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Trazodone for the treatment of insomnia: a meta-analysis of randomized placebo-controlled trials

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Abbreviations:

SE%=sleep efficiency
SL=sleep latency
TST=total sleep time
NAs=the number of awakenings
WASO=waking time after sleep onset
SQ=perceived sleep quality

Abstract

Objective: To assess the efficacy and tolerability of trazodone compared with placebo in patients with insomnia.

Methods: Electronic databases were searched and relevant reports were hand-screened to identify eligible trials. Only randomized placebo-controlled trials were included. Standardized mean differences (SMD) and the odds ratios (OR) were estimated using a random-effect model. Primary efficacy outcomes included sleep efficiency (SE%) and self-reported sleep quality (SQ). Secondary efficacy outcomes included sleep latency (SL), total sleep time (TST), the number of awakenings (NAs), waking time after sleep onset (WASO). Tolerability outcome was measured by the number of patients who discontinued for adverse events and acceptability outcome was measured by the number of patients who discontinued for all causes.

Results: Seven trials involving 429 patients were included. There was no significant improvement for trazodone in SE% (SMD=0.09, 95% confidence interval (CI) -0.19 to 0.38, *P*=0.53) with a non-significant heterogeneity (I^2=0%, *P*=0.59). However, patients receiving trazodone perceived better SQ than those receiving the placebo (SMD=-0.41, 95% CI -0.82 to -0.00, *P*=0.05) with a non-significantly moderate heterogeneity (I^2=65%, *P*=0.06). As to secondary efficacy outcomes, we only found a significant reduction for trazodone in NAs (SMD=-0.51, 95%CI -0.97 to -0.05) compared to the placebo, with non-significant differences found in SL, TST, or WASO between trazodone and placebo. Moreover, no significant difference was found in the outcome of tolerability or acceptability.

Conclusions: Trazodone was effective in sleep maintenance by decreasing the number of early awakenings and it could significantly improve perceived sleep quality, although no significant improvements in sleep efficiency or other objective measures. And trazodone presented good tolerance in the short-term treatment of insomnia for those patients with insomnia.

Keywords: insomnia; trazodone; efficacy; tolerability; meta-analysis

1. Introduction

Insomnia is the most common type of sleep disturbance in the general population [1]. According to different studies, almost one third of adults in western countries would be considered to have insomnia [2-4]. Clinically, insomnia is a subjective disorder that manifests as prolonged sleep latency, sleep maintenance disorder, more early awakenings, impaired total sleep time and decline in sleep quality; despite having an adequate opportunity to sleep, accompanied with distress and daytime dysfunction [5,6]. It is becoming evident that insomnia increases the risk of developing hypertension, stroke, reduced body immunity and mental disorders (including anxiety and depression) [7]. Treatment of insomnia is important for both the management and prevention of these comorbid disorders. There are two main treatments for insomnia: psychotherapy and pharmacotherapy. Psychotherapy, especially cognitive behavioral therapy for insomnia (CBT-i), is recommended as the first line in the management of chronic insomnia [8], however, few well-trained therapists and poor compliance have limited its clinical practice. Pharmacotherapy also plays an important role in the treatment of insomnia. Benzodiazepine drugs (BZDs) and nonbenzodiazepine compounds (non-BZDs) are often prescribed to treat insomnia and are clinically effective, however dependence, abuse potential, withdrawal syndrome and adverse effects to these drugs for long-term use are also common [9]. Antidepressants are often used in depressed patients with insomnia, yet studies had shown that when treated with selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, depressed patients frequently complained of exacerbating insomnia and daytime somnolence [10,11].

Trazodone, a second-generation triazolopyridine antidepressant, is well known as a sedative and hypnotic for its dose-dependent pharmacologic actions [12,13]. It can block the serotonin transporter, inhibit the reuptake of 5-hydroxytryptamine (5-HT), and function as an antidepressant. Because trazodone has weak affinity with serotonin transporter, it must be administered at a high dose of 150-600mg to act as an antidepressant [14-17]. However, trazodone is more commonly prescribed as a hypnotic clinically for sleep disturbances including primary insomnia, and secondary insomnia, which often caused by co-morbid psychiatric disorders, physical diseases, or medication [18-22]. This effect results from blockade of 5-HT_{2A} receptors, α1 adrenergic receptors and histamine H1 receptors, and these pharmacologic actions still function at high doses [14-17]. That is why trazodone can be used to treat depression and not induce sleep problems. Notably, the strongest indication of trazodone is insomnia with depression [13]. A low dose of 25-150mg is usually effective for treatment of sleep disturbances because of its potent binding affinities with those receptors [5].

