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Effectiveness and tolerability of citalopram for the treatment of depression and anxiety disorders in children and adolescents: an open-label study

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Abstract To assess the effectiveness and tolerability of citalopram for the acute treatment of children and adolescents suffering from depression and/or anxiety disorders. As much as 78 outpatients, aged 7–18 years with a diagnosis of depressive and/or anxiety disorder, completed an 8-week open trial with citalopram (20–40 mg/day). Outcome, side effects and suicidality were assessed weekly to bi-weekly using appropriate rating scales. At endpoint 56% of subjects were found to be responders (Clinical Global Impression-Improvement [CGI-I] Scale $\leq$ 2). Subjects with less severe psychopathology and subjects with anxiety disorders showed a more favorable response. As much as 43% of depressed and 51% of anxious subjects had a 50% or greater reduction in scores on our secondary outcome measures, Children's Depression Rating Scale-Revised (CDRS-R) and Screen for Child Anxiety Related Emotional Disorders (SCARED). Most reported adverse events were mild to moderate and did not affect medication adherence. No increase in suicidality was observed during the study. Citalopram was moderately effective, generally well tolerated and safe for the acute treatment of depressed and anxious children and adolescents.

Keywords Mood disorders · Depression · Anxiety disorders · Antidepressants · Selective serotonin reuptake inhibitors · Suicidality

Introduction

Affective and anxiety disorders are among the most common childhood psychiatric disorders. These disorders are often associated with family, school and social problems and substance abuse (Bernstein and Shaw 1997). Children and adolescents with depression are at increased risk for school failure and dropout (Simeon 1989) and for suicide (Brent 1993). Thus, effective treatment of depression and anxiety disorders in children and adolescents is an important mental health care priority.

The efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of pediatric depression and anxiety disorders has been demonstrated in several open-label and placebo-controlled trials (Ambrosini et al. 1999; Fairbanks et al. 1997; March et al. 2004; Birmaher et al. 2003).

Nevertheless, the extant data indicate that SSRIs would result in an adequate clinical response in only around 60% of patients (Emslie et al. 1997; Tsapakis et al. 2008).

Furthermore, reports of SSRI-induced agitation and suicidality have begun to emerge in recent years, and there

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is a growing concern regarding the safety profile of this class, especially in the pediatric population (Vitiello and Swedo 2004; Emslie et al. 2006a).

A meta-analysis of short-term placebo-controlled trials of antidepressant drugs, including the SSRIs, in children and adolescents with MDD, or other psychiatric disorders, showed an increased risk of suicidality during the first few months of treatment in those receiving antidepressants as compared to placebo (Hammad et al. 2006).

These findings suggest the need for additional treatment alternatives in this population. Given the paucity of data on alternative treatment options for these youths, further knowledge about different selective serotonin reuptake inhibitors in pediatric depression and anxiety is needed to broaden our pharmacological armamentarium.

The majority of studies evaluated the SSRIs fluoxetine, sertraline and paroxetine (Compton et al. 2001; Keller et al. 2001; Emslie et al. 2002). There is currently less information on the use of the SSRI citalopram in pediatric populations.

Citalopram has a more specific and selective pharmacological profile than other antidepressants of its class. It has the highest serotonin to norepinephrine ratio of all SSRIs and relatively weak interaction with the CYP 450 system, accounting for its minimal drug interaction potential (Hemeryck and Belpaire 2002; Lucki and O'Leary 2004).

Studies on the use of citalopram in adult populations have demonstrated its good tolerability, safety and effectiveness (Keller 2000). A limited number of studies have reported favorable results concerning the use of citalopram in the treatment of a range of pediatric depressive and anxiety disorders (Baumgartner et al. 2002; Wagner et al. 2004a, b; Shirazi and Alaghband-Rad 2005). Data from these studies suggest that citalopram is effective, safe and well tolerated in this group of children and adolescents and that further trials are warranted in this population.

As part of a larger trial investigating the impact of serotonin pathway genes on SSRI response in pediatric depression and anxiety, the objective of the study presented here was to expand our knowledge on the effectiveness, safety and tolerability of citalopram in a prospective study of youth suffering from acute affective and/or anxiety disorders. The pharmacogenetic findings of this trial were published earlier (Kronenberg et al. 2007).

