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Efficacy and tolerability of fluvoxamine in adults with social anxiety disorder

A meta-analysis

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Abstract

Background: No meta-analysis for estimating the comprehensive efficacy and tolerability of fluvoxamine in patients with social anxiety disorder (SAD) has been published.

Objective: To investigate the efficacy and tolerability of fluvoxamine in adults with SAD, trials meeting the following criteria were identified: population: ≥18 years of age with a diagnosis of SAD; intervention: fluvoxamine; study design: placebo-controlled randomized controlled trials (RCTs); outcomes: efficacy and tolerability outcomes.

Methods: We conducted a comprehensive search of PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and ClinicalTrials.gov for RCTs on January 3, 2018. Review Manager 5.3 and Stata Version 12.0 software were used for all statistical analyses. Mean differences (MDs) with 95% confidence intervals (CIs) were calculated for continuous variables, and odds ratios (ORs) with 95% CIs were calculated for dichotomous variables. Cochrane Collaboration's risk of bias tool was used to assess the likelihood of risk of bias. Efficacy was assessed by mean changes in the Liebowitz Social Anxiety scale (LSAS) total score and the Clinical Global Impression Severity of Illness (CGI-S) score as well as the response rate. Tolerability was mainly assessed by the discontinuation rate due to adverse events (AEs) and the incidence of most frequent treatment-emergent AEs (TEAEs).

Results: This meta-analysis included 5 RCTs. Mean changes in LSAS total and CGI-S scores were both significantly greater in patients treated with fluvoxamine than those treated with placebo (LSAS: MD = 11.90, 95% CI = 8.09–15.71, $P < .001$; CGI-S: MD = 0.52, 95% CI = 0.33–0.72, $P < .001$). Response rate was higher in fluvoxamine group as compared with placebo (OR = 1.71, 95% CI = 1.30–2.24, $P < .001$). Additionally, mean change in the Sheehan disability scale score was significantly greater in fluvoxamine group than placebo group (OR = 2.11, 95% CI = 1.03–3.18, $P < .001$). The discontinuation rate due to AEs was higher in patients that received fluvoxamine compared to those received placebo (OR = 5.99, 95% CI = 2.24–15.99, $P < .001$), as was the incidence of overall TEAEs (any AE) (OR = 2.66, 95% CI = 1.77–4.02, $P < .001$). However, the incidence of serious AEs was not significantly different between the 2 groups (OR = 0.99, 95% CI = 0.25–3.89, $P = .99$).

Conclusion: Fluvoxamine was found to be effective in adult patients with SAD, with acceptable tolerability.

Abbreviations: AE = adverse event, CENTRAL = Cochrane Central Register of Controlled Trials, CGI-I = Clinical Global Impression Improvement, CGI-S = Clinical Global Impression Severity of Illness, CI = confidence interval, DSM-III = Diagnosis and Statistical Manual of Mental Disorders, Third Edition, LSAS = Liebowitz Social Anxiety scale, MD = mean difference, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analyses, RCTs = randomized controlled trials, SAD = social anxiety disorder, SD = standard deviation, SE = standard error, SSRIs = selective serotonin reuptake inhibitors, TEAE = treatment-emergent adverse event.

Keywords: efficacy, fluvoxamine, meta-analysis, social anxiety disorder, tolerability

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1. Introduction

Social anxiety disorder (SAD) is one of the most common mental disorders, with a lifetime prevalence of 13% and a 12-month prevalence of 8% among adults.[1] The disorder has an early onset and is often chronic.[2] SAD is characterized by a persistent fear of social situations or performance activities in which the person is exposed to unfamiliar people.[3] As a result, individuals with SAD tend to show anxiety symptoms when facing social situations or possible scrutiny by others. In addition, SAD is associated with an increasing risk of comorbid mood disorders such as major depressive disorder, substance-use disorders, and avoidant personality disorder.[3,4]

Overall, available treatment options for SAD consist of pharmacologic and psychologic therapies. Pharmacotherapy is the mainstay of SAD treatment and mainly includes beta blockers, tricyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), pregabalin,[5] and venlafaxine.[6] In many countries, SSRIs are recommended as the first-line pharmacotherapy.[7]

Fluvoxamine, an SSRI, was initially confirmed to be effective for adults with SAD in 1994.[8] However, several subsequent randomized controlled trials (RCTs) investigating its efficacy and tolerability in patients with SAD have reported inconsistent results on tolerability or safety.[9,10] Moreover, there has been no meta-analysis of the efficacy and tolerability of fluvoxamine in SAD patients. Thus, to conduct such a meta-analysis, we systematically reviewed all RCTs exploring the use of fluvoxamine in adults with SAD.

2. Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) working group (See Reporting guidelines Checklist).[11] We followed the detailed methodology described in the protocol (See Appendix 1, Supplemental Content, which showed the study protocol, http://links.lww.com/MD/C340). All analyses were based on previous published studies, thus no ethical approval and patient consent was required.