The US Food and Drug Administration (FDA) has not approved the marketing of trazodone as a hypnotic in the USA because of insufficient evidence for its efficacy and tolerability [12]. However, several guidelines have recommended trazodone as a choice of hypnotics for clinical use [6,23-25]. Prescriptions of trazodone for treating sleep disorders have increased in USA. In recent years, further studies on the efficacy and tolerability of trazodone as a hypnotic have been accomplished. There is an urgent need to integrate these data and provide a best clinical evidence for trazodone in the treatment of insomnia. Therefore, we designed a meta-analysis to evaluate the efficacy and tolerability of trazodone on both primary and secondary insomnia in all randomized placebo-controlled trials.

2. Methods

2.1. Literature search and selection criteria

PubMed, Embase, Web of Science, Cochrane Library, and PsycINFO citations, as well as websites of clinicaltrials.gov were searched from inception to August 2017 employing the following keywords: ‘sleep’, ‘sleeplessness’, ‘insomnia’, ‘insomniac’, ‘dyssomnia’, and ‘trazodone’. The reference lists of identified articles and related publications were hand-searched for further relevant reports. No language, publication date, or publication status restrictions were applied.

Inclusions criteria of the trials were as follows: randomized controlled trials (RCTs), including crossover design, were chosen; patients suffering from insomnia regardless of primary or secondary disorders, as diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) [26-30], International Classification of Diseases [31,32], or International Classification of Sleep Disorders [33,34]. Trials that used predefined diagnostic criteria or diagnosed by a chief complaint of insomnia in participants were also included; comparisons were made between trazodone and placebo; and reporting data of objective sleep parameters or subjective measures in both trazodone and placebo groups. We excluded trials of: a quasi-random nature; where concurrent therapy was changed during study period; conducted in pregnant women (since trazodone may cause fetal harm) [35]; when data were still unavailable after attempting to contact the authors; and when two studies with overlapping populations or duplicated data.

Two authors (X.Y.Y. and X.Y.Z.) individually screened the titles and abstracts of all relevant studies. When meeting disagreements, consensus was reached through discussion by the two authors.

2.2. Data extraction and quality assessment

Data were extracted independently by two authors (X.Y.Y. and X.Y.Z.). A standard Data Extraction Form was made for reducing inconsistency of the two authors in collecting data. It was composed of general information (the first author, publication year, study country, study design, etc.), sample demographics (age, %female, co-morbid diseases, diagnostic criteria, dosage and duration of trazodone, outcome measures, etc.), study results (baseline data, post-treatment data, the discontinuation for all causes, the discontinuation for adverse events, etc.), and quality assessment of literature. When data were missing, we would calculate from exiting data if possible or one would email the authors to obtain data and detailed information [36]. Study quality was assessed by the Cochrane Collaboration's risk-of-bias method, rating as 'high bias', 'low' bias or 'unclear' in each domain [37].

2.3. Outcome measures

Sleep outcomes can be assessed by objective and subjective measures. Objective measures are mainly recorded by polysomnography (PSG), which is the gold standard instrument to appraise sleep disturbances, and actigraphy, which is a portable device developed in recent years [38]. Subjective measures are usually evaluated from scales, questionnaires and diaries. As reported in previous meta-analyses, objective measures, such as sleep efficiency (SE%, total sleep time (TST, min)/time in bed(min)*100%), sleep latency (SL, min), TST, the number of awakenings (NAs), waking time after sleep onset (WASO, min) and subjective measures, such as perceived sleep quality (SQ), were the most frequently used outcome measures [39-41]. In this meta-analysis, we chose SE% and SQ as the primary outcomes for efficacy, because they reflect the comprehensive outcomes of insomnia in objective measures and subjective measures, respectively. Furthermore, SL, TST, NAs and WASO were chosen as the secondary efficacy outcomes, because they would measure only one part of sleep disorder, such as sleep maintenance, difficulty in falling asleep, or insufficient sleep time. Moreover, outcome for tolerability was assessed by the number of patients who discontinued due to adverse events and acceptability outcome was assessed by the number of patients who discontinued due to adverse events.

