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REVIEW

Trazodone for Insomnia: A Systematic Review

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ABSTRACT

OBJECTIVE: While trazodone is approved for the treatment of depression, the off-label use of this medication for insomnia has surpassed its usage as an antidepressant. In this systematic review, we examined the evidence for the efficacy and safety of trazodone for insomnia. **METHODS:** A literature search was conducted using MEDLINE/PubMed databases from the past 33 years (1983–2016) and the keywords insomnia, trazodone, sedative, treatment, and hypnotics. The results were restricted to English language and human subjects. All randomized clinical trials, meta-analyses, observational studies, and placebo-controlled trials regarding trazodone for the treatment of primary or secondary insomnia were reported, per PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study selection process yielded a total of 45 studies. **RESULTS:** Evidence for the efficacy of trazodone has been repeatedly demonstrated for primary insomnia, as well as secondary insomnia, including for symptoms that are a result of depression, dementia, and being a healthy man. Earlier studies (1980–2000) focused on utilizing trazodone at high doses (≥100mg/d) for the treatment of insomnia among the depressed population; however, since the 2000s, the utility of trazodone has been expanded to treat secondary insomnia among the non-depressed population as well. The side effects are dose-dependent, and the most common is drowsiness. **CONCLUSION:** A review of the literature suggests that there are adequate data supporting the efficacy and general safety of the low-dose use of trazodone for the treatment of insomnia.

KEYWORDS: insomnia, hypnotics, treatment, trazodone, sedative

Insomnia is characterized by difficulty falling asleep, difficulty staying asleep, or waking too early[1] and is associated with significant impairments in daytime activities, which might occur despite adequate opportunities for sleep.[2–6] Primary insomnia is an organic illness in which sleep disturbances last longer than one month and have no identifiable etiology.[7] Secondary insomnia might be caused by psychiatric or medical disorders, environmental factors, changes in circadian rhythm, or medication use. Effective treatment requires appropriate diagnosis, as well as behavioral and pharmacological therapy. Currently, benzodiazepine receptor agonists (BzRAs), such as zolpidem (Ambien) have been the preferred treatment of insomnia. However, trazodone was recently among the most widely prescribed sleep aids in the United States, despite being approved for depression by the Food and Drug Administration (FDA).[8–10] Given this widespread use, it seems beneficial to evaluate the literature on the efficacy and safety of trazodone when administered for the treatment of insomnia. A MEDLINE search of the literature from 1983 through 2016 was conducted using the keywords insomnia, trazodone, sedative, and hypnotics and restricted to English language and human subjects. This strategy identified 173 articles that were screened; 55 were related to the topic. Two reviewers conducted a focused analysis using the full-text articles independently and reached a consensus on the studies to include in this review. The study selection process yielded 45 studies (Figure 1).

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ACKNOWLEDGEMENTS: Data used in the preparation of this article were obtained from MEDLINE/PubMed databases. The primary purpose of this research study was to determine the efficacy and safety of trazodone in the treatment of insomnia.

