 1% and 1.9% respectively[1]. Approximately 80% of adults with OCD reported an onset of symptoms before 18 years[2]. OCD appears to be similar in children, adolescents and adults in terms of clinical features and treatment[3,4]. The etiology of OCD has been explained by genetic, biological, behavioral and psychodynamic theories[5]. Tic disorder is the most common comorbid disorder in children with OCD. Assessment of the other disorders, particularly tics, is important and may help in determining treatment[6].

Several studies have established the safety and efficacy of the serotonergic tricyclic antidepressant clomipramine in children and adolescents with OCD[1,3]. Common side effects are generally related to the anticholinergic and alpha-adrenergic effects[5]. In recent years, there has been increasing interest in the use of specific serotonin reuptake inhibitors (SSRI's) in the treatment of OCD. Some studies have demonstrated that fluoxetine, a SSRI, is effective in reducing OCD symptoms in children and adolescents as well as in adults, but there is no follow-up study that evaluates the discontinuation period. The purpose of this study was to examine the efficacy and safety of fluoxetine in short-term and long-term treatment of OCD in children and adolescents.

Material and Methods

Twenty-three children and adolescents representing a consecutive series treated with fluoxetine for OCD with or without Gilles de la Tourette's syndrome (GTS) at the Child and Adolescents Psychiatry Department of the University of Hacettepe were the subjects of this study. The study design included an open-label trial for 20 weeks and an open discontinued follow-up period of 24 months. The study was approved by the institutional ethics committee and signed consent were obtained from parents.

All subjects were evaluated independently by two child and adolescent psychiatrists and all met the DSM-IV diagnostic criteria for OCD[7].

Ten of the subjects received an additional diagnosis of GTS according to the DSM-IV. No other comorbid diagnosis was made according to the DSM-IV criteria. The exclusion criteria were life-time and current mental retardation, psychotic disorders, major depressive disorder, organic or neurological problems and laboratory abnormalities.

The symptom severity of OCD was measured with the Maudsley OCD Scale[8] translated and standardized for Turkish population[9] and with the Clinical Global Impression Scale (CGI) at the beginning and end of the study. Severity ratings on the CGI scale was as follows: 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, 7 = extreme. The agreement between the interviewers was high (Kappa: 0.803).

At the first examination, medical assessments including physical and neurological examination weight and blood pressure measurement; and clinical laboratory studies including electrocardiogram (ECG), and routine clinical chemistry, blood count, and urinalysis were done. These variables were reassessed monthly in the treatment phase.

After these assessments, fluoxetine was administered at a fixed dose (20 mg/day) every morning. No other treatment was given (family therapy, individual psychotherapy, behavioral-cognitive therapy), except pimozide for GTS. Pimozide dose was stable for each patient with GTS (mean dose: 2 mg/day).

During the 20-week study period, patients were, evaluated by the clinicians every fourth week and the symptom severity was rated on the CGI scale. The safety of the treatment was also assessed monthly by monitoring vital signs, laboratory tests and ECG. Furthermore, a semi-structured interview according to a body-system classification was developed and applied every fourth week to record systematically all adverse events.

At the end of 20 weeks, fluoxetine administration was discontinued. Twenty-three patients were longitudinally followed-up for a total period of 24 months. They were evaluated every two months for the first 12 months and every six months for the last 12 months. OCD symptom severity was measured with the CGI. The Maudsley OCD scale was used to screen obsessive-compulsive symptoms at the end of the 12-month and 24-month period. Fluoxetine (20 mg/day) was the choice of drug in case of recurrences. The dosage of the drug was increased up to 60 mg/day for patients who did not respond to 20 mg/day, and side effects were assessed for all relapsing patients.

Statistical analysis was performed with a computer package program (Statistical Package for Social Sciences, For Windows Release 5.0.1, SPSS Inc., 1992). Chi-square test, Wilcoxon test, Kruskal Wallis test and Mann Whitney U test were used with non-parametric data and t-test with parametric data. Fisher's exact test was applied when necessary and all tests were two-tailed.

Results

The age range of the sample was from 8 to 16 years; the mean age was 12.0 years (SD=2.3). There were 13 females (56.5%) and 10 males (43.5%).

None of the subjects had prior history of treatment with psychotropic medication before receiving fluoxetine. As a concurrent medication, pimozide was used in 10 subjects (43.5%), for the treatment of comorbid GTS (Table I).

