The Effectiveness and Tolerability of Citalopram in a Turkish Sample of Children with Obsessive Compulsive Disorder

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ABSTRACT:
THE EFFECTIVENESS AND TOLERABILITY OF CITALOPRAM IN A TURKISH SAMPLE OF CHILDREN WITH OBSESSIVE-COMPULSIVE DISORDER

Objectives: The aim of the study was to describe efficacy, tolerability and side effects of citalopram in the treatment of child and adolescent obsessive-compulsive disorder (OCD). **Methods:** This open-label trial of citalopram (10-20 mg daily) included 23 cases. Maudsley Obsessive Compulsive Questionnaire (MOCQ), Child Depression Inventory (CDI), State and Trait Anxiety Inventory for Children (STAI-C) were given to all children during the detailed psychiatric interviews. The treatment response was evaluated using Clinical Global Improvement Scales (CGI). All cases were assessed by Diagnostic and Statistical Manual of Mental Disorder–Text Revision (DSM-IV-TR). **Results:** After the 8 weeks of citalopram treatment, statistically significant improvements were found in all scores. 20 subjects (86.95%) had comorbid diagnosis or conditions. Depression was the most common comorbid diagnosis (6 cases, 26.08%). 13 subjects (56.52%) had side effects, and all side effects were highly similar to those reported from the use of other selective serotonin reuptake inhibitors (SSRIs). However, sedation during the day-time was obvious in 5 of the cases (21.73%) during the first week. None the subjects worsened during citalopram treatment and none was excluded because of serious side effects during 8 weeks. **Conclusions:** These results suggested that citalopram has seemed to be quite effective and tolerable of child and adolescent with OCD, and comorbid anxiety disorders.

Key Words: citalopram, obsessive compulsive disorder, effectiveness, side effects, tolerability.

Bull Clin Psychopharmacol 2002;12:134-141

INTRODUCTION

Anxiety disorders (OCD, social phobia, selective mutism, panic disorder, separation anxiety, generalized anxiety disorder, simple phobia and post-traumatic stress disorder) are the most prevalent psychiatric disorders in children and adolescents, effecting as many as 10% of children (1,2). Current estimates suggest that 2% and 3% of children and adolescents are affected by OCD (3). Generally, symptoms exist an average of 7-8 years before reaching clinical attention (4). Main associated psychopathology with severe primary childhood OCD are major depression, Gilles de la Tourette syndrome (GTS), anxiety disorders, attention deficit/hyperactivity disorder (ADHD), conduct/oppositional disorder, eating disorders and alcohol substance abuse (5,6,7).

In children and adolescents, drug treatment for anxiety disorders have been seldom studied compare to adults. However, the effective and commonly used treatment of OCD is a combination of behavioral therapy and pharmacological treatment with a serotonin reuptake inhibitor (8).

The selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors (SSRIs), which are a new group of antidepressants used in mild to moderate cases of a spectrum of childhood psychiatric disorders (e.g. OCD, depression, eating disorders, GTS, ADHD, anxiety disorders, elective mutism, Asperger Syndrome), because of their efficacy, good side-effect profile, tolerability, and safety in overdose, as well as patient compliance (9-17). The best-documented SSRI to this area is sertraline. However, fluoxetine and fluoxamine have been studied in systematic trials in children and adolescents. Clomipramine has been proven effective, however, side effects caused by this agent would suggest that an SSRI is a better choice (18). In addition, although SSRIs are first-line pharmacological agents in children and adolescents with OCD, refractory symptoms can be treated by augmentation with neuroleptics or other agents (3,19).

Citalopram is the most selective of the SSRIs, and

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Date of acceptance: 26.05.2002

it has a half-life of approximately 33 hours (1,20). It is metabolized by cytochrome P450 (CYP) isozymes. However it has less inhibition of cytochrome P450 enzymes than other SSRIs, possibly giving it a lower potential for drug interactions (21-23).

In the studies reported that the main side effects of citalopram are headache, nausea, sedation, insomnia, dry mouth (17).

The aim of the present case study were; firstly, to investigate efficacy of citalopram and tolerance to it, secondly, to assess the pattern of adverse reactions of citalopram, lastly, to determine the frequency of mainly obsessive-compulsive symptoms and a comorbid diagnosis and conditions reported on citalopram in children.

