A Randomized, Double-blind, Placebo-controlled Study of Citalopram in Adolescents With Major Depressive Disorder

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Abstract: In a European, multicenter, double-blind study, 244 adolescents, 13 to 18 years old, with major depression were randomized to treatment with citalopram (n = 124) or placebo (n = 120). One third of the patients in both groups withdrew from the study. No significant differences in improvement of scores from baseline to week 12 between citalopram and placebo were found. The response rate was 59% to 61% in both groups according to the Schedule for Affective Disorders and Schizophrenia for school-aged children – Present episode version (Kiddie-SADS-P) (depression and anhedonia scores ≤2) and Montgomery Åsberg Depression Rating Scale (MADRS) (≥50% reduction). Remission (MADRS score ≤12) was achieved by 51% of patients with citalopram and 53% with placebo. A post hoc analysis revealed that more than two thirds of all patients received psychotherapy during this study. For those patients not receiving psychotherapy, there was a higher percentage of Kiddie-SADS-P responders with citalopram (41%) versus placebo (25%) and a significantly higher percentage of MADRS responders and remitters with citalopram (52% and 45%, respectively) versus placebo (22% and 19%, respectively). Mild to moderate treatment-emergent adverse events were reported in 75% citalopram and 71% of placebo patients, most commonly headache, nausea, and insomnia. Serious adverse events occurred in 14% to 15% in both groups. Suicide attempts, including suicidal thoughts and tendencies, were reported by 5 patients in the placebo group and by 14 patients in the citalopram group (not significant) with no pattern with respect to duration of treatment, time of onset, or dosage. In contrast, the suicidal ideation (Kiddie-SADS-P) single item showed worsening more frequently in the placebo (18%) than in the citalopram group (8%).

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D epression is a prevalent disorder affecting 2% to 6% of adolescents.[1,2] There is, therefore, a clear need for a safe and effective treatment for this group of patients. Most

selective serotonin reuptake inhibitors (SSRIs) are not generally approved for pediatric use, and there is still a rather limited body of evidence to support the efficacy and safety of SSRIs in the young.[3] Recently, a study demonstrating a positive effect of citalopram in the treatment of pediatric and adolescent depression was published.[4]

The present study of the efficacy of citalopram in the treatment of adolescent depression uses a flexible dose strategy, with a double-blind, randomized placebo-controlled design.

METHODS

This was a multicenter (31 European recruiting sites), 12-week, double-blind, randomized, placebo-controlled, parallel-group, flexible-dose study in patients under specialist care. The study was initiated in Sweden in November 1996 but was extended to the additional countries because of poor recruitment. The total duration of the study exceeded 4 years.

After the screening visit, patients were randomized to citalopram 10 mg or placebo. Assessments were made after 1, 2, 5, 9, and 12 weeks. The *CPMP Note for Guidance on Good Clinical Practice*[5], the *ICH guideline for Good Clinical Practice*[6] and the *Declaration of Helsinki*[7] were implemented in the design and conduct of the study. Local ethics committees approved the study before patient inclusion. Patients and guardian(s) had to give informed consent after procedures and possible side effects were explained to them before any study procedures.

Population

Inpatients or outpatients, 13 to 18 years, who had entered puberty (Tanner stage ≥3) with major depression with current episode 4 weeks to 1 year were recruited for the study. Initially, a Beck Depression Inventory (BDI) score of 21 or more[8] and a Global Assessment of Functioning (GAF), according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, score of 60 or less at the screening visit were required for inclusion. The entry criterion was changed after enrollment of approximately 15% of the patients to include boys with a BDI score of 16 or more.[9] At the same time point, Montgomery Åsberg Depression Rating Scale (MADRS) assessments[10] were added. Patients were excluded from the study if they had bipolar disorder, attention deficit hyperactivity disorder, or any other psychotic disorder, progressive neurological disorder, alcohol abuse problems influencing daily functioning, or primary eating disorder. They should not attend a

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special school for the mentally retarded, have a pervasive developmental disorder, or be pregnant. Treatment with neuroleptics or any antipsychotics, selegiline, or dextrometorphan was not allowed, although antipsychotics was initially allowed during the first phases of the study and only later proscribed in a protocol amendment. Antidepressants, buspirone, lithium, pimozide, phenytoin, sumatriptan, anticoagulants were not allowed including 2 weeks before screening. Allowed medications included benzodiazepines, hypnotics, stimulants, and anticonvulsants.

