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Inhibitor citalopram in the medicaments of burdensome issues: an open mark, multicenter research in China

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Abstract

Results of randomized, placebo- controlled trials with the selective serotonin reuptake inhibitor citalopram suggest that this agent is safe and effective for the treatment of depressive disorders. We investigated the safety and efficacy of citalopram in the treatment of Chinese patients with depressive disorders. An 8-week, open-label, multicenter study evaluated the safety and efficacy of citalopram in the treatment of patients with an ICD-10 diagnosis of depressive disorder or depressive episode of bipolar disorder. Efficacy measures included the Hamilton Rating Scale for Depression (HAMD) and the Clinical Global Impression (CGI). A total of 6080 patients (2553 men, 3527 women) (mean age 40.9 ± 15.6 years, range 18 – 92) participated in the study. Mean HAMD scores decreased significantly (p<0.001) after 2 weeks of treatment and at all subsequent study visits. Endpoint analyses showed that 89.9% of the patients demonstrated a clinical response, defined as a 50% reduction in HAMD scores. The mean daily dose of citalopram at endpoint was 23.65 mg. Nausea (7.6%), headache (3.7%) and dry mouth (2.9%) were the most frequently reported adverse events. Patients with bipolar depression and comorbid obsessive compulsive disorder (OCD) received a higher mean daily dose (26.4 and 27.7 mg, respectively), while patients with comorbid physical disorders received a lower dose (21.9 mg) than patients with simple depressive disorder. The results of this 8-week open-label study suggest that citalopram is safe and effective in the treatment of depression in Chinese patients. Limitations is an open-label and uncontrolled.

Keywords: Antidepressant, citalopram, depression, selective serotonin reuptake inhibitor.

INTRODUCTION

Citalopram is a highly selective serotonin reuptake inhibitor (SSRI) (IC_{50}- $_{NA}$/IC_{50}-$_{5\text{-}HT}$ = 3400), with only very weak effects on norepinephrine and dopamine reuptake (Hyttel, 1994; Sanchez and Hyttel, 1999; Hyttel, 1982), and the most selective antidepressive effect. The little or no affinity for a variety of receptor types Hyttel (1994) renders it relatively free of anticholinergic and cardiovascular side effects, properties that have limited use-fulness in tricyclic antidepressants. The drug is well absorbed after oral administration, exhibits linear phar-macokinetics and produces little inhibition of the major cytochrome P450 isoenzymes (Greenblatt et al., 1998; Baumann, 1996; Greenblatt et al., 1999) .

Citalopram has an elimination half-life of 1.5 days which allows for once-daily dosing and facilitates dosing compliance. Citalopram is metabolized by the liver; the principal metabolites occur in low concentrations and do not substantially contribute to citalopram's overall clinical activity. The safety and efficacy of citalopram as an antidepressant have also been established in a number of clinical trials, in comparison with placebo as well as reference antidepressant drugs (Mendels et al., 1999; Feighner and Overo, 1999; Montgomery and Djarv, 1996). Long-term studies have demonstrated that the drug can prevent the relapse and recurrence of depressive illness (Keller, 2000; Montgomery, 1993). Citalopram was approved for the treatment of depression in China in 1998; however, experience with the drug here is still limited. One reason for the limited usage is that citalopram has not yet been included in the category of State Medical Insurance-covered medication (approval pending). This study aimed to obtain information

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Table 1. Demographic and baseline clinical characteristics of patients with depressive disorder assigned to 8 weeks of open-label treatment with citalopram (n = 6080).

Variable	
Age (mean ± SD, years)	40.9±15.6
Range (years)	18~92 (median 38)
Female (%)	58.0
Primary diagnosis, n (%)	
Depressive disorder	5588 (91.9)
Depressive disorder + comorbid OCD	136 (2.2)
Depressive disorder + comorbid physical disorder	158 (2.6)
Bipolar depression	197 (3.2)
Duration of depressive disorder (mean ± SD, years)	2.3±4.2 (median 1.0)
Duration of current depressive episode (mean ± SD, months)	6.5±14.1 (median 3.0)
Recurrent, n (%)	2116 (34.8)
Prior antidepressant treatment, n (%)	1630 (26.8)
History of nonresponse, n (%)	1127 (69.1)
History of intolerance, n (%)	348 (21.3)

on the clinical safety and efficacy of citalopram in Chinese patients with depression.