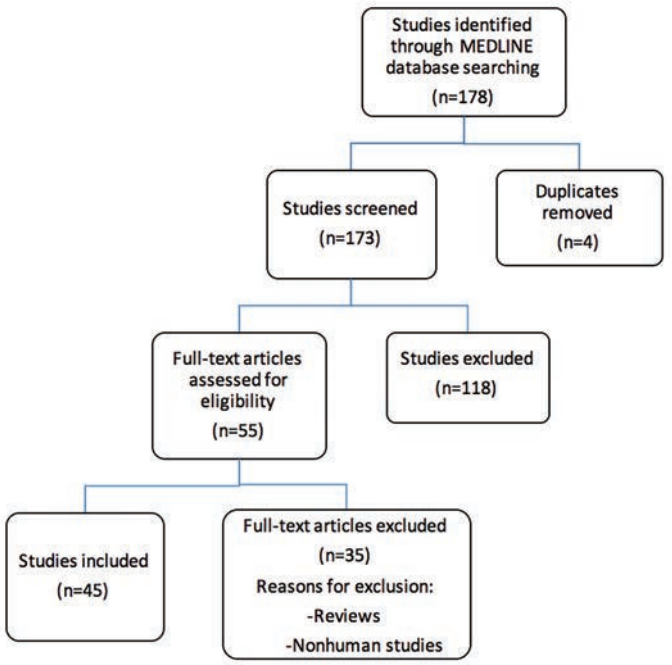
PHARMACOLOGY OF TRAZODONE

Trazodone is a triazolopyridine derivative that was approved in 1982 for the treatment of depression. It belongs to the class of serotonin antagonist and reuptake inhibitors (SARI). Trazodone behaves as an antagonist at the serotonin type 2 (5-HT2) receptors, an antagonist at the alpha1 (α1) adrenergic receptors, and as an inhibitor of serotonin reuptake transporter (SERT). Of note, another consistent finding in the literature is that trazodone moderates cortisol suppression of the hypothalamic-pituitary-adrenal axis, which likely contributes to the efficacy of trazodone for insomnia. In addition, trazodone has moderate antihistamine and low anticholinergic activity.[11] Although its mechanism of action is not fully understood, the main pharmacological action of trazodone is blockade of the serotonin 5-HT2A receptor (1mg of trazodone roughly blocked half of brain 5-HT2A receptors). Increasing trazodone dose (50mg) causes antagonism on histamine H1 and α1-adrenergic receptors. The blocking of the 5-HT2A, histamine H1, and alpha receptors is thought to produce the hypnotic effect reported for low doses of trazodone (25–100mg).[11] At these low doses, trazodone induces and maintains sleep without causing daytime drowsiness or tolerance, mainly because of its short half-life (3–6 hours).[11–13] For the medication's antidepressant effects to reach efficacy, simultaneous blocking of 5-HT2A and SERT is required, which occurs at higher doses (150–600mg).[11] Tolerance can occur during the combined antagonism actions of 5-HT2A and SERT.[11]

OVERVIEW OF INCLUDED STUDIES

A significant number of clinical trials have evaluated the hypnotic effectiveness of trazodone in the treatment of insomnia. We identified 45 previous studies that evaluated trazodone's effect on sleep outcomes

Figure 1: PRISMA* Flow Diagram for Systematic Review of Trazodone for Insomnia



*PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(Table 1).[14–58] Studies are grouped in the table from the most recent to the least recent and are also divided based on the type of insomnia studied (i.e., primary or secondary insomnia). The majority of these studies (95.5%, 43/45 studies) concluded that trazodone was effective in the treatment of insomnia. Only two studies did not support the use of trazodone for sleep.[26,47] Twenty-one of the studies were performed with depressed patient populations where insomnia was either secondary to depression or induced by antidepressants.[20,29,33,35,38,39,41,42,44,48,50–57] Of all studies included in the current review, 23 evaluated trazodone's effects in non-depressed patients with sleep disorders: five were performed in primary insomnia,[14–18] one for patients during pregnancy,[19] one for women post-menopause,[21] one with Alzheimer's disease patients,[22] one with cancer patients,[23] one with dementia patients,[25] one with methadone-maintenance patients,[26] four with healthy men,[28,31,43,49] three with alcohol-related participants,[30,36,37] one with somatoform pain disorder patients,[32] three with psychiatric patients,[24,34,40] and one with self-reported "poor sleepers."[57]

EFFICACY IN PRIMARY INSOMNIA

Five controlled clinical trials evaluated trazodone for the treatment of primary insomnia.[14–18] The original placebo-controlled, randomized clinical trial (RCT) was conducted by Walsh and colleagues and placed 306 subjects (21–65 years) to receive trazodone 50mg (n=100), zolpidem 10mg (n=102), or placebo (n=104) nightly for 14 days.[18] Sleep measures were assessed using subjective sleep questionnaires. During the first week, trazodone decreased the time to fall asleep (sleep latency) significantly more than placebo, and zolpidem decreased sleep latency more than either trazodone or placebo.[18] During the second week, sleep latency was still shorter in patients receiving zolpidem; however, the effects of

Table 1. Characteristics of included studies evaluating trazodone for primary and secondary insomnia

