Citalopram Treatment of Fluoxetine-Intolerant Depressed Patients

Joseph R. Calabrese, M.D.; Peter D. Londborg, M.D.; Melvin D. Shelton, M.D., Ph.D.; and Michael E. Thase, M.D.

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Corresponding author and reprints: Joseph R. Calabrese, M.D., Mood Disorders Program, Case Western Reserve University School of Medicine, 11400 Euclid Ave., Ste. 200, Cleveland, OH 44106 (e-mail: jrc8@po.cwru.edu).

Background: We assessed the tolerability of and response to citalopram in depressed patients who had discontinued fluoxetine treatment due to adverse events.

Method: Fifty-five outpatients with DSM-IV major depressive disorder and a confirmed history of intolerance to fluoxetine (mean final dose = 24.6 mg/day) were switched to citalopram (20 mg/day) after a 2- to 4-week single-blind placebo washout period. During a 6-week, open-label treatment protocol, citalopram could be titrated up to 40 mg/day. Safety and tolerability, including reemergence of symptoms that previously had been associated with fluoxetine, were assessed by recording all spontaneously reported or observed adverse events. Efficacy was evaluated using the Hamilton Rating Scale for Depression (HAM-D), the Clinical Global Impressions (CGI) scale, and several other measures. Response was defined as a CGI-Improvement score at endpoint of 1 or 2 (i.e., very much or much improved).

Results: Ninety-five percent of patients (N = 52) completed the citalopram trial. The only adverse events reported by more than 5 patients (≥ 10%) were pharyngitis (15%) and constipation (11%), and none of the 3 early terminations were attributed to adverse events. The rate of recurrence of the fluoxetine-associated adverse events was low, with headache (3 [27%] of 11 cases), nausea (2 [22%] of 9 cases), and decreased libido (5 [18%] of 28 cases) being the most common. Significant improvement from baseline HAM-D ($p < .001$) was observed by the first week of citalopram therapy and continued until study end. The intent-to-treat CGI response rate was 65% (36 of 55 patients) at study endpoint; 69% (36 of 52 patients) of the completers responded.

Conclusion: These data suggest that fluoxetine-intolerant patients can be treated effectively with citalopram.

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During the 1990s, selective serotonin reuptake inhibitors (SSRIs) surpassed the tricyclic antidepressants as first-line treatment for depression.[1,2] SSRIs have a wider margin of safety in overdose, and they lack the anticholinergic, antihistaminic, and anti–α_1-adrenergic side effects associated with the tricyclic agents. Despite the favorable safety and tolerability profile of SSRIs, adverse events commonly associated with SSRI therapy (e.g., nausea, diarrhea, headache, tremor, sedation, insomnia, and sexual dysfunction) can result in morbidity or discontinuation of treatment.[1,2] Typically 10% to 20% of patients who begin a 6- to 8-week trial with one of these agents discontinue treatment prematurely due to adverse events.[3,4]

There are no large-scale controlled studies examining the efficacy and tolerability of switching from one SSRI to another following intolerance. However, recent anecdotal and experimental evidence suggests that there are subtle but clinically meaningful differences in the adverse event profiles of the SSRIs.[5–10] Given the widespread use of the SSRIs, some clinicians prefer to switch a patient who cannot tolerate treatment with one SSRI to a second member of the class prior to initiating treatment with an alternate type of antidepressant.

Only 2 studies have been reported that specifically examined the effect of switching to a second SSRI following intolerance to an initial trial of SSRI. Brown and Harrison[5] reported on the tolerability and efficacy of sertraline in 113 patients who could not tolerate fluoxetine. Eighty-one percent of patients were able to complete the 8-week, open-label trial of sertraline, while 76% of patients (N = 62) who were evaluated for efficacy responded. More recently, Thase et al.[11] found that 84% of patients who could not tolerate paroxetine treatment were able to complete a 6-week therapeutic trial of citalopram,

of which 67% responded to treatment. In other studies of more heterogeneous patient populations who either had not benefited from or could not tolerate one SSRI, 35% to 60% responded to treatment with the second SSRI.[12–15]