Table I. Clinical Characteristics of the Subjects

		n	%
Age			
Mean Age	12.0 ± 2.3 years	23	100
Range	8-16 years		
Sex			
Male		10	43.5
Female		13	56.5
Comorbid Disorders			
GTS		10	43.5
None		13	56.5
Concurrent medication			
Pimozide (only for children with comorbid GTS)		10	43.5
None		13	56.5

GTS: Gilles de la Tourette's syndrome.

The age of onset for the OCD symptoms ranged from 7 to 15 years, mean 10.7 years (SD = 2.2). The interval between the onset of the symptoms and the diagnosis ranged from 3 to 48 months, mean 16.1 months (SD = 12.1). GTS symptoms started before OCD symptoms in ten patients with GTS.

Most of the patients (n: 11, 47.8%) were mild cases according to CGI scores and only one patient (4.3%) was rated as 'severe' by both clinicians. The severity of the OCD symptoms according to the Maudsley OCD scores showed a significant decrease in the treatment phase,

and did not change significantly at the end of the follow-up period. The symptomatic improvement during fluoxetine treatment was observed generally in the first month on the CGI scores. All patients' CGI scores continued to decrease monthly in the treatment phase. This decrease was statistically significant for every four-week interval except for the last month of the treatment phase. At the end of the treatment phase, 21 patients (91.3%) responded well to fluoxetine treatment according to CGI scores (patients who received 1 in CGI).

As 10 patients (43.5%) relapsed after the discontinuation of fluoxetine in the first 8-16 weeks (mean = 13.0, SD = 4.1 weeks), a statistically significant increase in the CGI scores in the second month of the follow-up period was observed. The CGI scores decreased in the eight month of the follow-up period with the recovery of these patients (Fig. 1 and Table II).

Fluoxetine (20 mg/day) was applied for all relapsed patients, but three of them needed an increase to 40 or 60 mg/day. All but one patient recovered completely in 16 to 40 weeks. This 13-year-old girl's subclinical symptoms remained. A 10-year-old boy showed an additional relapse eight months after recovery from his first relapse (Table III).

The associations between age, gender and other demographic variables, and clinical and therapeutic features such as comorbid diagnosis, concurrent medication, and onset of the illness were examined. Relapsing and non-relapsing patients did not differ in terms of age, sex, comorbidity of GTS or severity of OCD, therefore, no risk factors could be determined for relapses.

The relapsed patients required a significantly shorter time to achieve a '1' in the CGI scale during the treatment phase (mean: 3.4 months