METHODS

Subjects

23 children and adolescents with DSM-IV-TR diagnosis of OCD were included in this study. Subjects were 12 boys (52.2%) and 11girls (47.8%) with an age range of 8 to 15 years, and average age was 10.6±2.5 years.

Patients with mental retardation, psychosis, pervasive developmental disorders, neurologic disorder (e.g. seizure disorders), any known metabolic disease (e.g. Diabetes Mellitus), take of any medication within the prior 10 weeks excluded from this study. Main and comorbid psychiatric diagnoses were determined by clinical interviews of each child and parent by the same child and adolescent psychiatrist (FT). In additon, the selection of the subjects and determination of the effectiveness and tolerability were assessed by the same child and adolescent psychiatrist.

Methods

In this preliminary, open-label study, 23 children and adolescents with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (24) moderate to severe OCD were treated with citalopram during the 8 weeks. All parents informed about all procedures performing in the present study and their written consents were taken.

Citalopram was used as monotherapy at a dose of 20 mg. After the initial clinical interviews, the presence of OCD and comorbid diagnosis was investigated by the first author using DSM-IV-TR. In addition, indications and the clinical outcome of the treatment were determined by a consensus of the assessments by parents, psychiatric scale scores, interview with children every week. Maudsley Obsessive Compulsive Questionnaire (MOCQ), Beck Child Depression Inventory (CDI), State Anxiety Inventory for Children (SAI-C) and Trait Anxiety Inventory for Children (TAI-C) were applied to all children (25-28). The treatment response was evaluated using CGI on every week during the 8 weeks (29). MOCQ, it has 4 subscales; doubt, cleanness, control, slowness, CDI, State and Trait Anxiety Inventory for Children (STAI-C) are applied to all cases at the referral and again after 8 weeks of treatment with citalopram. The adverse effects were recorded every week with possible adverse effects questionnaire list. In addition, the effects of the drug were assessed with electrocardiogram (ECG) and blood pressure at baseline and at the end of 8 weeks. Before starting treatment with citalopram, electroencephalograms (EEG) of all cases were recorded. And also the case's developmental history indicated that normal milestones had been achieved.

Parents were asked about demographic and family issues. Information about school achievements was gathered from the teachers. In this study, using all psychometric tests were assessed by Turkish Health Ministry, and approved for the validity and reliability. As a result of this investigation in Turkish children, the cut off point for CDI was determined as 19 (27).

All cases were followed up with 8 weeks of treatment for OCD by the same child and adolescent psychiatrist. None of the subjects dropped out from the study.

Statistical Methods

Mental and medical health and social conditions of patients and their parents were compared by using chi-square test. The pre and post treatment clinical scores were compared by paired-samples t test. Repeated measurement of ANOVA was used to compare the data obtained from improvement and severity scales of OCD, registered weekly during the study. Gender was accepted as a factor and age was accepted as a covariate. The clinical scores between girls and boys were compared by using Mann-Whitney U test. Two tailed tests were used and $p<0.05$ was considered as significant.

RESULTS

Of the 23 subjects with OCD, 12 (52.2%) were boys and 11 (47.8%) were girls, revealing no statistically significant difference ($p>0.05$). The main age of children was 10.8±2.3 years (range from 8 to 15 years). The duration of education of cases was 5.66±2.5 years (ranged from 1 to 9 years). The time of walking was 14.4 months (ranged from 9 to 30 months), the time of speaking was 19.3±5.9 months (ranged from 11 to 36 months), the gaining of bowel control was 23.9±8.6 months (ranged from 11 to 36 months).

The average age at the onset of the symptoms was 8.3±2.5 (3 to 13 years). The age at the referral was 10.6±2.5 (6 to 15 years). The most common obsession was contamination. The most common compulsions were hand- washing and controlling (see Table 1).