2.4. Data analysis

All analyses were performed using RevMan 5.3 software (Cochrane Information Management System). Efficacy was evaluated by change values from baseline to end point data on each outcomes in this meta-analysis [42]. When standard error (SD) was missing in an article and could not contact the authors, it would be calculated from reported *P* values, t values, confidence intervals (CIs) or standard errors (SEs) [43]. A random-effects model was applied in this meta-analysis in order to get relatively robust results. Standardized mean differences (SMD) in continuous measure (SE%, SQ, SL, TST, NAs, and WASO), and the odds ratios (OR) in dichotomous measure (the number of discontinuation patients), as well as 95% CIs, were estimated by inverse variance models. Heterogeneity was evaluated with the test of inconsistency (I^2). It represented large, moderate and small heterogeneity when I^2 statistic was higher than 75%, 50% and 25%, respectively [44]. And we used subgroup analyses and sensitivity analyses to find possible sources of the heterogeneity. The publication bias was assessed by Egger tests (Stata 13.0, Stata Corp, College Station, TX, USA) [45]. A two-sided *P* value of less than 0.05 was considered statistically significant if not specifically stated. Where the crossover-design study reported the data of phase 1 and phase 2, respectively, we only extracted the data of phase 1. If not, we extracted the combined data of phase 1 and phase 2, and the number of participants was counted once for each arm in which they were included when analyzed [46].

3. Results

3.1. Search results

Through a full search of databases and manually search, totally 471 relevant citations were identified initially. After exclusion of duplicates, two authors scanned all the titles and abstracts independently, and screened out 15 potential trials. The 15 trials were reviewed for full-texts. Finally, seven RCTs involving 429 patients published between 1994 and 2014 were selected based on our inclusion and exclusion criteria [22,47-52]. The flow diagram was shown in Fig. 1.

3.2. Characteristics of included studies

Of the included trials, six (85.7%) [22,47,48,50-52] recruited patients from Europe and America, and only one (14.3%) [49] from Asia. Three trials (42.9%) were parallel RCTs [47,51,52], and four trials (57.1%) were crossover RCTs [22,48-50]. The sample size ranged from 7 to 204 patients, with a mean

sample size of 61 patients. The mean age was 46.1 years (range 38.2-81.0 years) and only one trial investigated patients over 65 years of age [47]. More than half of the sample population were female (131 [58.2%] of 225). The diagnosis included primary insomnia in two trials [50,52] and secondary insomnia in the remaining trials [22,47-49,51]. Only one trial was diagnosed by international standard criteria [50], four were diagnosed by predefined criteria [22,47,51,52], and two by insomnia symptoms [48,49]. Four trials had co-current pharmacological therapy [22,48,49,51]. The duration of trazodone administration varied from one weeks to four weeks (mean 1.7 weeks) and trazodone was administered at a low dose between 50-150mg/day in all trials. Five trials reported objective measures, of which four [48-51] were detected by PSG or sleep electroencephalograph (SEEG) and one [47] was detected by actigraphy. Furthermore, three trials [22,51,52] reported subjective measures. The characteristics of all included trials shown in Table 1.

3.2. Quality assessment

All of the included trials had mentioned assignment of patients with random, but only two trials of rating as ‘low bias’ reported the detailed instruments for random sequence generation [47,51]. Allocation concealment [47,48,50] were described in three trials hence rating as ‘low bias’. Four trials performed blinding of participants and personnel [47,48,50,51] and three trials performed blinding of outcome assessment [47,49,50]. In the domain of incomplete data, most trials (5/7, 71.4%) reported discontinuation rates and reasons for discontinuation and rated as ‘low bias’ [22,47-49,52]. Apart from one trial [50], most trials are rating as ‘low bias’ in the domain of selective reporting. Three trials were rated as ‘low bias’ in the domain of other bias for baseline consistency [47,51,52]. Overall, the summary quality assessment of the whole included trials was low to moderate (Fig. A.1).

3.3. Primary efficacy outcomes

Four trials yielded data on sleep efficiency (SE%) in the trazodone group compared with placebo group with a total of 177 completed patients [47,49-51]. Trazodone was not more beneficial than placebo in sleep efficiency with the pooled SMD of 0.09 (95%CI -0.19 to 0.38, P=0.53) and a small heterogeneity (I^2=0%, P=0.59) (Fig. 2). Moreover, we conducted subgroup analyses stratified by age, race, study design, type of insomnia, and dosage and duration of trazodone, while there were no statistical significance in any of the subgroups. Results for subgroup analyses were shown in Table 2. A sensitivity analysis excluding the trial that used actigraphy as measure instrument was performed,

however no trial significantly affected our results. No publication bias was found by the Egger test (*P*=0.259).

Only three trials [22,51,52] reported data on perceived sleep quality (SQ), among which two were measured by the Pittsburgh Sleep Quality Index (PSQI) [22,51] and one was measured by a morning questionnaire [52]. Patients receiving trazodone perceived significantly better SQ than those receiving the placebo (SMD=-0.41, 95%CI -0.82 to -0.00, *P*=0.05; Fig. 2). A non-significantly moderate heterogeneity (I^2=65%, *P*=0.06) was seen in the outcome of SQ. No publication bias was found by the Egger test (*P*=0.088).