Study (Year)	Population Features (N)	Study Design	Trazodone Dosage mg/d (N)	Duration	Sleep Measures (Subj/Obj)	Conclusions	Strengths and Limitations
Morin et al[14] (2016)	Primary insomnia Age ≥21 (N=224)	Randomized controlled trial 2-tx stages	50–150 mg/d (N=not indicated)	6 weeks	-sleep diaries -PSG -(Subj/Obj)	Ongoing	Strengths: Dual-site RCT; large target sample size; remitters will be followed for 12 months; use of both clinically relevant primary outcomes; inclusion of insomnia patients with and without psychiatric comorbidity. Limitations: N/A
Roth et al[15] (2011)	Primary insomnia Age range 18–65 (N=16)	Randomized double-blind, placebo-controlled	50mg/d (N=16)	3 weeks	-PSG (Obj)	Trazodone is efficacious for sleep maintenance but may be associated with motor and cognitive impairments	Strengths: Strict inclusion of primary insomniacs; use of polysomnography to confirm diagnosis. Limitations: Small sample; of the 63 individuals who gave informed consent, 47 did not complete the study; no a priori justification of sample size.
Zavesicka et al[16] (2008)	Primary insomnia Mean age 46 (N=20)	Randomized comparative trial CBT vs. CBT+Traz	100mg/d (N=10)	8 weeks	self-reported -PSG (Subj/Obj)	CBT monotherapy & combined with trazodone are effective for short-term management of chronic primary insomnia	Strengths: Randomized design; comparative clinical trial to CBT. Limitations: Single-site study; effects of trazodone were not compared with placebo; small treatment groups
Wichniak et al[17] (2007)	Primary insomnia Mean age 46 (N=20)	Randomized comparative trial CBT vs. CBT+Traz	25–150 mg/d (N=28)	3 months	-LSEQ (Subj)	Trazodone improves sleep quality and daytime functioning	Strengths: Three-month study; inclusion of multiple patient-reported sleep scales. Limitations: Small sample size.
Walsh et al[18] (1998)	Primary insomnia Age range 21–65 (N=306)	Randomized, double-blind, placebo- controlled	50mg/d (N=100)	2 weeks	Sleep Question (Subj)	Trazodone improves subjective sleep latency, sleep duration, & quality	Strengths: Double-blind, placebo-controlled RCT; large sample size; robust exclusion criteria. Limitations: Only single dose of each drug was included; no inclusion of PSG measures.
Giannaccini[20] (2016)	Secondary insomnia: Mood disorder Middle-age (N=17)	Pilot study	10–20 mg/d (N=17)	1 month	HAM-D (Subj)	Trazodone would rebalance sleep and mood by interacting with melatonin	Strengths: Initial pilot study to investigate the involvement of melatonin system in low-dose efficacy of the typical antidepressant, trazodone on insomnia patients with mood disorders; inclusion of medication serum levels. Limitations: Small sample size.
Eraslan et al[21] (2014)	Secondary insomnia: post-menopausal Mean age 51 (N=83)	Open and randomly assigned to trazodone or zopiclone	50–100mg/d (N=28)	4 weeks	HAM-D (Subj)	Both trazodone & zopiclone improved sleep quality and sexual dysfunction	Strengths: Homogenous cohort of post-menopausal women; exclusion of women taking psychotropic drugs known to cause sleep problems. Limitations: Mild attrition; small sample size; did not control for extraneous variables (e.g., hormone levels).
Camargos et al[22] (2014)	Secondary insomnia: Alzheimer Age >60 (N=36)	Randomized, double-blind placebo-controlled	50mg/d (N=15)	2 weeks	Actigraphy (Obj)	50mg was safe and effective in the treatment of insomnia	Strengths: First double-blind, placebo-controlled study of trazodone in patients with Alzheimer's disease. Limitations: No a priori power calculations; small sample size; no use of PSG data; problems with daily diary recordings.
Tanimukai et al[23] (2013)	Secondary insomnia: Cancer patients Mean age 61 (N=267)	Observational study	12.5–50 mg/d (N=30)	Not defined	Request of insomnia prescription (Subj)	Trazodone may be effective in treatment of insomnia and nightmares in patients with cancer	Strengths: Homogenous cohort of advanced cancer patients. Limitations: Single site; small sample; 7-day study duration for each participant; lack of objective measures.
Khazaie et al[19] (2013)	Secondary insomnia: 3rd trim pregnancy (N=67)	Randomized, placebo-controlled	50mg/d (N=20)	6 weeks	Actigraphy (Obj)	Trazodone improved sleep quality during pregnancy	Strengths: First RCT to assess the effect of trazodone in pregnant women; homogenous cohort. Limitations: Relatively small sample; no long-term follow-up past 6 weeks; drug serum levels were not measured; only 3 nights of actigraphy monitoring.

Abbreviations: PSG = polysomnographic, Obj = objective, Sub = subjective, CBT = cognitive behavioral therapy, VAS = visual analogue scale, HAM-D = Hamilton Depression Scale, PSQI = Pittsburgh Sleep Quality Index, EEG = electroencephalogram, LSEQ = Leeds Sleep Evaluation Questionnaire, NPI = neuropsychiatric inventory, SPD = somatoform pain disorder, SASAQS = Self-assessment of Sleep & Awakening Quality Scale

Doroudgar et al[24] (2013)	Secondary insomnia: Psychiatric inpatients age 18–65 (N=64)	Observational study	102mg (12.5–300mg/d) (N=30)	Up to 2 weeks	Patient interview and sleep log (Subj)	Trazodone was preferred over quetiapine for improvement of total sleep	Strengths: Stringent exclusion criteria. Limitations: Small sample; variable medication regimen across treatment groups; observational study; no objective measures; single-site study.
Stein et al[26] (2012)	Secondary insomnia: methadone-maintenance Mean age 38 (N=137)	Randomized, double-blind placebo-controlled	50–150mg/d Self-titrate (N=69)	6 months	PSQI PSG (Subj/Obj)	Trazodone did not improve subjective or objective sleep disturbance	Strengths: First placebo-controlled RCT for opiate dependent persons; participant follow-up; sufficient power; use of PSG measure. Limitations: Smaller sample size.
Camargos et al[25] (2011)	Secondary insomnia: Dementia Mean age 79 (N=178)	Retrospective study	50mg/d (N=34) 100mg/d (N=1)	Not defined	Not defined	Trazodone is effective in treating for insomnia associated with dementia	Strengths: Representative cohort of older adults with dementia; longitudinal follow-up over 1 year of the study; strict exclusion criteria; comprehensive demographic characteristics provided. Limitations: No objective measures; observational study; absence of a placebo-controlled group
Galecki et al[27] (2010)	Insomnia	Article in Polish	Article in Polish	Article in Polish	Article in Polish	Trazodone can be effective in the treatment of insomnia with small adverse reactions	Strengths: N/A Limitations: N/A
Paterson et al[28] (2009)	Healthy men Age range 21–34 (N=12)	Randomized, double-blind placebo-controlled	100 mg/d + caffeine (N=12)		PSG EEG (Obj)	Trazodone improved sleep latency & total sleep time	Strengths: Use of PSG measure; double-blind study. Limitations: Small sample size.
Sheehan[29] (2009)	Secondary insomnia: Depressed patients (N=412)	Randomized placebo-controlled	150–375mg/d (N=206)	8 weeks	HAM-D (Subj)	Trazodone improved middle & late insomnia	Strengths: Large randomized study sample; inclusion of intent-to-treat analysis. Limitations: No follow-up after 8 weeks of study.

