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Efficacy and Tolerability of High-Dose Escitalopram in Posttraumatic Stress Disorder

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Abstract:

Background: Open-label trials suggest that escitalopram (up to 20 mg/d) is an effective treatment for some, but not all posttraumatic stress disorder (PTSD) patients. Higher doses of escitalopram effectively reduced major depression symptoms in patients who had not responded to regular doses. The current study examines the efficacy, tolerability, and adherence to high-dose escitalopram in PTSD.

Methods: Forty-five PTSD patients received 12 weeks of gradually increasing doses of escitalopram reaching 40 mg daily at 4 weeks. Among those, 12 participants received regular doses of antidepressants at study onset including escitalopram (n = 7). The Clinician-Administered PTSD Scale (CAPS) evaluated PTSD symptoms severity before treatment, at 3 months (upon treatment termination), and at 6 months (maintenance effect). A 20% reduction in CAPS scores was deemed clinically significant.

Results: Adverse events and medication adherence were monitored at each clinical session. Linear mixed-models analysis showed a significant reduction of mean CAPS scores (11.5 ± 18.1 points) at 3 months and maintenance of gains by 6 months ($F_{2,34.56} = 8.15$, $P = 0.001$). Eleven participants (34.3%) showed clinically significant improvement at 3 months. Only 9 participants (20%) left the study. There were no serious adverse events and few mild ones with only 2 adverse events (diarrhea, 11.1%; drowsiness, 11.1%) reported by more than 10% of participants.

Conclusion: High doses of escitalopram are tolerable and well adhered to in PTSD. Their beneficial effect at a group level is due to a particularly good response in a subset of patients.Variability in prior pharmacological treatment precludes a definite attribution of the results to high doses of escitalopram.

Key Words: civilian trauma, escitalopram, PTSD, SSRI

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Selective serotonin reuptake inhibitors (SSRIs) are a commonly used pharmacologic treatment for posttraumatic stress disorder (PTSD). Clinical evidence shows that treatment with SSRIs (eg, paroxetine, sertraline) leads to a reduction in PTSD symptoms, with small to medium effect sizes.[1] Open-label trials suggest that escitalopram, another commonly prescribed SSRI (off-label use in treating PTSD), may also be effective in treating PTSD[2–4] in some patients. Previous escitalopram studies followed a recommended daily dose of up to 20 mg. However, in obsessive-compulsive disorder[5] and major depression,[6] higher doses were effective in patients who did not respond to regular doses. The use of higher doses of escitalopram has not been systematically evaluated in PTSD.

This study examined the efficacy, adherence to, and tolerance of high-dose escitalopram (up to 40 mg/d) in the treatment of PTSD. The study examined escitalopram's immediate effect after 3 months of treatment and its role as maintenance treatment after 6 months. We predefined *efficacy* as statistically significant reduction of PTSD symptoms at group level and a *clinically significant effect* as a 20% reduction in PTSD symptoms at the level of the individual. We used the proportion of prescribed drug taken and the 3- and 6-month completion rate as a measure of adherence, and the prevalence and severity of adverse effects as indices of tolerability.

METHODS

Study Participants

Participants (N = 45) were treatment-seeking civilian PTSD patients recruited from 2 psychiatric outpatient clinics in Jerusalem, Israel. Eligible participants were not included if they had prior adverse reactions to SSRIs; current neurological, endocrine, renal, or liver disease disorders; medication counterindicating the use of SSRIs; or lifetime history of psychosis or manic episodes. Prior treatment with SSRIs was not used as an exclusion criterion. The Clinician-Administered PTSD Scale (CAPS) for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* measured PTSD symptom severity and provided a PTSD diagnosis. Thirty-six participants had at least 2 efficacy assessments (see study flowchart in Figure 1). The study was approved and monitored by the Hadassah University Hospital institutional review board. Written informed consent was obtained after explaining the study's procedures and possible adverse effects. The study was registered at ClinicalTrials.gov (identifier: NCT00736021).

Intervention and Procedure

Escitalopram (Lexapro; Lundbeck Pharmaceuticals, Copenhagen, Denmark) treatment was started with an initial oral dose of 10 to 20 mg daily and gradually increased to the target dose of 40 mg daily over the first month. For medication at study onset (n = 12), SSRIs other than escitalopram were discontinued during a 2-week washout period prior to study onset, and existing escitalopram dose (n = 6) was progressively augmented to 40 mg daily. Escitalopram efficacy, adherence, and tolerability were sanctioned after 12 weeks (3 months) of treatment, during which time only supportive counseling and nonpsychiatric medication were allowed. Treatment was extended by 3 additional months to explore a longer-term (maintenance) effect and sustained adherence and tolerability (Fig. 1). Participants were seen by a psychiatrist every week during the first month, biweekly during the second and third months, and monthly after that. Leftover medication tablets were counted and recorded at each visit to indicate dose actually taken, and adverse effects were evaluated using a checklist.

