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Secondary prevention of chronic PTSD by early and short administration of esitalopram: a prospective randomized controlled double blind trial

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*Running title: PTSD prevention with SSRI*
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Abstract

Objective. Prospective studies have not identified a viable pharmacological strategy for secondary prevention of posttraumatic stress disorder (PTSD). We examined whether preventive intervention via early and short-term administration of a selective-serotonin reuptake inhibitor (SSRI), within one month of exposure to a traumatic event (before diagnosis of PTSD could be made), may reduce the severity of PTSD symptoms according to DSM-IV at 13-months follow-up.

Method. Over 25,000 screening calls performed between June 2006 and December 2008 yielded 353 participants who were recruited within the month following traumatic event (before diagnosis of PTSD could be made). Participants were randomly enrolled in a double-blind design to escitalopram (n=176) or placebo (n=177). The per-protocol analysis comprised 198 participants (escitalopram, n=102; placebo, n=96) who received treatment for 12 to 24 weeks and were available for follow-up at week 56.

Results. The primary outcome measure, the Clinician Administered PTSD Scale (CAPS) revealed no prevention effect. However, a secondary outcome, Pittsburg Sleep Quality Inventory (PSQI) showed better results for the SSRI group than the placebo. For a sub-set of participants who experienced intentional trauma (missile attacks, rape, and physical assault, n=50) the prevention effect was found on both primary and secondary measures (CAPS, sleep quality, depression, and global severity).

Conclusions. Early and short-term administration of escitalopram was not shown to prevent PTSD, although it did improve sleep quality. In a sub-group of participants who experienced intentional trauma, this approach may be effective as secondary prevention. This is the first large study to investigate the preventive effect of early administration of escitalopram on
PTSD. It highlights the relevance of the type of trauma (intentional versus unintentional) to the outcome.

**Trial Registration:** ClinicalTrials.gov identifier: NCT00300313.

**Introduction**

Posttraumatic stress disorder (PTSD) is a debilitating condition that affects 10-20% of those who are exposed to a traumatic event\(^1\). Due to its chronic and disabling course, PTSD is highly detrimental to the quality of life and productivity of those afflicted and their families\(^2\). Unlike most psychiatric disorders, PTSD is typically triggered by a remarkable event. This affords a "window of opportunity" for secondary prevention, comparable to the window of opportunity available in the "golden hours" for conditions such as ischemic stroke and myocardial infarction\(^3\).

Researchers have studied treatment of PTSD using psychological approaches such as debriefing, modified prolonged exposure (PE)\(^4,5\), and cognitive therapy (CT)\(^4\). Debriefing may be beneficial for some patients\(^6\), yet may actually *increase* the likelihood of developing PTSD for others, such as for individuals with high anxiety levels\(^7\). More focus and support are currently apportioned to PE and CT\(^4,5\).

Pharmacological treatment protocols to prevent PTSD have generally not been successful. In some cases, the use of Benzodiazepine has been found to be associated with an increased prevalence of PTSD, both in humans\(^8\) and in an animal model\(^9\). While an earlier pilot study supported the beneficial role of early propranolol administration in preventing PTSD\(^10\), a later placebo controlled trial\(^11\) failed to demonstrate a significant treatment effect. Some evidence based on a retrospective case review study suggest that morphine during early resuscitation and trauma care of US soldiers was significantly associated with a lower risk of PTSD after injury\(^12\). In a small retrospective study, the dose of morphine was found to
positively correlate with the amount of change in PTSD symptoms from admission to 6-months follow-up, among children with burns\textsuperscript{12A}. Naturalist studies\textsuperscript{13-15} and a small pilot study\textsuperscript{16} suggest preventive effects of hydrocortisone.

PTSD has been linked to the hippocampus\textsuperscript{17}. Selective serotonin reuptake inhibitors (SSRIs) stimulate hippocampal neurogenesis\textsuperscript{18}. Indeed, early administration (1 day after exposure) of the SSRI sertraline, was associated with a significant decrease in PTSD-like behavior (extreme behavioral response [EBR]) in rats\textsuperscript{19}. Based on this finding, a pilot retrospective study\textsuperscript{20} examined whether early administration of sertraline (one to three months after an earthquake) would change the trajectory of PTSD in a group of 56 survivors. In that study those who received sertraline exhibited fewer signs and symptoms of PTSD at six to nine months follow up, than did those who were not treated. However, two small studies that compared patients who received escitalopram versus placebo (n=19 and 17 in one study and n=12 and 17 in the second, respectively) showed no benefit of escitalopram at the nine-month or 13-month follow up\textsuperscript{5,21}.