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Friedmann et al[30] (2008)	Secondary insomnia: Alcohol-detox Ages 18–65 (N=173)	Randomized, double-blind, placebo-controlled	50–150mg/d (N=88)	12 weeks	PSQI (Subj)	Trazodone was associated with improved sleep quality, but can lead to increased drinking when stopped	Strengths: Double-blind, placebo-controlled RCT; reasonable follow-up; robust statistical analysis for missing data; stringent exclusion criteria. Limitations: Small sample; single site; no objective measures; study attrition.
Paterson et al[31] (2007)	Healthy men & rats Age range 21–34 (N=12)	Randomized, double-blind placebo-controlled	100 mg/d + caffeine (N=12)	4 weeks	PSG LSEQ (Subj/Obj)	Both zolpidem and trazodone improved subjective sleep latency	Strengths: Established an effective model of onset insomnia; experimental design; use of PSG monitoring. Limitations: Translational model; did not account for sensitivity to caffeine; small sample size.
Saletu et al[32] (2005)	Secondary insomnia: somatoform pain disorders (N=11)	Sleep laboratory study	100 mg/d (N=6)		PSG Psychometry (Subj/Obj)	SPD induced changes in subjective & sleep quality which was mitigated by trazodone	Strengths: Use of PSG monitoring; homogenous cohort. Limitations: Small sample size.
Kaynak et al[33] (2004)	Secondary insomnia: Depressed women age range 20–50 (N=12)	Double-blind, crossover, placebo-controlled	100 mg/d (N=6)	14 days	PSG PSQI (Subj/Obj)	Trazodone is effective in the treatment of antidepressant-associated insomnia	Strengths: Clinician rating scale used; objective measures included; PSG recordings were scored blinded; random assignment to treatment; homogeneous female cohort. Limitations: Small sample size; single dose amount.
Schwartz et al[34] (2004)	Secondary insomnia: psychiatric inpatients (N=15)	Open and randomly assigned to trazodone or zaleplon	50–100mg/d (N=15)	As-needed basis		Trazodone may be a better agent to promote longer, deeper subjective quality sleep for psychiatric inpatients with insomnia	Strengths: Random assignment; flexible-dosing schedule; homogenous inpatient cohort. Limitations: Small sample size.

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Saletu-Zyhlarz et al[35] (2003)	Secondary insomnia: depressed patients all age groups (N=549)	Open-label study	50–300mg/d controlled-release (N=549)	6 weeks	HAM-D Self-rating (Subj)	Insomnia was ranked to be the most improved symptom after treatment of trazodone	Strengths: Large sample; multicenter study across 80 outpatient clinics; small attrition rate. Limitations: No inclusion of objective measures.
Karam-Hage & Brower[36] (2003)	Secondary insomnia: Alcohol-dependent Mean age 44 (N=50)	Open pilot study	(105 =/- 57 mg) at bedtime (N=16)	4–6 weeks	Sleep problems questionnaire (Subj)	Significant sleep improvement was reported during treatment with either trazodone or gabapentin	Strengths: First study to compare gabapentin and trazodone for treating insomnia in alcohol-dependent patients; required 4 weeks of abstinence to initiate participation in the study; included study follow-up. Limitations: Small sample; non-randomization; no placebo control; non-blinded; 2 patients admitted to drinking during the study period.
Le Bon et al[37] (2003)	Secondary insomnia: Alcohol-dependent (N=16)	Double-blind, placebo-controlled	Titrated up to 200 mg/d (N=8)	4 weeks	PSG (Objective)	Trazodone can be potentially helpful in the treatment of alcohol post-withdrawal insomnia	Strengths: PSG monitoring; inclusion of secondary measures (HRSD); robust inclusion and exclusion criteria to ensure a homogenous cohort. Limitations: Small sample size.
Saletu-Zyhlarz et al[38] (2002)	Secondary insomnia: Depressed patients Healthy controls (N=22)	Single-blind, crossover, placebo-controlled	100mg/d (N=11)	1 night	-PSG -SASAQS (Subj/Obj)	100mg trazodone increased total sleep and sleep efficiency, but not sleep latency	Strengths: Objective and subjective measures; placebo-controlled design; homogenous cohort. Limitations: Small sample size; short observation duration; no follow-up; evening and morning blood pressure was higher in depressed patients.
Saletu-Zyhlarz et al[39] (2001)	Secondary insomnia: Dysthymic patients mean age 50 +/- 14 (N=22)	Single-blind, crossover, placebo-controlled	100mg/d (N=11)	1 night	-PSG -SASAQS (Subj/Obj)	100mg trazodone improved objective and subjective sleep and awakening quality (increased slow-wave sleep)	Strengths: PSG monitoring and subjective measures; placebo-controlled design; homogenous cohort. Limitations: Small sample.

