Fluvoxamine for the Treatment of Child and Adolescent Depression: An Open Label Trial

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Objective: Major depressive disorder is a severe disorder that has a significant impact on the psychological and social functioning of children and adolescents. Considering current limitations in the treatment of this disorder, the present study was performed to evaluate the efficacy of fluvoxamine in the treatment of children and adolescents with major depressive disorder.
Method: In an open trial, the efficacy of fluvoxamine (50-200 mg/d) on children and adolescents with major depressive disorder or dysthymic disorder was evaluated using the "Children's Depression Inventory", the "Hamilton Anxiety Rating Scale", the "Children – Global Assessment Scale", the "Clinical Global Impression Scale", and the "Drug Side Effect Questionnaire" at the beginning and 2, 4, and 8 weeks after the beginning of the treatment. The frequency of suicidal ideas was evaluated as well.
Results: Treatment with fluvoxamine caused statistically significant improvement in all of the above scales. The frequency of suicidal ideas decreased from 88.9 percent to zero after 8 weeks. No significant side effects were observed.
Conclusion: Fluvoxamine can be used as a safe and effective drug in the treatment of major depressive disorder and dysthymic disorder of children and adolescents.
Key Words:
Adolescents, Children, , Fluvoxamine, Major Depressive Disorder, Treatment outcome

Iran J Psychiatry 2008; 3: 11-15

Depression in children and adolescents is a severe disorder with significant impacts on psychosocial functioning which increases the risk of suicide (1). Manifestations of depression in this age group include loss of interest to participate in plays or exercises, not to engage in friendship or educational activities, and to have generalized feelings of worthlessness. The main manifestations of major depressive disorder in children and adolescents are similar to those of adults, but presentations are variable with regards to the age and developmental level of the given patients (2, 3).

The prevalence of major depressive disorder is about 2 percent in school age children and 5 percent in adolescents, and the prevalence of dysthymic disorder that manifests itself as depressed moods or irritability (for at least one year) is estimated to be 2.5 to 3 percent. The occurrence of depressive disorders in childhood is accompanied by increasing recurrence, severity, chronicity, and complications as compared to adults. Children and adolescents may also have secondary complications such as conduct disorder, substance or alcohol abuse, antisocial behaviors, or even attempting or committing suicide. Children and adolescents with major depressive disorder may have hallucinations or delusions (2), anxiety disorders or symptoms (4).

On the other hand, the risk of suicide in depressed children is very high, being 3 times more than the normal population and 2 times more than patients with anxiety disorders (2).

Currently, there is no clear consensus regarding the treatment of depression in children and adolescents. In contrast to adults, for this age group there are limited studies relating to the pharmacological treatment of depression (3, 5). Although selective serotonin reuptake inhibitors are now the first line drugs used for the treatment of depressive disorders (6), only two studies compare their effects with placebos in children and adolescents with depression. While there is not enough evidence regarding the efficacy of these drugs, it appears that they are effective in the treatment of depression in children and adolescents and could be drugs of choice due to their favorable side effect profile.

Among the selective serotonin reuptake inhibitors, fluoxetine is studied more than others in these age groups and is shown to be effective in 56 percent of the children and adolescents with depressive disorders (7). Considering the fact that each selective serotonin reuptake inhibitor has distinct structural and pharmacological properties, fluvoxamine also has unique therapeutic effects, side effect profile, and tolerability (8). Taking into account the above-

mentioned observations and bearing in mind that failure to respond to one of these drugs does not mean that the patient does not respond to another drug of this category, the authors aimed at studying the efficacy of fluvoxamine in the treatment of depressive disorders in children and adolescents.

Materials and Method

Study design

The present study is interventional and semi-experimental and conducted as an open trial. The studied population consisted of 6 to 18 year old patients with the impression of major depressive or dysthymic disorders who were referred to the child and adolescent psychiatry inpatient ward or outpatient clinic of Imam Hussein Hospital, Tehran, 2006-2007.

Sampling was done using the simple method. After validation of the diagnosis by two child and adolescent psychiatrists, and clinical interviews based on DSM-IV-TR, 18 patients were selected for the study once written consent from their parents was obtained. To manage possible problems or drug side-effects, the treating physicians were available round the clock or directly after a phone call.

Case selection

Patients with an IQ higher than 70 who had the defined criteria for major depressive disorder (MDD) or dysthymic disorder without psychotic features according to DSM-IV-TR, were included in the study. However, those with any other major psychiatric disorder including psychosis, bipolar mood disorder, catatonic features, conduct disorder, attention-deficit/hyperactivity disorder, or substance abuse were excluded from the study. Patients who had severe or debilitating physical disorders or other intervening medical disorders, those who used other medications with known interactions with fluvoxamine or other anti-depressive drugs were also excluded from the study.