Methods

Subjects

As much as 103 subjects, aged 7–18 years, diagnosed with Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) depressive or anxiety disorders of at least moderate severity (Clinical Global Impression-Severity [CGI-S] Scale ≥ 4) were recruited from a pediatric psychiatric outpatient clinic.

Inclusion criteria were mood disorders—major depressive disorder (MDD) and dysthymic disorder—and anxiety disorders. All subjects were medication-treatment naïve and were not receiving psychotherapy during the treatment trial period.

Exclusion criteria included mental retardation, organic brain syndrome, pervasive developmental disorder, history of hypomania or mania, psychosis, eating disorder, substance abuse and treatment with a CNS-acting agent.

Evaluation

Subjects were assessed at intake, 2, 4, 6 and 8 weeks. Diagnoses were established using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for school-aged children—Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997; Shanee et al. 1997). Overall clinical severity and improvement were assessed using the Clinical Global Impressions-Severity and Improvement subscales, respectively (CGI-S/CGI-I) (Guy 1976). Continuous measures of depression and anxiety were obtained using the Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al. 1985), the Beck Depression Inventory (BDI) for youth $\geq$13 years (Smucker et al. 1986), the Children's Depression Inventory (CDI) for children <13 years (Ambrosini et al. 1991) and the Screen for Child Anxiety Related Emotional Disorders (SCARED) (Birmaher et al. 1997, 1999). Suicidality was assessed using CDRS-R-Item 13 (assessing "suicidal ideation" from a score of 1—"understands the word suicide, but does not apply the term to himself/herself" to a score of 7—"has made a suicide attempt within the last month or is actively suicidal") and an 8-item short version of the Suicide Ideation Questionnaire (SIQ; assessing suicidality from a score of 56—defined as no suicidality to a score of 0—defined as maximal suicidality; Reynolds 1987). Clinicians also reported any event of self-harm. Side effects were rated on a five-point severity scale using a self-developed questionnaire based on reported side effects in recent literature (Emslie et al. 2005; Kronenberg et al. 2007).

Drug response was defined as CGI-I ≤ 2—much or very much improved—(primary outcome measure) and/or a decrease in scores of 50% or more from baseline on CDRS-R or SCARED (secondary outcome measures).

Procedure

Written informed consent was obtained from participants and their parents and the limitations of an open-label study

were explained to both. Following diagnostic assessment, participants received citalopram 10 mg/day for one week, which thereafter was increased to 20 mg/day through week 4. An additional increase to 40 mg/day was made at the end of week 4, if improvement was only minimal (CGI-I $\geq$ 3). Subjects were seen weekly by an experienced child psychiatrist, who assessed clinical response (bi-weekly) and side effects (weekly) using the aforementioned instruments.

Data analysis

All datasets were tested for normalcy using Kolmogorov-Smirnov test for normal distribution. Data with a normal distribution were analyzed using paired-samples *t* test, and data not normally distributed were analyzed using Wilcoxon, Mann–Whitney *U* and Kruskal-Wallis *H* tests. Fisher's exact test was used to analyze nominal datasets (e.g., responders vs. non-responders). Data analysis was performed for the intent-to-treat sample using last observation carried forward (LOCF).

Results

Characteristics of the study sample

As much as 103 subjects entered the trial and were started on medication. Eight subjects were disqualified due to protocol breach or non-attendance at first follow-up. The intent-to-treat population consisted of the remaining 95 subjects, of which 78 completed the full 8-week trial. A total of 7 subjects dropped out before completion of the trial for unknown reasons, 10 subjects stopped the medication due to side effects. Table 1 presents age and gender distribution of the study sample, as well as the distribution of subjects' primary psychiatric disorders and their severity.