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Warner et al[40] (2001)	Secondary insomnia: PTSD patients (N=74)	Survey on usefulness of trazodone	dose range 50–200 mg/d (N=74)		Empirically designed question (Subj)	Trazodone was effective in patients with chronic PTSD, insomnia, and frequent nightmares	Strengths: Homogeneous cohort. Limitations: No control group; moderate levels of participant discontinuation due to priapism or daytime sedation; no objective measures; single institution.
Mashiko et al[41] (1999)	Secondary insomnia: Depressed patients (N=75)	Dose-finding study; randomized non-controlled	50, 75, or 100mg/d (N=75)	6 weeks	Self-rating for sleep (Subj)	Trazodone at dosage 50–100mg/d improved sleep disorders and most effective at 100mg/day	Strengths: First dose-finding study on trazodone that excluded concomitant use of hypnotics during depressive state; multi-dose comparison groups. Limitations: Limited demographic characteristics provided.
Haffmans & Vos[42] (1999)	Secondary insomnia: Depressed patients with brofaromine-induced insomnia (N=17)	Randomized, double-blind, crossover, placebo-controlled	50mg/d (N=7)	1 week	PSG HAM-D (Subj/Obj)	Low doses of trazodone may be safe and effective in the treatment of MAO-I induced insomnia	Strengths: Double-blind, placebo-controlled design with random assignment; exclusion of participants on other psychoactive medications. Limitations: Small sample with large variability in sleep parameters.
Yamadera et al[43] (1999)	Healthy men (N=12)	Non-randomized, non-controlled	50–100 mg/d (N=12)	2 nights	PSG (Obj)	Trazodone increased slow-wave sleep	Strengths: PSG monitoring. Limitations: Small sample; non-randomized single-blind study method.
Arriaga et al[44] (1997)	Secondary insomnia: Major depression (N=9)	Single-blind	50–250 mg/d (N=9)	5 weeks	EEG (Obj)	Trazodone improved objective insomnia and increased amounts of slow-wave sleep	Strengths: PSG monitoring; longer duration study with 2-week placebo run-in period. Limitations: Small sample size; single-blind study method.
Nierenberg et al[45] (1994)	Secondary insomnia: Depressed fluoxetine bupropion-induced insomnia (N=17)	Randomized, double-blind, crossover, placebo-controlled	50–100 mg/d (N=17)	6.5 days (mean)	PSQI (Subj)	Trazodone is an effective hypnotic for patients with antidepressant-associated insomnia	Strengths: Double-blind crossover trial; homogenous cohort. Limitations: Small sample size; no objective measures.

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Parrino et al[46] (1994)	Secondary insomnia: Dysthymic patients middle aged (N=6)	Non-randomized, non-controlled, single-blind	50–100 mg/d (N=6)	6 weeks	PSG VAS (Subj/Obj)	No significant sleep initiation and maintenance, while significant increase of slow-wave sleep and reductions of stage 2	Strengths: PSG monitoring; homogenous cohort; 6-week phase schedule with increasing dosing schedule. Limitations: Small sample size.
Van Bemmel et al[47] (1992)	Secondary insomnia: Depressed outpatients (N=8)	Non-randomized, non-controlled, single-blind	300–400 mg/d (N=8)	5 weeks	PSG (Obj)	Trazodone did not influence slow-wave sleep but did suppress REM sleep	Strengths: PSG monitoring. Limitations: Small sample size and non-randomized design.
Scharf & Sachais[48] (1990)	Secondary insomnia: Depressed patients (N=6)	Non-randomized, non-controlled, single-blind	150–400 mg/d (N=6)	8 weeks	PSG (Obj)	Trazodone significantly improved symptoms of depression and polysomnographic sleep architecture	Strengths: Double-blind, crossover study design; PSG monitoring; 4 dosing schedules. Limitations: Small sample size.
Ware & Pittard[49] (1990)	Healthy men (N=6)	Double-blind, crossover, placebo-controlled	50–200 mg/d (N=6)	4 nights	PSG (Obj)	Trazodone significantly increased time spent in deep sleep without affecting normal sleep architecture	Strengths: Double-blind, crossover study design; PSG monitoring; 4 dosing schedules. Limitations: Small sample size.
Jacobsen[50] (1990)	Secondary insomnia: Major depression-MAOI-induced insomnia (N=48)	Open trials	50–75 mg/d (N=48)			Low-dose trazodone may be safe and effective for treating MAOI-induced and other insomnias	Strengths: Homogenous depressed cohort treated with MAOIs. Limitations: Small sample size.
Botros et al[55] (1989)	Secondary insomnia: Depressed patients (N=20)	Randomized, double-blind, parallel-group	50mg/d (N=10)	3 weeks	Sleep questionnaires	Trazodone improved sleep quality	Strengths: Randomized, double-blind design; compared efficacy of trazodone with amitriptyline; robust exclusion criteria; investigated the effect of trazodone on cognition and psychomotor functioning. Limitations: Small sample size.
Davey[51] (1988)	Secondary insomnia: Depressed patients (N=183)	Randomized, double-blind, parallel-group	50mg/3x/d (N=87) 150mg/d (N=95)	6 weeks	LSEQ (Subj)	150mg trazodone produced greater benefit to sleep and quality of sleep during first few weeks	Strengths: Multicenter, double-blind, randomized trial; larger sample; efficacy study of 2 dosing regimens; Limitations: No objective measures.