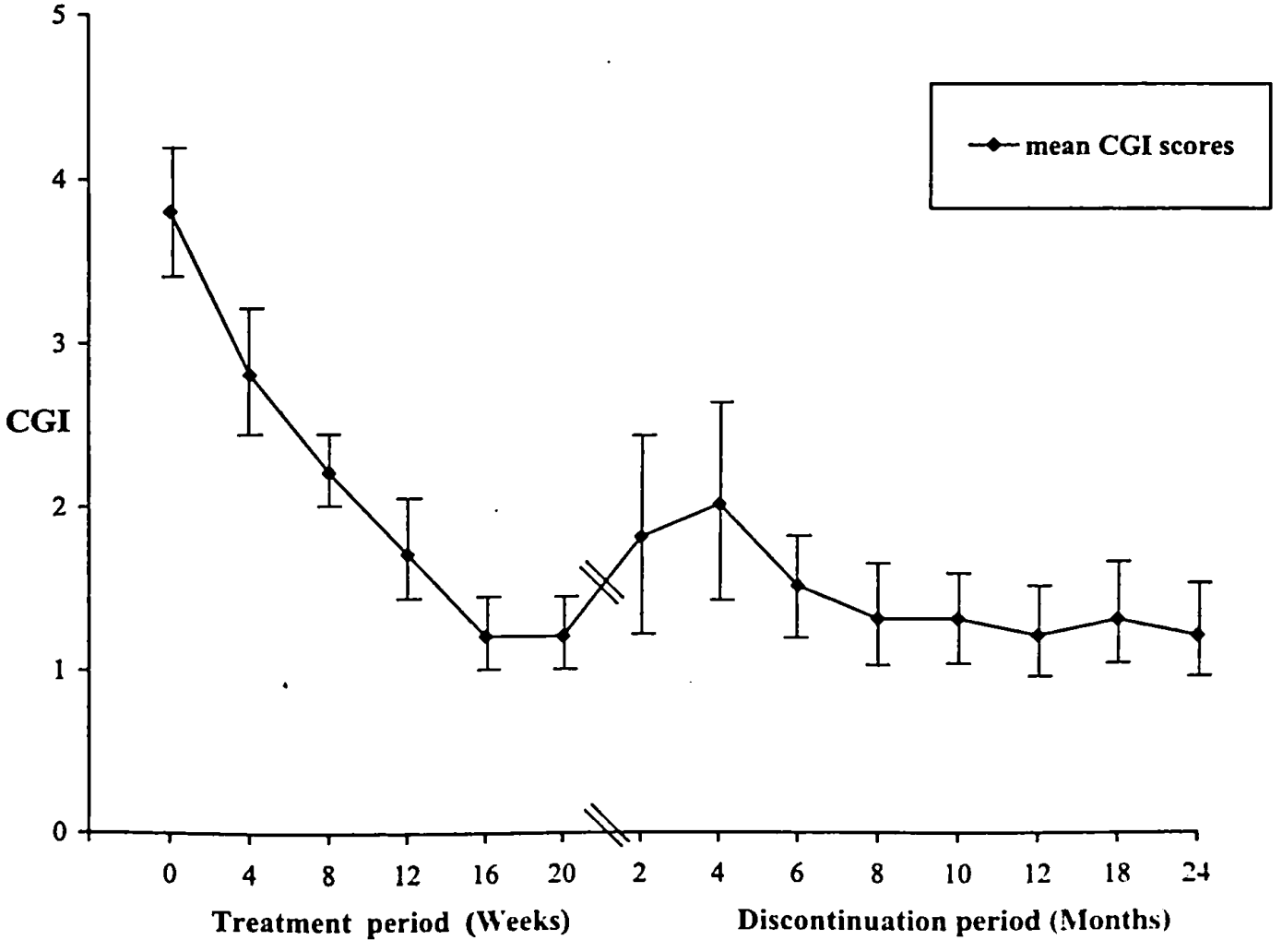

Fig. 1. Mean CGI Scores during the Treatment and Discontinuation Periods.

SD = 0.7) than in the follow-up phase (mean: 5.5 months SD = 2.1) (z: 2.37 p: 0.018). However, the recovery time in the treatment phase of these patients (n: 10, mean: 3.4 months SD = 0.7) and of the patients who did not relapse (mean: 3.5 months SD = 0.5) was similar (z: 0.42, p: 0.68).

Fluoxetine was generally well tolerated. Side effects reported in our sample included dyspepsia and nausea in three patients (13.0%) and skin rash in one patient (4.3%). Those side effects were relatively mild and not severe enough to discontinue the drug. They appeared during the first few days of treatment and disappeared in almost one week. No side effects were noticed during the use of fluoxetine in recurrences, even with high dosages. There were no significant ECG changes, laboratory abnormalities, or blood pressure or weight changes during the study.

Table II. Symptom Severity During the Treatment and Discontinuation Periods

	CGI scale[a]	t	df	Maudsley OCD scale[a]	t	df
Baseline	3.8 ± 0.9			21.6 ± 4.4		
4th Week	2.8 ± 0.9[b]	9.18	22			
8th Week	2.2 ± 0.4[b]	4.60	22			
12th Week	1.7 ± 0.7[b]	4.49	22			
16th Week	1.2 ± 0.4[b]	4.90	22			
20th Week	1.1 ± 0.3[NS]			9.3 ± 4.2[b]	16.56	22
2th Month	1.8 ± 1.2[b]	3.01	22			
4th Month	2.0 ± 1.1[NS]					
6th Month	1.5 ± 0.7[b]	3.87	22			
8th Month	1.3 ± 0.6[c]	2.47	22			
10th Month	1.3 ± 0.5[NS]					
12th Month	1.2 ± 0.5[NS]			8.9 ± 4.2[NS]		
18th Month	1.3 ± 0.6[NS]					
24th Month	1.2 ± 0.5[NS]			8.8 ± 3.8[NS]		

[a] : All statistical comparisons were made with the former measurement.
[b] : $p < 0.001$.
[c] : < 0.05.
[NS]: not significant.
CGI: Clinical Global Impression, OCD: Obsessive-compulsive disorder.