Instruments

Selected patients were evaluated using instruments such as Raven's IQ, Children's Depression Inventory (CDI), Hamilton Anxiety Rating Scale (HARS), Children – Global Assessment Scale (CGAS), Clinical Global Impression Scale - Improvement (CGI), Drug Side Effect Questionnaire, a checklist for diagnostic criteria of major depressive and dysthymic disorders according to DSM-IV-TR and the participants' demographic feature checklists. CDI was used to evaluate the severity of depressive symptoms in the selected patients. Suicidal ideas were evaluated through clinical interviews. A fellow of child and adolescent psychiatry performed all the evaluations.

Intervention

Before initiating the treatment (T0) the CDI, HARS, CGAS, and CGI questionnaires and the written consent forms were completed. Subsequently, the patients were treated with fluvoxamine 25 mg/d. The administered drug dosage reached to 50 mg/d after 3 days. The maximum daily dosage was equal to 200 mg/d, administered in the case of patients' clinical non-responsiveness. The mean of administered dosage was 2.9±1.3 mg/kg. The subjects took a full dosage during nights.

The patients were visited at the end of the first week and their probable drug side-effects were evaluated. They were also visited in the second, forth, and eighth week and CDI, CGI-I, CGAS, and drug side-effects questionnaires were completed in each visit.

Statistical analysis

The data obtained from the questionnaires were tabulated and analyzed using SPSS Win 15.0. Analysis of Variance (ANOVA) and Chi Square tests were used to compare the results when appropriate. The significance level was determined to be 0.05.

Results

Twenty five patients participated in the present study. Among them, 7 patients were excluded from the study without reporting any side-effects due to lack of cooperation. Ultimately, 18 patients were studied and their responses to the treatment were analyzed; 16 patients completed the study up to week 8, but the other 2 continued only until week 6 and did not show up for the last visit, therefore, final evaluation in the 8th week was not possible.

Three patients were selected from the inpatient ward and 15 from the outpatient clinic of Tehran Imam Hussein Hospital. Thirteen patients (72.2%) had comorbid anxiety disorders and 5 (27.8%) had only depressive disorders; these results were confirmed by clinical interview, using the DSM-IV-TR checklist

The scores of the patients on CDI and its subscales, Hamilton Anxiety Inventory, GAF scale, and CGI-I during different evaluation times are shown in Table 2.

Table 1. Demographic features of the studied patients

Features	Frequency (%)
Sex	
Male	10 (55.6)
Female	8 (44.4)
Age	
<11y	6 (33.3)
>11y	12 (66.7)
Duration	
≤1y	9 (50)
>1y	9 (50)
Family history of Depressive disorders	
Positive	17 (94.4)
Negative	5 (5.6)
Comorbid condition	
GAD	4 (22.2)
Enuresis	3 (16.7)
Panic attack	2 (11.1)
OCD	1 (5.6)
Tic disorder	1 (5.6)
Trichotilomania	1 (5.6)
Social phobia	1 (5.6)
Specific phobia	1 (5.6)

Table 2. Scores of different scales during the study

Scale	Beginning of the study	2nd week	4th week	8th week	P value
Children's Depression Inventory	28.61	17.82	11.27	7.06	< 0.001
Negative mood	6.33	3.33	1.77	0.75	<0.001
Interpersonal problem	3.05	1.66	1.16	0.75	< 0.001
Ineffectiveness	4.44	3.33	2.16	1.31	< 0.001
Anhedonia	9.88	6.16	4.11	2.93	< 0.001
Negative self-esteem	5	3.33	2.05	1.31	< 0.001
Children Global Assessment Scale	37.8	53.6	69.2	84.1	< 0.001
Hamilton Anxiety Rating Scale	30.5	14.6	8.4	6.4	< 0.001
Clinical Global Impression Scale	-	1.44	2.61	3	< 0.001
Frequency of Suicidal Ideas (%)	16 (88.9)	10 (55.6)	2 (11.2)0	0 (0)	< 0.001

As shown, the changes of all scores in the 8th week in the repeated measures of ANOVA were statistically significant ($P < 0.001$). In other words, fluvoxamine caused significant improvement in the scores of all the scales. It is also noteworthy that the frequency of suicidal ideas decreased from 88.9 percent from the beginning of the study to zero in week 8 ($P < 0.001$). No statistically significant relationships were found between the age or sex of the patients and their responses to the treatment ($P > 0.05$).

The probable side-effects were also studied. No statistically significant changes in systolic or diastolic blood pressure of the studied patients ($P > 0.05$) were found.

However, the medication caused a significant increase in body weight (the patients' weight was 45.36±16.34 kg before treatment that reached to 45.87±16.26 kg after treatment; $P < 0.001$). Generally speaking, fluvoxamine was tolerated very well. Only one patient had mild dizziness, one had drowsiness, and one experienced gastrointestinal upset (with previous history of such problem). The remarkable finding was that fluvoxamine improved headaches, enuresis and decreased appetite in patients with previous history of such complaints.