The current randomized, double-blind, placebo-controlled trial was designed to examine, in a sufficiently powered study, whether early SSRI administration (within the first month after a traumatic event) would result, at 13-months follow-up, in reduced severity of PTSD symptoms. Being a secondary prevention study, the effect size that are expected are different (smaller) from treatment studies\textsuperscript{21A}. 
Methods

Study design and participants

Over 25,000 recruiting phone calls were made between June 2006 and December 2008 to individuals who were either self-referred or referred by medical personnel to a hospital emergency department (ED), in one of five medical centers in Israel or one medical center in Cape Town, South Africa (Figure 1). A total of 353 participants from five medical centers distributed across Israel, and one center in South Africa were recruited (333 from Israel and 20 from South Africa). Enrolled participants were randomized to treatment and placebo arms.

The local Internal Review Board (IRB) of each participating medical center approved the study. Telephone screening for study eligibility was conducted after individuals gave oral consent to answer a few questions regarding their state following admission to the ED. During the screening visit, all persons who were recruited to the study signed written informed consent. The study was registered at ClinicalTrials.gov (identifier: NCT000123456)

Inclusion criteria required that participants had undergone a traumatic event within the month prior to enrollment (before diagnosis of PTSD could be made), were between the ages of 18 and 65, and met at least two DSM-IV criteria for acute stress disorder (ASD), namely re-experiencing and hyper-arousal. Study exclusion criteria were serious injury (Abbreviated Injury Scale ≥ 3)\textsuperscript{22}; a diagnosis of bipolar disorder, schizophrenia, or personality disorder; a history of alcohol or drug abuse, mental retardation, or dementia; having significant suicide risk or a past serious suicide attempt, as evaluated by the Mini International Neuropsychiatric Interview (MINI)\textsuperscript{23}; the intake of psychiatric medications, such as medications for depression, psychosis, or relapse prevention (mood stabilizers); participation in psychotherapy; electroconvulsive treatment (ECT) within the previous year;
sensitivity to citalopram or escitalopram; any major physical illness; being pregnant or lactating; and being of childbearing age and not using contraceptives.

**Randomization and masking**

Participants who met study criteria were assigned to either escitalopram or placebo in a randomized, double-blind procedure. The randomization was conducted by Trialog Clinical Trials, Ltd., an independent company that was not involved in the study except for the randomization procedure. Each center received the medications (escitalopram and placebo) directly from Trialog, with participant numbers marked on them.

**Procedure**

The study was divided into two phases: a short treatment phase (12 to 24 weeks, starting within the first 30 days following the traumatic event) and a long no-treatment follow-up phase, which ended 13 months after the event (at week 56). Week 56 (13 months) was chosen in order to avoid effects stemming from the first year anniversary of the traumatic event. Participants received their first medication within the first 30 days following the traumatic event. During the first four weeks of treatment, participants were instructed to take one daily capsule of 10 mg escitalopram or placebo, and were titrated gradually up to 20 mg. After four weeks of drug adjustment, all participants received the maximal dosage (20 mg) for up to 24 weeks (but not less than 12 weeks). Medication intake and psychiatric status were monitored every two to four weeks by trained psychiatrists. No-treatment follow-up continued from completion of medication until week 56, about 13 months after the traumatic event. No additional trauma (that would fit criteria A of PTSD in DSM IV TR) was recorded for any of the participants during the study follow-up.
Outcome measures

The primary measure assessing PTSD prevention was the difference, from baseline to follow-up, in each participant’s score on the Clinician Administered PTSD Scale (CAPS)\textsuperscript{24}. The CAPS includes 17 interviewer-rated items that cover the core symptoms of PTSD according to the DSM-IV criteria, and rates the frequency and the intensity of the symptoms on a 5-point scale (0-4).

Secondary measures included the following: (a) a 17-item self-report PTSD Symptoms Scale (PSS-sr) that measures DSM-IV diagnostic criteria rated by frequency of occurrence\textsuperscript{25}; (b) the Pittsburgh Sleep Quality Index (PSQI)\textsuperscript{26}, which records sleep disturbances, sleep quality, and sleep duration and habits; (c) the ten-item Montgomery Asberg Depression Rating Scale (MADRS)\textsuperscript{27}, rated by clinicians; (d) the Clinical Global Impression Scales of Severity (CGI-S) and Improvement (CGI-I)\textsuperscript{28}, rated by clinicians; and (e) the self-reported Visual Analogue Scale for Depression (VAS-D) and Anxiety (VAS-A)\textsuperscript{29}.