3.4. Secondary efficacy outcomes

We also assessed other sleep parameters and found the the number of awakenings (NAs) in trazodone group was significantly reduced than that in placebo group, with a pooled SMD of -0.51 (95%CI -0.97 to -0.05, *P*=0.03; n=4 studies) with small heterogeneity (I^2=0%, *P*=0.63). However, no significant improvements were found in the following sleep parameters: SL, TST, or WASO. Results are presented in Fig. 3.

3.5. Tolerability outcome and acceptability outcome

In terms of tolerability, there was no significant difference between the trazodone group and the placebo group in the outcome of discontinuation for adverse events (OR=0.86, 95%CI 0.28 to 2.63, *P*=0.80; I^2=0%, *P*=0.41). In terms of acceptability, there was no significant difference between the trazodone group and the placebo group in the outcome of discontinuation for all causes (OR=1.61, 95%CI 0.72 to 3.57, *P*=0.24; I^2=0%, *P*=0.98). Meta-analysis results for these outcomes are shown in Fig. 4.

4. Discussion

To our knowledge, this was the first meta-analysis focused on efficacy and tolerability of trazodone on both primary and secondary insomnia compared to placebo. Our analysis indicated that patients receiving trazodone perceived more benefits in sleep quality, although no improvement was seen in sleep efficiency in the treatment of insomnia. We also found that trazodone was more effective in maintaining sleep by decreasing the number of early awakenings, whereas having no effects in sleep onset or sleep length. Therefore, we hypothesized that better subjective sleep might result from reduction of early awakenings during sleep. Moreover, trazodone was well

tolerated as evidenced by no significant difference existed between trazodone and placebo in the outcomes of discontinuation.

Similar to the antidepressant doxepin, which was approved for insomnia by the FDA in 2010, trazodone was mainly effective in sleep maintenance insomnia at a low dose. But significant effects of doxepin were seen in improvement of SE%, TST and WASO, although not in decreasing NAs [53]. BZDs can be administered in both sleep onset insomnia and sleep maintenance insomnia [54]. A meta-analysis by Holbrook et al. reported that BZDs showed greater improvement in TST by 61.8 min, but whether NAs could be decreased was not investigated [46]. Notably, they found that patients receiving BZDs reported more adverse events, such as daytime drowsiness, dizziness, and even cognitive function impairment. Previous meta-analyses indicated that non-BZDs and melatonin agonist were featured in sleep onset insomnia with small effect in reducing SL (four-six min), which were different from trazodone [40,55,56].

No serious adverse events, including suicides and suicide attempts, were reported in patients receiving trazodone in the included trials. All adverse events were mild to moderate in short term use, such as daytime sleepiness, gastrointestinal discomfort, dizziness and dry mouth, which were consistent with other trials [57,58]. Furthermore, discontinuation rates for all causes as well as adverse events were not significantly higher than placebo, which indicated that trazodone was well tolerated in the treatment of insomnia. Although trazodone is known to have little cardiovascular toxicity, recent studies indicate that trazodone may have cardiovascular side effects, such as hypotension, QT prolongation, delayed atrioventricular conduction [59,60]. However, in the seven studies included in this review, none had reported cardiovascular adverse events caused by trazodone; possibly due to small sample sizes and short-term follow-up. Therefore, safety of trazodone, especially regarding cardiovascular system, still requires further validation.

Our meta-analysis have several limitations. First, the number of eligible trials and sample size was too small. Only seven trials with 429 participants were included in this review. Although trazodone was well tolerated as a hypnotic in our analysis, adverse events, such as those related to cardiovascular system, were rarely reported in the included trials; which were frequently indicated in recent studies [59,60]. There was lacking enough evidence of safety of trazodone for insomnia. Thus, the quality assessment of all included trials was low to moderate. Most of them had inadequate description of randomization, allocation concealment and blinding method. This greatly limited the interpretation of the results in this meta-analysis. Second, trazodone does not have patent reserves. Therefore, the scarcity of studies on the chronic use of trazodone is a reflection of the lack of interest by health authorities and pharmaceutical industries to develop controlled studies with placebo and double-blind groups. To assess the effectiveness and safety of trazodone in