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Moon & Davey[52] (1988)	Secondary insomnia: Depressed outpatients (N=39)	Randomized, double-blind, parallel-group	150mg/d (N=19)	6 weeks	HAM-D LSEQ (Subj)	150mg trazodone improved ease of getting to sleep and quality of sleep	Strengths: Double-blind, randomized trial; homogeneous depressed cohort; Limitations: Small sample.
Mouret et al[53] (1988)	Secondary insomnia: Depressed inpatients (N=10)	Non-randomized, non-controlled	400–600mg/d (N=10)	5 weeks	PSG (Obj)	Trazodone would be indicated for depressed individuals with insomnia	Strengths: Homogeneous depressed inpatient cohort; PSG monitoring; plasma levels of trazodone monitored. Limitations: Small sample size.
Blacker et al[54] (1988)	Secondary insomnia: Depressed outpatients (N=227)	Randomized, double-blind, parallel-group	150mg/d	6 weeks	LSEQ (Subj)	Trazodone improved sleep quality and ease of getting to sleep and was associated with lower incidence of dry mouth and drowsiness	Strengths: Multicenter, double-blind, randomized trial; larger sample; compared efficacy of trazodone to mianserin, dothiepin, and amitriptyline. Limitations: No objective measures.
Ather et al[56] (1985)	Secondary insomnia: Elderly depressed (N=149)	Randomized, double-blind, parallel-group	100–300 mg/d (N=51)	6 weeks	VAS (Subj)	Trazodone improved subjective reports of sleep	Strengths: Randomized, double-blind design; homogenous elderly cohort. Limitations: Small sample size.
Wheatley[57] (1984)	Secondary insomnia: depressed patients (N=146)	Randomized, controlled trial	100–150 mg/d (N=146)	6 weeks	HAM-D VAS (Subj)	Trazodone administered as a single or twice daily dosage improved sleep	Strengths: Larger sample size; randomized, controlled trial. Limitations: No objective measures.
Montgomery[58] (1983)	Self-reported "poor sleepers" mean age 61 (N=9)	Non-randomized, non-controlled	150mg/d (N=9)	3 weeks	PSG VAS (Subj/Obj)	Trazodone improved subjective sleep ratings during the first 2 weeks	Strengths: Objective measures; initial 2-week placebo dosing schedule. Limitations: Small sample size; non-randomized.

Abbreviations: PSG = polysomnographic, Obj = objective, Sub = subjective, CBT = cognitive behavioral therapy, VAS = visual analogue scale, HAM-D = Hamilton Depression Scale, PSQI = Pittsburgh Sleep Quality Index, EEG = electroencephalogram, LSEQ = Leeds Sleep Evaluation Questionnaire, NPI = neuropsychiatric inventory, SPD = somatoform pain disorder, SASAQS = Self-assessment of Sleep & Awakening Quality Scale

trazodone on sleep latency were comparable with placebo.[18]

Approximately a decade later, three additional studies examined trazodone's effects in the treatment of insomnia.[15–17] Roth and colleagues examined the hypnotic efficacy and daytime effects of trazodone in a randomized, double-blind, placebo-controlled crossover study that enrolled 16 adults.[15] They found that 50mg of trazodone administered 30 minutes before bedtime was effective for sleep maintenance but that it was possibly associated with motor and cognitive impairments.[15] Zavesicka et al evaluated the clinical efficacy of cognitive behavioral therapy (CBT) alone and in combination with trazodone in a randomized comparative trial of 20 subjects, and they reported that CBT+trazodone was the most effective for management of primary insomnia.[16] Wichniak et al studied long-term insomnia treatment by treating 28 subjects with trazodone (dosed ranges 25–150mg/d) for three months and concluded that trazodone improved sleep quality and daytime functioning.[17] In a recent randomized controlled trial conducted across two phases, 224 adults were randomized to receive either behavioral therapy or zolpidem in phase 1, while those who were unable to achieve remission were randomized to a second six-week treatment involving trazodone (50–150mg/d), zolpidem, or behavioral therapy; this clinical trial is currently ongoing and expected to provide new information about the optimal treatment for managing insomnia.[14]

