Fluoxetine as a treatment for post-traumatic stress disorder

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ABSTRACT

الأهداف: تقييم مدى فعالية عقار الفلوكسيتين في علاج اضطرابات ما بعد الصدمة النفسية لدى البالغين.

الطريقة: أُجريت هذه الدراسة التحليلية لمجموعة من التحاليل الإحصائية في مستشفى الصين الغربي، شينغدو، الصين خلال الفترة من أبريل 2008م إلى ديسمبر 2010م، حيث قمنا بتحليل كافة التجارب السريرية المعشاة التي قامت بدراسة عقار الفلوكسيتين ومدى فعاليته في علاج اضطرابات ما بعد الصدمة. لقد جمعنا هذه التجارب التي أُدخلت حتى سبتمبر 2010م في قواعد البيانات التالية: ميدلاين، إيبسكو، إيمبيس، إلسيفير. ومن ثم تمت معاينتها من قبل متخصصين من أجل تقييم معايير الدخول في الدراسة، والبيانات التي تم جمعها، ومدى جودة التجربة، وهكذا فقد شملت الدراسة 7 تجارب سريرية معشاة من أجل التقصي عن فعالية عقار الفلوكسيتين في علاج اضطرابات ما بعد الصدمة.

النتائج: أظهرت نتائج التحاليل التي كانت عالية من الناحية الإحصائية في كافة التجارب السريرية المعشاة التي تضمنتها الدراسة احتمال فعالية عقار الفلوكسيتين في علاج اضطرابات ما بعد الصدمة النفسية (الاستجابة: الخطر النسبي= 1.21، 95% مدى الأمان الإحصائي: 1.43–1.03، ومؤشر مقياس دافيدسون للصدمات النفسية: متوسط الفروق الموزونة= 7.73–، 95% مدى الأمان الإحصائي: 3.76–11.69–). بالإضافة إلى ذلك فقد ظهرت بعض الآثار الجانبية الخفيفة التي تسبب بها العقار بين المرضى المصابين باضطرابات ما بعد الصدمة النفسية.

خاتمة: اقترحت نتائج الدراسة الجامعة احتمالية فعالية عقار الفلوكسيتين في علاج اضطرابات ما بعد الصدمة النفسية، مع احتمال تسببه ببعض الآثار الجانبية الخفيفة.

Objective: To assess the effectiveness of fluoxetine in the treatment of post-traumatic stress disorder (PTSD) in adults.

Methods: A meta-analysis was conducted between April 2008 and December 2010 at West China Hospital, Chengdu, China. Any randomized controlled trials (RCTs) in which fluoxetine were used for PTSD were considered through computerized databases up to September 2010 such as MEDLINE, EBSCO, EMBASE, and ELSEVIER. The RCTs were strictly assessed by investigators for inclusion in the study, collated trial data, and trial quality. The results of 7 RCTs included were combined in this meta-analysis to determine the effectiveness of fluoxetine on PTSD.

Results: Significant findings from the randomized and placebo-controlled trials suggest that fluoxetine could be an effective medication for PTSD (Respond: relative risk=1.21, 95% confidence interval [CI]: 1.03-1.43; Davidson Trauma Scale total score: weighted mean differences=-7.73, 95% CI: -11.69-3.76). In addition, fluoxetine can cause fairly mild adverse effects for those PTSD patients.

Conclusion: Findings suggest that fluoxetine is an effective treatment for PTSD, with mild adverse effects on individuals.

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Post-traumatic stress disorder (PTSD) has been regarded as a chronic disorder associated with exposure to traumatic events, and which has a high rate of lifetime prevalence at 8-9%.[1,2] This common disorder can be diagnosed with 3 major symptom clusters including re-experience, hyper arousal, and avoidance.[1] The most common treatment for PTSD is the selective serotonin reuptake inhibitors (SSRIs), which have been considered the first-line medication choice.[3] However, existing evidence fails to ensure the efficacy of various

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kinds of SSRIs in treating PTSD. Fluoxetine is one kind of SSRI that has been used widely in the treatment of different psychiatric disorders, but its effectiveness in treating PTSD remains questionable.[4] Existing studies conclude that both psychotherapy and SSRIs are effective in treating PTSD.[5-7] However, it is not clear whether fluoxetine can effectively reduce the symptoms of PTSD. In addition, it is shown that fluoxetine causes less severe adverse effects on serotonin reuptake in comparison with most of the other types of SSRIs.[8] However, it is also uncertain whether the adverse effects it causes in the treatment of PTSD are tolerable by individuals. The main purpose of the present study was to examine the effectiveness of fluoxetine in the treatment of PTSD in addition to the adverse effects that it could cause.

