Open-Label Trial of Escitalopram in the Treatment of Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is a highly prevalent, disabling illness. Selective serotonin reuptake inhibitors (SSRIs) are considered first-line medication treatment, with sertraline, paroxetine, and fluoxetine being the most studied. More limited but favorable data suggest that citalopram, an SSRI, may also have a role in the treatment of PTSD. Its *S*-enantiomer escitalopram, which may have faster onset and greater magnitude of effect than citalopram in other conditions, has not yet been investigated in PTSD.

Objective: To assess the efficacy, safety, and tolerability of escitalopram in the treatment of PTSD.

Method: A 12-week, prospective, open-label trial of escitalopram was conducted from January 2003 through August 2004 in military veterans with PTSD. Escitalopram was initiated at 10 mg daily for 4 weeks, then increased to 20 mg daily for the remainder of the study. Concomitant psychiatric medications were discontinued at least 2 weeks prior to enrollment. The primary outcome variable was the change from baseline to endpoint in global Clinician-Administered PTSD Scale-Symptom version (CAPS-SX) score. Secondary efficacy measures included the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales, the Hamilton Rating Scale for Depression (HAM-D), and the Davidson Trauma Scale (DTS). Posttraumatic stress disorder and comorbid diagnoses were established using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition.

Results: Twenty-four of 25 patients were evaluated for efficacy. The mean global CAPS-SX score decreased from 79.4 (SD = 15.7) at baseline to 61.2 (SD = 24.7) at the end of the study (p = .0002). The CAPS-C avoidance/numbing and CAPS-D hyperarousal subscale scores decreased significantly from baseline to endpoint (CAPS-C, p = .0171; CAPS-D, p = .0001), with trend-level reductions observed in CAPS-B reexperiencing subscale scores (p = .0593). Forty-five percent of patients (9/20) were much or very much improved at the end of the study (CGI-I of 1 or 2). The HAM-D and DTS also significantly improved (p = .0063 and p = .0004, respectively). Mild to moderate gastrointestinal disturbances were the most common side effects. Only 4 patients discontinued early because of adverse effects.

Conclusions: This preliminary open-label study suggests that escitalopram is both efficacious and well tolerated in PTSD patients. However, randomized controlled studies are needed to confirm these results and to further define its potential role in the treatment of PTSD.

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Posttraumatic stress disorder (PTSD) is a disabling illness that affects up to 7.8% of the general population, with a much higher incidence in certain trauma populations such as combat veterans.[1,2] Selective serotonin reuptake inhibitor (SSRI) antidepressants are the most studied medication treatment for PTSD and are considered first-line treatment options.[3,4] Two SSRIs, sertraline and paroxetine, are the only Food and Drug Administration–approved medications for treating PTSD. Citalopram, another SSRI, is well tolerated and has minimal drug interactions. Thus, it is widely used for the treatment of depression and anxiety disorders.[5] Favorable data

from case reports[6] and open-label[7] and controlled trials[8] suggest that it may have a role in treating PTSD. However, as observed with other SSRIs, its effects may be less robust in military veterans with chronic PTSD.[9] Escitalopram, its *S*-enantiomer, may have a faster onset and better efficacy than citalopram,[10,11] but it has yet to be investigated in PTSD.

METHOD

Study Design

The study was a 12-week, prospective, open-label trial of escitalopram conducted from January 2003 through August 2004 in military veterans with PTSD. The research protocol was approved by the Medical University of South Carolina institutional review board and the Ralph H. Johnson VA Research and Development committee. All study-related procedures were performed after patients gave written informed consent.

Subject Inclusion/Exclusion Criteria

Subjects were recruited predominantly through the PTSD clinic but also through other outpatient clinics at the Ralph H. Johnson VA Medical Center.

Patients had to meet the following inclusion criteria: (1) outpatients 18 years of age or older; (2) competence to give written informed consent; (3) meeting DSM-IV[12] criteria for PTSD; (4) negative pregnancy test and using a medically approved contraceptive method for women of childbearing age; and (5) no psychotropic medications within 2 weeks prior to study entry except fluoxetine (6 weeks), monoamine oxidase inhibitors (4 weeks), depot neuroleptics (4 months), or any investigational drug within 30 days prior to study enrollment. A minimum Clinician-Administered PTSD Scale-Symptom version (CAPS-SX)[13] score was not required for entry into the study.

Patients were excluded from the study if they had any of the following: (1) history of sensitivity to citalopram or escitalopram; (2) failure to respond to a prior adequate trial of 2 SSRIs or citalopram or escitalopram in the past; (3) unstable medical conditions; (4) alcohol or drug abuse or dependence within 1 month of study entry; (5) DSM-IV[12] diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; or (6) active suicidality or homicidality or other clinically significant dangerousness.

