Citalopram Treatment of Fluoxetine Nonresponders

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Background: We assessed the tolerability and utility of switching fluoxetine nonresponders to citalopram the day that fluoxetine therapy was stopped.

Method: Fifty-eight outpatients with DSM-IV major depressive episode and prospectively confirmed nonresponse to fluoxetine (mean final dose = 31 mg/day) were switched directly to citalopram (20 mg/day). Of the 58 patients, 44 (76%) had never been successfully treated with antidepressant medication. During a 12-week open-label treatment period, citalopram could be titrated up to a maximum dose of 60 mg/day. Response was evaluated using the Clinical Global Impressions (CGI) scale, the 24-item Hamilton Rating Scale for Depression, and several other measures.

Results: Eighty-one percent (N = 47) completed the trial, and citalopram (mean dose = 38.8 mg/day) was well tolerated. The intent-to-treat CGI response rate was 46% (26/57) at week 6 and 63% (36/57) at study endpoint; the completer response rate was 76% among the 47 patients who completed the 12-week trial. Improvement from baseline on all dependent measures was statistically significant after the first week of citalopram treatment.

Conclusion: Fluoxetine nonresponders can be quickly switched to citalopram, with good tolerability and reasonable chance of therapeutic benefit. Further work is necessary to assess the merits of this treatment strategy relative to other options.

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The selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants in the United States, Canada, and most of Europe.[1,2] Each of the SSRIs has an intent-to-treat response rate of 50% to 60% in randomized clinical trials, and there is no compelling evidence that one is more effective than any of the others.[3–5] Despite comparable efficacy, however, the 5 members of this class do not appear to be fully interchangeable. For example, clinicians frequently encounter patients who do not respond to a particular SSRI but subsequently respond to a different member of the same class.

Four published, open-label studies have reported on switching nonresponders from one SSRI to another.[6–9] With one possible exception,[9] these reports support the utility of trying at least one other SSRI. However, several studies included SSRI-intolerant patients rather than, or in addition to, nonresponders. Moreover, none of the studies prospectively demonstrated nonresponse to the first SSRI.

Two of the SSRIs in clinical use today for the treatment of depression are fluoxetine and citalopram. Although the 2 antidepressants are thought to have the same primary pharmacologic mechanism of action, they are different in several ways. For example, preclinical studies have shown that citalopram is approximately 70-fold more selective than fluoxetine on ratio measures of serotonin reuptake versus catecholamine neurotransmitters.[10–13] The clinical significance of this difference is uncertain, but it is possible that some depressed patients respond better to highly selective drugs, while others respond better to agents that affect multiple neurotransmitter systems.

Fluoxetine also has a somewhat more complex pharmacokinetic profile, making the switch to another anti-

depressant potentially problematic.[13–15] Considerations include the long elimination half-life of its active metabolite, norfluoxetine, as well as nonlinear pharmacokinetics, and potent inhibition of CYP2D6.[16] As a result, patients who discontinue fluoxetine immediately preceding treatment with a medication that is metabolized by CYP2D6 are still at some risk of drug interactions.[17] However, it is not clear if such an immediate switch from fluoxetine to another SSRI would actually complicate treatment.

In the present study, we examined the tolerability and clinical utility of a direct switch to citalopram among patients documented to be nonresponsive to fluoxetine.

METHOD

Overview

This is an 8-center, open-label, standardized, prospective study of citalopram treatment of depressed outpatients who were confirmed prospectively to have failed to respond to fluoxetine.