2.1. Search strategy

Relevant studies were collected on January 3, 2018 from PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL) hosted by the Cochrane Library, and the registry of Clinical Trials (www.ClinicalTrials.gov). The search terms used were fluvoxamine OR faverin OR

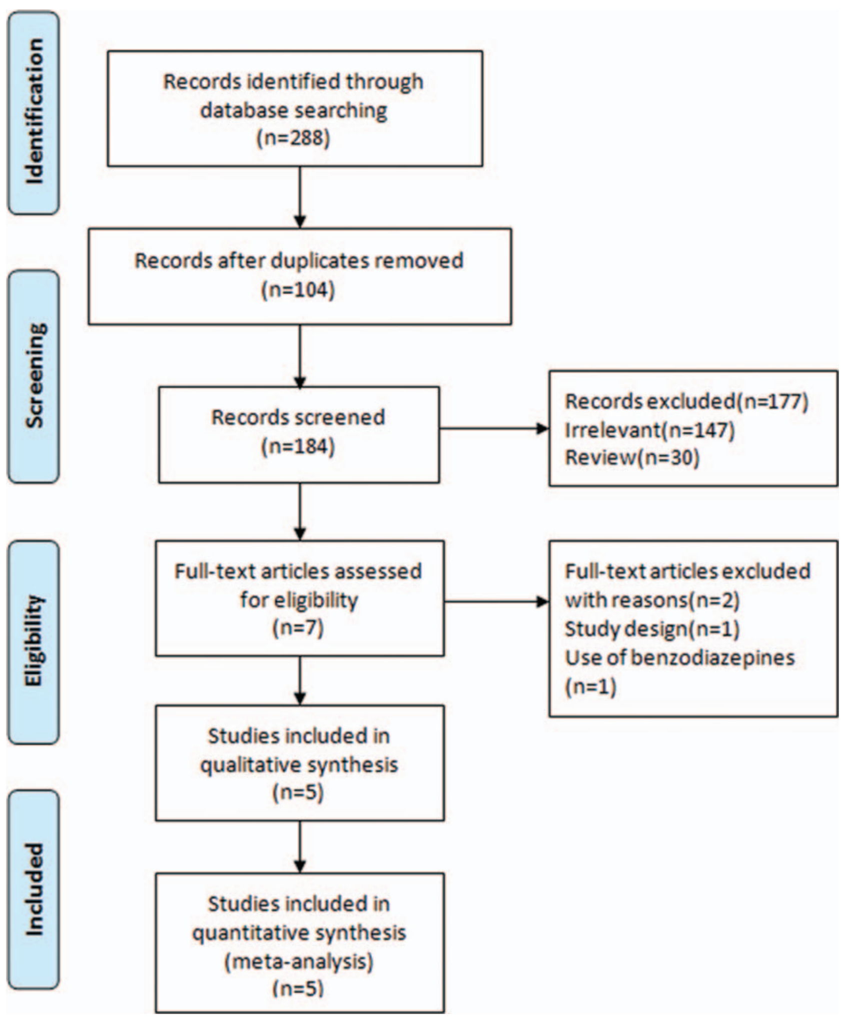

Figure 1. Flow diagram of study selection.

fevarin OR floxyfral OR luvox AND social anxiety disorder OR social anxiety OR social phobia OR SAD (See Appendix 2, Supplemental Content, which showed detailed search strategy, http://links.lww.com/MD/C340). Study types were restricted to RCTs. To avoid missing important studies, we contacted the first author of the included RCTs and further searched the reference lists of relevant articles.[12] An additional search was conducted on March 9, 2018, using the same search engines. There was no restriction on the language or date of publication.

2.2. Inclusion and exclusion criteria

Trials meeting the following inclusion criteria were selected: patients at least 18 years old meeting the criteria for GAD from the Diagnosis and Statistical Manual of Mental Disorders, Third Edition (DSM-III)[13] or later editions[14]; use of fluvoxamine or fluvoxamine XR plus antidepressants lasting ≥10 weeks; use of a placebo control; efficacy and tolerability data; and an RCT.

We excluded trials based on the following criteria: DSM-IV primary diagnosis of psychiatric disorders other than SAD (major depressive disorder, bipolar disorder, or other psychotic disorders) within the previous 6 months; use of any neuroleptic, antidepressants, or other psychotropic medications within 2 weeks of baseline (30 days for fluoxetine); history of alcohol or substance abuse within the past 6 months; patients at risk of suicide; previous treatment with fluvoxamine before randomization; patients who required cognitive behavioral therapy to treat social anxiety symptoms within the previous month; any clinically significant medical condition or required medications placing patients at risk for taking fluvoxamine; patients with clinically significant abnormal laboratory or electrocardiogram findings at baseline; and treatment outcomes not available.

2.3. Data extraction

Two authors (Xinyuan Li and Xue Liu) independently assessed the quality of the selected studies and extracted data using data extraction forms. Disagreements were resolved by consensus through a third author. The extracted data mainly included the first author's name, year of publication, age, sex distribution, number of enrolled participants, study design, intervention details, treatment duration, and efficacy measures.