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W.Q. and M.G. contributed equally to this study.

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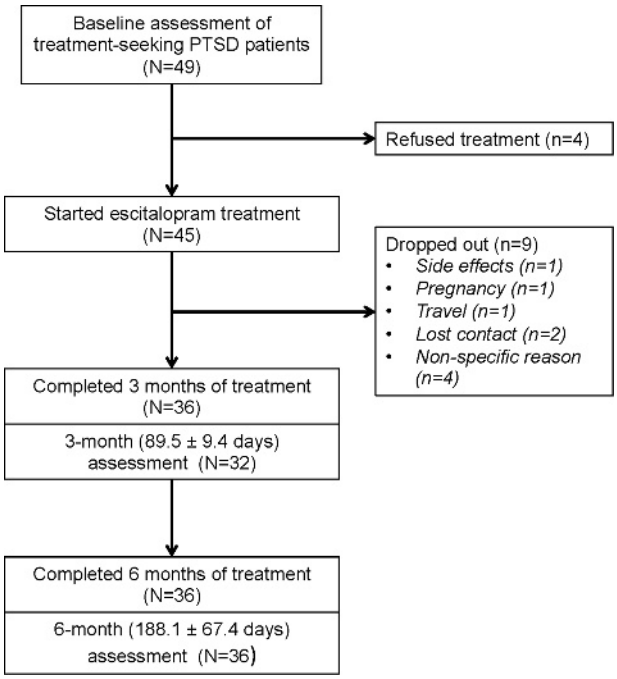

FIGURE 1. Study flow diagram.

Instruments

PTSD Symptom Severity

The CAPS is a clinical interview considered the criterion standard for diagnosing PTSD. The main outcome measure in this study was the total severity score (range, 0–136), a summation of frequency and intensity scores for the 17 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*–defined symptoms of PTSD.[7]

Depression

The severity of depression was measured with the Beck Depression Inventory (BDI), a 21-item self-report scale (range, 0–63).[8]

Adverse Events

Emerging adverse events were evaluated by a 14-item checklist of common adverse events of antidepressants, which also included an "other" category for participants to report possible adverse medication effects that were not on the list.

Outcome Measures

The study's main outcome measure was the severity of PTSD symptoms at 3 and 6 months as recorded by the CAPS. Following a previous study,[4] we used a predefined threshold of 20% reduction in symptom to infer clinically significant improvement. In addition, tolerability is expressed as percentage of participants reporting (*a*) serious adverse events, (*b*) mild adverse events at multiple assessments, and (*c*) any adverse event during the study. Indices of adherence include (*a*) proportion of participants who completed 3 and 6 months of treatment and (*b*) the proportion of prescribed dose actually taken by the participants.

Data Analysis

We used data from participants who at least completed 1 follow-up CAPS assessment (n = 36) for analysis. Baseline characteristics were compared between completers (n = 36) and dropouts (n = 9) using *t* test and χ^2 test. To test the effect of treatment on symptoms, we used SPSS 20.0 (IBM Corp, Armonk, NY) mixed-models procedure with maximum likelihood estimation, an autoregressive covariance structure, and a random intercept, separately for PTSD symptoms and depression. Time was entered as a fixed factor in these analyses. We also compared symptom differences between 2 adjacent time points using post hoc pairwise comparisons. Across all analyses, $P < 0.05$ (2-tailed) was considered statistically significant.

RESULTS

Baseline Characteristics

Baseline characteristics are presented in Table 1. Dropouts did not differ from followed participants in any baseline features, including age, sex, time from trauma, trauma type, BDI total score, and CAPS total score (Table 1).

High-dose escitalopram treatment was started an average of 2.7 (SD, 1.73) years after the traumatic event that triggered current PTSD. One-third of the participants were on stable treatment with SSRIs at study onset, including 7 participants (19.4%) treated with escitalopram (10–20 mg/d), 3 (8.3%) with citalopram (20–40 mg/d), and 2 (5.6%) with paroxetine (20 mg/d).

Efficacy

At 3 months, the mean CAPS scores for study participants were significantly lower than those recorded at baseline ($F_{2,34.56} = 8.15$, $P = 0.001$). The average decrease in PTSD symptoms for the entire group was 11.5 (SD, 18.1) points. These results were sustained at the 6-month assessment (Table 2, Fig. 2). All PTSD symptom clusters decreased by a similar degree (Table 2), with a mean decrease after 3 months of treatment of 3.87 points (18.5%) in intrusion, 3.97 points (14.1%) in avoidance, and 4.63 points (19.4%) in hyperarousal. Beck Depression Inventory scores showed similar and significant reduction at 3 months ($F_{2,35.25} = 4.28$, $P = 0.022$), decreasing by an average of 4.2 points. The results were sustained at 6 months (Table 2).