MATERIALS AND METHODS

Study design

This was an open-label, multicenter, post-marketing surveillance conducted in 300 psychiatric sites in China. Outpatients or inpatients, at least 18 years of age who met ICD-10 criteria for depressive disorder or depressive episode of bipolar depression and had a minimum score of 16 or more on the 17-item HAMD, were eligible for participation [13]. Specific exclusion criteria included pregnant or nursing patients, patients planning to become pregnant during the study period, patients with a history of a hypersensitivity reaction to citalopram or another SSRI, and those with a high risk of suicide. Patients who had abused alcohol or drugs in the past 6 months and patients who had taken a monoamine oxidase inhibitor in the previous 2 weeks also were excluded. Patients who experienced psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder) or personality disorders, or who were currently participating in other clinical trials were also excluded. Other considerations for patient selection were derived from warnings and precautions from the Cipramil® package insert. All patients provided written informed consent, and the study protocol for each site was approved by the review board of the Peking University Institute of Mental Health. Participating psychiatrists attended the investigator meetings at which the details of the study protocol, case record form and general information on the safety and efficacy of citalopram were presented. This study was conducted from March to December 2003.

Assessments

This was an 8-week study, which included a baseline visit and follow-up visits after 2, 4, 6 and 8 weeks, or upon study withdrawal (the last available observation). At the baseline visit, demographic information (including age, sex, duration of illness and previous episodes) and a medical history were obtained. Antidepressant treatment history and concomitant medications were also recorded. Efficacy was assessed using the 17-item HAMD and the Clinical Global Impression (CGI), which demonstrates the severity of illness and degree of improvement. The responder was defined as a subject with 50% reduction in HAMD score. Safety assessments were performed at the end of each study week and consisted of reports or observations of adverse events.

Treatment

After giving written informed consent and completion of the pretreatment evaluation, all eligible patients were dispensed open-label commercial citalopram at starting doses of 10 – 40 mg/day depending on the severity of disease. The once-daily dose was increased in 10 or 20 mg increments up to the maximum tolerated dose, with a maximum of four tablets per day (80 mg). Concomitant medications during the study were recorded in detail on the case record form, including the dosage and indications.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science 11.0 software program (SPSS, Inc., Chicago, IL). All statistical tests were two-sided with a p value of ≤ 0.05 regarded as statistically significant.

RESULTS

Study population

A total of 6080 patients from 300 psychiatric sites were enrolled in this study. Table 1 presents the demographic and clinical features of the sample: 58.0% (3527) were female, the mean age was 40.9 years (median 38 years), and 9.7% (588) were 65 years of age. Nearly all of the patients met ICD-10 criteria for depressive disorder; 2.2% of patients had comorbid obsessive and compulsive disorders (OCD); 3.2% had a depressive episode of bipolar disorder; 2.6% had an ongoing mild general medical ill-

Table 2. Mean daily dose of open-label citalopram according to clinical diagnosis in an 8-week trial in depressive patients.

	Depressive disorder N = 5239	Comorbid OCD N=136	Comorbid physical disorder N=197	Bipolar depression N=158
Starting dosage	19.1±3.7	19.4±2.4	18.4±3.8*	18.9±3.6
End of Week 2	22.5±6.7	24.1±7.9**	21.9±6.9	22.9±7.0
End of Week 4	24.5±8.6	27.7±10.5**	23.2±8.3	26.0±9.3*
End of Week 6	24.4±8.9	28.3±10.9**	22.9±8.4*	26.4±10.9*
End of Week 8	23.5±8.4	27.7±10.7**	21.9±7.1*	26.4±10.8*