2.4. Outcomes and definitions

For efficacy and tolerability analysis, the last-observation-carried-forward approach was applied. The primary efficacy outcomes were the mean changes in the Liebowitz Social Anxiety scale (LSAS) total score and the Clinical Global Impression Severity of Illness (CGI-S) score from baseline to endpoint. The key secondary efficacy outcome was the response rate, defined as very much improved (score = 1) or much improved (score = 2) on the Clinical Global Impression Improvement (CGI-I) scale.[15] With regard to tolerability analysis, the primary tolerability outcome was discontinuation rate due to AEs; the incidence of common treatment-emergent adverse events (TEAEs) as well as serious adverse events (SAEs) were assessed as the key secondary tolerability outcomes.

2.5. Quality assessment

Two authors (Xinyuan Li and Congxiao Zhang) independently assessed the risk of bias in the included studies, and disagreements were resolved by consensus through a third author. According to the Cochrane Collaboration's risk of bias tool,[16] the likelihood

Table 1

Characteristics of the included studies.

Study	Design	Sample size (N*)	Male/female (N*)	Diagnosis criteria	Treatment/control	Age, y (mean ± SD)	Fluvoxamine dose, mg/d	Duration, wk	Entry score	Baseline LSAS total score (mean ± SD)	Mean change in LSAS total score (mean ± SD)	Baseline CGI-S score (mean ± SD)	Response, %†	Location
Stein et al (1999)[20]	Double-blind	92	59/33	SAD, DSM-IV	Fluvoxamine/placebo	39.1 ± 11.2/39.7 ± 9.9	50–300	12	BSPS≥20	–	−22.0 ± 22.7/ −7.8 ± 19.4	–	42.9/22.7	USA
Stein et al (2003)[9]	Double-blind	109	58/51	GSAD, DSM-IV	Fluvoxamine/ placebo	36.3 ± 10.5/38.0 ± 11.6	100–300	24	LSAS≥60	98.2 ± 18.7/97.7 ± 16.7	−59.1 ± 29.9/ −49.5 ± 27.7	5.0 ± 0.7/4.7 ± 0.7	80.0/74.0	Europe, South Africa, and USA
Davidson et al (2004)[21]	Double-blind	279	179/100	GSAD, DSM-IV	Fluvoxamine CR/placebo	37.3 ± 11.8/37.2 ± 10.6	100–300	12	LSAS≥60	90.1 ± 17.7/89.4 ± 18.9	−26.7 ± 28.6/ −12.9 ± 18.0	4.6 ± 1.2/4.6 ± 1.2	33.9/16.7	USA
Westenberg et al (2004)[10]	Double-blind	300	143/157	GSAD, DSM-IV	Fluvoxamine CR/placebo	38.6 ± 11.0/37.3 ± 11.0	100–300	12	LSAS≥60	94.8 ± 18.3/94.8 ± 22.1	-36.1 ± 32.6/ −27.3 ± 29.2	4.8 ± 1.2/4.7 ± 1.2	48/44	Europe, South Africa, and USA
Asakura et al (2007)[22]	Double-blind	265	179/86	GSAD, DSM-IV	Fluvoxamine/ placebo	39.3 ± 11.0/37.9 ± 11.5	50–300	10	LSAS≥60	87.9 ± 18.2/87.0 ± 18.8	−29.3/−21.2	–	45.1/30.3	Japan

BSPS = Brief Social Phobia scale, CGI-I = Clinical Global Impression Improvement scale, CGI-S = Clinical Global Impressions Severity of Illness scale, CR = controlled release, LSAS = Liebowitz Social Anxiety scale, SD = standard deviation.

* Number treated.

† Response defined as very much improved (score = 1) or much improved (score = 2) of CGI-I.

of risk of bias included selection bias (random sequence generation, allocation concealment), detection bias (blinding of outcome assessors, participant/personnel), reporting bias (selective reporting), and attrition bias (incomplete outcome data).

2.6. Statistical analysis

Statistical analysis was performed using Review Manager 5.3 software provided by the Cochrane Collaboration (London, UK), and all analyses were conducted on intent-to-treat populations. The significance of the pooled estimates was determined by the Z statistic, and statistical significance was set at a 2-tailed $P<.05$.[17] Continuous data were analyzed using mean differences (MDs) with 95% confidence intervals (CIs). Therefore, the mean and standard deviation (SD) were calculated for each selected study.

Dichotomous data were analyzed using odds ratios (ORs) with corresponding 95% CIs. Study heterogeneity was evaluated using the I^2 statistic: a value of 0% indicated no heterogeneity, 50%