Table 1 Demographic and clinical characteristics of study sample

Age	
Mean ± SD (range) [years]	13.9 ± 2.8 (7–18)
≥13 years	62 (65.3%)
≤12 years	33 (34.7%)
Gender	
Boys	47 (49.5%)
Girls	48 (50.5%)
Primary psychiatric disorder	
Depressive disorder	30 (31.6%)
Anxiety disorder	43 (45.3%)
Comorbid anxiety and depressive disorders	22 (23.2%)
Severity of primary psychiatric disorder	
Moderate—CGI-S = 4	27 (28.4%)
Marked—CGI-S = 5	57 (60%)
Severe—CGI-S = 6	11 (11.6%)

CGI-S clinical global impression-severity

Medication response (effectiveness)

The rate of improvement as defined by our primary outcome measure (CGI-I $\leq$ 2, much or very much improved) for the total sample, and for the depressed and anxious subjects separately, at 2, 4, 6 and 8 weeks is shown in Table 2. Based on the CGI-I, significant improvement was observed in 53 out of 95 subjects (55.8%) at the end of the 8-week trial.

For patients diagnosed with depression, scores of depression severity decreased significantly from baseline to endpoint on all three measures of depression, i.e., CDRS-R ($t = 9.1$, $df = 50$, $P < 0.001$), BDI ($t = 6.7$, $df = 38$, $P < 0.001$) and CDI ($t = 3.4$, $df = 12$, $P = 0.005$, Table 2). Of 51 subjects diagnosed with depression, 22 (43.1%) showed a significant reduction in symptoms of depression (at least 50% reduction in severity of symptoms) measured by the CDRS-R. Using a CDRS-R-score of ≤28 as remission (Emslie et al. 2006b; Kennard et al. 2006), we found that 23.5% of subjects with depression in our study sample attained remission at endpoint.

For patients diagnosed with anxiety disorders, SCARED scores declined significantly from baseline to endpoint ($t = 9.0$, $df = 64$, $P < 0.001$, Table 2). The decline was detected in all five SCARED domains (generalized anxiety disorder, panic disorder, social phobia, school anxiety and separation anxiety disorder; all Ps < 0.001). Significant improvement of anxiety symptoms in patients with anxiety disorders (at least 50% reduction in SCARED scores from baseline to endpoint) was observed in 33 out of 65 subjects (50.8%).

Mean dose of citalopram for subjects who completed at least 4 weeks of the trial ($n = 86$) was 30.2 ± 10.1 mg/day at week 4. Mean citalopram dose at week 8 for responders (53 out of 86 subjects) was 25.3 ± 8.9 mg/day and for non-responders (33 out of 86 subjects) 38.2 ± 5.8 mg/day. The average medication dose of responders indicates that most subjects responded to 20 mg/day of citalopram and did not require a dose increase to 40 mg/day at week 4.

A significantly lower rate of response was detected in patients with comorbid anxiety and depressive disorder versus depressive and anxiety disorder alone: 8/22 (36.3%) versus 15/30 (50%) versus 30/43 (69.7%), respectively; $P < 0.05$. We also found a negative association between severity of anxiety and depressive disorders and response rate to citalopram treatment. Adequate clinical response at the end of the 8-week trial was detected in 23 out of 27

Table 2 Response rate (CGI-I) and symptom reduction (CDRS-R, BDI, CDI, SCARED) after 2, 4, 6 and 8 weeks for total sample, depressed and anxious subjects

Week	Total sample	Depressed subjects				Anxious subjects	
	Responders CGI-I ≤ 2 *N* (%)	CDRS-R Mean ± SD	BDI Mean ± SD	CDI Mean ± SD	Responders CGI-I ≤ 2 *N* (%)	SCARED Mean ± SD	Responders CGI-I ≤ 2 *N* (%)
0	–	58.0 ± 9.5	23.4 ± 8.5	22.8 ± 10.4	–	33.5 ± 8.9	–
2	19 (20.0)	48.6 ± 11.7	15.8 ± 9.4	16.9 ± 12.9	12 (23.1)	25.5 ± 10.4	11 (16.9)
4	41 (43.2)	46.4 ± 13.2	15.4 ± 0.4	16.6 ± 13.1	20 (38.5)	21.8 ± 13.3	29 (44.6)
6	46 (48.4)	43.8 ± 14.7	13.4 ± 10.5	17.5 ± 12.6	23 (44.2)	19.6 ± 13.3	35 (53.8)
8	53 (55.8)	42.2 ± 15.7	13.4 ± 10.2	12.9 ± 13.8	28 (53.8)	18.7 ± 14.1	38 (58.5)

CGI-I clinical global impression-improvement, *CDRS-R* children's depression rating scale-revised, *BDI* Beck depression inventory, *CDI* children's depression inventory, *SCARED* screen for child anxiety related emotional disorders

(85.1%) patients with moderate illness (CGI-S = 4), 27 out of 57 (47.3%) patients with marked illness (CGI-S = 5) and in only 3 out of 11 (27.2%) patients with severe illness (CGI-S = 6) ($P < 0.001$). No significant association was found between response rate and age (children vs. adolescents), gender, ethnicity and body mass index.