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[18] diagnosis of major depressive episode, (2) completion of at least 6 weeks of treatment with fluoxetine at a dose of ≥ 20 mg/day, (3) no intolerable side effects during fluoxetine treatment, (4) a score of ≥ 18 on the 24-item version of the Hamilton Rating Scale for Depression (HAM-D-24)[19,20] on 2 consecutive evaluations, (5) current Patient Global Evaluation and Clinical Global Impressions (CGI) scale[20] scores of 3 or greater (no more than minimal improvement) during fluoxetine therapy, and (6) aged between 18 and 65 years. Exclusion criteria included the following: (1) current use of psychotropic medications other than fluoxetine, (2) prior treatment with citalopram, (3) pregnancy or breast-feeding, (4) unwillingness to use contraception, (5) any lifetime history of psychosis, (6) abuse of drugs or alcohol within the past year, and (7) severe or unstable medical illness or neurologic disease, or required therapy associated with such conditions. Medical status was confirmed by a history and physical examination, 12-lead electrocardiogram (ECG), urine drug test, complete blood count, blood urea nitrogen (BUN), creatinine, electrolytes, liver enzymes, thyroid-stimulating hormone (TSH), urinalysis, and (if appropriate) urine and serum pregnancy tests. Patients with Cluster A or B DSM-IV personality disorders were excluded if the investigator judged the condition to be severe. Patients could not have had a depot neuroleptic within 6 months, electroconvulsive therapy (ECT) within 3 months, or any psychotropic medication (other than fluoxetine) within 2 weeks of beginning study medication. Finally, patients who had failed (by history) to respond to an adequate trial of any SSRI other than fluoxetine were excluded, as were those who had failed 2 or more trials with other antidepressants. In many cases, patients had already taken fluoxetine for 6 or more weeks when referred to study doctors, who confirmed nonresponse prospectively over at least 2 weeks before switching medications.

Treatment Protocol

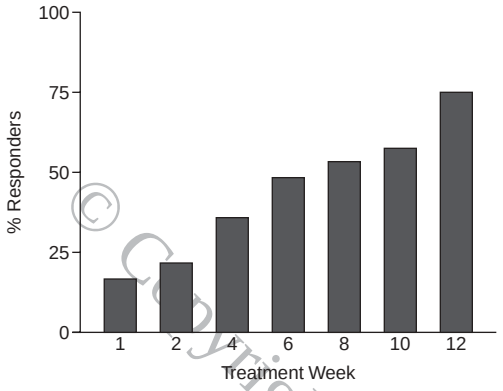
After providing informed consent and meeting study eligibility, patients were instructed to continue to take fluoxetine (without dosage change) for the next week. At that time, if eligibility was confirmed, patients were instructed to stop fluoxetine treatment, without any tapering, and to begin citalopram treatment on the day following the last fluoxetine dose. Citalopram was initiated at 20 mg/day. After 2 weeks of therapy, the dose could be increased to 40 mg/day if response was not adequate. Similarly, after 2 weeks of therapy at 40 mg/day, the dose could be advanced to 60 mg/day. Dosage reductions of 20 mg/day were permitted if there were significant side effects, although to remain in the study, patients had to be able to tolerate 20 mg/day of citalopram.

Clinical evaluations were performed at weeks 1, 2, 4, 6, 8, 10, and 12 of citalopram treatment. Blood work and ECGs were repeated at week 12 or endpoint. Side effects were recorded based on spontaneous patient report. In addition to the HAM-D-24, response was evaluated at each visit by the CGI scale.[20] A response was defined by a CGI-Improvement score of 1 or 2 (very much improved or much improved). Secondary dependent measures, including the Patient Global Evaluation scale,[20] the Hamilton Rating Scale for Anxiety (HAM-A),[21] a quality of life questionnaire,[22] and the Beck Depression Inventory,[23] were collected at week 0 and week 12 or endpoint. Primary analyses followed the intent-to-treat principle, utilizing endpoint scores (last observation carried forward) whenever necessary. Data were analyzed using paired t tests, with results presented as the means ± standard deviations.