**t* test, comparison with patients with depressive disorder, $p<0.05$; ***t* test, comparison with patients with depressive disorder, $p<0.001$. OCD = obsessive compulsive disorder

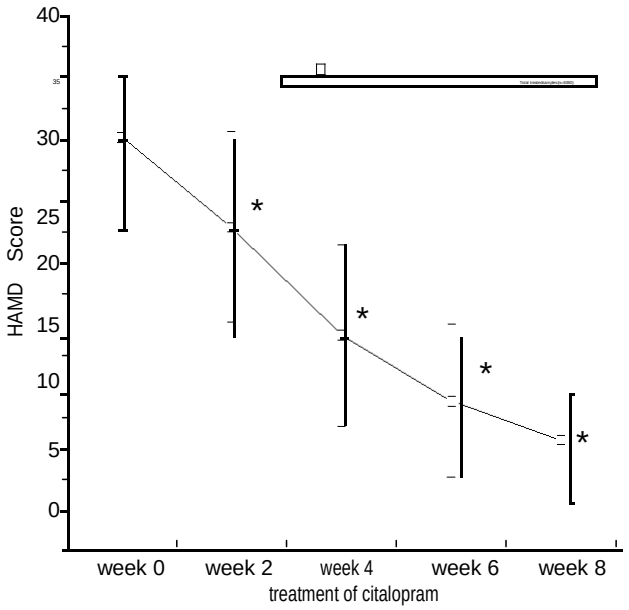

Figure 1. Baseline-to-endpoint changes in HAMB scores of patients with depressive disorder who received citalopram for 8 weeks (* P < 0.001). HAMB = Hamilton Rating Scale for Depression.

ness; 34.8% (2116) had recurrent depressive episodes; 26.8% (1630) had been previously treated with other antidepressants; 69.1% (1127) were non-responsive to previous treatment; and 21.3% were intolerant to other antidepressants. The treated population was further subdivided into mild (baseline HAMD score <24 and CGI-S of 3, n = 1488), moderate and severe (baseline HAMD score 24) or depressive disorders (n = 4592), as well by age into non-elderly adult (age <65 years, n=5492) and elderly (age 65 yrs, n = 588) groups. The median duration of the treated patients' current depressive disorder episode was approximately 3 months. The demographics of these various subpopulations were similar to those of the entire study population.

Treatment

The overall mean starting dose was 19.1 mg (20 mg in 88.7%), and the mean dose at study endpoint was 23.6 mg. The most frequently prescribed dose in this study was 20 mg/day. Compared with patients with depressive disorder, the mean daily doses of citalopram at the endpoint were significantly higher for patients with comorbid OCD (27.7 mg/day) or bipolar depressive disorders (26.4 mg/day), and significantly lower for patients with comorbid general conditions (21.9 mg/day) (Table 2). Mean daily doses of citalopram were significantly higher for patients with severe depression than for those with mild depression from the end of week 2 ($P<0.0001$) . The mean daily dose was unrelated to gender, but was significantly higher in the non- elderly group (starting dose 17.3 mg/day vs. 19.3 mg/day, endpoint dose 23.6 mg/day vs. 24.6 mg/day, respectively). The mean daily dose of citalopram for patients who experienced >2 depressive episodes was significantly higher than those with first-episode from the 2nd week of treatment, with the trend continuing to the endpoint ($P<0.0001$). The mean daily endpoint dose of citalopram for the first-episode and recurrent patients was 24.1 and 23.1 mg/day, respectively.

Clinical outcomes

Intent to treat population

HAMD scores decreased significantly over the 8-week period of treatment with citalopram (Figure 1). The mean HAMD at baseline was 30.2 and decreased to 5.7 at endpoint ($F=31197.75$, $P<0.0001$) in the group. The intent-to-treat response rate was 89.9%. Strict criteria for remission (HAMD ≤ 7) were met by 73.0% of the patients (Frank et al., 1991).