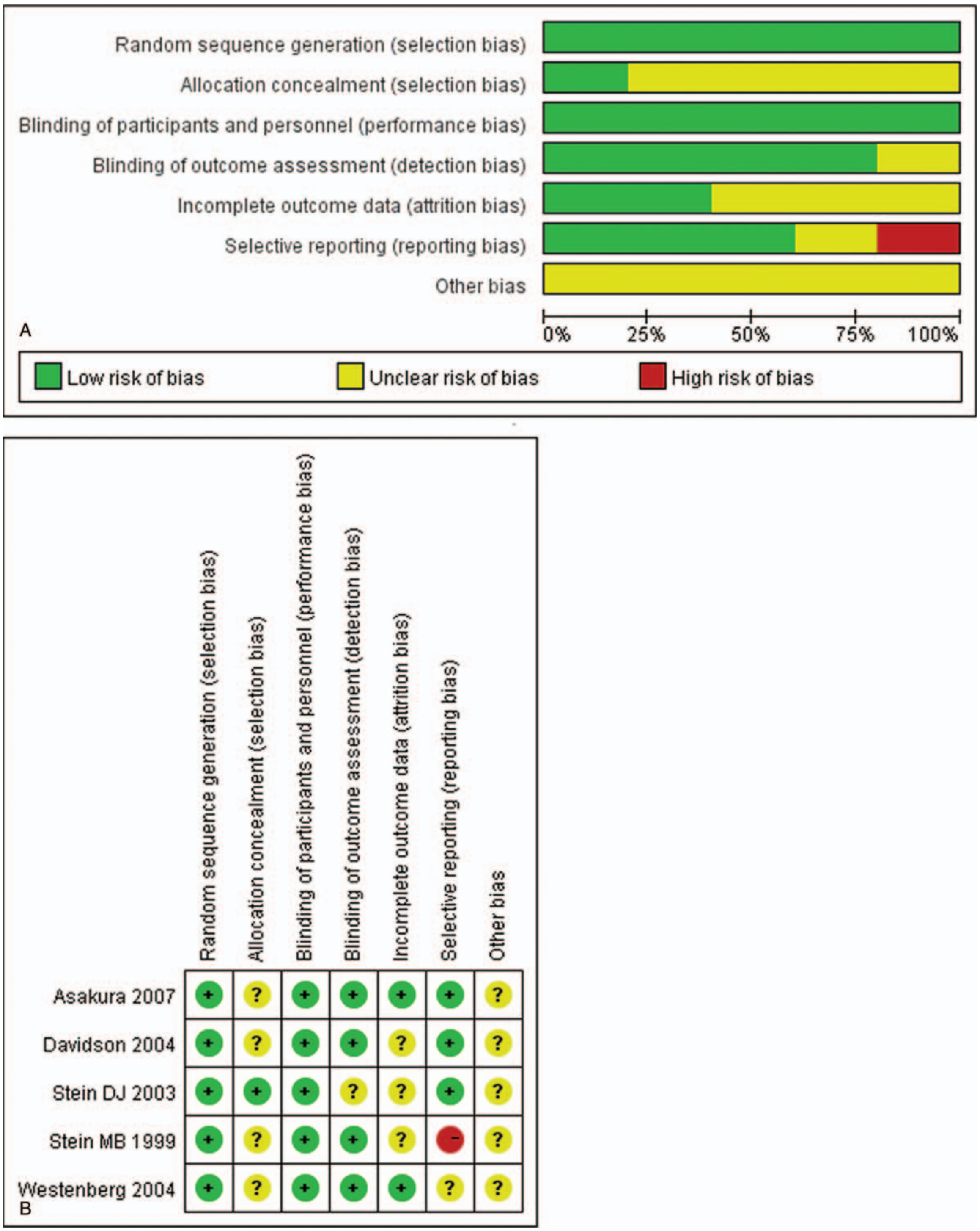

Figure 2. Risk of bias in the included studies.

indicated moderate heterogeneity, and 75% indicated high heterogeneity. In general, substantial heterogeneity was defined as $P<.05$ and $I^2 \geq 50\%$.[18] A random-effects model was used to pool data with substantial heterogeneity. Publication bias was assessed by a funnel plot and Egger test[19] using Stata Version 12.0 software. We also conducted sensitivity analyses to evaluate the stability of the main outcomes.

3. Results

3.1. Characteristics of the included studies

Our literature search (PubMed, Embase, Web of Science, CENTRAL) yielded a total of 288 articles. We excluded 147 irrelevant articles, 104 duplicates, and 30 reviews based on the title or abstract review, and 2 articles after full-text reading. Ultimately, 5 eligible articles (5 RCTs) were included in the analysis. The flowchart shown in Figure 1 depicted the detailed process of eligible article inclusion. In the comparison of duloxetine (541 patients) with placebo (460 patients), the meta-analysis included a combined sample of 1001 adults with SAD who fulfilled the eligibility criteria. All selected studies were conducted between 1999 and 2007; we summarize the main features of these 5 RCTs in Table 1. Three studies lasted 12 weeks, 1 lasted 10 weeks, and 1 lasted 24 weeks. There was no restriction regarding whether doses were fixed or flexible. Three studies included flexible doses of 100–300 mg/d, and 2 studies involved flexible doses of 50–300 mg/d.

3.2. Quality assessment

Figure 2 shows the authors' judgments according to the Cochrane Collaboration's risk of bias tool.

3.3. Publication bias

According to a funnel plot (Fig. 3) and the result of Egger test, there was no possibility of publication bias ($P=.984$).