Table III. Clinical Characteristics of the Relapsed Patients

	Age	Sex	GTS	Relapsed (CGI=3) at week	Recovered (CGI=1) at week
Case 1	12	female	–	8	32[b]
Case 2	10	female	–	8	32[b]
Case 3	9	male	–	16	- [c, m]
Case 4	13	female	–	8	- [c, s]
Case 5	10	male	–	8	32[a, r]
Case 6	8	male	+	8	24[a]
Case 7	13	male	+	16	32[a]
Case 8	13	male	+	8	48[c]
Case 9	9	male	+	16	32[a]
Case 10	14	female	+	8	24[a]

Recovered with: [a] 20 mg/day, [b] 40 mg/day, [c] 60 mg/day fluoxetine.
[m]: recovered partially and remained with mild symptoms (CGI = 3).
[s]: recovered partially and remained with subclinical symptoms (CGI = 2).
[r]: relapsed again at week 72 but responded well to 20 mg fluoxetine.
GTS: Gilles de la Tourette's syndrome, CGI: Clinical Global Impression.

Discussion

The results of this open-label clinical study suggest that fluoxetine is an effective treatment in children and adolescents with OCD. A decrease in the severity of OCD symptoms was reflected in the Maudsley OCD scores and CGI scores. These results were similar to those of previously reported studies[10-15]. The symptomatic improvement during fluoxetine treatment was generally observed in the first month, both clinically and on the CGI scores. A plateau in

improvement was noticeable in the last month. Riddle et al.[14] reported that OCD symptom severity decreased about 30 to 45% after eight weeks. This result suggests that fluoxetine is effective for short-term treatment of OCD.

Several controlled studies established the efficacy of clomipramine in the short-term treatment of children and adolescents with OCD[3,16]. Leonard et al.[17] also showed the efficacy of clomipramine in the long-term treatment of children and adolescents with OCD. However, clomipramine was associated with anticholinergic adverse effects, intolerable for some patients. Fluoxetine treatment was generally well tolerated. A significant number of subjects (83%) did not report any side effects. Dyspepsia and nausea were also the most common side effects in previous studies, and were generally transient[10,14], as in our sample. Also, a study in children and adolescents with another SSRI (citalopram) suggested that side effects were minor and transient[18]. The absence of side effects during the use of fluoxetine in recurrences supports the safety of this drug for long-term use in children and adolescents.

There were no significant ECG changes, laboratory abnormalities, or blood pressure or weight changes during the study, as expected from previous reports[10,13-14]. However, there is no data on long-term effects of fluoxetine on these variables. This report supports that fluoxetine may be safe alternative treatment for children and adolescents with OCD, both in the short-and long-term.

Ten recurrences were observed during the follow-up period. Relapsing and non-relapsing patients did not differ in terms of age, sex, comorbidity of GTS or severity of OCD; therefore, no risk factors could be determined for relapses.

The same dose (20 mg/day) was readministered to patients who relapsed. However, the need for doses as high as 40-60 mg/day in three patients elongated the recovery time compared to the first treatment period, suggesting a development of tolerance to the medicine.

Although there are no objective data, the clinical observations of the clinicians following-up these cases suggested that families of relapsing patients were less supportive and less involved with their child compared to those of other patients. Family attitudes as a factor influencing the prognosis of OCD have been reported in some studies[19].

The duration of medical treatment in OCD is controversial. Some clinicians advise at least six months' treatment in order to improve subclinical findings and prevent relapses[20]. The occurrence of relapses after 8-16 weeks of the discontinuation of fluoxetine suggests that 20 weeks' treatment may be too short, and that the treatment should be extended even in the absence of symptoms to prevent relapses.

Despite its two major limitations, its open-label design and fixed dosage, this study is one on the largest series of children and adolescents treated with fluoxetine. However, the most important aspect of this study is that a follow-up, evaluating long-term effects and side effects in fluoxetine treatment, could be conducted so that the rate of recurrences could be established. The findings indicate that fluoxetine is effective and safe in short-term and long-term treatment of OCD in children and adolescents. Future studies should determine the effective blood levels of fluoxetine and the minimum duration of treatment in children and adolescents.

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