Methods. A meta-analysis was conducted between April 2008 and December 2010 in the West China Hospital, Chengdu, China in order to test the research hypotheses.

Identification of clinical trials. Any trial that used fluoxetine for treating PTSD patients and could be searched through the computerized databases up to September 2010 such as MEDLINE, EBSCO, EMBASE, and ELSEVIER was included. Trials that were published in any language were included. Additional trials were also searched in the reference lists of retrieved studies and other relevant review articles. All randomized controlled trials (RCTs) that used fluoxetine for the treatment of PTSD were included for further analysis. An RCT trial is a type of scientific experiment that involves the procedure of random allocation of different interventions (treatments or conditions) to subjects. One of the advantages of the randomization is that it helps to eliminate selection bias as well as to balance both the known and unknown prognostic factors in the assignment of treatments.[9] The RCTs from the search were independently evaluated for the involvement of 2 investigators, which were based on the information from a trial report formed earlier. Any disparities in assessment were resolved by discussion. Only studies performed on patients who met the threshold of the Diagnostic and Statistical Manual of Mental Disorders-III, III-R, or IV criteria for PTSD were included in our research. Analysis was also restricted to trials on adult participants while studies with children or the predominately elderly were excluded for the purpose of assessing the dosage levels of the adult patients.

Data extraction. The effectiveness of fluoxetine was measured by the improvement of symptoms and the number of responders in treatment, and these data was collected from the included studies. The levels of symptom severity was assessed by the Davidson Trauma Scale (DTS) as versus the Clinician Administered PTSD Scale (CAPS), which has not been widely used in the literature included in the present study.[10,11] The effectiveness of treatment was assessed by the Treatment Oriented PTSD Scale (TOP-8), the Clinical Global Impression of Severity Scale (CGI Severity), and the Duke Global Rating for PTSD Scale (Duke).[12-14] Effective treatment in the present study was defined by 4 outcomes including TOP-8 decrease >50%, CGI = 1 or 2, patients no longer meeting DSM-IV PTSD criteria, and Duke=1 or 2. Martenyi et al[15] used 2 different dosages of fluoxetine, and the study was divided into 2 parts when assessing PTSD symptoms and adverse effects of fluoxetine. The adverse effects were measured by the number of adverse events such as headache and nausea. Barnett et al[16] and van der Kolk et al[17] only provided information on the side effects of fluoxetine, and the effectiveness of the drug was not mentioned. We considered the methodological quality of the selected studies according to the recommendations of the Cochrane Collaboration Handbook.[18] We assessed the quality of trials including adequacy of sample size, allocation concealment, clear description of treatment, representative source of subjects, use of diagnostic criteria or clear specification of inclusion criteria, and either outcome measures described clearly, or use of validated instruments. We considered the study as poor quality when none of these components were mentioned in the research. Information included in trials was identified independently by 2 reviewers, while disagreements in assessment and collation were resolved by discussion.

Data synthesis. The software Review Manager (RevMan version 4.2) was used to analyze data collected in each trial. In addition, the weighted mean differences (WMDs) for continuous measures and the relative risks (RRs) for dichotomous outcomes were examined. Furthermore, the number of treatments required was also included in the data analysis procedure. The Q statistic was used to assess heterogeneity.[18] Instead of using standard deviation in trials, standard error was used for computation ($SD=SE^*\sqrt{N}$). The funnel plot analysis was used to detect publication bias. Two-sided *p*-values of less than 0.05 were regarded as statistically significant.

Results. *Description of studies included.* Seventy-three studies met the initial criteria, but only 7 articles[15-17,19-22] were included in the present study (**Figure 1**). There were totally 966 participants in these 7 studies, and their responses were assessed accordingly, as stated in **Table 1**. Only the adverse effects of fluoxetine were examined by Barnett et al[16] and van der Kolk et al[17] due to limited information.

Quality of studies included. The studies included in this review met the minimum quality criteria, which meant that they had at least one of the key components among methodological quality. All trials passed through funnel plot analysis, which was used to measure the effectiveness and adverse effects of fluoxetine for PTSD.

Improvement of fluoxetine as a treatment for PTSD. Findings obtained from the present study confirm fluoxetine to be more effective (**Figures 2 & 3**) by displaying higher responder status and less severe PTSD symptoms at trial endpoint than their counterparts in the placebo groups (Respond: RR=1.21, 95% CI: 1.03-1.43; DTS total score: WMD=-7.73, 95% CI: -11.69-3.76).