Treatment Regimen

Patients randomized to citalopram took a daily dose of 10 mg during the first week with a possible 10 mg increase at the end of weeks 1, 2, 5, and 9, to a maximum of 40 mg if the GAF score had decreased by 10 units for any of the 4 items or was unchanged since last visit. At any time, the investigator could decide to decrease the dose in case of adverse events.

Psychotherapy, which was not predefined (could both be ongoing and initiated during the study, and of varying type and duration), was allowed during the study.

Efficacy Assessments

The prospectively defined primary measure of efficacy was based on the 9-item total score of the Schedule for Affective Disorders and Schizophrenia for school-aged children–Present episode version (Kiddie-SADS-P) (scored 0–56)[11] and MADRS (scored 0–60)[10] were carried out at baseline and weeks 2, 5, 9, and 12. Patients with a score of 2 or less on the Kiddie-SADS-P depression and anhedonia items or with a reduction of 50% or more from baseline of the MADRS total score were defined as responders. Patients with a score of 3 or more on either the Kiddie-SADS-P depression or the anhedonia item were defined as nonresponders. Remission was defined as MADRS total score of 12 or less.[12] The raters were trained in the use of the Kiddie-SADS-P in corating sessions.

Other secondary measures of efficacy included the BDI (scored 0–63) and GAF (scored 100–1), which were assessed at screening and weeks 1, 2, 5, 9, and 12. The GAF scale measured 4 areas: activities, relationships, personal care and symptoms, analyzing the mean value of the scores.

Tolerability Assessments

Standard clinical laboratory tests were taken at screening, and weeks 1 and 12. Electrocardiography was recorded at screening and week 2. Physical examination including weight, height, and vital signs was made at baseline, and except for height, at weeks 1, 2, 5, 9, and 12. All adverse events observed either by the investigator or reported spontaneously by the patient were recorded. The patient was also asked at each visit whether he/she had experienced any adverse events.

Statistics

Efficacy analyses were conducted on the intent-to-treat population, which included all randomized patients who took at least one dose of double-blind medication and who had at least one valid postbaseline Kiddie-SADS-P assessment. The primary efficacy parameter was adjusted mean change from baseline of the Kiddie-SADS-P total score using an observed case (OC) analysis. This was analyzed by means of analysis of covariance for the change from baseline to final assessment, and by repeated measures, taking all visits into account.

As a secondary efficacy measure, the proportion of responders and the percentage of patients in full remission were examined. These measures were analyzed by categorical methods. Because of the overall difference in withdrawal rate in the subgroups, the last observation carried forward (LOCF) method was used for the post hoc analyses. Safety analyses were conducted for the all-patients-treated set, which included all randomized patients who took at least one dose of double-blind medication.

RESULTS

A total of 244 patients were randomized to treatment, 124 to citalopram and 120 to placebo, and 233 took at least one dose of double blind treatment (citalopram = 121; placebo = 112) and comprised the safety population (all-patients-treated set). Overall, 14% of the patients were hospitalized at the entry of the study; patients enrolled during the first half of the study period tended to be more ill than those entered later. Patient baseline characteristics were similar for the 2 treatment groups. Mean age was 16 ± 1 years; mean Kiddie-SADS-P score, 32 ± 5; mean MADRS score, 30 ± 5/6; and mean GAF score, 55 ± 7.

There was no significant difference between groups (placebo [36%] and citalopram [28%]) in the proportion of patients who had previously received treatment for a major depressive episode. Slightly more patients on citalopram (23%) versus those on placebo (16%) had earlier been hospitalized for a psychiatric disorder and 30% of patients in both groups had previously attempted suicide.

Approximately one third of the patients in each group withdrew from the study; 79 citalopram and 74 placebo patients completed. Withdrawal due to lack of efficacy was more frequent in the placebo group than the citalopram group (16% vs. 9%, respectively), whereas withdrawals due to adverse effects were slightly more common in the citalopram group (8% vs. 11%, respectively). Approximately 70% of the patients were treated for at least 60 days. After week 5, patients in the citalopram group received 20 mg (37 patients), 30 mg (20 patients), and 40 mg (24 patients), and at last assessment, the mean dose was 26 mg.

Efficacy

Intent-to-treat Population

A decrease from baseline in the prospectively defined primary parameter Kiddie-SADS-P total score over time was found for both groups, with no significant differences between the groups (Fig. 1). The proportion of Kiddie-SADS-P responders increased during the study and was remarkably high at week 12 in both the placebo (61%) and

citalopram groups (60%) (OC). Response rate at each visit did not differ significantly between the treatment groups. Analysis of the suicidal ideation single item (Kiddie-SADS-P item 9) showed similar improvements from baseline to week 12 for citalopram compared with placebo (−0.88 vs. −0.76). Worsening of this item was seen more frequently in the placebo group (17/95; 17.9%) than in the citalopram group (8/103; 7.8%), reflecting a relative risk of 0.43 ($P = 0.052$).