Study Procedures

During the screening visit, patients received a comprehensive psychiatric evaluation, physical examination, electrocardiogram, and laboratory tests (complete blood count with white count differential, serum electrolytes, glucose, creatinine, blood urea nitrogen, liver function tests, urinalysis, and urine drug screen). Efficacy and safety assessments, including vital sign measurements and recording of adverse events, were performed biweekly until week 8 and then at week 12, with weekly phone contacts between office visits to monitor tolerability. Posttraumatic stress disorder and comorbid diagnoses were assessed at screening with the Structured Clinical Interview for DSM-IV.[14]

Escitalopram was initiated at 10 mg daily for 4 weeks, then increased to 20 mg daily for the remainder of the study. Concomitant psychiatric medications were discontinued at least 2 weeks prior to enrollment and were not allowed during the study period except for minimal, intermittent use of hypnotics during the first 2 weeks of the study.

Outcome Variables

The primary efficacy variable was the change from baseline to endpoint in global CAPS-SX score.[13] Secondary efficacy measures consisted of the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales,[15] the Hamilton Rating Scale for Depression (HAM-D),[16] the Davidson Trauma Scale (DTS),[17] the Pittsburgh Sleep Quality Index (PSQI)[18] and Addendum for PTSD (PSQI-A),[19] the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[20] and the proportion of responders on the CAPS-SX. Response was defined a priori as a 20% or greater decrease from baseline to endpoint in total CAPS-SX score. Response was defined this way in view of the severe, chronic, relatively treatment-resistant PTSD that is characteristic of the military veteran population.

Primary and secondary outcome assessments were performed at screening and at weeks 2, 4, 6, 8, and 12, except for the CGI-I (not administered at screening) and the PSQI, PSQI-A, and Q-LES-Q (not administered at weeks 2 and 6).

Statistical Analyses

Sample-size calculations were based on obtaining 90% power to detect at least a 20% decrease in total CAPS-SX score from baseline to final visit using a 2-sided Wilcoxon signed rank test. A mean ± SD baseline total CAPS-SX score of 79.9 ± 15.6, as reported in the original citalopram PTSD study,[7] was used. The estimated sample size of 20 subjects was increased to 25 subjects, as we anticipated a 20% dropout rate.

Primary and secondary outcomes were analyzed using the Wilcoxon signed rank test. The last-observation-carried-forward (LOCF) method was used for missing data for subjects who had at least 1 postbaseline efficacy assessment (efficacy analysis).

RESULTS

Twenty-five patients were enrolled in the study. Demographics and psychiatric comorbidities are listed in

Table 1. Demographic Characteristics and Comorbid Psychiatric Diagnoses of Patients in a Trial of Escitalopram for Posttraumatic Stress Disorder

Variable	Escitalopram Study Sample[a] (N = 25)
Age, mean (SD), y	55.6 (7.68)
Gender, male	25 (100)
Race	
White	17 (68)
African American	8 (32)
Marital status	
Married	17 (68)
Divorced	5 (20)
Separated	2 (8)
Never married	1 (4)
Employment status	
Employed	15 (60)
Retired	3 (12)
Disabled	5 (20)
Unemployed	1 (4)
Student	1 (4)
Comorbid Axis I diagnoses	
Major depressive disorder	19 (76)
Other anxiety disorders	5 (20)
History of alcohol abuse/dependence	11 (44)
History of drug abuse/dependence	3 (12)

[a]Values are shown as N (%) except where indicated otherwise.

Table 2. Mean Baseline and Endpoint Scores for Primary and Secondary Efficacy Variables (LOCF) (N = 24)

Variable	Baseline, Mean (SD)	Endpoint, Mean (SD)	p Value
CAPS-SX	79.42 (15.70)	61.21 (24.65)	.0002
CAPS-B (reexperiencing)	20.54 (7.76)	15.87 (9.27)	.0593
CAPS-C (avoidance/numbing)	31.88 (8.36)	25.42 (13.80)	.0171
CAPS-D (hyperarousal)	27.00 (4.84)	19.92 (6.57)	.0001
HAM-D	21.58 (7.16)	17.00 (7.59)	.0063
CGI-S	4.50 (0.88)	4.25 (0.85)	.1094
DTS	78.58 (19.13)	61.20 (24.53)	.0004
PSQI	12.67 (2.65)	11.20 (3.50)	.0616
PSQI-A	7.59 (4.15)	7.58 (4.92)	.4315
Q-LES-Q	40.74 (7.28)	44.10 (9.29)	.1047

Abbreviations: CAPS-SX = Clinician-Administered PTSD Scale-Symptom version, CGI-S = Clinical Global Impressions-Severity of Illness scale, DTS = Davidson Trauma Scale, HAM-D = Hamilton Rating Scale for Depression, LOCF = last observation carried forward, PSQI = Pittsburgh Sleep Quality Index, PSQI-A = Pittsburgh Sleep Quality Index-Addendum for PTSD, PTSD = posttraumatic stress disorder, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

Table 1. Twenty-four patients had at least 1 postbaseline efficacy evaluation and thus were included in the efficacy analysis.