Adverse effect of fluoxetine as a treatment for PTSD. The adverse effects of fluoxetine were measured by the number of adverse events collected in trials (**Figure 4**). It is shown that fluoxetine might induce a greater number of side effects (RR=1.45, 95% CI: 1.22-1.74). However, this finding was not revealed in every adverse event. The RR of headache is 0.83 (95% CI: 0.83-1.58) suggesting that patients who receive fluoxetine do not display a greater number of symptoms such as headache than patients given placebo in addition to somnolence, rhinitis, and thirst. However, the RR for nausea is 1.57 (95% CI: 1.09-2.27) suggesting that nausea is more frequent in individuals after taking fluoxetine, as is the case also for diarrhea.

Discussion. The present study was intended to examine the effectiveness of fluoxetine in the treatment of PTSD in addition to the adverse effects that it

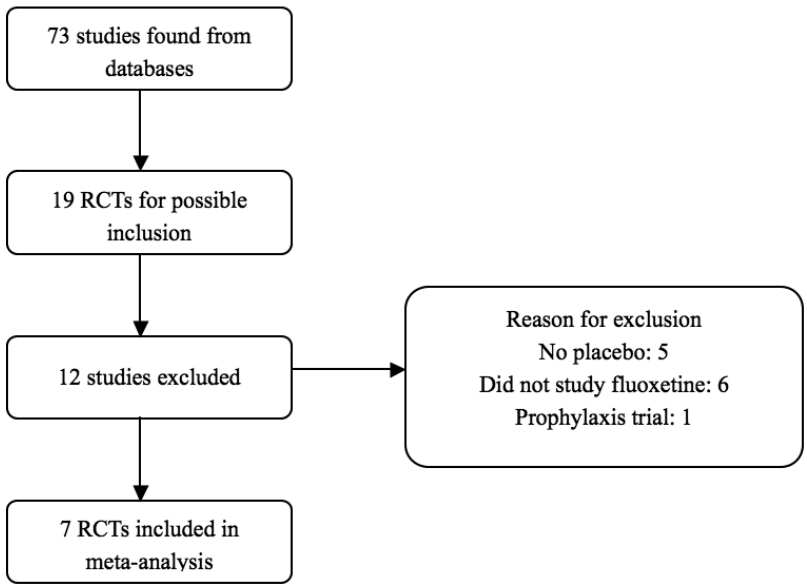

Figure 1 - Number of studies from the initial search.

Table 1 - Features of 7 randomized trials comparing fluoxetine with placebo for PTSD.

Study	Study period (weeks)	Sample size	Male ratio (%)	Dose (mg)	Outcome
Martenyi et al (2007)[15]	12	411	28.4	20, 40	TOP-8, CGI, DTS, CAPS
van der Kolk et al (2007)[19]	8	59	13.5	10-60	CAPS
Martenyi et al (2002)[20]	12	301	81.4	20-80	TOP-8, CGI, CAPS, DTS,
Barnett et al (2002)[16]	12	65	-	10-60	--
Hertzbelg et al (2000)[21]	12	12	100.0	10-60	DTS, SDS, SIP
Connor et al (1999)[22]	12	54	9.3	10-60	SIP, DTS, SDS, Duke
van der Kolk (1994)[17]	5	64	56.3	20-60	CAPS

PTSD - Post-traumatic stress disorder, TOP-8 - Treatment Oriented PTSD Scale, CGI - Clinical Global Impression of Severity Scale, DTS - Davidson Trauma Scale, CAPS - Clinician Administered PTSD Scale, SDS - Self-rating Depression Scale, SIP - Structured Interview for PTSD, Duke - Duke Global Rating for PTSD Scale