Discussion

With the introduction of Selective Serotonin Reuptake Inhibitors (SSRIs) as a new generation of anti-depressive drugs in the 1990s, research regarding the treatment of depressive disorders has switched from tricyclic antidepressants to this class of medications. The first controlled trial of SSRIs concerning children and adolescent depressive disorders was conducted by Emslie et al. (7). They treated 96 depressed children for 8 weeks with fluoxetine and observed significant improvements in their scores on CGI and CDRS scales. In this study, 56 percent of the children improved significantly and the disorder remitted for 31 percent. Compared to this study, in the present research, fluvoxamine had a better improvement rate (equal to 100%). However, it is suggested that the study be replicated in double blind clinical trials for a further verification.

In a meta-analysis performed by Wallace et al. (6) it was suggested that SSRIs generally, and fluoxetine and citalopram more specifically, are effective in the treatment of childhood depressive disorders and have favorable side-effect profiles. In another review by Hamrin and Scahill (9), it was noted that SSRIs drugs had moderate effects on childhood depressive disorders and were accompanied by increased risk of suicide and self injurious behavior. They concluded that whenever SSRIs were to be used in children and adolescents, accurate diagnostic assessments, evaluations of comorbid conditions and close observation should be performed, being more intensive in the first week of drug prescription (10). In the present study, contrary to the above-mentioned studies, no increase in suicidal trends was observed. Moreover, fluvoxamine caused these trends to disappear in the studied patients. This difference may be due to small sample size, difference in the epidemiologic features of the studied populations, or real difference due to the efficacy of medication in the patients who used fluvoxamine.

DeVane and Sallee noted that SSRIs are only effective in the treatment of childhood depression and obsessive-compulsive disorders and considering their probable behavioral side-effects, they must be prescribed to this age group with precaution (11). In the present study, such behavioral side-effects were not observed. However, considering the small sample-size, making such a judgment is difficult.

There is more evidence for the efficacy of other SSRIs than that of fluvoxamine for the treatment of patients with depressive disorders. The majority of these

studies are performed with reference to fluoxetine (12). In a study performed in France, fluoxetine was found to be more effective than sertraline and paroxetine in treating childhood depression (13). The efficacy of fluoxetine in this study is comparable to the results regarding fluvoxamine in the present research. Hjalmarsson, Corcos, and Jeammet considered a 1 or 2 CGI score as improvement (13). If this index is considered as progress in our study as well, it can be concluded that all of the studied patients had improved in their depressive disorders, which can, in turn, be interpreted as the favorable effectiveness of fluvoxamine in the treatment of childhood and adolescence depressive disorders.

In previous studies, it is shown that more than 95 percent of the patients with depressive disorders have at least one anxiety symptom and up to 65 percent of the patients with anxiety disorders become depressed (14). On the other hand, it is shown that fluvoxamine can alleviate manifestations of both disorders simultaneously (15), and in treating anxiety disorders, it has an efficacy equal to benzodiazepines in the long run (15-17). Therefore, it can be concluded that fluvoxamine may be the drug of choice in the treatment of anxiety disorders, especially obsessive-compulsive disorder (18).

In a study performed by Gothelf et al the efficacy of fluvoxamine in cancerous children with depressive and anxiety disorders was studied (19). The authors concluded that in an open labeled study, like the present one, fluvoxamine has a favorable efficacy in the treatment of depressive and anxiety manifestations in children.

In the present study, it was observed that the benefits of fluvoxamine appear somehow rapidly, and contrary to other studies that recommended 4 to 6 weeks for its effects to appear, the patients' improvement after 2 weeks was significant. However, this rapid mode of action can be related to placebo effect. Other studies also suggest that fluvoxamine acts faster than other antidepressants (20).

There is some controversy regarding suicide risk with using SSRIs. In a small number of studies it is mentioned that some SSRIs (such as paroxetine) may increase suicidal attempts or thoughts, but others (such as fluoxetine or citalopram) are safe (6). On the other hand, in a study performed in New Zealand in 1993, it was suggested that fluvoxamine has a more rapid mode of action in decreasing suicidal thoughts than imipramine or maprothyline (21). Nevertheless, it is recommended that drug prescription be performed with precaution, and the risk of suicide be notified to the patient and his/her family until the safety of fluvoxamine concerning suicidal risks is established by studies such as the present where it was shown to have reduced such risk.

It is also worth mentioning that fluvoxamine is a relatively safe drug for children and adolescents (22). In the present study, no significant side-effects were observed. However, due to small sample size, the results on drug side-effects must be interpreted with caution.

Limitations

The lack of a control group in the present study causes difficulty for the interpretation of the results regarding the efficacy of fluvoxamine in the treatment of children and adolescents with depressive disorders. In addition, considering the short duration of the study (8 weeks), long term efficacy and side-effects of fluvoxamine in children and adolescents with depressive disorders could not be determined.

Conclusion

Fluvoxamine can be a favorable drug in the treatment of children and adolescents with depressive disorders. However, further studies (preferably double blind, placebo controlled ones) with larger sample sizes are recommended to approve its efficacy and probable side-effects.

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