OCD is typically co-morbid with serious medical illness, and often co-morbid with complicating

Table 1. Obsessive-compulsive symptoms in childhood and at follow-up in 23 patients with childhood obsessive-compulsive disorder

Cases Onset	Age of Onset	Age at Referral	Main Obsessive-Compulsive Symptoms	Comorbid Diagnosis or Condition	OCPD or OCDin First Degree Relatives
1 (M)	11y	13y	Checking, symmetry, hand-washing	GTS Somnambulism	Y
2 (F)	8y	12y	Checking, death	Claustrophobia, low-Self-esteem	Y
3 (M)	12y	15y	Dirt, hand-washing	GTS	N
4 (M)	8y	9y	Control, death	Separation anxiety, Somnambulism	N
5 (F)	7y	8y	Dirt, doubt	Depression	N
6 (F)	10y	14y	Death, doubt	Social phobia	Y
7 (M)	4y	8y	Death, doubt	PNE separation anxiety	N
8 (M)	8y	11y	Contamination (antrax) Dirt, hand-washing	Motor tic disorder	N
9 (F)	11y	13y	Dirt, hand-washing contamination, control	PNE	Y
10 (M)	4y	8y	Control, contamination	School phobia	Y
11 (F)	12y	14y	Control, contamination, Doubt	Depression, low-self esteem	Y
12 (M)	5y	10y	Checking, handwashing	ADHD, PNE	N
13 (F)	10y	13y	Contamination, dirt, hand-washing	None	Y
14 (F)	7y	11y	Control, symmetry	Depression, low-self esteem	N
15 (F)	3y	9y	Control, death, dirt	Seperation anxiety	Y
16 (M)	10y	10y	Death, illness	eye blinking, depression	N
17 (M)	13y	14y	Checking, hand-washing	Conduct disorder, motor tic disorder	N
18 (M)	7y	10y	Contamination (antrax), control, hand-washing	Phobies	N
19 (F)	7y	8y	Contamination, control, counting	Phobies	Y
20 (F)	6y	8y	Death, doubt,phobia	Depression	Y
21 (M)	7y	9y	Contamination (antrax)	ADHD, depression	N
22 (F)	8y	9y	Control, death	None	N
23 (M)	10y	12y	Contamination, hand-washing	None	N

ADHD: Attention deficit hyperactivity disorder
PNE: Primary nocturnal enuresis
OCDP: Obsessive-compulsive personality disorder
GTS: Gilles de la Tourette syndrome

emotional disorders. In our study, 20 of cases (87%) had some psychiatric problems (see Table 1).

Family history of psychiatric disorders was reported in 7 mothers (two OCD, five obsessive-compulsive personality disorder, two depression), (x^2:3.5, p=0.06), in 6 fathers (one OCD, two obsessive-compulsive personality disorder, two alcohol dependent, two depression), (x^2:5.3, p=0.022). 10 children (43.5%) had positive family history of OCD or obsessive-compulsive personality disorder in the first degree family members. Family members of OCD with girls (34.8%) had much more OCD or obsessive-compulsive personality disorder than family members of OCD with boys (8.7%) (see Table 1). No siblings of both girls and boys with OCD had psychiatric disorders.

All children and adolescents had high scores on the all scales before starting treatment of citalopram and it was obvious that a significant reduction on all scores at the end of 8 weeks was found (see Table 2).

Electrocardiogram of all cases was assessed at the referral and at the end of 8 weeks. No significant effect on the electrocardiogram (ECG) has been reported during short-term controlled studies of citalopram. In addition, a physical examination, routine biochemical investigations, and EEG were all proved normal before initiation of citalopram trial.

Efficacy and tolerability of citalopram

20 of cases were treated with 20mg/day citalopram during the 8 weeks. While taking 20 mg/day citalopram, cases 2, 4, and 5 had hypomania

Table 2. The results of psychometric assessments of 23 cases with obsessive-compulsive disorder

Scales	All Scores At Baseline	All Scores at 8 Weeks	p	t
CDI	15.3±9.1	9.1±5.7	0.000	7.3
TAI-C	40.5±7.0	29.8 ±7.7	0.000	8.4
SAI-C	37.0±7.9	29.3±6.3	0.000	13.2
MOCQ	20.65±4.3	11.1±2.4	0.000	18.1
Doubt subscale (MOCQ)	7.0±2.0	3.9±1.4	0.000	13.7
Cleanness subscale (MOCQ)	5.1±1.8	2.3±1.2	0.000	10.5
Control subscale (MOCQ)	4.5±2.2	2.5±1.2	0.000	7.6
Slowness subscale (MOCQ)	3.9±1.5	2.4±1.2	0.000	6.1
Severity scores of CGI	5.5±0.9	2.05±0.5	0.000	21.1
Improvement scores of CGI	4.0±0.0	1.7±0.7	0.000	15.8