The raters in the study were psychiatrists who were trained in attaining research measurements. Inter-rater reliability for the different scales was between 0.6 and 0.7. The data were monitored by a Research Management company to ensure that none of the information on the questionnaires was missing.

Statistical analysis

As per the protocol the study was designed to examine secondary prevention; specifically, to test the hypothesis that participants treated with escitalopram for 12 to 24 weeks would exhibit significantly less symptoms of PTSD at 56 weeks. A power analysis that was conducted prior to the study’s initiation, assuming a reduction of ~15 points in CAPS (SD=25 points), indicated that 100 participants would be needed to complete each study arm. The hypothesis was tested using ANCOVA to compare change from baseline to week 56 among
those treated for 12 to 24 weeks with placebo or active treatment, while controlling for baseline, age, sex, sociodemographic status (SES), and medical center. Effect size (Cohen’s d) was derived from Eta Square ($d = 2\frac{\eta^2}{\sqrt{1-\eta^2}}$). Analysis was first conducted on all types of trauma together (n=198). The course and outcome of PTSD among people who experience intentional trauma (such as a terror attack or physical or sexual assault) have been shown to differ from the course and outcome for persons who experience traumatic events that were unintended (such as car accidents and natural disasters)$^{30,31}$. A separate analysis included only individuals who experienced intentional trauma (n=50).

Safety data were collected for all persons who were randomized to one of the study arms, irrespective of the length of treatment or availability for follow-up.
Results

Participants who completed the study (i.e., the per-protocol sample, n=198) differed from those who did not (n=155), in sex distribution: 62.3% of the males were completers, compared to only 50.8% of the females (Odds Ratio 1.60, p=.029). No statistically significant differences (p<.16) were observed between the study arms regarding age, SES, marital status, CAPS score at baseline, or type of trauma (intentional or unintentional).

Background characteristics

Background characteristics at baseline for the escitalopram and placebo groups are presented in Table 1. No statistically significant differences were found between the groups in mean age, education, CAPS total score at baseline, and type of trauma. Regarding the latter, 74.7% of the entire cohort was in a car accident, while the rest were victims of intentional trauma such as terror attacks (Israel, n=5), missile attacks (Israel, n=26), physical assault including rape (Israel, n=8, South Africa, n=11). In the escitalopram group, there were significantly more males and slightly more individuals of lower SES, with near statistical significance (see Table 1). The intentional trauma group was marginally younger than the car accident group (mean 36.6 SD 12.43 vs. 40.2 SD 12.7, p=.08) and had a slightly lower proportion of females than males (40%, n=20/50 vs. 52%, n=77/148, p=.14). Notably, no differences were found in mean values of education, baseline CAPS score, and SES, between those who experienced intentional or unintentional trauma.

Treatment effect

Ninety-one percent (180/198) of the participants who completed the study underwent the full 24-weeks of treatment. The remaining 18 completers underwent at least 12 weeks of treatment. At the end of the treatment phase (12 to 24 weeks), no significant effect was
observed, of escitalopram compared to the placebo, on the outcome measures investigated: CAPS, PSS-sr, MADRS, PSQI, VAS anxiety and depression, CGI-I and CGI-S, in an analysis that included the entire sample, and in a sub-analysis of participants who experienced intentional trauma (Table 2).

Secondary prevention effect

Table 2 presents the mean differences of outcomes for the escitalopram and placebo groups at the end of the treatment phase and at the end of follow up. Of the 198 participants who completed follow-up, 102 (52%) were in the escitalopram and 96 (48%) in the placebo group. A significant prevention effect was observed on the PSQI (p=.009, ES=.39, Figure 2a). Although there were no statistically significant effects for CAPS, PSS-sr, MADRS, VAS anxiety and depression, CGI-I and CGI-S, modest effect sizes were found for the CAPS, PSS-sr, CGI-I and CGI-S (between .20 and .28) (Table 2). An 11% difference favoring escitalopram over placebo emerged for a mean CAPS change from baseline to the end of follow-up (Figure 2b, Table 2). A separate analysis on sleep-related items revealed significant lower scores for the escitalopram than the placebo group at the end of the follow-up phase. These results were obtained in items related to sleep from the CAPS (item 13, F=3.367, p=.046) and PSS (item 13, F=3.351, p=.042), but not at the MADRS (item 4, F=1.553, p=.107), and not in items related specifically to dreams (CAPS, item 2, F=1.414, p=.118; PSS-sr, item 2, F=1.369, p=.121; PSQI, item 5.8, F=.389, p=.733)