Fluoxetine and citalopram are 2 widely used SSRIs for the treatment of depression. Although both agents potently block 5-HT reuptake, they differ in several key ways. Preclinical data indicate that citalopram is at least 70-fold more selective than fluoxetine on ratio measures of potency of reuptake blockade of serotonin versus catecholamine neurotransmitters.[16–19] In addition, fluoxetine has a more complex pharmacokinetic profile than does citalopram. Fluoxetine and its active metabolite norfluoxetine have long half-lives (7 and 15 days, respectively). Both moieties are cleared by the cytochrome P450 2D6 system, and both potently inhibit CYP2D6 activity, thereby inhibiting their own metabolism as well as the metabolism of other concomitantly administered 2D6 substrates. In contrast, citalopram has a less complicated pharmacokinetic profile. The half-life of the parent compound is approximately 24 to 48 hours, and there are no active metabolites.[20–23] Further, citalopram has little inhibitory effect on the cytochrome system.[24] The clinical significance of these pharmacologic and kinetic differences has not been clearly established. However, it is likely that some patients will achieve good therapeutic results with a more selective agent such as citalopram, while others will benefit from agents such as fluoxetine that have a more complex in vivo profile.

In this article, we report the findings from a clinical investigation of the efficacy and safety of citalopram when administered to depressed patients who were intolerant of fluoxetine.

METHOD

Overview

This was a prospective, open-label study of citalopram treatment of depressed outpatients who failed to tolerate fluoxetine. Patients (recruited from 11 sites in the United States) began citalopram therapy if their fluoxetine-associated symptoms had resolved after a placebo washout period of 2 to 4 weeks.

Patients

Patients were eligible for this study if they provided informed consent for research participation and met all of the following inclusion criteria: (1) current principal DSM-IV diagnosis of major depressive episode both at the start of fluoxetine therapy and at entry into the current study (i.e., start of single-blind placebo treatment); (2) inability to tolerate fluoxetine treatment at a dose of at least 20 mg/day for at least 1 week; and (3) aged between 18 and 80 years. There was no minimum threshold depression symptom severity score required for study entry.

Table 1. Adverse Events Reported to Have Led to Discontinuation of Fluoxetine in 55 Patients With Major Depressive Disorder[a]

	Incidence	
Adverse Event	N	%
Decreased libido	23	42
Anorgasmia[b]	9	23[b]
Insomnia	12	22
Somnolence	10	18
Headache	9	16
Nausea	8	15
Ejaculation disorder[c]	2	13[c]
Fatigue	6	11
Diarrhea	6	11
Dry mouth	6	11
Nervousness	6	11

[a]Reported prevalence > 10%. Some patients attributed discontinuation to more than 1 adverse event.
[b]Reported prevalence in female patients (N = 40).
[c]Reported prevalence in male patients (N = 15).

Exclusion criteria included the following: (1) inability to tolerate any SSRI other than fluoxetine; (2) prior treatment with citalopram; (3) pregnant or breast-feeding; (4) unwilling to use contraception; (5) any lifetime history of psychosis; (6) abuse of drugs or alcohol within the past year; (7) seizure disorder; (8) severe or unstable medical illness or neurologic disease; and (9) treatment with a depot neuroleptic within 6 months, electroconvulsive therapy within 3 months, or any psychotropic medication (other than fluoxetine) within 2 weeks of beginning study medication. Medical status was confirmed by a history and physical examination, 12-lead ECG, urine drug test, complete blood count, BUN, creatinine, electrolytes, liver enzymes, TSH, urinalysis, and (when appropriate) urine and serum pregnancy tests.

Treatment Protocol

After providing informed consent and meeting study eligibility, patients were asked to identify the adverse event(s) that led to discontinuation of fluoxetine. No formal rating scale was used; patients were simply asked to name the adverse event that led to their discontinuation of the drug. These fluoxetine-associated adverse events are shown in Table 1. Patients then began a minimum 2-week, single-blind placebo washout period. Patients whose intolerable side effects had resolved by the end of this 2-week period began open-label citalopram treatment. For patients in whom side effects did not resolve, single-blind placebo administration could continue up to 2 more weeks (i.e., maximum of 4 weeks of single-blind placebo administration) in an effort to allow fluoxetine side effects to resolve. Any patients whose fluoxetine-associated symptoms had not resolved by the end of the 4-week washout period were excluded from study participation.