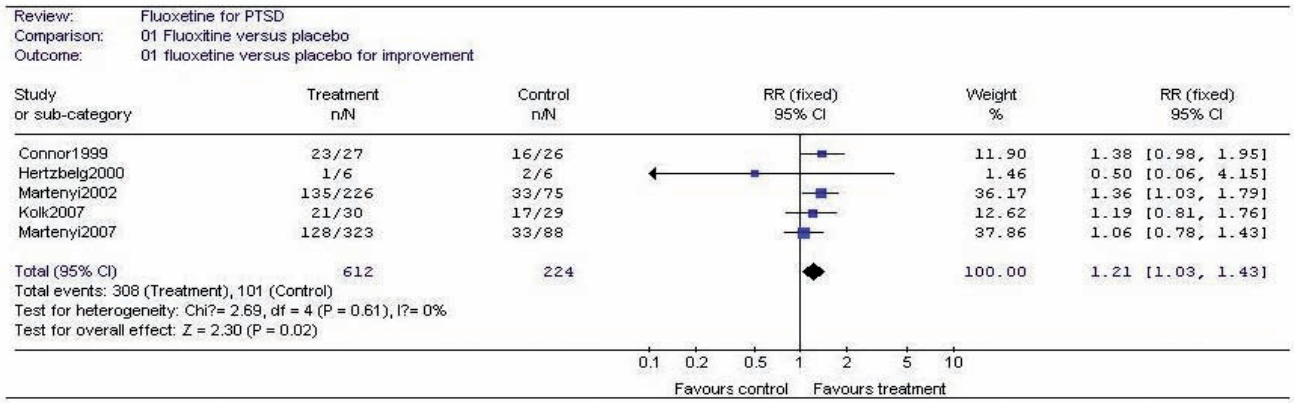

Figure 2 - Fluoxetine versus placebo for responder. PTSD - post-traumatic stress disorder

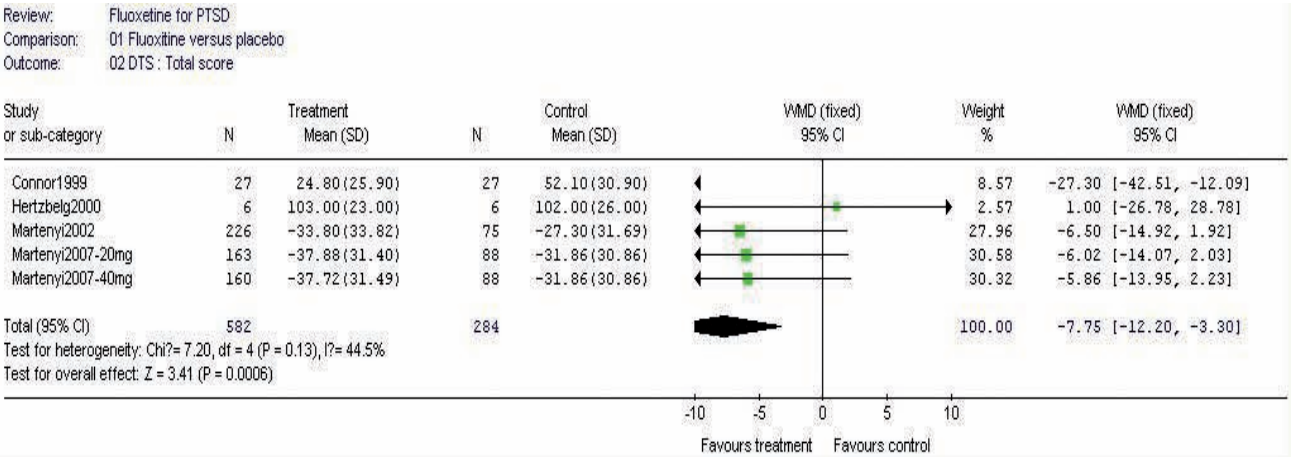

Figure 3 - Fluoxetine versus placebo for post-traumatic stress disorder symptom severity.

might cause. Findings suggest that fluoxetine can be an effective drug in treating PTSD in comparison with the placebo groups as evidenced by response to treatment and symptom severity levels. Although the adverse effects of fluoxetine are found to be more severe in participants from experimental groups than placebo groups, but not every adverse event is more frequent in experimental groups.

Evidence obtained in the present study confirms that fluoxetine can be effective in treating PTSD. Although the cause of PTSD is still unclear, the neurochemical abnormalities definitely have a crucial influence on developing the disorder. Most existing studies revealed that PTSD was affected by the levels of serotonin, catecholamine, and dopamine.[23-25] Fluoxetine is a selective inhibitor of neuronal serotonin reuptake, which could increase the synaptic levels of serotonin in order to facilitate serotonergic neurotransmission.[26] Furthermore, it is revealed that fluoxetine is not only effective for serotonin but also noradrenaline and dopamine, which could help to explain the complicated relationship between fluoxetine and its effect on PTSD.[26]

Findings revealed in the present study show that fluoxetine causes adverse effects, but not at significant levels. Fluoxetine is less effective on serotonin reuptake than most of the SSRIs.[8] As a result, it might cause less adverse effects on individuals such as somnolence, rhinitis, and thirst.

The present study has included most of the studies using a RCT design in examining the effectiveness of using fluoxetine for PTSD. However, there are several limitations to this research. First, the methods of assessing PTSD symptoms are varied in the present study, which might result in bias of assessment. It is suggested to use a unified measurement standard to evaluate PTSD symptoms in future studies. In addition, it would be beneficial to assess the effect of fluoxetine if the sample RCTs involved had more homogeneity in the sample groups. Several factors such as gender and the type of trauma could influence the treatment of PTSD.