these patients [61]. Thus, the National Institutes of Health and other public agencies could prioritize funding studies of new uses that industry has little incentive to conductance [62]. Third, outcome measures for insomnia varied between studies. Five trials reported objective measures, whereas four recorded SE%, TST and NAs, and three recorded SL and WASO. With respect to subjective measures, only three trials reported self-reported SQ. This may reduce the strength of a single outcome. Notably, measure instruments were also different. Regarding to objective measurements, one trial conducted in demented patients had chosen actigraphy [47]. PSG use relies on patients' cooperation and understanding, however, they are hardly conducted in the demented population. Ancoli-Israel et al. reported the inaccuracy of SEEG use in patients with dementia [63]. Actigraphy is more comfortable, feasible, and have better compliance. The correlation for TST between actigraphy and PSG ranged from 0.81 to 0.91 in demented populations [63]. In this review, we did not find great heterogeneity between studies and sensitivity analyses presented robust results. Therefore, difference in measure instruments had limited influence in our results. Fourth, a very important concern in studying a hypnotic medication is that does it improve the patient's next-day ability. However, only one study evaluated self-reported morning sleepiness and ability to concentrate [52], which had not been evaluated in the other 6 include studies. Therefore, data on those outcomes could not be combined. Finally, due to lacking data for long-term use and follow-up, we could not make recommendations on treatment duration of trazodone based on available evidence. However, an observational studies reported that the average time of use of trazodone for the treatment of sleep disorders in demented patients was 8.1(±4) months [64].

5. Conclusion

In summary, trazodone was an effective and well-tolerated hypnotic for those patients with primary and secondary insomnia. In this review, trazodone was effective in sleep maintenance by decreasing the number of early awakenings and it could significantly improve perceived sleep quality, although no improvements in sleep efficiency and other objective measures. Thus, trazodone presented good tolerance in the short-term treatment of insomnia for those patients with insomnia. But with limited data, small sample sizes and relatively low quality of the included studies, they would limit its generalization. Furthermore, because of a lack of clearly established efficacy and safety data as well as a lack of approval by the FDA for its use as a hypnotic, we should be with much caution about trazodone use in insomnia.

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Table Legends

Table 1 Characteristics of the 7 included studies on efficacy and safety of trazodone for treating insomnia.

Table 2 Subgroup analyses of SE% comparing between trazodone group and placebo group.

Figure Legends

Fig. 1. Flow diagram indicating the process of selecting literature for meta-analysis.

Fig. 2. Meta-analysis results for primary efficacy outcomes of trazodone compared with placebo: (a) SE%=sleep efficiency; (b) SQ=sleep quality.

Fig. 3. Meta-analysis results for secondary efficacy outcomes of trazodone compared with placebo: (a) SL=sleep latency; (b) TST=total sleep time; (c) NAs=the number of awakening; (d) WASO=waking time after sleep onset.

Fig. 4. Meta-analysis results for safety outcomes of trazodone compared with placebo: (a) Discontinuation for adverse events; (b) Discontinuation for all causes.

Table 1 Characteristics of the seven included studies on efficacy and tolerability of trazodone for treating insomnia.

Study	Country	Study design	Setting	Age(years, mean±SD)	%Female	Co-morbid diseases	Concurrent therapy	Diagnostic Criteria	n[a], dosage, duration	Measure instruments	Outcome measures
Camargos 2014 [47]	Brazil	parallel	outpatients	81±7.5	66.7	Alzheimer's disease	none	predefined criteria	n=36, 50mg/day, 2 weeks	actigraphy	SE%, TST, NAs, WASO
Haffmans 1999 [48]	Netherlands	crossover	outpatients	44	42.9	MDD	brofaromine	insomnia symptoms	n=7, 50mg/day, 1 weeks	SEEG	TST, SL, NAs, WASO
Kaynak 2004 [49]	Turkey	crossover	outpatients	42±9	100	MDD	SSRIs	insomnia symptoms	n=12, 100mg/day, 1 weeks	PSG	SE%, TST, SL, NAs
Nierenberg 1994 [22]	USA	crossover	inpatients and outpatients	41.9±16	40	MDD or bipolar depression	fluoxetine or bupropion	predefined criteria	n=17, 50-100mg/day, 1 weeks	PSQI	SQ
Roth 2011 [50]	USA	crossover	outpatients	44±11	75	primary insomnia	none	DSM-IV	n=16, 50mg/day, 1 weeks	PSG	SE%, SL, NAs, WASO
Stein 2012 [51]	USA	parallel	outpatients	38.2±8.6	53.3	opioid dependence	methadone	predefined criteria	n=137, 50-150mg/day, 4 weeks	PSG and PSQI	SE%, TST, SQ
Walsh 1998 [52]	USA	parallel	outpatients	NR	NR	primary insomnia	none	predefined criteria	n=204, 50mg/day, 2 weeks	predetermined questionnaire	SQ