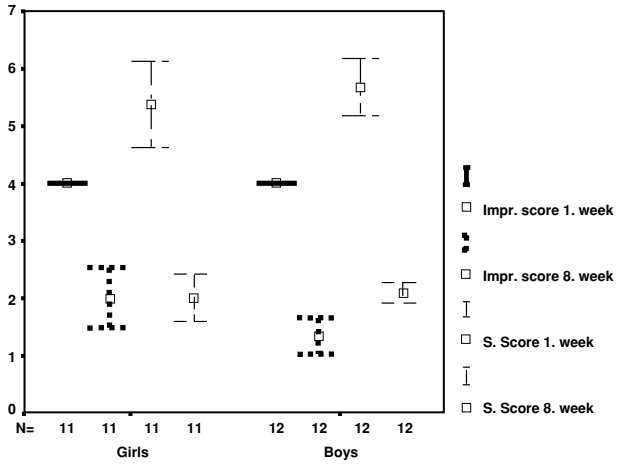

Figure 1. Pretreatment and posttreatment Clinical Global Impressions Scale scores in both genders

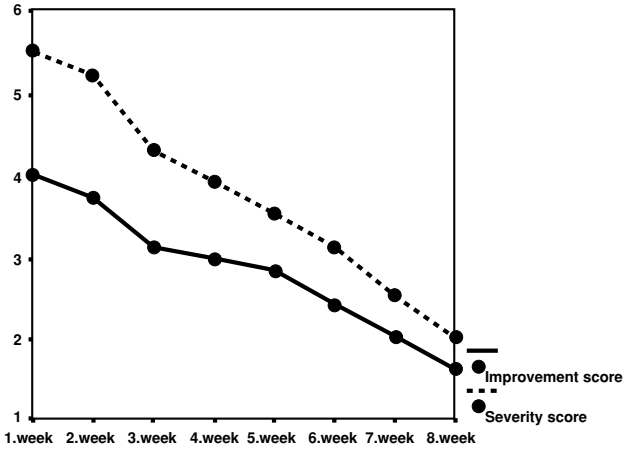

Figure 2. Effectiveness of citalopram according to Clinical Global Impressions scale scores

during third weeks. Therefore, these cases took 10mg/day citalopram rest of the treatment. Final citalopram dose for the cases was 18.7 mg/daily (ranged from 10 to 20 mg/day). Although there was hypomania on some cases, there were no increase symptoms of ADHD on two cases 12,21. It was obvious that citalopram was quite effective on phobias.

Cases 1 and 3, who had GTS, were more resistant to OCD treatment by citalopram, and these cases may have needed treatment with higher doses of citalopram or combination of other medications. However, there were not any increase of tics on four cases 1,3,8,17.

Effectiveness of citalopram is represented in Figure 1 and Figure 2. Clinically, although cases 1 and 3 had only a slight improvement, the other cases had a marked improvement at the end of 8 weeks period. A large proportion of treated cases showed full or almost full remission (1 or 2 on CGI) at the end of study (Figure 1 and Figure 2).

There were not differences in total MOCQ, CDI, SAI-C and TAI-C scores between boys and girls at the baseline or at the end of 8 weeks. However, improvement of boys with OCD was statistically higher than girls with OCD (p=0.03, according to CGI) (Table 3).

Side effects

The most often reported adverse reaction was sedation (n=5, 21.7%). Sedation was the most obvious in the first weeks. 2 of 5 cases, who had sedation, had serious problem at school because of they slept on the desk many times in the first weeks. Most of side effects decreased or vanished in the second and third weeks of treatment. Interestingly, all symptoms of hypomania on three cases (case 2, 4 and 5) occured in third weeks. Hypomania resolved when citalopram was decreased to 10 mg per day (see Table 4).

DISCUSSION

The results of this study showed apparently that citalopram was effective and tolerable in children and adolescents with OCD, and comorbid other anxiety children and adolescents.