Adverse events and sucidality

The most common adverse events reported with citalopram are listed in Table 3. Adverse events were reported by a substantial number of subjects. Although most side effects were experienced as mild or moderate and did not affect drug adherence, 10 subjects reported side effects severe enough to warrant discontinuation of the medication. Both psychological and motor agitation were more common in males than in females (both *P*s < 0.05).

No suicide attempts were conducted during the entire study period. Severity of disorder was significantly associated with higher Item 13 baseline scores (moderate disorder vs. marked disorder vs. severe disorder: 1.9 ± 1.4 vs. 2.9 ± 1.8 vs. 3.0 ± 1.8; $P = 0.041$).

Table 3 Adverse events reported with citalopram

Adverse event	*N*	%
Fatigue	30	31.6
Motor agitation	24	25.3
Appetite decrease	20	21.1
Headache	19	20.0
Gastric discomfort	16	16.8
Insomnia	15	15.8
Psychological agitation	14	14.7
Hypersomnia	10	10.5
Sweating	10	10.5

A decrease in suicidal ideation from baseline to end point was observed on CDRS-R- Item 13 scores (from 2.7 ± 1.8 to 1.9 ± 1.5, $P < 0.001$) and SIQ scores (from 47.1 ± 12.5 to 49.0 ± 12.0, $P = 0.054$). The type of psychiatric disorder was significantly associated with both baseline ($P < 0.001$) and endpoint suicidal ideation ($P = 0.001$). Subjects with only depression had lowest SIQ scores (meaning highest suicidality), whereas subjects with only anxiety disorders were least suicidal at both time points.

Discussion

Effectiveness

In this open-label trial citalopram was found to be moderately effective (overall response rate = 56%). The clinical results of our study are similar to those of other studies investigating the efficacy of SSRIs in children and adolescents. The TADS response rate to fluoxetine, based on a CGI-I score of 1 or 2 was 60.6% (March et al. 2004). Wagner et al. found a CGI-I-response rate of 47% to citalopram and 63% to sertraline and Emslie et al. reported a CGI-I-response rate of 48.5% to paroxetine treatment in children and adolescents with major depressive disorder (Wagner et al. 2003; 2004b; Emslie et al. 2006b). Trials with anxious youth produced somewhat higher response rates of 61% to fluoxetine (Birmaher et al. 2003) and 77.6% to paroxetine treatment (Wagner et al. 2004a).

We found two clinical factors that seemed to have an impact on citalopram response.

First, subjects suffering from milder depressive or anxiety disorders had a significantly better response than those suffering from a more severe disorder. Second, psychiatric disorder affected response rate in our sample. Subjects with anxiety alone responded better than those with depression

alone, who in turn responded better than those with comorbid anxiety and depression. These results are consistent with current literature, where numerous reports state a more favorable drug response for less severe disorders and for anxiety disorders (Brent 1993; Emslie et al. 1998; Hamilton and Bridge 1999).

Citalopram was associated with moderate response rates for depression and anxiety disorders in our sample, i.e., about 50% of subjects significantly improved with citalopram treatment and remission rate for depressed subjects was 23.5%. This is again consistent with response and remission rates in previous studies with SSRIs (Wagner et al. 2003, 2004b; von Knorring et al. 2006; Kennard et al. 2006; Emslie et al. 2006b).

Tolerability

A somewhat higher rate of SSRI-related side effects was reported in our study as compared to recently published trials with citalopram and fluoxetine (March et al. 2004). Four side effects: fatigue, motor agitation, decreased appetite and headache were each reported in more than 20% of our study subjects. In our study population 10.5% of patients discontinued medication due to severe subjective or objective side effects. No association was found between citalopram dose and rate or severity of reported side effects. However, in our sample we found that males were more susceptible to develop akathisia-like symptoms. This finding is novel and requires replication in future studies.