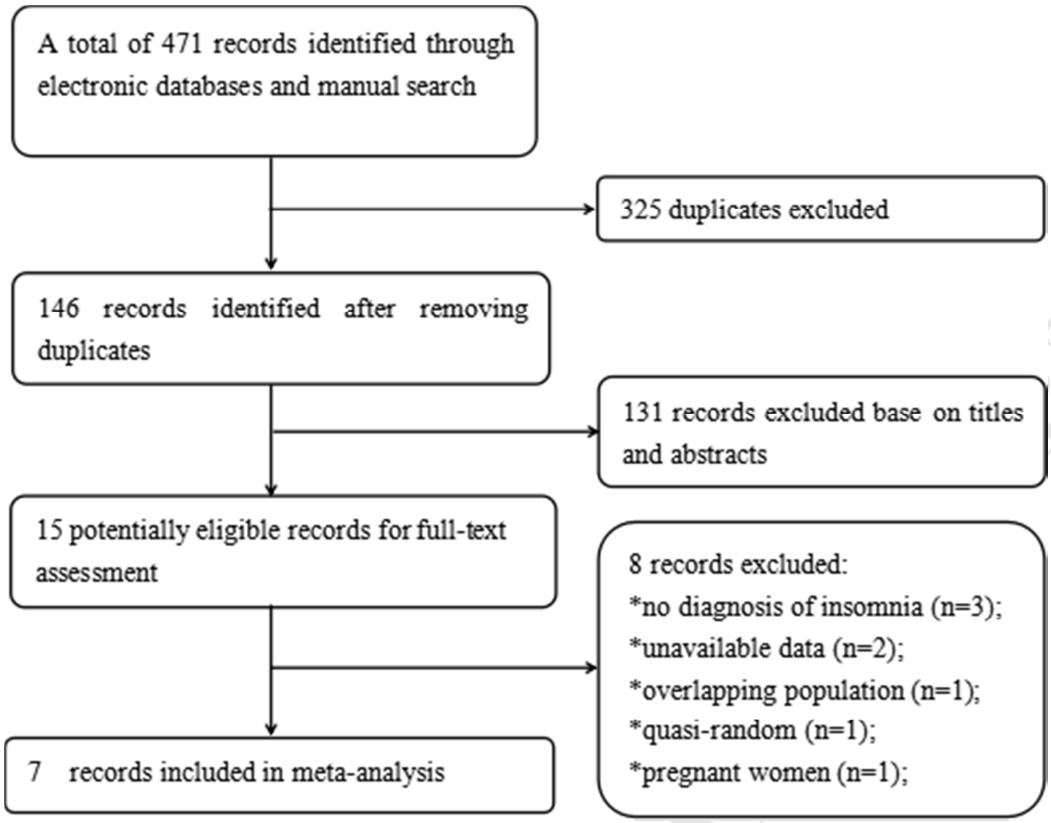
[a] number of patients who were assigned randomly. We only recorded the number of phase 1 in the crossover trials.

DSM: the Diagnostic and Statistical Manual of Mental Disorders; MDD: major depressive disorder; NAs: the number of awakening; PSG: polysomnography; PSQI:

Pittsburgh sleep quality index; SEEG: sleep electroencephalograph; SE%: sleep efficiency; SL: sleep latency; SQ; sleep quality; SSRIs: selective serotonin reuptake inhibitors; TST: total sleep time; WASO: waking time after sleep onset; NR: not reported.

Table 2 Subgroup analyses of SE% comparing between trazodone group and placebo group.

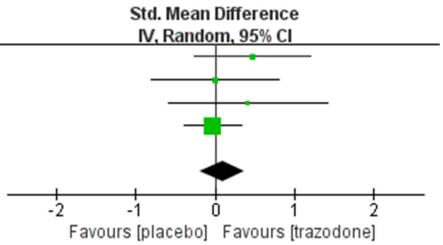
Subgroups	Trials	Overall effect		Heterogeneity	
		SMD (95%CI)	*P*	I^2 (%)	*P*
Age					
＜60 years	Kaynak 2004; Roth 2011; Stein 2012	0.02 (-0.29, 0.33)	0.89	0	0.72
⩾60 years	Camargos 2014	0.47 (-0.25, 1.20)	0.20	/	/
Race					
Asian	Kaynak 2004;	0.00 (-0.80, 0.80)	1.00	/	/
Caucasian	Camargos 2014; Roth 2011; Stein 2012	0.11 (-0.20, 0.41)	0.50	0	0.40
Study design					
Crossover	Kaynak 2004; Roth 2011	0.16 (-0.46, 0.79)	0.61	0	0.52
Parallel	Camargos 2014; Stein 2012	0.12 (-0.32, 0.56)	0.60	31	0.23
Type of insomnia					
Primary	Roth 2011	0.42 (-0.58, 1.42)	0.41	/	/
Secondary	Camargos 2014; Kaynak 2004; Stein 2012	0.06 (-0.24, 0.36)	0.68	0	0.48
Dosage of trazodone					
⩽50mg/day	Camargos 2014; Roth 2011	0.45 (-0.14, 1.04)	0.13	0	0.93
＞50mg/day	Kaynak 2004; Stein 2012	-0.02 (-0.35, 0.31)	0.90	0	0.96