RESULTS

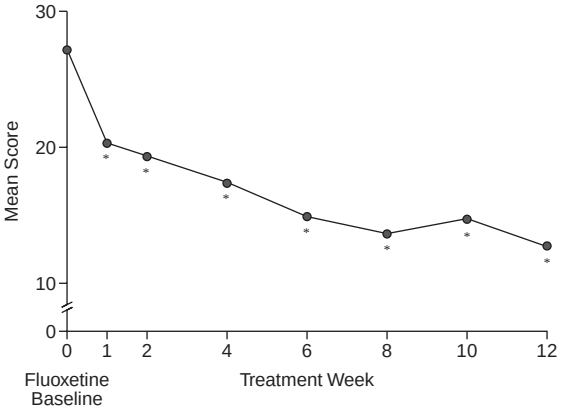
A total of 58 consenting patients (35 female/23 male) enrolled in this study. These patients had a mean ± SD age of 43.9 ± 11.4 years. The entire study group was white. The patients were taking a mean dose of 30.9 mg of fluoxetine at study entry (range, 20–80 mg/day). The median duration of fluoxetine treatment was 5.9 months. The mean ± SD HAM-D-24 score at entry was 27.5 ± 4.6 despite ongoing fluoxetine treatment. The distribution of CGI ratings of the response to fluoxetine treatment was 28% minimally improved, 60% unchanged, and 12% worse. For 29 patients (50%), the failed fluoxetine trial was their first antidepressant treatment. Among the remainder, 14 (24%) had previously responded to an antidepressant and 15 (26%) had not. Thus, 76% of the patients

Figure 1. Percentage of Citalopram-Treated Patients Classified as Responders on the Clinical Global Impressions-Improvement scale (CGI-I) by Treatment Week Among 47 Completers[a]



[a]Observed case analysis (cell size range from 57 at week 1 to 46 at week 12). Response was defined as CGI-I = 1 or 2, very much improved or much improved. Improvement was rated relative to the patient's condition on the last day of fluoxetine treatment.

Figure 2. Mean Score on the Hamilton Rating Scale for Depression During Citalopram Treatment[a]



[a]Significant improvement relative to baseline was observed beginning in the first week after initiation of citalopram therapy.
*Significantly different from baseline, p < .001 (last observation carried forward, intent-to-treat population, N = 57).

(44/58) had never been successfully treated with antidepressant medication.

A total of 47 patients (81%) completed the 12-week trial. The mean duration of treatment was 75.3 days and the mean ± SD dose of citalopram was 38.8 ± 11.3 mg. Reasons for premature discontinuation included adverse events (N = 3), insufficient response (N = 3), lost to follow-up (N = 3), withdrawal of consent (N = 1), and protocol violation (N = 1).

Postbaseline outcome data were documented for 57 patients, constituting the intent-to-treat sample. A total of 36 patients (63%) met CGI response criteria at study endpoint (week 12 or last observation). Of these, 26 (46% of all patients) had responded by week 6. For the 47 patients who completed the trial, the CGI response rate was 76% (Figure 1). Thirty patients (53% of the intent-to-treat sample; 65% of the completers) judged themselves to be much or very much improved according to the Patient Global Evaluation.

Overall, the mean HAM-D-24 score decreased from 27.5 ± 4.6 to 14.6 ± 8.2 ($p < .001$), a 47% reduction in depressive symptoms. Twenty-six patients (46% of the intent-to-treat sample and 57% of completers) had a ≥ 50% reduction in HAM-D-24 scores. As illustrated in Figure 2, symptomatic improvement was most dramatic during the first week of citalopram treatment, with a steady linear trend between week 1 and week 8. Thereafter, HAM-D-24 scores did not improve significantly. Improvement at weeks 6 and 12, as measured by the percent change in HAM-D scores, was not related to the dose or duration of prior fluoxetine treatment.

HAM-A scores improved from 16.9 ± 4.9 to 9.4 ± 6.4 (N = 46; $p < .001$). Beck Depression Inventory scores similarly fell from 16.1 ± 5.6 to 8.8 ± 6.5 (N = 46; $p < .001$). Mean CGI-Severity ratings decreased from 4.1 ± 0.4 (i.e., moderately to markedly ill) to 2.6 ± 1.0 (borderline to mildly ill) (N = 46; $p < .001$). Quality of life total scores improved from 39.4 ± 8.8 to 52.2 ± 11.3 (N = 46; $p < .001$), with significant improvement on all 16 subscales.

