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FROM	:	Heydorn, William
TO	:	Olanoff, Lawrence; Gergel, Ivan; Flicker, Charles; MacPhee, John; Greene, Nefertiti; Jin, James; Kfo@Lundbeck. Com (E-mail); Lawrence, Jeffrey
CC	:	Kilbane, Julie
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SUBJECT	:	Secodn draft of Citalopram pediatric manuscript
FOLDER	:	Outlook Folders\Personal Folders\Sent Items April - June 2002
SOURCE	:	Heydorn, Bill
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MESSAGEID	:	<2F54E33330409943BEFC912FC7DCB3EB018C81F1@MAIL-NYC>
BODY	:	Attached for your review is the second draft of the citalopram pediatrics manuscript.

During your review, please note the following:

1) The publications committee discussed target journals, and recommended that the paper be submitted to the American Journal of Psychiatry as a Brief Report. The rationale for this was the following: 1) We'd like to see the paper published quickly and in a top tier journal; 2) Jack Gorman (editor) has seen the results on the primary endpoint and was impressed; 3) This is the third report of a positive effect of an SSRI in young patients; and 4) As a Brief Report, we feel we can avoid mentioning the lack of statistically significant positive effects at week 8 or study termination for secondary endpoints.

2) In the results section, the response stratified by age group is presented. This showed a postive drug effect in adolescents but (due to a greater level of placebo response) no drug effect in children. This information was not included in the first draft.

Please review the attached paper and return any comments to me by April 24.

Thanks

Bill

PS - James - for statistical comparisions, the journa requires us to insert the F value and degrees of freedom along with the p value. Please supply this information in the paper where needed. Thanks

1477 words, 1 figure

A placebo-controlled trial of citalopram for the treatment of major depression in children and adolescents ~~with major depressive disorder~~

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ABSTRACT

Objective: The authors investigated the efficacy of citalopram versus placebo in the treatment of children and adolescents with depression.

Method: ~~suggest that is~~ An 8-week, randomized, double-blind study compared ~~multicenter, parallel group,~~ flexible doses of citalopram (20-40 mg/day) with placebo in the treatment of children (ages 7-11, n=83) and adolescents (ages 12-17, n=91) with major depressive disorder. ~~major depressive disorder; the dose could be increased to 40 mg/day at week 4, if necessary.~~ The primary outcome measure was the Children's Depression Rating Scale-Revised (CDRS-R) at endpoint, and response was defined as a CDRS-R score ≤ 28.

Results: Compared with placebo, mean CDRS-R scores in the citalopram treatment group decreased significantly from ~~b~~baseline beginning at ~~w~~Week 1 and continuing at every observation point to the end of the study. ~~—~~The difference in response rate at ~~w~~Week 8 between placebo (24%) and citalopram (36%) also was statistically significant ($p < 0.05$).

Conclusion: In this population of adolescents and children, citalopram treatment reduced depressive symptoms to a significantly greater extent than did placebo.

INTRODUCTION

Approximately 1% of children and 5% of adolescents meet diagnostic criteria for depression, with incidence increasing markedly after puberty.[1] Like adult depression, pediatric depression is associated with significant social and functional impairment[2] and suicide risk.[3] Furthermore, early-onset depression frequently continues into adulthood, resulting in considerable morbidity and mortality.[4]

The few published studies of antidepressant pharmocotherapy in the pediatric population have shown mixed results. Trials with tricyclic antidepressants have demonstrated a poor risk/benefit ratio,[5, 6] whereas studies with selective serotonin reuptake inhibitors (SSRIs) suggest these agents may be effective and well tolerated.[7, 8]

Citalopram is an SSRI shown to be effective in the treatment of depression in the adult population, with a favorable safety and tolerability profile.[9] The objective of this study was to compare efficacy of citalopram with placebo in the treatment of children and adolescents with major depressive disorder (MDD).