Among participants who had experienced intentional trauma (escitalopram, n=24; placebo, n=26), prevention effects with noteworthy effect size were found on the CAPS (ES=.58, p=.09, Figure 2b), PSS-sr (ES=.78, p=.10), PSQI (ES=.59, p=.08, Figure 2a), MADRS (ES=.73, p=.03), and CGI-S (ES=1.12, p=.02) (Table 2).
Table 3 presents adverse event data for all participants who were randomized to a study arm. The 20 mg dose of escitalopram for up to 24 weeks was well tolerated. In fact, there were no differences in the total number of serious adverse events (SAE) between the escitalopram and the placebo arms (nine in each).
Discussion

This double-blind placebo-controlled, random-assignment, study showed that early, short-term administration of SSRI: 1) did not prevent PTSD in a general sample of individuals who experienced different types of trauma; 2) may be effective as secondary prevention for quality of sleep; and 3) a decrease with noteworthy effect size in PTSD severity, in a subgroup of participants, namely, those who experienced intentional trauma.

This is the first study to test the secondary prevention effect of SSRI in a large sample. In smaller studies, an effect of SSRI vs. placebo in preventing PTSD was not found\textsuperscript{5,21}. Interestingly, the difference in CAPS score between the treatment and placebo groups found in the present study, is the same as shown in a previous study\textsuperscript{5}; an 11\% difference between escitalopram and placebo groups at 6 to 9 months follow-up.

During the study period (2006 to 2008), the catchment area of two of the participating Israeli centers was exposed to missile attacks (the Second Lebanon War, and Operation Cast Lead). This afforded the opportunity to analyze separately the effects of missile attacks together with other intentional traumas such as physical assault and rape. Previous studies suggested that the course and outcome of PTSD among individuals who experienced intentional trauma is different and more severe than among people who experienced any type of trauma\textsuperscript{30,31}. In the current study, individuals who experienced intentional trauma exhibited greater benefit from the intervention than did those who experienced any trauma. Lange and colleagues\textsuperscript{32} also reported different responses to an intervention based on the type of trauma (intentional vs. non-intentional). Hence, the type of trauma should be considered when establishing protocols for early intervention.

Previous prevention studies did not assess the effect of early administration of SSRI on sleep quality, a prominent symptom of PTSD. In the current study, examining sleep quality, another benefit emerged; the escitalopram treated group scored significantly better
than the placebo group on PSQI. This effect probably reflects alteration in the development of the disorder, rather than a direct effect of escitalopram on sleep quality, as it was measured 6-9 months after escitalopram had been stopped. This effect was specific to sleep quality, as was observed in the relevant items of the two PTSD questionnaires (CAPS and PSS). This finding lends further support to the secondary prevention effect of early administration of escitalopram on sleep. However, not a specific change in nightmare was found in this sub-set of participants. This effect should be taken into consideration when assessing the effect of early intervention on PTSD.

The findings for the entire cohort raise the question of whether an 11% (ES=.20) difference in CAPS is of clinical significance. The authors debated this issue. The effect sizes that are usually employed in secondary prevention are quite small; for example, vaccines are administered to millions in order to prevent infection of thousands, and serious complications in hundreds. Along this line, the effect size observed in the current study (0.20) should be compared to the effect size of secondary prevention, and not to the effect size of a treatment. Also, the design of the study, namely the assessment of the long-term effect of SSRI intake starting during the first month post-exposure, and for 3 to 6 months, raises issues regarding the administration of treatment for a disorder before it materializes. In such a situation, the therapeutic effect needs to be superior to spontaneous recovery (the time effect). Moreover, since the primary outcome measure – CAPS at 13 months post-trauma – was assessed at 6 to 9 months after the intervention was stopped, the secondary prevention effect does not appear to be a carry-over of the treatment.