There were no statistically significant differences in the mean MADRS total score between the treatment groups over time. The adjusted mean reduction in MADRS total score from baseline to week 12 (OC) was 16 points in both groups. In the analysis of change from baseline to last assessment, the explanatory variables age, body mass index, weight, sex, and center were included. None of these had a statistically significant impact on the change in MADRS total score. After 12 weeks, the proportion of responders was 59% of the placebo group and 61% of the citalopram group (OC). Remission was achieved by 53% of placebo patients and 51% of citalopram patients after 12 weeks (OC). At last assessment (LOCF), the proportion of patients in remission was 36% (placebo) and 33% (citalopram).

The adjusted mean changes in the BDI total score from baseline to each visit were not significantly different between the 2 groups. After 12 weeks, the mean reduction was 16 points in both treatment groups. The mean GAF scores did not show any significant differences between the 2 groups. After 12 weeks, the adjusted mean increase was 18 points in both groups.

Subgroup Analyses

In a post hoc analysis patients with higher baseline Kiddie-SADS-P or MADRS total scores (severe group defined as Kiddie-SADS-P >32 and MADRS ≥30, respectively) showed a greater improvement than patients with lower scores. However, there were no significant differences between the treatment groups.
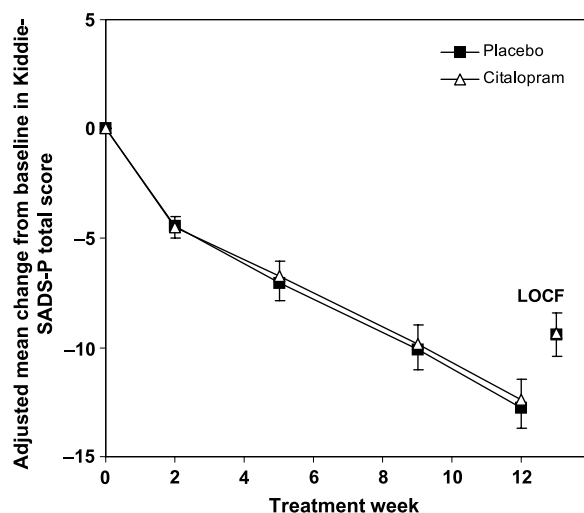

FIGURE 1. Primary efficacy parameter, the adjusted mean change ± SE in Kiddie-SADS-P total score from baseline, shown for each visit (OC) and last assessment (LOCF).

Another post hoc analysis revealed that more than two thirds of all patients were receiving psychotherapy during the study, distributed as 65% placebo (73/112) and 72% citalopram (87/121) patients. Baseline characteristics were similar for the 2 subgroups. For those patients not receiving psychotherapy, a higher percentage of Kiddie-SADS-P responders were found with citalopram at week 12 (41%; 12/29) versus placebo (25%; 9/36) (not significant [NS], LOCF).

Consistent with these data, a higher percentage was found of MADRS responders at week 12 in favor of citalopram. This difference was statistically significantly greater for citalopram (52%; 15/29) versus placebo (22%; 8/36) ($P = 0.019$, LOCF). In addition, there was a significantly higher percentage of patients achieving remission with citalopram at week 12 (45%; 13/29) than placebo (19%; 7/36) ($P = 0.034$, LOCF). There was a clinically relevant difference in favor of citalopram over placebo in the adjusted mean change from baseline in MADRS total score of −6.25 points ($P < 0.05$, LOCF).

Results from patients receiving psychotherapy showed a slightly better effect of placebo. There was a higher percentage of Kiddie-SADS-P responders at week 12 with placebo (53%; 38/72) versus citalopram (44%; 38/86) (NS, LOCF). Consistent with these data, there was a higher percentage of MADRS responders at week 12 in favor of placebo: citalopram (35%; 30/86) versus placebo (49%; 35/72) (NS, LOCF). In addition, there was a significantly higher percentage of patients achieving remission with placebo at week 12 (44%; 32/72) than with citalopram (29%; 25/86) ($P < 0.05$, LOCF). There was a small difference between placebo and citalopram groups in the adjusted mean change from baseline in MADRS total score of −2.2 points (LOCF) in favor of placebo.