Individual Differences

Eleven participants (34.4%) showed clinically significant improvement at 3 months (Fig. 2), including 3 of 10 participants who received escitalopram or citalopram at study onset and 1 of 2 participants on paroxetine.

At 6 months, 15 participants (41.7%) showed clinically significant improvement including all 11 subjects who improved by 3 months, 3 who improved between 3 and 6 months, and 1 subject who had not been assessed at 3 months. Importantly, more than half of participants did not show clinically relevant improvement during the trial.

There were no significant differences in age, sex, trauma type, days since trauma, and baseline PTSD symptoms between participants with significant responses (responders) and others (nonresponders) at 3 months. Responders, however, had a lower mean BDI score at baseline (responders' mean = 19.64 [SD, 9.78] and nonresponders' mean = 27.90 [SD, 10.30]; $P = 0.037$). Responders also showed larger decrease in depression symptoms at 3 months (respectively for responders and nonresponders BDI mean = 13.67 [SD, 7.86] vs BDI mean = 25.05 [SD, 12.08]).

Adherence and Tolerability

Thirty-six (80%) of the 45 participants continued taking escitalopram for 3 months, and all of them further continued

TABLE 1. Baseline Characteristics

	Followed (n = 36)	Dropout (n = 9)	*P*
Age, mean (SD), y	43.5 (13.4)	41.6 (13.1)	0.695
Time from trauma mean (SD), d	988.7 (630.0)	795.8 (367.7)	0.245
Gender, n (%)			0.530
Male	18 (50.0)	4 (44.6)	
Female	18 (50.0)	5 (55.4)	
Trauma type n (%)			0.320
Motor vehicle accident	29 (80.6)	7 (77.8)	
Terrorist attack	3 (8.3)	0	
Work accident	2 (5.6)	2 (22.2)	
Other	2 (5.6)	0	
BDI, mean (SD)	25.7 (10.7)	29.6 (11.5)	0.400
CAPS, mean (SD)	71.8 (14.3)	77.8 (11.6)	0.208

treatment until 6 months. Compliance was high, as participants took 95% of prescribed dose (Table 2). No serious adverse effects have been recorded during the study. Only 1 participant (2.2%) listed an adverse reaction as the reason for dropping out (at a dosage of 10 mg/d). Other reasons for dropping out included pregnancy (n = 1 [2.2%]), travel (n = 1 [2.2%]), loss of contact (n = 2 [4.4%]), and unspecified (n = 4 [8.8%]). Among those who completed the study (n = 36), 16 participants (44%) did not report any adverse event during 6 months of treatment. Nine participants (25%) reported a mild adverse event in more than 1 visit, and an additional 11 (30.6%) reported a mild adverse event in 1 clinical visit only. Diarrhea and drowsiness were most commonly reported (Table 2).

DISCUSSION

This open-label study investigated the efficacy, tolerability, and treatment adherence of high-dosage escitalopram in adult civilians with chronic PTSD. The results show significant reduction in mean PTSD symptom at 3 months, which was sustained at 6 months. However, this effect is driven by a subgroup of good responders, whereas the majority of participants remain unchanged.

TABLE 2. Treatment Dosage, Adverse Events, and Symptom Severity Over Time

	Before Treatment	3 mo	6 mo
Dosage			
Prescribed, mean (SD), mg		38.33 (5.07)	38.61 (4.87)
Taken, mean (SD), mg		36.53 (6.64)	37.78 (5.40)
Adverse events, n (%)		21 (58.3)	6 (16.7)
Change in appetite		2 (5.6)	0
Weight loss/gain		2 (5.6)	1 (2.7)
Abdominal pain		3 (8.3)	2 (5.6)
Diarrhea		4 (11.1)	0
Constipation		1 (2.8)	0
Dry mouth		2 (5.6)	1 (2.8)
Restlessness		0	0
Drowsiness		4 (11.1)	1 (2.8)
Insomnia		1 (2.8)	0
Headache		3 (8.3)	0
Vertigo		3 (8.3)	0
Sweating		2 (5.6)	0
Palpitations		1 (2.8)	0
Tremor		0	0
Sexual dysfunction		0	0
Other		15 (42)	3 (8.3)
CAPS total, mean (SD)	71.80 (14.29)	60.53 (24.60)	60.08 (25.86)
Intrusion	20.93 (4.41)	17.06 (7.34)	16.89 (7.79)
Avoidance	28.16 (8.08)	24.19 (11.96)	23.36 (12.31)
Hyperarousal	23.91 (3.84)	19.28 (6.80)	19.83 (6.91)
BDI, mean (SD), kg/m^2	25.71 (10.71)	21.52 (11.84)	21.86 (13.53)