First-episode and recurrent patients

Among the treated population, 2116 of the subjects were recurrently depressed. These patients had more severe depression at baseline and experienced a significantly lower response from the treatment at week 4 than the first-episode patients, a trend that continued to the first-episode patients, a trend that continued to the endpoint

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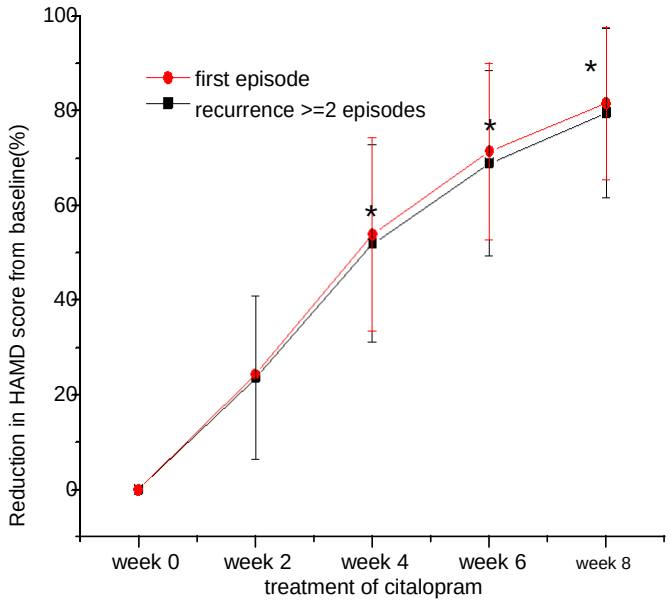

Figure 2. Baseline-to-endpoint changes in HAMB scores of first episode patients and recurrent patients who received citalopram for 8 weeks (* P < 0.001) Hamilton Rating Scale for Depression.

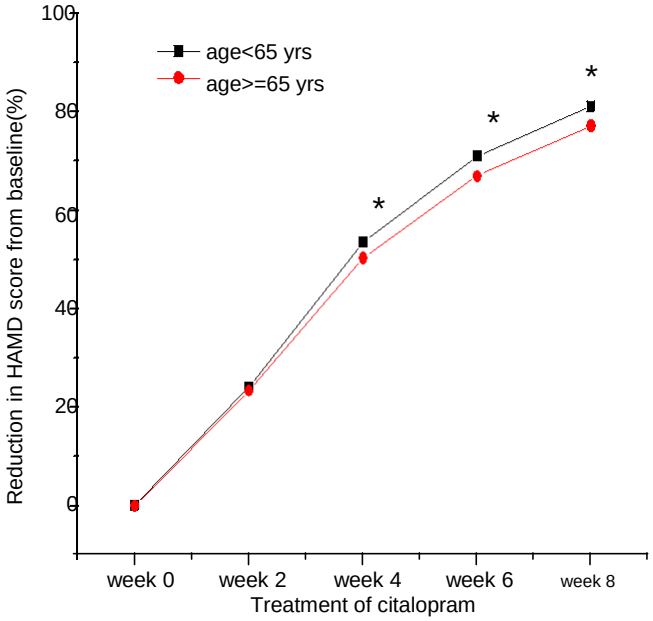

Figure 3. Baseline-to-endpoint changes in HAMB scores of patients = 65 years < 65 years who received citalopram for 8 weeks (* P < 0.001) HAMB = Hamilton Rating Scale for Depression.

endpoint (79.6 vs. 81.6% HAMD score reduction at endpoint; Figure 2).

Non-elderly adult and elderly patients

The 588 elderly patients had more severe depression than the non-elderly patient group at baseline. Younger patients also experienced a significantly higher response to treatment at week 4 than the elderly patients, a trend that continued to the endpoint (81.1 vs. 77.2% HAMD score reduction at endpoint; Figure 3).

Naïve and pretreated patients

About a quarter (26.8%) of the patients were treated with other antidepressants before this study and were switched to citalopram because of non-response or intolerance. This subgroup had more severe depression than the non-pretreated patients at baseline, and experienced a significantly lower response to treatment, a trend that continued to the endpoint (78.4% vs. 81.6% HAMD score reduction at endpoint; Figure 4).