3.4. Outcomes

3.4.1. Primary efficacy outcomes.

Mean change in LSAS total score was shown in Figure 4. Four studies[9,10,20,21] with a total of 736 patients were included in the analysis; 1 study[22] was excluded because it did not provide SD or standard error (SE). The baseline LSAS total score had no significant differences between fluvoxamine and placebo groups (MD = 0.53, 95% CI = −1.91 to 2.96, $P=.67$). The results revealed that patients with SAD that received fluvoxamine experienced a greater reduction than those received placebo (MD = 11.90, 95% CI = 8.09–15.71, $P<.001$) and there was no heterogeneity ($P=.67$, $I^2=0\%$). Severity of illness was measured by mean change in CGI-S, and the results were presented in Figure 4. Three studies[9,10,21] with a total of 650 patients were included in the analysis; 2 studies[20,22] were excluded due to lack of information. The baseline CGI-S did not significantly differ between fluvoxamine and placebo groups (MD = 0.14, 95% CI = −0.02 to 0.30, $P=.08$). Patients in fluvoxamine group had a significantly larger reduction than did those in placebo group (MD = 0.52, 95% CI = 0.33–0.72, $P<.001$) and there was no heterogeneity ($P=.81$, $I^2=0\%$).

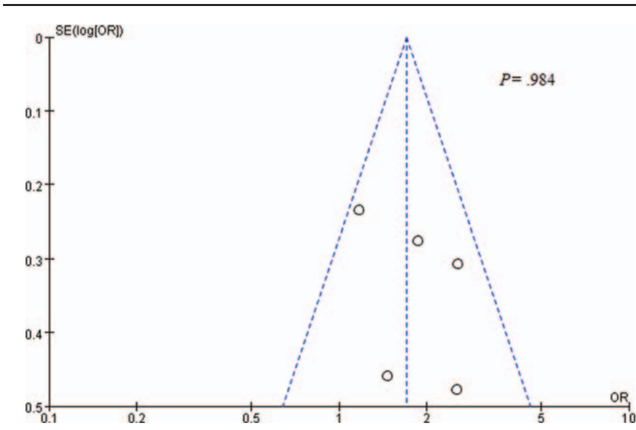

Figure 3. Funnel plot of publication bias. OR = odds ratio, SE = standard error.

3.4.2. Secondary efficacy outcomes.

Five studies[9,10,20–22] were included in the analysis of response rate, and the results showed a better response for patients treated with fluvoxamine than those treated with placebo (OR = 1.71, 95% CI = 1.30–2.24, $P<.001$); substantial heterogeneity was not identified ($P=.27$, $I^2=23\%$) (Fig. 5). In addition, psychosocial impairment was assessed by SDS total score, and the results from analysis of 4 studies[9,10,21,22] showed that the mean change from baseline to endpoint was significantly greater for patients treated with fluvoxamine than those treated with placebo (OR = 2.11, 95% CI = 1.03–3.18, $P<.001$). No heterogeneity was found ($P=.61$, $I^2=0\%$) (Fig. 5).

3.4.3. Primary tolerability outcome.

Four studies[9,10,20,21] reported discontinuation rate due to AEs, with a higher rate in fluvoxamine group than placebo group (OR = 5.99, 95% CI = 2.24–15.99, $P<.001$) (Fig. 6). Heterogeneity was identified ($P=.09$, $I^2=54\%$), and a random-effects model was used.

3.4.4. Secondary tolerability outcomes.

Three studies[9,10,22] reported overall TEAEs (any AE), and the incidence was higher in fluvoxamine group than placebo group (OR = 2.66, 95% CI = 1.77–4.02, $P<.001$). However, the incidence of SAEs was not significantly different between the 2 groups (OR = 0.99, 95% CI = 0.25–3.89, $P=.99$) (Fig. 6). The most frequently reported TEAEs mainly included nausea, somnolence, insomnia, headache, and abnormal ejaculation. The incidence of nausea, somnolence, insomnia, and abnormal ejaculation was all significantly higher in patients treated with fluvoxamine than those treated with placebo (Table 2). Interestingly, the incidence of headache was not significantly different between 2 groups (OR = 1.29, 95% CI = 0.93–1.79, $P=.13$). In addition to TEAEs, 3 studies reported weight variation. However, there was no significant difference between fluvoxamine and placebo groups with respect to markedly abnormal changes in body weight (MD = 0.05, 95% CI = −0.31 to 0.41, $P=.79$).

3.5. Sensitivity analysis

We conducted sensitivity analyses of the main outcomes to identify heterogeneity, and the results were robust and stable (Fig. 7).

4. Discussion

To the best of our knowledge, this is the first meta-analysis to evaluate the efficacy and tolerability of fluvoxamine in adults with SAD. There were some important results indicating that