(a) SE%

Study or Subgroup	Trazodone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Camargos 2014	4.7	15.7	15	-3	16	15	15.5%	0.47 [-0.25, 1.20]
Kaynak 2004	-1	7.5	12	-1	12.1	12	12.8%	0.00 [-0.80, 0.80]
Roth 2011	0.2	11.1	9	-4.6	10.6	7	8.2%	0.42 [-0.58, 1.42]
Stein 2012	2.3	12.1	63	2.6	12.1	56	63.4%	-0.02 [-0.38, 0.34]
Total (95% CI)			**99**			**90**	**100.0%**	**0.09 [-0.19, 0.38]**

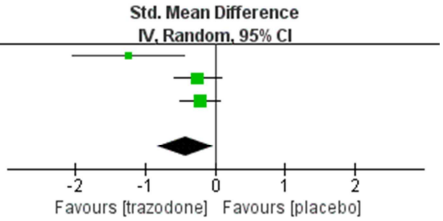
Heterogeneity: Tau² = 0.00; Chi² = 1.91, df = 3 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)



(b) SQ

Study or Subgroup	Trazodone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Nierenberg 1994	-4.6	4	15	0.8	4.5	15	17.9%	-1.23 [-2.02, -0.44]
Stein 2012	-3.9	4	67	-2.9	4	67	39.4%	-0.25 [-0.59, 0.09]
Walsh 1998	-0.48	0.59	90	-0.36	0.52	97	42.7%	-0.22 [-0.50, 0.07]
Total (95% CI)			**172**			**179**	**100.0%**	**-0.41 [-0.82, -0.00]**

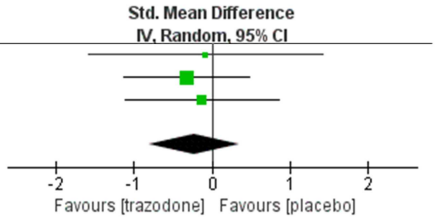
Heterogeneity: Tau² = 0.08; Chi² = 5.79, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 1.97 (P = 0.05)



(a) SL

Study or Subgroup	Trazodone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Haffmans 1999	3	10	3	5.5	30.6	4	14.8%	-0.09 [-1.58, 1.41]
Kaynak 2004	-3	20.1	12	9	45.9	12	51.2%	-0.33 [-1.13, 0.48]
Roth 2011	-2.1	25.5	9	1	17.4	7	34.0%	-0.13 [-1.12, 0.86]
Total (95% CI)			**24**			**23**	**100.0%**	**-0.22 [-0.80, 0.35]**

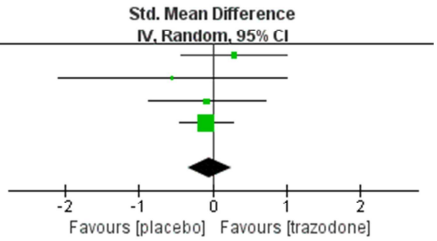
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)



(b) TST

Study or Subgroup	Trazodone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Camargos 2014	31.7	97	15	-1	118.5	15	16.6%	0.29 [-0.43, 1.01]
Haffmans 1999	-4.7	10	3	37.5	83.3	4	3.5%	-0.55 [-2.11, 1.01]
Kaynak 2004	-7	36.8	12	-3	57.2	12	13.4%	-0.08 [-0.88, 0.72]
Stein 2012	-4.2	118.3	63	6.6	118.3	56	66.4%	-0.09 [-0.45, 0.27]
Total (95% CI)			**93**			**87**	**100.0%**	**-0.04 [-0.34, 0.25]**

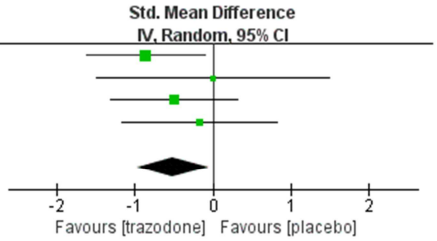
Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 3 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.28 (P = 0.78)