Depressed patients and patients with other comorbidities

Efficacy of treatment in various other subgroups was also analyzed. Treatment efficacy in depressed patients was similar to those with comorbid OCD, physical disorders and bipolar depressive disorders. Patients with severe depression experienced the same extent of improvement as the mildly depressed patients. Chronic patients (duration of illness >1 year) experienced a lower response than acute patients (duration of illness <1 year) after 6 weeks of treatment (p<0.01).

Adverse effects

Treatment- emergent adverse events (AEs) were experienced by 22.4% (1362) of patients. The AEs most frequently reported were gastrointestinal complaints, psychiatric signs and symptoms, and nervous system disorders. These included nausea and vomiting (7.6%), headache (3.7%), dry mouth (2.9%), fatigue and weakness (1.5%), constipation (1.4%), perspiration (1.4%), insomnia (1.0%), fidgeting (0.8%), tremors (0.2%), agitation (1.3%), bradycardia (0.1%), sexual dysfunction (0.1%) and somnolence (0.1%). Most (80.1%) AEs occurred in the initial 2 weeks of treatment, and were mild in severity. One patient developed seizures and another had suicidal ideations. The incidence of AEs did not show any relationship to dose, age, gender, or comorbidities. AEs were more common in first-episode or naïve patients than in recurrent or pretreated patients.

Discontinuations

Of the 6080 patients, 95.0% completed 8 weeks of treatment. Discontinuations were most commonly attributed to lack of efficacy (n = 149, 49.5%), AEs (n = 81, 26.9%), or lost to follow-up (n = 71, 23.6%).

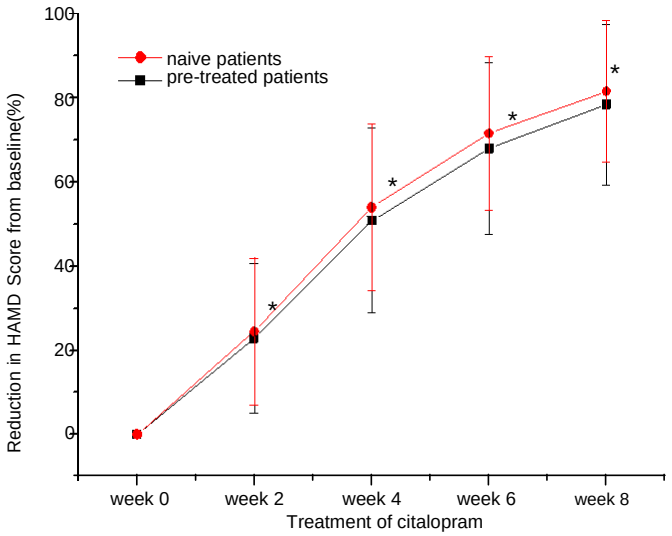

Figure 4. Baseline-to-endpoint changes in HAMB scores of Treatment- naïve patients and pretreated patients who received citalopram for 8 weeks (* P < 0.001) HAMB = Hamilton Rating Scale for Depression.

Concomitant medications

In the entire treatment population, 60.1% (3657) of pa-tients received concomitant medications; 51.3% (3116) received a combination with one other medication, while 8.9% (541) received two other kinds of medication. The most frequently prescribed combination medication was a benzodiazepine (n = 2959, 80.9%). Other drugs used were sedative medications (n = 142, 2.3%), other anti-depressants (n = 120, 2%), anxiolytic agents (n = 71, 1.2%), and TCA (n = 71, 1.2%). A significant improvement in efficacy at the end of 4 weeks was found in the combi-nation of citalopram with benzodiazepines (HAMD reduc-tion were 54.2% for combination group, 52.3% for non-combination, p<0.001), which suggests that this combina-tion was helpful in improving sleep and anxiety and had augmentation effects. Citalopram was combined with other medications to treat AEs and psychotic symptoms that manifested during the course of the study.