Considering the above, the authors submit that the criteria for employing secondary prevention might be different from those used for treatment, and should attempt to balance potential harm with potential benefit. Criteria to be considered in determining secondary
treatment (in this case, short-term administration of SSRI) include: a) the clinical effect; b) risk and discomfort; and c) the available options:

a. *The clinical effect*: a significant clinical effect on quality of sleep (which is a major complaint of PTSD patients), together with some improvement of PTSD symptoms (a reduction of 11% in CAPS, ES=.2).

b. *Risk and discomfort*: The risk and discomfort of taking 20 mg of escitalopram for three to six months are fairly low. In terms of SAE, they were minimal.

c. *Available options*: No known pharmacological options have been found to be effective as secondary PTSD prevention. Psychological techniques were found to be effective\(^7,8\); however, differences in methodological research strategies (defining the placebo group, blinding of the therapies, etc.) hamper comparison to the findings in the present study. Moreover, some of the treatments that are often given for PTSD (i.e., debriefing and benzodiazepines) may interfere with the normal potent recovery process, while early intervention with escitalopram does not interfere, and promotes sleep quality along with some improvement.

The current study was not without limitations. Among those who were eligible for the study, 45% declined treatment. This number is in line with a previous study that reported a 42.6% refusal rate to pharmacotherapy, and is typical of recruiting from the general population\(^8\).

Fifty-six percent of the participants who enrolled in the study completed the protocol. Most of those who did not complete the study were lost to follow-up (49%). This high dropout rate might be expected for a population who did not have any diagnosed disorder for which they would sense improvement with time. Vaccination studies report on increase in dropout rates according to the number of follow-up sessions that are required by the study protocol (e.g., 32.36% - 89.12% for 4 – 6 sessions\(^{32A,32B}\)). Therefore, the dropout rate in the current study
(19 sessions) can be expected. In addition, when considering the present study results, one should bear in mind that the study was carried out on participants that were exposed to a single and discrete event. Therefore the results are relevant for these type of events. Secondary prevention for other types of PTSD, including repetitive and continuous traumas, should be studied.

**Conclusions**

Early administration of escitalopram (before diagnosis of PTSD could be given, i.e. in the first month following a traumatic event) have three important implications: 1) it does not prevent PTSD but slightly decreases its severity; 2) it is associated with better quality of sleep; and 3) for a sub-group of PTSD patients (i.e., individuals exposed to intentional trauma), it may be beneficial. The potential clinical utility of this approach needs to take into account the relatively few side effects of short term administration of escitalopram and other frequently used options (e.g., benzodiazepines and debriefing).
References


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Potential conflicts of interest

Joseph Zohar and Leah Fostick design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Joseph Zohar has received grant/research support from Lundbeck, Servier and Pfizer, has served as a consultant or on advisory boards for Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca and Roche, and has served on speakers’ bureaus for Lundbeck, Roche, and Abbott.

Leah Fostick has no financial interests or other conflicts to disclose.

Alzbeta Juven-Wetzler has served on speakers’ bureaus for Pfizer.

Zeev Kaplan has no financial interests or other conflicts to disclose.

Hadar Shalev has served on speakers’ bureaus for Elli Lilly and Unifarm between 2008-2011

Gavriel Schreiber has no financial interests or other conflicts to disclose.

Natalie Miroshnik has no financial interests or other conflicts to disclose.

Arieh Shalev has no financial interests or other conflicts to disclose.

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Sharain Suliman MRC Anxiety Disorders Unit, Department of Psychiatry, Stellenbosch University. I have received research grants from: the Stellenbosch University Faculty of Health Sciences, Hendrik Vrouwes Research Scholarship, and South African National Research Foundation (Thuthuka).

Ehud Klein has no financial interests or other conflicts to disclose.
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<th>Placebo (n=96)</th>
<th>( t_{(196)} = 0.22, \ p = 0.82 )</th>
<th>( \chi^2_{(1)} = 5.14, \ p = 0.023 )</th>
<th>( \chi^2_{(3)} = 1.99, \ p = 0.37 )</th>
<th>( \chi^2_{(2)} = 5.11, \ p = 0.08 )</th>
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<td></td>
</tr>
<tr>
<td>Religiosity</td>
<td></td>
<td></td>
<td>( \chi^2_{(2)} = 1.23, \ p = 0.54 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observant</td>
<td>18 (18.8%)</td>
<td>19 (21.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partially observant</td>
<td>26 (27.1%)</td>
<td>28 (32.2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-observant</td>
<td>52 (54.2%)</td>
<td>40 (46.0%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event type</td>
<td></td>
<td></td>
<td>( \chi^2_{(1)} = 0.33, \ p = 0.56 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intentional</td>
<td>78 (76.5%)</td>
<td>70 (72.9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintentional</td>
<td>24 (23.5%)</td>
<td>26 (27.1%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPS total score</td>
<td>71.9 (22.1)</td>
<td>72.8 (21.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2 Mean (standard error) differences in outcome measures between the medication and placebo groups (ANCOVA), for treatment and prevention effects.