Citalopram treatment was initiated at 20 mg/day. The initial dose could be reduced to 10 mg/day if necessary, although a minimum dose of 20 mg/day was required by

Table 2. Baseline Characteristics of Citalopram-Treated Patients (N = 55)[a]

Characteristic	Value
Age, mean (range), y	43 (19–73)
Gender, N (%) female	40 (73)
Race, N (%) white	47 (85)
Weight, mean, lb (kg)	180 (81.65)
Baseline scores, mean (SD)	
HAM-D-24	19.4 (7.4)
CGI-Severity	3.7 (0.82)

[a]Baseline defined as the start of citalopram treatment.
Abbreviations: CGI = Clinical Global Impressions scale, HAM-D-24 = 24-item Hamilton Rating Scale for Depression.

week 4 of therapy. Thereafter, citalopram dose could be increased to 40 mg/day if response was not adequate.

Clinical evaluations were performed at weeks 0 (baseline week—start of citalopram therapy) and at weeks 1, 2, 4, and 6 of citalopram treatment. Blood work and ECGs were repeated at week 6 or at endpoint. Response was evaluated at each visit using the 24-item Hamilton Rating Scale for Depression (HAM-D-24) and the Clinical Global Impressions (CGI) scale.[25] A response was defined by a CGI-Improvement score of 1 or 2 (very much improved or much improved). Secondary dependent measures, including the Hamilton Rating Scale for Anxiety (HAM-A),[26] the Beck Depression Inventory (BDI),[27] and the Quality of Life Scale (QLS) questionnaire,[28] were collected at week 0 and week 6, or endpoint (the QLS measure was also collected at week 2). In addition, the Patient Global Evaluation scale[25] was administered at screening and week 6. All adverse events, including those spontaneously reported by patients and those observed by the investigator and his/her staff, were recorded. Primary analyses followed the intent-to-treat principle, utilizing endpoint scores (last-observation-carried-forward) when necessary. Data were analyzed using paired t tests and are presented as means ± standard deviations.

RESULTS

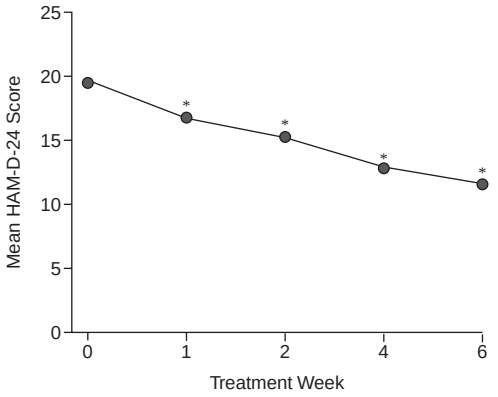
The baseline characteristics of the 55 patients who enrolled in this study are shown in Table 2. All patients completed at least 4 weeks of treatment with citalopram; 52 patients (95%) completed the entire 6-week trial. Three patients (5%) were discontinued after week 4: 1 because of a protocol violation, 1 for lack of efficacy, and 1 who was lost to follow-up. No patients discontinued citalopram treatment because of adverse events.

Prior Antidepressant Experience

The mean duration of fluoxetine therapy in this patient population was 13.4 months. Patients had taken a mean daily dose of 24.6 mg of fluoxetine (range, 10–60 mg/day), and the mean washout period was 17.4 days prior to beginning citalopram. For 43 patients (78%), fluoxetine washout was completed in 2 weeks; 8 patients (15%) required a 3-week washout period and 4 patients (7%) required the full 4 weeks for washout.