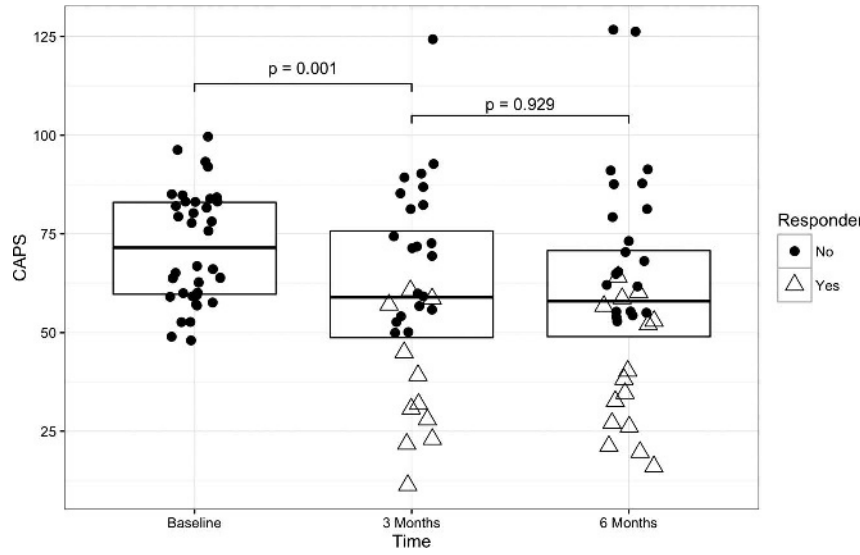

FIGURE 2. Posttraumatic stress disorder symptom scores before, after 3 months, and after 6 months treatment with escitalopram. Box plots including individual observations of post traumatic stress disorder (PTSD) symptom scores measured with the CAPS (y-axis, higher scores mean more symptoms) before the start of high-dose escitalopram treatment (baseline, n = 36), after initial treatment (3 months, n = 32) and after sustained treatment (6 months, n = 36). Individual observations are coded to different shapes to reflect treatment response (triangle, >20% decrease in symptoms relative to individual baseline; dot, non-response at that time point).

Escitalopram treatment also led to a limited reduction in depression symptoms, which could reflect the absence of response of depression symptoms among nonresponders. Adverse events were mild and mostly transient, with rates similar to those reported in studies of low-dose escitalopram.[4] These results are also in line with a study of major depression, in which escitalopram was well tolerated up to 40 mg. In that study, however, the tolerance declined with doses greater than 40 mg.[6] As indicated by the limited dropout rate and high compliance with medication, treatment adherence was good.

While the main treatment effect was significant, with a 16% decrease in mean PTSD symptoms, the mean effect was not superior when compared with decreases of 23% to 58% reported in studies that examined low doses.[2–4] The reported improvement of 4 participants on regular doses of SSRI suggests that higher-dose escitalopram might be beneficial to some individuals who do not improve on lower doses.

The heterogeneity in responses, in this work, is remarkable: the mean symptom reduction was driven by a subgroup of treatment responders, whereas greater than 50% of the participants did not improve. Among those who improved, 9 participants reached levels of PTSD symptoms (22–40 total CAPS score) considered as mild. This finding reveals a major limitation of the prevalent use of group average responses in clinical trials, which does not discern responders from nonresponders. Reporting response heterogeneities and exploring their sources might lead to better targeting treatment intervention and cost-effective treatments.[9,10]

Identifying treatment responders remains a major challenge. In this work, for example, treatment outcome was not predicted by initial PTSD symptom severity and trauma type. Yet unexplored genetic and neurobiological features[11,12] might help in improving such predictions: Genetic polymorphisms of cytochrome P450 enzymes have been shown to influence the metabolism of escitalopram and other antidepressants,[13,14] and brain-derived neurotrophic factor levels were found to be associated with greater treatment response to escitalopram in veterans with PTSD.[2] Harnessing such information into predictive models requires further work.

Several limitations of this work are worth considering when interpreting its results. Being an open-label trial without a control group, our results cannot be definitely attributed to the treatment provided. The study's small sample did not allow a thorough investigation of uncommon or rare adverse effects related to higher doses. Because participants were reassessed only at 3 months, the study does not allow an intent-to-treat analysis. While the sample was all civilians and quite homogeneous in baseline symptom levels, there were variations in previous treatment that preclude a reliable statement about the effect of increasing the dose of escitalopram. Finally, the study has not revealed specific predictors of improvements, and as such, the sources of better responding remain a future challenge. The study nonetheless shows a potential benefit of high-dose escitalopram in a subset of treatment candidates along with satisfactory tolerability and adherence. It stresses the importance of investigating the mechanisms underlying heterogeneous treatment response.

AUTHOR DISCLOSURE INFORMATION

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