EFFICACY IN SECONDARY INSOMNIA

Evidence of trazodone's effect in depressed subjects with insomnia. The first RCTs that evaluated the efficacy of trazodone for the treatment of insomnia among depressed populations originated from two studies in the 1980s.[56,57] Since that time, the interest in the hypnotic effects of trazodone has significantly increased. Likewise, the clinical efficacy of trazodone for treating patients suffering from insomnia associated with depression has been discussed in more depth recently.[51–55] Of the 21 studies in the current review that examined depressed patient populations,[20,29,33,35,38,39,41,44,46–48,51–57] seven were conducted in the 1980s[51–57]; these studies primarily focused on the antidepressant activity of trazodone (high dose ≥100mg) and included subjective measures of sleep endpoints as a secondary analysis (Table 1). Wheatley et al and Ather et al used a visual analogue scale (VAS) to subjectively assess patients' quality of sleep, and both of these studies reported improved sleep quality for participants, with drowsiness being the most commonly reported side effect.[56,57] Three clinical trials employed the Leeds Sleep Evaluation Questionnaire and reported "ease of getting to sleep" and "quality of sleep" following six weeks of treatment with trazodone (150mg/d).[51,52,54]

More recently, eight studies were performed with depressed or dysthymic patients, and these studies focused on the effects of trazodone in treating medication-induced or depression-associated insomnia.[41,42,44–48,50] In an open-label, six-week RCT, the effective dose of trazodone was evaluated in 75 subjects, with a 50mg/d trazodone dose for two weeks, and then participants were randomized to receive 50, 75, or 100mg/d for the remaining four weeks. All doses improved sleep symptoms, as rated by sleep items on the Hamilton Depression Rating Scale (HAM-D), while the optimal result was achieved at 100mg/d of trazodone.[41] Three trials evaluated trazodone's effects with medication-induced insomnia, such as monoamine oxidase inhibitors or selective serotonin reuptake inhibitors; it was reported that trazodone was effective and safe for treating antidepressant-induced insomnia.[42,45,50] The remaining four studies had small sample sizes (6–9 subjects) with unconventional methodology, making it difficult to analyze the results.[44,46–48]

Finally, the sedative effects of trazodone were evaluated in four studies conducted in dysthymic and depressed patients during the 2000s.[29,35,38,39] In a placebo-controlled, crossover study, one night of treatment with trazodone (100mg) was reported to increase slow-wave sleep but not sleep latency or total sleep time.[39] A subsequent study from the same authors reported that 100mg of trazodone increased the total sleep time but did not shorten sleep latency.[38] In a multicenter open-label study, Saletu-Zyhlarz and colleagues treated 549 patients with 50 to 300mg of controlled-release trazodone, and patients reported significant improvement on the HAM-D across the six-week study.[35] In a randomized placebo-controlled study, 206 subjects were randomized to receive 150 to 375mg of trazodone and reported improvements in middle and late insomnia.[29] In a pilot study conducted in 2016, Giannaccini et al investigated the relationship between melatonin and trazodone in a group of 17 patients suffering from insomnia associated with mood disorders and reported that trazodone normalized sleep and mood by interacting with melatonin.[20]

Evidence of trazodone's effect in non-depressed subjects with insomnia. As indicated in Table 1, 19 studies enrolled non-depressed subjects with secondary insomnia.[19,21–28,30–32,34,36,37,40,43,49,58] Three of these studies were conducted with healthy men and employed objective polysomnographic (PSG) measures, which revealed improved time spent in deep sleep (increased slow wave) without affecting normal sleep architecture.[31,43,49] Three additional studies were conducted with alcohol-dependent subjects.[30,36,37] In a small, placebo-controlled trial, Le Bon et al treated 16 patients with 50mg of trazodone initially and gradually increased the dosage to 200mg; the PSG measures demonstrated improved sleep efficiency for patients on Day 3 but not on Day 28.[37] In a larger, placebo-controlled trial conducted over 12 weeks, 88 patients with alcohol dependence were prescribed 50 to 150mg of trazodone, and study

findings revealed that trazodone significantly improved sleep, as measured by the Pittsburgh Sleep Quality Index (PSQI).[30] Interestingly, discontinuation of trazodone was associated with increased drinking.[30]

In the past 10 years, the treatment efficacy of trazodone for primary insomnia has been well documented.[14–16] In addition, the efficacy of trazodone for treating secondary insomnia related to depression, post-menopause, advanced cancer, dementia, methadone maintenance, post-traumatic stress disorders (PTSD), and somatoform pain disorders also has been demonstrated.[21,23,25,26,32,40]