<table>
<thead>
<tr>
<th></th>
<th>Treatment effect</th>
<th>Prevention effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any trauma³</td>
<td>Intentional trauma⁴</td>
</tr>
<tr>
<td>CAPS</td>
<td>2.21 (4.02),</td>
<td>9.51 (7.03),</td>
</tr>
<tr>
<td></td>
<td>p=.58; ES=.09</td>
<td>p=.19; ES=.50</td>
</tr>
<tr>
<td>PSS-sr</td>
<td>.71 (1.94),</td>
<td>4.62 (4.22),</td>
</tr>
<tr>
<td></td>
<td>p=.71; ES=.06</td>
<td>p=.40; ES=.42</td>
</tr>
<tr>
<td>PSQI</td>
<td>.81 (7.6),</td>
<td>.28 (1.38), p=.84;</td>
</tr>
<tr>
<td></td>
<td>p=.29; ES=.18</td>
<td>ES=.06</td>
</tr>
<tr>
<td>MADRS</td>
<td>.64 (1.52),</td>
<td>3.41 (2.35),</td>
</tr>
<tr>
<td></td>
<td>p=.67; ES=.06</td>
<td>p=.16; ES=.53</td>
</tr>
<tr>
<td>VAS depression</td>
<td>.10 (.46), p=.82;</td>
<td>.55 (.83),</td>
</tr>
<tr>
<td>VAS anxiety</td>
<td>.22 (.47), p=.64;</td>
<td>.84 (.92),</td>
</tr>
<tr>
<td>CGI-I</td>
<td>.17 (.19), p=.37;</td>
<td>.52 (.46),</td>
</tr>
<tr>
<td></td>
<td>ES=.14</td>
<td>p=.27; ES=.41</td>
</tr>
<tr>
<td>CGI-S</td>
<td>-.02 (.21),</td>
<td>.68 (.34),</td>
</tr>
<tr>
<td></td>
<td>p=.91; ES=.01</td>
<td>p=.06; ES=.76</td>
</tr>
</tbody>
</table>

ANCOVA tested for escitalopram vs. placebo, controlling for baseline, gender, medical center, sociodemographic status (SES), and age.

Note: CGI-I rescored to 7 Very much improved; 1 Very much worse. CGI-S and VAS increase from least to most severe.

¹24 weeks for 91% (n=180) of participants, 12-23 for the others (n=18)
²Week 56.

³Data was analyzed for participants who experienced any trauma
⁴Data was analyzed for the subgroup of participants that experienced intentional trauma

Abbreviations.
CAPS=Clinician Administered PTSD Scale; CGI-I= Clinical Global Impression Scales of Improvement; CGI-S=Clinical Global Impression Scales of Severity; ES=effect size
MADRS=Montgomery Asberg Depression Rating Scale; PSQI=Pittsburgh Sleep Quality Index; PSS-sr=PTSD Symptoms Scale- self-report; VAS=Visual Analogue Scale
Table 3 Serious Adverse Events: Number of participants with each event (duplicate events per patient were not counted)

<table>
<thead>
<tr>
<th>Event</th>
<th>Active (n=176)</th>
<th>Placebo (n=178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal bleeding</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Crohn's Disease</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fracture hand and finger (amputation of finger-tip)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Inflammatory pelvic disease</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Menometrorrhagia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infraction</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Nephrolithiasis Bilateral</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Perianal abscess superficial invasion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9</strong></td>
<td><strong>9</strong></td>
</tr>
</tbody>
</table>

Note: No patient had more than one serious event.
Figure 1. CONSORT diagram of the recruitment process
Figure 2. Mean changes from baseline (ANCOVA) for escitalopram and placebo groups at the end of follow-up (prevention effect) for participants who experienced any type of trauma (n=198) and participants who experienced intentional trauma (n=50), for (a) PSQI and (b) CAPS.