DISCUSSION

The results of this multicenter, open label, 300-site study prospectively evaluated the prescription patterns of a newly introduced antidepressant medication, citalopram, in Chinese psychiatric clinical practice. Overall, citalo-pram was associated with favorable outcomes and was generally well tolerated among patients with chronic, recurrent depression, with or without other comorbid psy-chiatric or physical conditions, including a significant proportion of subjects who had a history of non-response or intolerance to other antidepressants.

A major limitation of this study is that it was open-label and uncontrolled. Firstly, the patients recruited for the study had a heterogenous clinical profile (Table 1). Secondly, both physician and patient ratings of efficacy were performed openly. Consequently, it was impossible to evaluate the true magnitude of the clinical effect, or to estimate the contribution of the placebo effect to the observed response rates. On the other hand, this study closely resembles actual clinical practice. The most commonly prescribed dose of citalopram was 20 mg/day, which is consistent with clinical trial evidence supporting the effectiveness of treatment of depression (Montgomery and Djarv, 1996; Montgomery et al., 1994; Montgomery, 1995). The observed response rates in both the entire treatment population and the various subgroups are similar to rates reported in randomized, controlled trials with citalopram (Mendels et al, 1999; Patris et al, 1996; Ekselius, 1997). However, the dose of citalopram used to treat cases of depression with comorbid OCD or bipolar depressive disorder was higher than for the single depressive disorder alone. These data closely resemble those reported in a previous study (Stein et al., 2001).

The first-episode, non- elderly adult and naïve subgroups of patients had better outcomes in terms of efficacy of treatment, an observation consistent with those of pre-vious studies (Vaswani et a,l 2003; Roose et al 2004). Various guidelines, such as those proposed by the (American Psychiatric Association, 2000) and the (Chinese Psychiatric Association 2003) have recom-mended that patients with chronic and/or recurrent epi-sodes of depression should have a longer consolidating therapy and maintenance antidepressant therapy. For patients >45 years of age, with a high risk of developing comorbid physical disorders and a low tolerability to medication, the response is usually slower than in younger patients. The dose in this population should be lowered and then titrated slowly. A marked improvement in these patients can be expected after 4 weeks of citalopram treatment (Hranov and Assenov, 1997).

The safety profile of citalopram in this study was generally comparable to what has been reported for other SSRIs (Roose et al., 2004; Masand, 2003) and it was well tolerated. The most common AEs were gastrointes-tinal and CNS symptoms. AEs occurred in the earlier period of treatment and usually were relieved imme-diately. Eighty-one (1.3%) patients withdrew due to AEs. In patients with recurrent depressive episodes or with a history of previous antidepressant treatment, AE rates were significantly lower than in those who had their first depressive episode or had no prior treatment. These findings reinforce the observation that patients who do not tolerate or respond to one kind of antidepressant, including the SSRIs, may benefit from switching to other antidepressants, or even another SSRI (Vaswani et al., 2003; Calabrese et al., 2003). (Kupfer et al., 2001) reported that citalopram was efficacious for the improve-ment of depression symptoms in combination with mood stabilizers for the treatment of bipolar depression. They

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suggested that citalopram was an effective drug for the treatment of bipolar I and II disorders. Also, the risk of citalopram-induced manic episode is significantly lower than that of mianserin and maprotiline (Barak et al., 2000) Studies on citalopram recently published in China were small-size (recruiting 20–88 subjects). Result showed that citalopram was an effective and a fast-onset antidepressant (Wang et al., 2004). Another study, which analyzed pharmacoeconomic aspects of fluoxetine, paroxetine and citalopram, showed that citalopram has a relatively better cost-effectiveness in China (Lin, 2004)
In summary, the results of this study suggest that citalopram is effective in the treatment of depressive disorders in Chinese patients, including a heterogeneous and clinically complicated group of patients who are initially difficult to treat. The most common dose of citalopram (20 mg/day) exhibited significant therapeutic benefit and a favorable safety profile in the broad population of 6080 patients. Response rates were comparable to those reported in randomized, double-blind clinical trials composed of fewer chronic or medically complex patients.

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