A total of 30 patients (55%) reported either no response or a poor response to the prior fluoxetine therapy. Sixteen patients (29%) had never taken an antidepressant other than fluoxetine; of the remainder, 13 (24%) previously had responded to an antidepressant; the other 26 patients (47%) had not responded to previous courses of therapy with antidepressant agents. Eleven (20%) had discontinued trials with antidepressants other than SSRIs due to intolerance.

Figure 1. Mean Rating on the 24-Item HAM-D at Baseline and Each Treatment Week (LOCF) in 55 Citalopram-Treated Patients[a]



[a]Baseline defined as the start of citalopram treatment.
*p < .001.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, LOCF = last-observation-carried-forward.

Experience With Citalopram

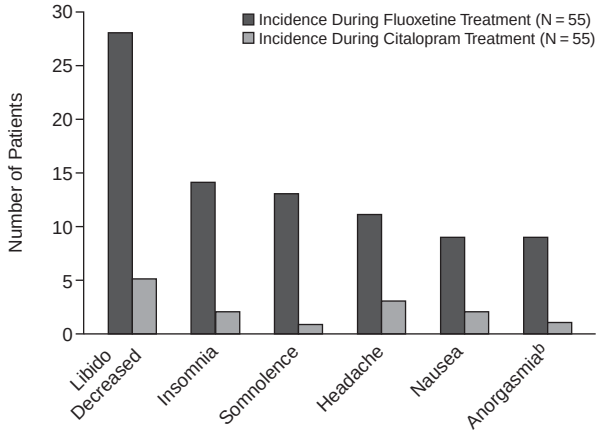
Most patients improved during open-label citalopram therapy. As shown in Figure 1, significant improvement in the primary efficacy measure, the HAM-D-24 score, was observed at each timepoint. The effects of citalopram on efficacy outcome measures are summarized in Table 3. Significant improvements were observed on both the 17- and 24-item versions of the HAM-D, as well as the CGI-Severity of Illness, BDI, and HAM-A scales. At endpoint, the mean CGI-Improvement score was 2.3 (median = 2.0; SD = 1.09; range, 1–6). A total of 36 patients (65%) met CGI response criteria at study endpoint. For those patients who completed the trial, the CGI response rate was 69% (36 of 52 patients). On the self-reported Patient Global Evaluation, 32 patients (62% of completers) reported being much or very much improved. The QLS total score for the intent-to-treat population improved from 47.8 (SD = 9.06) at baseline to 56.3 (SD = 10.4) at endpoint (p < .001). The mean duration of citalopram treatment in this study was 43 days (range, 34

Table 3. Improvement in Measures of Depression and Anxiety During Citalopram Therapy (N = 55)[a]

Dependent Measure	Week 0 Mean (SD)	Week 1 Mean (SD)	Week 2 Mean (SD)	Week 4 Mean (SD)	Week 6 Mean (SD)
HAM-D-24	19.4 (7.4)	16.6* (7.7)	15.2* (7.9)	12.7* (7.4)	11.4* (6.5)
HAM-D-17	14.4 (5.4)	12.6* (5.8)	11.8* (5.9)	9.8* (5.1)	9.1* (4.9)
CGI-S	3.7 (0.8)	3.3* (1.0)	3.2* (1.0)	2.9* (1.1)	2.6* (1.1)
BDI	11.0 (5.3)	ND	ND	ND	6.2* (4.3)
HAM-A	12.3 (5.0)	ND	ND	ND	7.5* (4.8)

[a]Scores are for the intent-to-treat sample (last-observation-carried-forward).
*p < .001, paired t test.
Abbreviations: BDI = Beck Depression Inventory, CGI-S = Clinical Global Impressions-Severity of Illness, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 and -24 = Hamilton Rating Scale for Depression (17-item and 24-item scales, respectively), ND = not determined.

Figure 2. Recurrence of Fluoxetine Adverse Events During Citalopram Treatment[a]



[a]Incidence of adverse events reported by at least 15% of the patients on fluoxetine therapy. Shown are the numbers of patients who reported each adverse event on fluoxetine therapy together with the subset of patients who reexperienced the event during citalopram treatment.
[b]Female patients only (N = 40).

to 54 days). Among the intent-to-treat sample, the mean overall dose of citalopram was 24.6 mg/day, and the mean-endpoint dose was 33.8 mg/day.