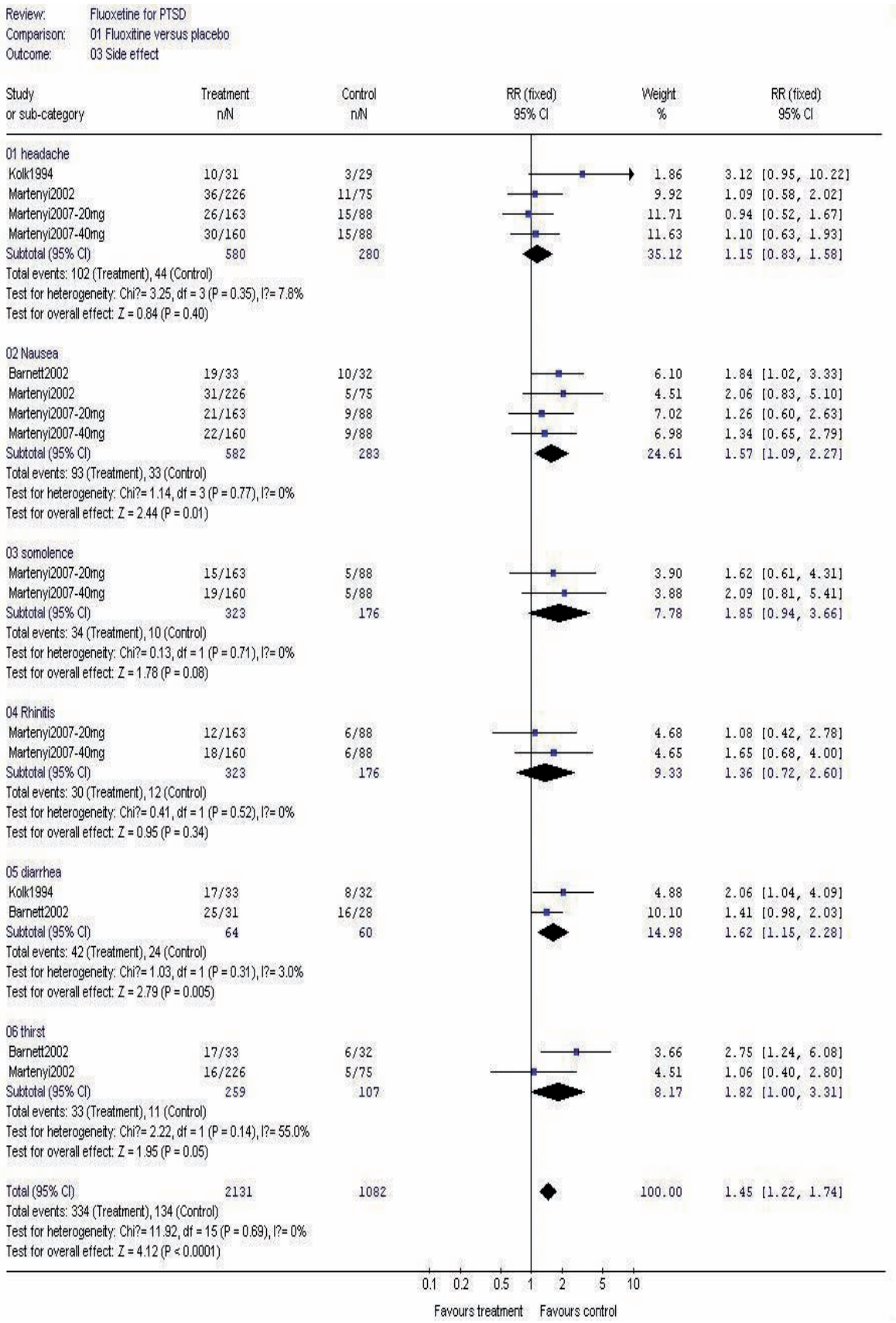

Figure 4 - Adverse effects of fluoxetine versus placebo for post-traumatic stress disorder symptom severity.

In conclusion, the findings of this study provide important information for the treatment of PTSD patients. This will be beneficial for planning more suitable treatment of PTSD in the future, as evidenced by the reduction of PTSD symptoms. In addition, fluoxetine causes mild levels of adverse effects. It is fair to conclude that fluoxetine should be considered as part of the treatment of PTSD, and more trials on the effectiveness of fluoxetine with large samples should be conducted in the future.

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