The older antidepressants seem to be effective but they often cause many adverse effects (30). In addition, the older antidepressants are not less expensive and no more effective than SSRIs. There is no advantage in restricting cases from treatment with SSRIs, which have fewer adverse effects and a decreased risk of a lethal

Table 3. The results of psychometric assessments in girls and boys

Scales	Baseline (Boys)	8 Weeks (Boys)	Baseline (Girls)	8 Weeks (Girls)	p1	p2
CDI	13.7±6.7	8.5±4.7	17.1±11.2	9.8±6.9	NS	NS
TAI-C	41.8±4.6	30.4±8.3	39.1±8.9	29.2±7.4	NS	NS
SAI-C	38.8±5.6	31.0±5.2	35.1±9.8	27.5±7.1	NS	NS
MOCQ	20.6±4.6	10.8±2.4	20.6±4.1	11.5±2.4	NS	NS
Doubt subscale (MOCQ)	6.6±2.2	3.6±1.3	7.5±1.7	4.3±1.4	NS	NS
Cleanness subscale (MOCQ)	5.4±1.7	2.5±1.1	4.7±1.9	2.2±1.4	NS	NS
Control subscale (MOCQ)	4.4±2.6	2.4±1.2	4.6±1.8	2.5±1.3	NS	NS
Slowness subscale (MOCQ)	4.2±1.6	2.3±0.9	3.7±1.5	2.5±1.4	NS	NS
Severity scores of CGI	5.6±0.8	2.08±0.8	5.4±1.1	2.0±0.6	NS	NS
Improvement scores of CGI	4.0±0.0	1.3±0.5	4.9±0.0	2.0.88±	NS	0.03

NS: Not significant (p>0.05)

TAI-C: Trait anxiety inventory for children

SAI-C: State anxiety inventory for children

CGI: Clinical global impressions scale

MOCQ: Maudsley obsessive-compulsive quesionnaire

p1: At baseline

p2: At 8 weks

Table 4. Side effects of citalopram treatment in Turkish children and adolescents cases with obsessive-compulsive disorder

	1.W	2.W	3.W	4.W	5.W	6.W	7.W	8.W
1. Sedation	5	4	3	3	1	1	-	-
2. Hypersomnia	3	3	3	2	2	1	-	-
3. Nausea	2	2	1-	-	-	-	-	-
4. Vomit	2	1	-	-	-	-	-	-
5. Hypomania	-	-	3	3	-	-	-	-
6. Decreased Appetite	1	1	1	-	-	-	-	-
7. Increased dreaming	1	1	-	-	-	-	-	-

W: Week

Note: Figures represented as the number of cases with OCD

overdosage in comparison with tricyclic antidepressants. The first choice of treatment in the psychopharmacological approach to OCD in children and adolescents are the SSRI agents, which have been documented as being effective as well as well-tolerated in children and adolescents (18). To date, primary studies consist of prospective investigations and case studies of citalopram (31,32). Therefore, we wanted to use citalopram in Turkish children and adolescents with OCD.

Table 1 shows, for each patient, sex, age of onset of obsessive-compulsive symptoms, age at referral, main obsessive-compulsive symptoms, comorbid DSM-IV-TR diagnosis and conditions at referral, and presence of obsessive-compulsive personality disorder or OCD in the first -degree relatives.

Children with OCD often have other psychiatric symptoms. In our study, most of cases had comorbid diagnosis or conditions (n= 20, 87%) (see Table 1). This comorbid diagnosis was quite similar to other studies (4,33). Depression in child and adolescent is a serious psychiatric disorder with a considerable impact on psychosocial functioning, and an associated risk of mortality due to suicide. The potential interest of SSRIs for child and adolescent depression treatment is now well recognized. Open studies have shown a response rate to SSRI from 60% to 75% and their efficiency was demonstrated through a controlled trial of high methodological quality, conducted (34). In this study, the most common comorbid diagnosis was depression (n=6, 26.0%). End of the 8 weeks, citalopram's efficacy in treating depression was evident on cases 5,11,14,16,20,21 (at the beginning of the treatment mean CDI scores of these 6 cases were 19.3, after 8 weeks mean CDI scores of these 6 cases decreased to 10.6). It was reported that low doses of citalopram were effective in cases with school phobia (35,36). To similar these studies, citalopram were quite effective on cases 6 and 10 with school phobia.