Citalopram therapy was well tolerated. The only adverse events reported by more than 5 patients were pharyngitis (15%; N = 8) and constipation (11%; N = 6); no patients terminated treatment because of adverse events. Most adverse events were rated as mild or moderate during citalopram therapy. All patients were able to tolerate at least 20 mg/day. Systolic blood pressure (baseline, 118 mm Hg; endpoint, 119 mm Hg), diastolic blood pressure (baseline, 76 mm Hg; endpoint, 75 mm Hg), and weight (baseline, 180 lb [81.65 kg]; endpoint, 179 lb [81.19 kg]) were unaffected by treatment. Pulse (baseline, 74 bpm; endpoint, 70 bpm) was slightly decreased by citalopram. There were no reports of clinically significant ECG changes.

Recurrence of the most common adverse events that had led to fluoxetine discontinuation was low (Figure 2). Those with the greatest rates of recurrence were headache (3 [27%] of 11 cases), nausea (2 [22%] of 9 cases), and decreased libido (5 [18%] of 28 cases).

DISCUSSION

Several studies have examined the utility of treatment with a second SSRI following intolerance and/or nonresponse to the first SSRI. However, this is only the third study that specifically examined patients who had been unable to tolerate previous SSRI therapy, and the first study to examine the utility of citalopram in patients intolerant of fluoxetine. In this study, treatment with citalopram in patients with a documented history of fluoxetine intolerance was effective and very well tolerated. Ninety-five percent of patients completed a 6-week therapeutic trial, and no patients discontinued due to adverse events. Further, using the definition of response as a CGI-Improvement score of 1 or 2, 65% of patients in the current study responded to citalopram treatment. While it is important to be cautious when comparing response rates across studies, it should be noted that these results are similar to the findings of Brown and Harrison,[5] who switched fluoxetine-intolerant patients to sertraline therapy, as well as those of Thase et al.,[29] who switched paroxetine-intolerant patients to citalopram.

The tolerability and efficacy observed in our study, as well as the findings of Thase et al.,[29] are similar to the results reported in double-blind clinical trials of citalopram. In controlled clinical trials, response rates to citalopram of at least 50% have been repeatedly observed.[30,31] This observation suggests that an inability to tolerate fluoxetine or paroxetine does not predict therapeutic failure during a subsequent trial of citalopram.

The low attrition rate and good tolerability of citalopram in this study may be attributable to several factors. It is possible that pharmacokinetic differences between citalopram and fluoxetine account for different tolerability profiles in this population.[32–34] A second factor that may have contributed to improved tolerability of citalopram is the relatively slow titration schedule, in which doses above 20 mg/day were not permitted until after

completion of 4 weeks of treatment. Thus, patients who did not tolerate a previous trial of fluoxetine due to rapid dose titration may have responded well to the current trial with citalopram. Finally, the fluoxetine-intolerant patients in this study may have been particularly motivated to stay on citalopram therapy in order to achieve symptom relief. It is also true that the patient selection process may have isolated a group that is more sensitive to lower plasma drug levels and therefore might have had a better response to low-dose citalopram treatment than an unselected study group.

Several additional factors limit our interpretation of these data. As noted above, this study did not use randomized assignment or a double-blind design including a comparator arm. Open-label treatment could account for the robust effect seen as early as week 1. Open-label designs have been used in most published studies examining the efficacy and safety of switching patients intolerant or nonresponsive to one SSRI to a second member of this class. As a result, findings from these trials should be interpreted with caution. Moreover, although the data may be relevant to other SSRIs, we did not address that question. However, taken together with the other published switch studies, our results suggest that patients who are unable to tolerate one SSRI can be successfully treated with another agent from this pharmacologic class. In light of the well-known safety of these agents and their widespread use, within-class switching has clinical merit. Therefore, the preliminary results reported here warrant further study and, if replicated by a randomized controlled trial, could provide meaningful guidance to a vast array of generalists and specialists.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft).

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