Baseline CAPS-SX scores ranged from 48 to 106. There was a significant decrease in the mean global CAPS-SX score from 79.4 (SD = 15.7) at baseline to 61.2 (SD = 24.7) at study endpoint (p = .0002). The CAPS-C avoidance/numbing and CAPS-D hyperarousal scores decreased significantly from baseline to endpoint, with

Table 3. Most Frequent Treatment-Emergent Adverse Events

Adverse Event	Escitalopram Study Sample[a] (N = 25)
Any gastrointestinal disturbance	11 (44)
Nausea	6 (24)
Diarrhea	4 (16)
Sedation	6 (24)
Sexual dysfunction	6 (24)
Sweating	4 (16)
Nervousness	4 (16)
Insomnia	3 (12)
Headache	3 (12)
Weight gain	2 (8)
Arthralgia	2 (8)

[a]Values are shown as N (%).

trend-level reductions observed in CAPS-B reexperiencing scores (Table 2). There was a positive rank correlation between changes in total CAPS-SX and HAM-D scores (Spearman rank = 0.61).

The proportion of responders was 37.5% (9/24) in the intent-to-treat sample and 45% (9/20) in patients who completed the study. The mean CAPS-SX score in the 9 responders decreased from 83.1 (SD = 12.6) at baseline to 39.8 (SD = 19.7) at endpoint.

Forty-five percent (9/20) of completers were much or very much improved at the end of the study (CGI-I of 1 or 2). The CGI-S score decreased by at least 1 point in 25% (6/24) of patients in the intent-to-treat sample.

Safety

Escitalopram was well tolerated. Treatment-emergent side effects are listed in Table 3; most were mild to moderate and usually transient.

Eight of 25 patients discontinued early: 4 discontinued because of side effects (apathy [N = 1], nervousness [N = 1], sedation [N = 1], and odd dreams [N = 1]), 1 each discontinued for lack of efficacy and noncompliance, and 2 were lost to follow-up.

DISCUSSION

As observed with other SSRIs,[21,22] treatment with escitalopram significantly improved PTSD symptoms on clinician- and patient-rated scales, with specific improvement also noted in avoidance/numbing and hyperarousal symptoms. The reduction in reexperiencing symptoms did not reach statistical significance but was noteworthy given the conflicting results or delayed onset of effect observed with other SSRIs.[21,22] As expected, escitalopram was effective at reducing depressive symptoms, but the effect was modest. This is not surprising, given that depression comorbid with PTSD tends to have a less robust response than depression alone. The trend-level improvement in sleep disturbances noted in this study is encouraging. Unlike sertraline,[23] escitalopram does not appear to

worsen sleep disturbances associated with PTSD but may actually improve such symptoms, more consistent with effects reported with fluvoxamine[24] and paroxetine.[25] Escitalopram was well tolerated, with few patients discontinuing because of intolerable side effects.

Despite the improvement described above, the sample's mean PTSD symptoms and overall severity of illness were moderate to severe after 12 weeks of treatment with escitalopram, with most patients still exceeding minimum CAPS-SX inclusion criteria utilized in PTSD studies.[22,23] Nonetheless, a substantial proportion of patients (37.5%) responded to the treatment and were considered much or very much improved overall. Our a priori responder criterion of 20% decrease in total CAPS-SX scores is different than the 30% used in several large studies.[21–23] In contrast to these studies involving primarily civilian PTSD populations, trials with veterans have typically failed to show benefits, or have shown only minimal benefits, from antidepressants.[21,26–28] We selected our response definition accordingly in the setting of a traditionally chronic, treatment-resistant PTSD population. A post hoc analysis based on 30% total CAPS-SX score decrease yielded a slightly lower response rate of 33.3% (8/24) in the intent-to-treat sample and 40% (8/20) for completers. Posttraumatic stress disorder symptomatology for these responders was reduced from extreme to mild with escitalopram treatment. Hence, the benefits observed with escitalopram are promising, given the symptom chronicity and typically less responsive PTSD population, but again they suggest that optimum PTSD treatment in veterans may not be achieved with monotherapy.[29] Our results must be interpreted in the context of the open-label design of the study and lack of a placebo-control group.

CONCLUSIONS

Results from this open-label study suggest that escitalopram may be effective at reducing PTSD symptoms, with specific improvement in avoidance/numbing and hyperarousal symptoms. Escitalopram was well tolerated, with few patients discontinuing because of intolerable side effects. Randomized controlled studies are needed to confirm these preliminary results and to further define the potential role for escitalopram in the treatment of PTSD.

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

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