(c) NAs

Study or Subgroup	Trazodone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Camargos 2014	-5.2	10	15	3.4	9.5	15	37.3%	-0.86 [-1.61, -0.11]
Haffmans 1999	-2	2.7	3	-2	3.2	4	9.4%	0.00 [-1.50, 1.50]
Kaynak 2004	-1	11.3	12	6	15.7	12	31.8%	-0.49 [-1.31, 0.32]
Roth 2011	-3.5	8.6	9	-1.6	12.8	7	21.5%	-0.17 [-1.16, 0.82]
Total (95% CI)			**39**			**38**	**100.0%**	**-0.51 [-0.97, -0.05]**

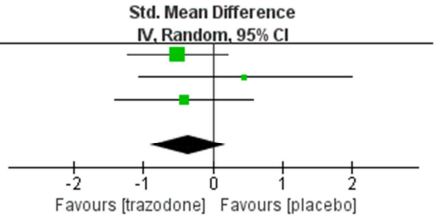
Heterogeneity: Tau² = 0.00; Chi² = 1.72, df = 3 (P = 0.63); I² = 0%
Test for overall effect: Z = 2.19 (P = 0.03)



(d) WASO

Study or Subgroup	Trazodone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Camargos 2014	-41	91.2	15	7.1	92	15	57.0%	-0.51 [-1.24, 0.22]
Haffmans 1999	6.7	47.6	3	-22.8	57.3	4	12.8%	0.46 [-1.08, 2.00]
Roth 2011	1.1	53.4	9	24.9	53.4	7	30.2%	-0.42 [-1.42, 0.58]
Total (95% CI)			**27**			**26**	**100.0%**	**-0.36 [-0.91, 0.19]**

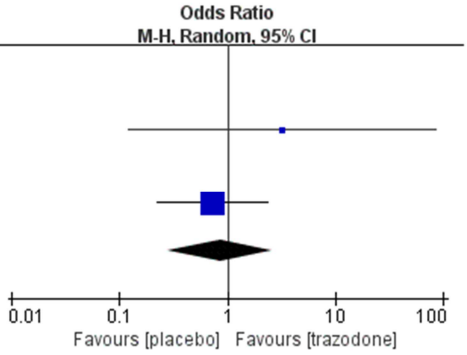
Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.28 (P = 0.20)



(a) Discontinuation for adverse events

Study or Subgroup	Trazodone Events	Trazodone Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Camargos 2014	0	19	0	17		Not estimable
Haffmans 1999	0	3	0	4		Not estimable
Kaynak 2004	0	12	0	12		Not estimable
Nierenberg 1994	1	17	0	17	11.6%	3.18 [0.12, 83.76]
Roth 2011	0	9	0	7		Not estimable
Stein 2012	0	69	0	68		Not estimable
Walsh 1998	5	100	7	104	88.4%	0.73 [0.22, 2.38]
Total (95% CI)		**229**		**229**	**100.0%**	**0.86 [0.28, 2.63]**
Total events	6		7			

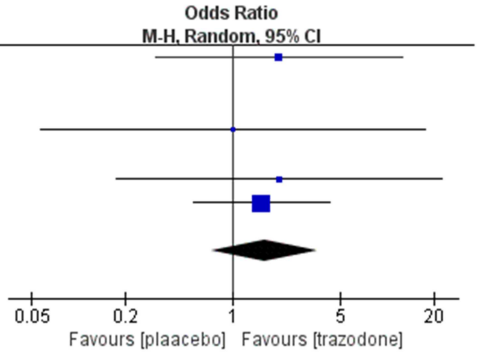
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)



(b) Discontinuation for all causes

Study or Subgroup	Trazodone Events	Trazodone Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Camargos 2014	4	19	2	17	18.7%	2.00 [0.32, 12.62]
Haffmans 1999	0	3	0	4		Not estimable
Kaynak 2004	0	12	0	12		Not estimable
Nierenberg 1994	1	17	1	17	7.8%	1.00 [0.06, 17.41]
Roth 2011	0	9	0	7		Not estimable
Stein 2012	2	69	1	68	10.8%	2.00 [0.18, 22.59]
Walsh 1998	10	100	7	104	62.6%	1.54 [0.56, 4.22]
Total (95% CI)		**229**		**229**	**100.0%**	**1.61 [0.72, 3.57]**
Total events	17		11			

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.17 (P = 0.24)



Highlights

1. This was the first meta-analysis focused on efficacy and tolerability of trazodone on insomnia.
2. Trazodone was effective for the treatment of insomnia, especially in maintaining sleep by reducing the number of early awakenings, and improving perceived sleep quality.
3. Trazodone was well tolerated in short term use for insomnia.