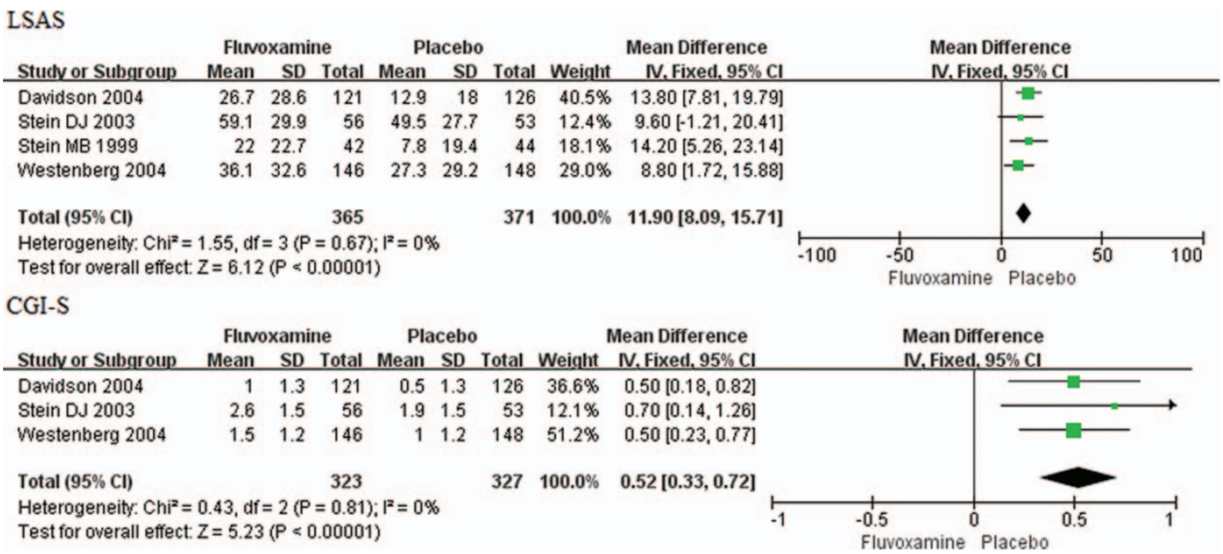

Figure 4. Mean changes in LSAS total score and CGI-S score. CGI-S = Clinical Global Impression Severity of Illness, CI = confidence interval, LSAS = Liebowitz Social Anxiety scale, SD = standard deviation.

fluvoxamine was effective and well-tolerated. Mean changes in LSAS total and CGI-S scores were both higher in patients treated with fluvoxamine than those treated with placebo. Additionally, response rate was greater in fluvoxamine group than placebo group. The result of response rate was inconsistent with a previous mixed-treatment meta-analysis[23] indicating there was no significant difference between fluvoxamine and placebo groups. This inconsistency can be explained by small sample size of the previous analysis.

With regard to tolerability, discontinuation rate due to AEs was higher in fluvoxamine group than placebo group. Most frequent TEAEs mainly comprised nausea, somnolence, insomnia, abnormal ejaculation, and headache. The incidence of nausea, somnolence, insomnia, and abnormal ejaculation was all higher in patients treated with fluvoxamine than those treated with placebo. However, it should be noted that the incidence of headache was not significantly different between the 2 groups. Additional meta-analyses are warranted to explore the incidence

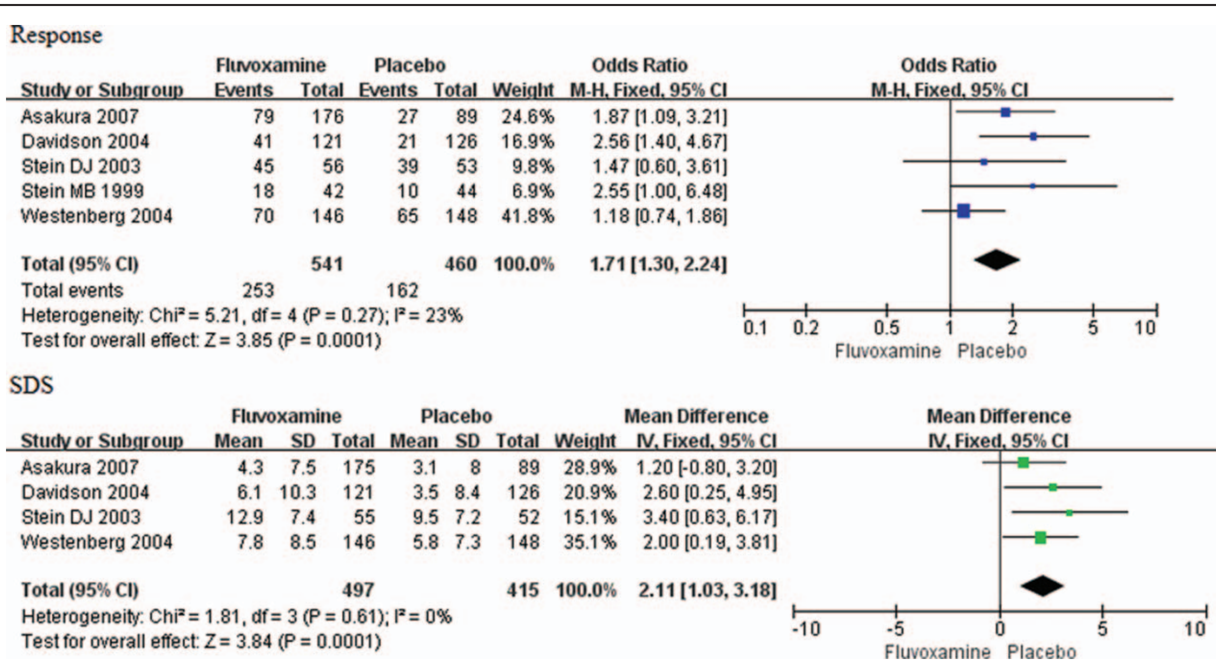

Figure 5. Forest plots of response rate and mean change in SDS total score. CI = confidence interval, SD = standard deviation, SDS = Sheehan disability scale.