Overall, reported rates of side effects differ widely across the literature, which may be the result of different measures being used to evaluate side effects in different studies and the lack of standardized instruments with sound psychometric properties. The instrument used in our study for the assessment of side effects (SEPI) was developed by the investigators and based on commonly reported side effects of SSRIs in recent literature. Thus, our results seem to be within the range of previous reports. As medication was confined to 8 weeks in this trial, no conclusion can be drawn as to potential long-term side effects of citalopram treatment.

Suicidality and switch to mania

No harm-related events were noted in our study as opposed to reports thereof in two recently published RCTs with fluoxetine and sertraline (March et al. 2004; Wagner et al. 2003). Two patients in our study sample developed hypomanic symptoms and had to discontinue medication. None of the patients in our study sample attempted suicide. Using the SIQ, a self-rating scale for suicidal ideation, we found a 21.6% decrease in suicidal ideation from baseline to endpoint. On CDRS-R-Item 13, a clinician rated item for suicidal ideation and behavior, a 44.8% decrease from baseline to endpoint was observed. However, 25.3% of patients reported motor agitation and 14.7% reported psychological agitation. Many clinicians believe these side effects to be risk factors for future suicidal behavior and perhaps for switching to mania (Apter et al. 2005; Lim et al. 2005).

The idea that SSRIs may increase the rate of self-harm behavior, suicidality and completed suicides is extremely controversial. Evidence of an increased rate of completed suicides in association with the use of paroxetine, or other SSRIs is limited and contradictory (Beasley et al. 1991; Jick et al. 1995; Khan et al. 2003). A recent study by Jick et al. (2004) found that the risk of suicidal behavior among patients treated with amitriptyline, dotiepin, fluoxetine and paroxetine was similar. Recent meta-analyses of RCTs indicated no increase in the risk of completed suicide for SSRIs compared with either TCAs or placebo (Fergusson et al. 2005; Bridge et al. 2007). However, one study indicated an increased risk for suicide attempts with SSRIs compared with placebo but not compared with TCAs (Fergusson et al. 2005). There is evidence that antidepressants ameliorate suicidal tendencies, but also that treatment emergent suicidal ideation can occur (Teicher et al. 1993).

Our results are within the range of previous reports; however, they are limited, as we did not have a placebo arm. On the one hand, we did not detect any events of self-harm or increased suicidality; on the other hand many patients reported increased motor and psychological agitation, which may put them at risk for future suicidal behavior or switch to mania.

Limitations

As we used an open-label design for the study, all patients knew they were taking an active drug with proven efficacy for the treatment of depression and anxiety and placebo effects cannot be disregarded. The open design may, however, be an advantage by mimicking the real life situation. In addition, clinical results from this prospective study are similar to the active-drug arm of a recent RCT with citalopram (Wagner et al. 2004b).

Although we regularly checked medication compliance, we did not measure drug blood levels. Therefore, there is a possibility that some of the non-responders simply did not adhere to protocol.

In our study non-responders received a dose increase to a maximum dose of 40 mg/day at the end of week 4. It can be argued that some of the non-responders would have become responders later on and that we rather differentiated between fast-responders and slow-responders, and not

necessarily between responders and non-responders at week 4. However, our data shows that 72.2% of non-responders at week 4 remained non-responsive at week 8, and this despite the dose increase. Our finding is also in line with a recent open trial with fluoxetine, which showed that a significant symptom reduction was needed by week 4 in order to achieve remission at the end of the 12-week-trial (Tao et al. 2009).

Due to the limited duration of this trial (8 weeks) no statement can be made about the long-term effectiveness. Our study included a heterogeneous sample of patients with depressive and/or anxiety disorders, which is in contrast with most other studies that investigated drug efficacy separately for depressed or anxious youth. Although we performed separate statistical analyses for the depressive and anxiety subgroups for primary and secondary outcome measures, there is limited power in the separate analyses given the sample size.

Conclusion

The findings of our open-label prospective study suggest that citalopram is moderately effective, generally well tolerated and safe for the acute treatment of child and adolescent depression and anxiety. Future trials in a prospective double-blind placebo-controlled design with larger samples and of longer duration are warranted to substantiate our findings.

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Conflict of interest statement The authors declare that they have no conflict of interest.

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