METHODS

Children (ages 7-11) and adolescents (ages 12-17) who met DSM-IV criteria for MDD and whose current episode was at least 4 weeks in duration were eligible for participation in this multicenter study. The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)-Present and Lifetime was used to establish a diagnosis of depression and to rule out other psychiatric diagnoses. A score of ≥ 40 on the Children's

Depression Rating Scale-Revised (CDRS-R) was required at the screening and baseline visits.

Following a 1-week, single-blind, placebo lead-in period, patients were randomized to 8 weeks of citalopram or placebo. Citalopram was initiated at 20 mg/day, with increases to 40 mg/day permitted anytime after Week 4. Evaluations were scheduled after 1, 2, 4, 6 and 8 weeks of treatment.

The primary endpoint in this study was the change from baseline in the CDRS-R score at week 8 or early termination. Treatment differences were assessed using an analysis of covariance (ANCOVA) model, with treatment, study center, and age group as factors, and the baseline score as covariate. A response was defined as a CDRS-R score ≤ 28. A Cochran-Mantzel-Haenszel (CMH) test controlling for center and age group was applied for between-treatment comparison with respect to the response rate for CDRS-R responders. All analyses were carried out using the last observation carried forward (LOCF) approach.

RESULTS

A total of 178 patients enrolled in the study. Three children and one adolescent were lost to follow-up and did not receive study medication. Thus, the intent-to-treat population comprised 174 patients, 89 randomized to citalopram and 85 randomized to placebo. There were no significant differences in demographic data or depression history between groups. In both treatment groups the mean age was 12.1 years, with a slightly higher

proportion of boys (54% in the placebo group, 53% in the citalopram group) than girls. Mean CDRS-R scores at baseline were 57.8 and 58.8, respectively, in the placebo and citalopram groups.

Citalopram treatment showed statistically significant improvement compared with placebo on the CDRS-R as early as week one ($p < 0.02$), which persisted throughout the study (Figure 1). Additionally, at endpoint more citalopram-treated patients (36%) met criteria for response than did placebo-treated patients (24%), a difference that was statistically significant ($p < 0.05$).

Stratification by age group showed a similar response to citalopram in children ($n = 45$) and adolescents ($n = 44$). However, a greater level of placebo response was observed in children ($n = 38$); consequently, the placebo-drug difference in children was not statistically significant. In adolescents, the difference between placebo ($n = 47$) and citalopram was statistically significant at every time point including endpoint ($p = 0.0135$).

Citalopram was well tolerated. Nausea (13%), rhinitis (13%) and abdominal pain (11%) were the only adverse events occurring in ≥ 10% of citalopram-treated patients. The rate of discontinuation due to adverse events was comparable in the placebo and citalopram groups (5.6% vs. 5.9%, respectively). No serious adverse events were observed in patients treated with citalopram in this study.

DISCUSSION

This trial provides evidence that citalopram produces statistically and clinically significant improvement in depressive symptoms in children and adolescents. Citalopram was superior to placebo on the CDRS-R as early as Week 1, with efficacy continuing throughout the trial. Citalopram also was well tolerated.

The results of this trial are in agreement with earlier open-label studies[10] and case reports[11] that suggest citalopram is efficacious and safe in children and adolescents with depression, as well as with previously reported controlled trials with SSRI antidepressants.[6, 7]

Of interest, early and sustained improvements in CDRS-R scores were observed with citalopram treatment in this study, despite a relatively high rate of placebo response (which is common in pediatric trials with antidepressants). Although not powered to detect treatment differences by age group, a post hoc analysis suggested a greater response to placebo among children than adolescents, a dynamic that warrants investigation in future studies. Other methodological limitations include the low number of patients with comorbid conditions and concomitant medication use, both of which are common in younger patients.

In conclusion, in this study citalopram was safe and well tolerated, and significantly improved depressive symptoms within one week of treatment, suggesting the potential usefulness of this agent in children and adolescents with depression.