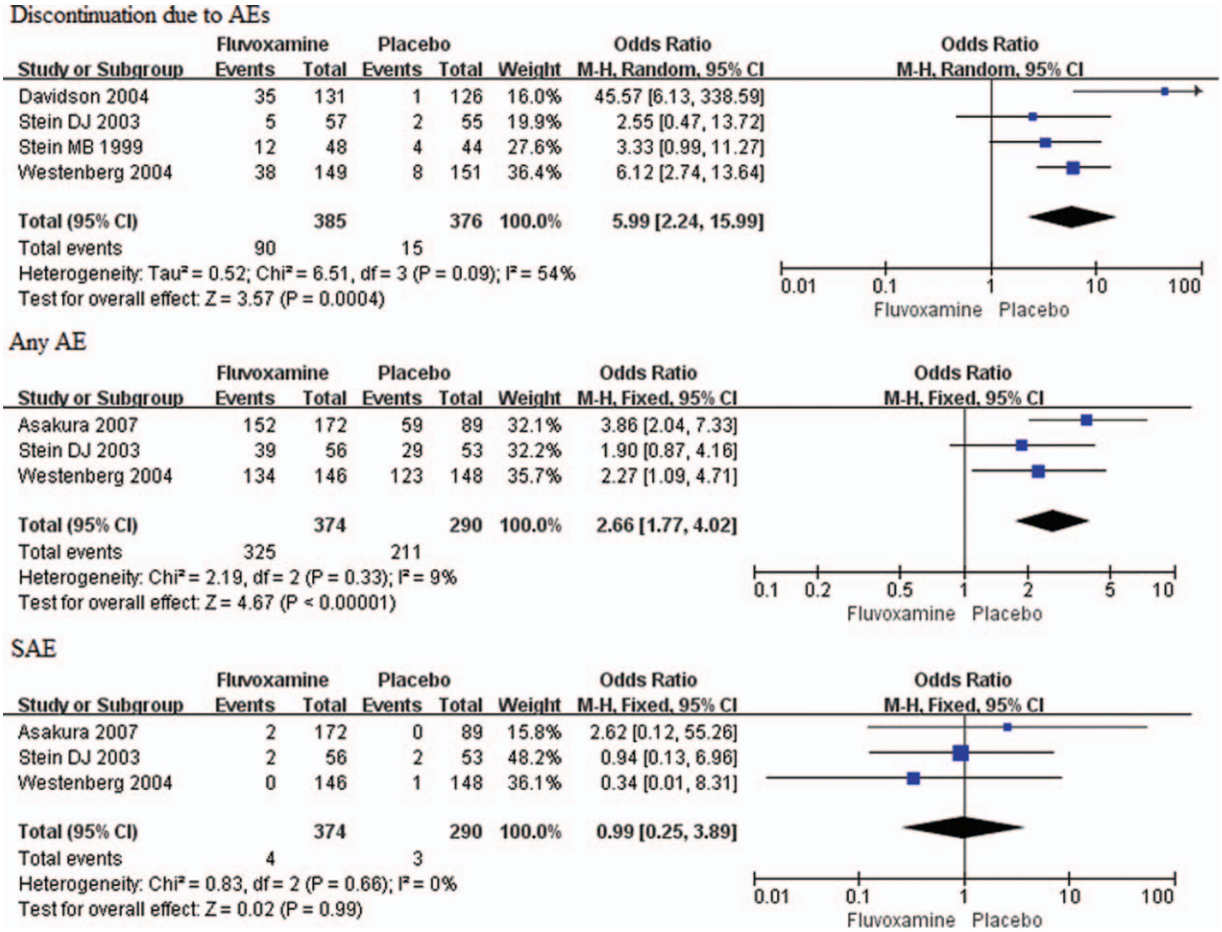

Figure 6. Discontinuation rate due to AEs; the incidence of any AE and SAE. AE=adverse event, CI=confidence interval, SAE=serious adverse event.

of headache in patients receiving fluvoxamine compared to placebo.

Several mixed treatment meta-analyses have been conducted to compare the efficacy of different classes of drugs including fluvoxamine for SAD.[24–26] Findings from a network meta-analysis of pharmacotherapy and psychotherapy for adults with SAD indicated no differences in efficacy were observed between SSRIs and SNRIs.[26] However, we were unable to extract data for the comprehensive efficacy of fluvoxamine. Moreover, these mixed meta-analyses failed to investigate the tolerability or safety of fluvoxamine in treating SAD, and the choice of medications was dependent on efficacy and tolerability. Based on these considerations, we believe that our meta-analysis of fluvoxamine will contribute strongly to the SAD treatment landscape.

Our meta-analysis had several advantages. First, we set strict inclusion and exclusion criteria that included only trials that were RCTs; one study[8] with history or concomitant usage of oxazepam was excluded. Second, we conducted manual searches of the reference lists of all relevant articles and contacted the corresponding authors of some RCTs for missing information. Third, we also searched ClinicalTrials.gov to identify eligible trials that were registered but not yet published.

There were also some limitations that should be noted. First, no restriction on the treatment duration of fluvoxamine was set,

Table 2

Meta-analysis of most frequent treatment-emergent adverse events.