Citalopram treatment was well tolerated. During the first week of therapy on citalopram, 20 mg/day, no patients discontinued because of adverse events, and only 4 adverse events were reported by more than 3 patients (i.e., ≥ 5% of the study group). These more common side effects were headache (9%), dyspepsia (7%), insomnia (7%), and somnolence (7%). Across the full 12-week protocol, the following adverse events were reported by more than 6 patients (i.e., ≥ 10% of the study group): headache (22%), diarrhea (21%), pharyngitis (19%), somnolence (19%), dry mouth (16%), nausea (14%), and insomnia (12%). Five patients (9%) reported decreased libido, and 2 men (9%) and 1 woman (3%) reported orgasmic dysfunction. There were no significant changes in body weight, pulse, blood pressure, laboratory, or ECG parameters.

DISCUSSION

This is the fifth study to address the outcomes of patients switched from one SSRI to another. As in 3 of the 4 preceding reports, the clinical outcomes of patients were reasonably good: 63% of the intent-to-treat sample and 76% of the completers had responded by week 12. Unlike in previous reports, fluoxetine nonresponse was documented prospectively and patients were switched abruptly, without any tapering or cross-titration. Overall,

our findings provide further evidence that a within-class switch from one SSRI to another is a viable strategy for patients who have not responded to an initial trial.

In spite of the immediate switch from fluoxetine to citalopram, no patients discontinued because of adverse events during the first week of citalopram treatment. Over the entire trial, only 3 patients (5%) dropped out due to side effects. Thus, although it is likely that most patients had clinically significant norfluoxetine levels for at least the first several weeks of citalopram treatment, potential pharmacokinetic or pharmacodynamic interactions between these compounds did not adversely affect the initiation of citalopram therapy. It should be noted that such good tolerability may have been facilitated by enrolling patients who had already tolerated, on average, months of fluoxetine treatment. Such findings are similar to those in a previous study of a heterogeneous group of fluoxetine-treated patients switched abruptly to paroxetine.[24] A second study by our group evaluating citalopram treatment of patients with a history of SSRI intolerance has been completed and will be reported separately.[25]

It is noteworthy that the patients showed the greatest symptom reduction in the first week of citalopram treatment, when both fluoxetine and norfluoxetine levels were still likely to be high. One possible explanation of this pattern is that there might be pharmacokinetic or pharmacodynamic synergism between these SSRIs. Much more extensive evaluation of this issue is necessary, however, before the unorthodox strategy of combining SSRIs could be recommended. It is also possible that such initial rapid symptom reduction reflected the patients' expectations for improvement following the switch to a new medication. In any event, we found no evidence of amplification of adverse effects during the first week of citalopram treatment, which was our more immediate clinical concern.

Several limitations affect the interpretation of this study. Although it is likely that these data are relevant to switches involving other SSRIs, such possibilities were not directly addressed. Moreover, this study, like the previous 4, did not use random assignment or a double-blind design including a comparative treatment. The use of unblinded evaluations, open-label medication, and a long 12-week treatment period are likely to have maximized the nonspecific (i.e., placebo-expectancy and spontaneous remission) elements of treatment response. Nevertheless, the positive results obtained do suggest that citalopram should be more systematically evaluated as an option for patients who do not respond to other SSRIs.

It is a challenge to assess the relative merits of a switch within the SSRI class compared with the myriad other strategies available for antidepressant nonresponders. For example, reasonable alternatives to a within-class switch include increasing the ineffective antidepressant to supratherapeutic doses, switching to a different class of antidepressant, and augmentation with agents such as thyroid hormone, lithium, or pindolol.[26] On the one hand, the SSRIs are safe and widely prescribed medications that are used with confidence by specialists and generalists alike. Moreover, the results of 4 ambulatory studies now suggest that 50% to 65% response rates can be expected when switching patients who have not responded to one SSRI to a second "class-mate." On the other hand, relatively poorer outcomes were observed in the one relevant inpatient study,[9] which enrolled patients with severe symptoms of depression and extensive comorbidity. A subgroup of SSRI nonresponders undoubtedly requires more intensive treatment strategies. Although more methodologically rigorous studies of the switch from one SSRI to another have yet to be published, our study demonstrates that fluoxetine nonresponders can be switched, immediately and safely, to citalopram with good tolerability and a reasonable expectation of therapeutic benefits.

Drug names: citalopram (Celexa), fluoxetine (Prozac), paroxetine (Paxil).

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