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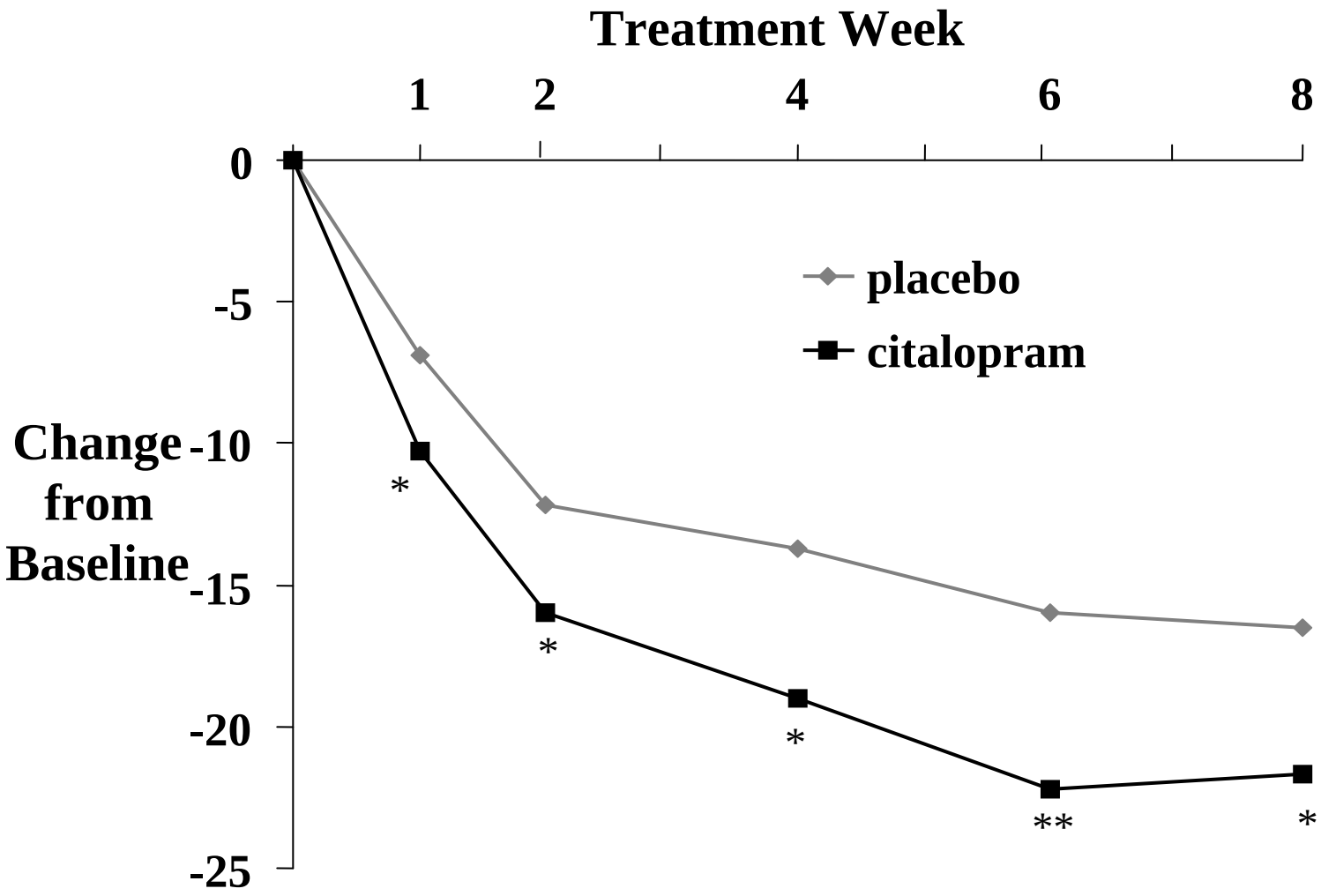
FIGURE LEGEND

Figure 1. Change from baseline over time in mean CDRS-R score, LOCF analysis. *$p < 0.05$, ** $p < 0.01$.


Treatment Week
1
2
4
6
8
0
-5
-10
-15
-20
-25
Change from Baseline
placebo
citalopram
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