TEAEs	Included studies (N)	OR	Heterogeneity	Effect model	Merger value	95% CI
Nausea	4	7.12	$P=.31$, $I^2=17\%$	Fixed	$P<.001$	4.56–11.13
Somnolence	3	3.58	$P=.91$, $I^2=0\%$	Fixed	$P<.001$	2.43–5.26
Insomnia	3	3.33	$P=.53$, $I^2=0\%$	Fixed	$P<.001$	2.18–5.10
Abnormal ejaculation*	3	2.25	$P=.58$, $I^2=0\%$	Fixed	$P=.05$	1.01–4.99
Headache	3	1.29	$P=.75$, $I^2=0\%$	Fixed	$P=.13$	0.93–1.79

CI=confidence interval, OR=odds ratio, TEAEs=treatment-emergent adverse events.
* Corrected for gender.

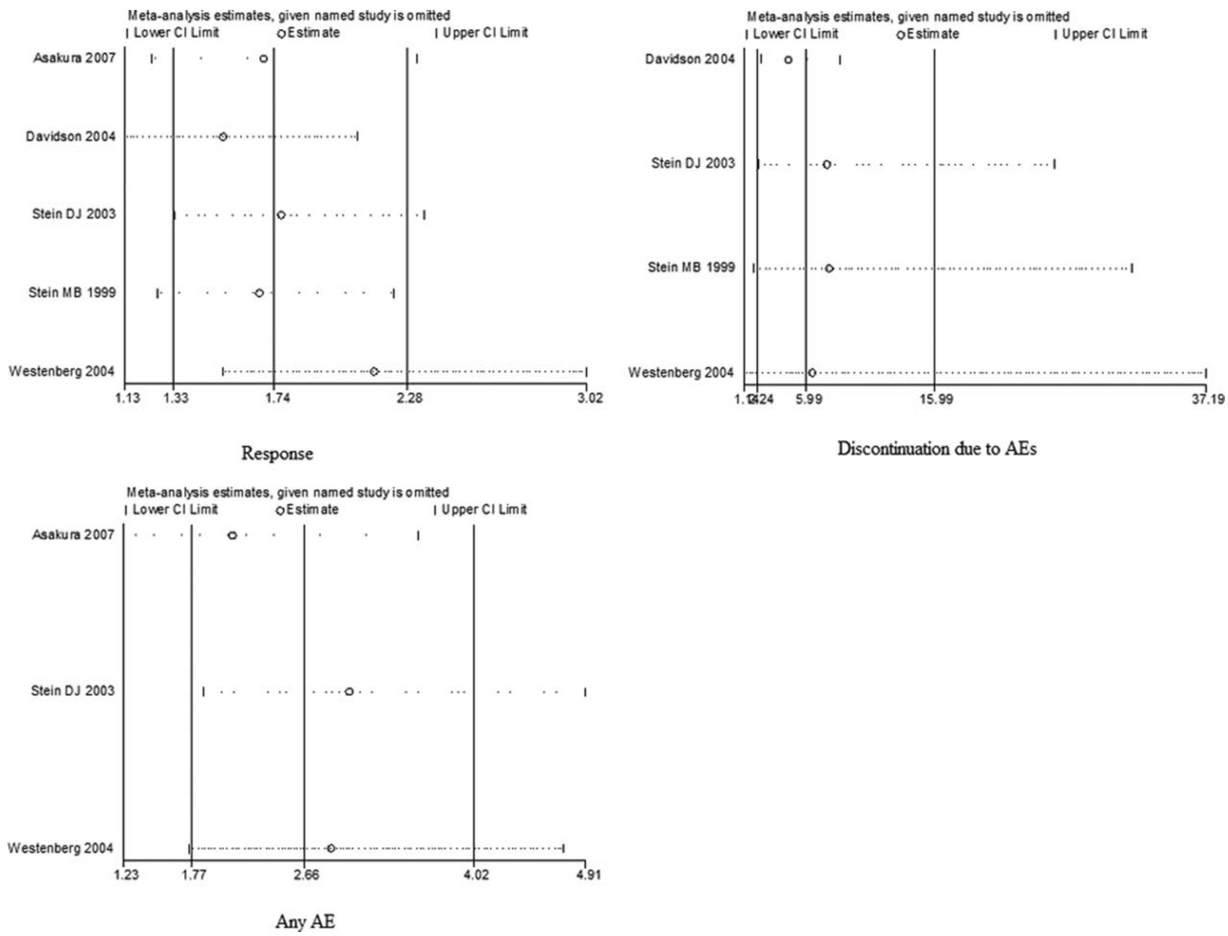

Figure 7. Sensitivity analyses of the main efficacy and tolerability outcomes. AE=adverse event.

which may have introduced heterogeneity. However, we attempted to overcome this limitation by conducting sensitivity analysis, and the results were robust. Second, some trials had a high risk of reporting bias because they were sponsored by pharmaceutical companies. Third, we generated a funnel plot to assess potential publication bias, though in general funnel plots should be used to assess publication bias only in reviews that include ≥10 trials.[27]

In conclusion, fluvoxamine was found to be an effective and well-tolerated treatment option in adults with SAD.

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