Most studies show that the most common obsession is dirt and the most compulsion is hand-washing (37,38). In this study, the most common obsessions were fear of contamination, death, dirt, doubt, and illness, and phobia. The most frequent compulsions were hand-washing, controlling, checking, symmetry, and counting. Interestingly, 3 of 9 cases, had obsession about contamination of anthrax

because when these cases at referral there were many news about anthrax (after September 11) (see Table 1).

At the end of 8 weeks, core OCD symptoms (eg. controlling, hand washing symptoms) showed statistically significant improvement, and scores of MOCQ, subscales of MOCQ, CDI, SAI-C, TAI-C and CGI were statistically decreased. As a result, all 23 children and adolescent completers were rated as much improved or very much improved on CGI scores. However, boys showed much more improvement than girls on improvement scores of CGI. That was only one difference between boys and girls on these scales (Table 2,3).

Side effects of SSRIs are similar to those described in adults and about 10% of children and adolescents treated have had to stop the treatment, because of side effects (8). Side effects of SSRIs include gastrointestinal disturbances, headache, sedation, decreased sleep, increased dreaming, hypomania, weight gain, impaired memory, excessive perspiration, paresthesia, and sexual dysfunction (13,39,40). In therapeutic use, citalopram has all been associated with apparent anticholinergic-like side effects (dry mouth, constipation, nausea etc.), despite the very low antimuscarinic activity of citalopram in vitro (30). In this study, side effects of citalopram were found similar to previous study (see Table 4). None of the subjects dropped out because of the side effects. Hypomania on 3 cases vanished after dose of citalopram was decreased to 10 mg/perday. Like some other studies, SSRI-induced hypomania found to be dose-dependent (19,41-43).

Results of both prospective and retrospective analyses showed that the only effect of citalopram on ECG findings is a small reduction in heart rate (8 beats per minute). There were no significant effects on PQ, QRS, or QTc intervals, indicating that citalopram has no effect on cardiac conduction and repolarization during short- or long-term treatment (20,44). Rodriguez et al. (45) observed cases of first-degree atrioventricular block, prolonged QTc interval, and orthostatic hypotension in SSRI-treated patients. Therefore, all ECGs were assessed at referral end of the 8 weeks, and no significant effects were observed on ECG and heart rates.

One possible side effect of SSRIs is the exacerbation of nervous tics in some cases (46). Though the symptoms of tics on cases 1,3,8,16, and 17, intensity of the symptoms did not increase during 8 weeks.

It is possible that the effects of SSRI on platelet functioning may cause bleeding in some patients and/or that a separate coagulopathy is present and contributing to bleeding (47). These adverse effects are still poorly known and rarely reported. In this study, routine blood examination (e.g., kidney functions tests, liver functions tests) was done at baseline and at 8 weeks. The results of these assessments revealed no significant abnormality.

The clinical outcomes of citalopram was satisfactory, well tolerated overall with reported adverse experiences being relatively benign, and its demostrated less need for concomitant anxiolytics/hypnotics (18,38,48,49).

Despite the fact that the use of medical treatment achieves a reduction in obsessive-compulsive symptoms rather than a total remission, medical treatment should always be combined with other treatment methods such as family counselling or family therapy, behavioral therapy, medications, and the cognitive behavioural therapy. The cognitive behavioral therapy is the best documented. However, we should be more alert about side effects if patients use combination therapy with medications (50).

Based on a few long-term follow-up studies on OCD children and adolescents there was not evidence that all children and adolescents suffer a lifetime course of the disease. It is therefore recommended that discontinuation is attempted after 1-1.5 years of successful treatment (18). Ideally the combination of behavioral therapy with drug discontinuation may prevent such relapses. Therefore, we planned that our cases are going to take citalopram with behavioral therapy in future, in addition we planned this treatment would take several more months.

Our results suggest that, low doses of citalopram, given in the morning, were effective, reasonably safe, with side-effects, that are more common and tolerable. We also hypotesized that children and adolescents would be most likely to show an early antidepressant and anxiolytic response and would also be more likely to develop manic or hypomanic symptoms with use of citalopram. These results, should be interpreted with caution because of the open nature of the study. Hence, there is a need for more systematic investigations to evaluate the safety and efficacy and proper use dimensioning of citalopram treatment in children and adolescents with OCD.

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