Tolerability

Treatment-emergent adverse events including the Utvalg for Kliniske Undersøgelser-collected adverse events were reported by 91 (75%) with citalopram and 79 (71%) with placebo. Most were considered by the investigator to be mild or moderate.[13] Headache (26% and 25%), nausea (19% and 15%), and insomnia (13% and 11%) were the most common in both groups. Only fatigue was significantly more frequent in the citalopram group (6%) than in placebo group (1%) ($P = 0.02$, Fisher exact test).

Serious adverse events after the start of double-blind treatment were reported by 18 with citalopram and 16 with placebo. Hospitalization due to psychiatric disorders was the most common serious adverse events (14/18 and 9/16 for citalopram and placebo, respectively). No deaths occurred. Withdrawal due to adverse events was reported in 13 (11%) with citalopram and 9 (8%) with placebo.

A previous history of suicide attempt was common in the study population, accounting for nearly one third of patients. Suicide-related events, including cases of suicidal thoughts or tendencies that did not involve an actual suicide attempt, were reported by 14 with citalopram and 5 with placebo (relative risk = 2.6; $P = 0.06$, Fisher exact test). No pattern with respect to duration of treatment or dosage at the time

of suicide-related events was observed. Most patients with suicide-related events continued in the study and recovered.

There were no clinically relevant findings within or between treatment groups with respect to changes in clinical laboratory values, electrocardiographic values, vital signs, or weight.

DISCUSSION

The benefits and risks of SSRI treatment of depression in children and adolescents have been the subject of much recent debate, both in scientific and regulatory domains. Rather discrepant views have been voiced,[3,14–16] although there is general agreement that careful monitoring of patients is necessary and further data are needed. The present trial provides no evidence that citalopram results in a statistically significant reduction in depressive symptoms compared with placebo in this population of adolescent patients. This is in contrast to another pediatric study with citalopram.[4] However, the results of these 2 citalopram studies in pediatric depression should be viewed in the context of adult depression studies, of which more than half failed to show significant effect of established antidepressants.[17] Inappropriate methodology could be one explanation because there is much less experience regarding studies with adolescents. Considering the number of studies with less clear-cut outcome in this population, there is a need to address methodological issues in future studies.

The prolonged study period of more than 4 years rather than the planned 2-year recruitment period, the larger number of participating countries (7 vs. the planned single country), and several adjustments to inclusion criteria and assessments undoubtedly contribute to the overall variance in the study data. The high placebo response may also in part be attributed to the use of concomitant psychotropic medication allowed in the study. However, the enrollment of patients undergoing psychotherapy or initiating it during the study, may have been a more important factor in the high response of the placebo group.

More than two thirds of the patients in the present study were receiving psychotherapy, the type and duration of which was not controlled. The addition of citalopram treatment in the present study did not benefit patients receiving psychotherapy. In patients not receiving psychotherapy, however, there was a significant effect of citalopram. This is in contrast to the study, in which cognitive behavior therapy and fluoxetine treatment were initiated simultaneously.[19]

The patients in this study had moderate to severe depression, with a mean MADRS total score of almost 30, which is much higher than most adolescent outpatients with depression.[20] The mean citalopram dose was similar to the mean dose shown to be effective in Wagner and Robb's study.[4] Given that our study population was severely ill with, among other things, a higher rate of comorbidity, it would seem likely that higher doses could have been beneficial. A signal of citalopram efficacy could be in the finding of fewer withdrawals due to lack of efficacy and in the post hoc analysis of patients not receiving psychotherapy.

A history of previous suicide attempts was common in the study population. A numerically higher proportion of suicide-related events in the citalopram group than in the placebo group was recorded in this study, but not in the other placebo-controlled study with citalopram, where both inpatients and patients who were considered a suicide risk were excluded.[4,18] No completed suicides occurred in either study. In the present study, there was no specific pattern or time-cluster relative to time-to-event after start of treatment or days since dose change for either treatment group. Thus, there was apparently no specific time frame during treatment with an increased risk of suicidality. Furthermore, the Kiddie-SADS-P and the MADRS single item scores of suicidal thoughts showed no difference between treatment groups with respect to change from baseline to last assessment, and a beneficial effect of citalopram was indicated as worsening of this item was seen more frequently in the placebo group than in the citalopram group. Thus, consistent indications that the higher frequency of suicide-related events in the citalopram group could be associated with treatment were not identified.

In conclusion, our study reflects the methodological difficulties with studies in adolescents and differs in outcome from another study.[4] Additional studies in adolescents are clearly needed to clarify both the therapeutic benefits and the recent concern regarding suicide-related behavior upon initiation of treatment. Adolescents with major depression remain a difficult-to-treat group without well-established treatment recommendations.

ACKNOWLEDGMENTS

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