More recently, the effectiveness of trazodone was compared to quetiapine among psychiatric inpatients, and trazodone was reported to be more effective than quetiapine for improvement of total sleep.[24] A recent double-blind, controlled trial randomized 36 patients to receive either trazodone or matching placebo for two weeks and showed that 50mg/d was safe and effective in the treatment of insomnia for patients with Alzheimer's disease.[22]

Finally, the sedative effects of trazodone for the treatment of insomnia were evaluated in 67 pregnant patients who were randomized to receive one of the following: trazodone (50mg/d), diphenhydramine, or placebo. The researchers used a wrist actigraphy to record total sleep time and assess sleep efficiency, and the team concluded that the use of trazodone or diphenhydramine to treat insomnia during the third trimester of pregnancy could help prevent postpartum depression.[19]

SAFETY

The most common adverse side effects of trazodone are relatively mild and include daytime sleepiness, headache, and orthostatic hypotension.[59] As trazodone is an α1-adrenergic antagonist, trazodone might carry the risk of causing hypotension, namely postural hypotension. Therefore, in clinical practice, clinicians are encouraged to consider the risk of hypotension when patients take trazodone. Postural hypotension can be a potentially serious condition, particularly in the elderly, who might fall and injure themselves when they get up, especially at night. In a double-blind, two-week, placebo-controlled study, the effective dose of 50mg/d was evaluated in 15 Alzheimer's patients; trazodone was well tolerated, and adverse effects were transient, mild, and safe.[22] Although impaired next-day memory performance, equilibrium, and muscle endurance have not been mentioned in the literature,[22] findings from this study were consistent with other previous studies.[18,19,33,38] Nonetheless, the literature has reported some adverse problems, both clinically and in prior clinical trials, although it is not common or problematic for the majority of older adult patients. Roth and colleagues reported cognitive and motor impairments after three weeks of 50mg/d trazodone use.[15] In a recent double-blind, placebo-controlled study conducted over six months, 69 subjects were prescribed trazodone (50–150mg/d), and findings revealed that trazodone was safe and well tolerated in combination with methadone.[26] Similar results (little to no adverse effects) have been observed in studies with low doses (25–100mg/d) of trazodone for the treatment of insomnia in non-depressed populations.[16,17,20,22,23,25] At higher doses of trazodone (>100mg/d), drowsiness has been reported.[52,54,56] As drowsiness has been a reported side effect of trazodone, there is the concern that patients might "nod off" while driving. Given the sedative nature of trazodone, patients should be encouraged to refrain from driving while taking the medication. Rarely, trazodone can cause priapism (between 1 in 1,000 and 1 in 10,000), and increased libido has been reported in clinical practice, which is one of the primary reasons it has been considered effective in the treatment of sexual dysfunction.[60,61] Gastric distress, nausea, vomiting, and decreased appetite are rarely reported as side effects for trazodone.[62] Trazodone presents with minimal anticholinergic features, and it is known to have fewer cardiovascular side effects than tricyclic antidepressants (TCAs).[63] Nevertheless, Rausch and colleagues reported that one young woman developed significant QT prolongation after acute trazodone overdose.[64] In sum, trazodone is generally safe and well tolerated, but it carries some risk and has a side-effect profile that differs from other widely used hypnotics, including but not limited to QT prolongation, abnormal bleeding, hyponatremia, priapism, acute angle glaucoma, neuroleptic malignant syndrome (particularly in older women), problems in select cardiac patients, drug-drug interactions (especially via 3A4), and switches into mania/hypomania. Furthermore, upswitching into impulsive suicidality can occur. For more information pertaining to the safety of trazodone, readers are encouraged to examine additional review studies that were not included in the current manuscript.[65,66]

DISCUSSION

The relevant studies demonstrate that trazodone is effective in decreasing sleep latency and increasing sleep duration. Furthermore, trials with active treatment periods from 6 to 12 weeks reported significant improvement in quality of sleep.[16,17,19,29,30,35,41,52,54] The majority of earlier studies have focused on utilizing high doses of trazodone (e.g., >100mg/d) for insomnia among depressed patient populations.[47,48,52–54,56] However, since the 2000s, the utility of low doses of trazodone (25–100mg) has been expanded to treat secondary insomnia among the non-depressed population as well. For example, trazodone has been shown to improve sleep in healthy adults who initially developed insomnia as a result of chronic caffeine intake.[28] Trazodone can

improve sleep in patients who experience insomnia comorbid with other general conditions as well (e.g., somatoform pain disorder) and has been shown to be highly effective in the treatment of insomnia among patents with Alzheimer's disease, pregnant women with insomnia, and patients with other comorbid psychiatric conditions. It also has been particularly effective for patients who have insomnia comorbid with PTSD. In cases where insomnia is a feature and result of a depressive episode, trazodone is the preferred recommended therapeutic, especially among patients with cardiac disorders.[67]

LIMITATIONS

One limitation of the current review was the lack of systematic analysis of measuring insomnia. Depending on the location of the study, some measurement questionnaires have been adapted by previous investigators so that foreign subjects could better comprehend items on the questionnaires or measures used in each study. Another limitation stems from myriad subjective and objective measurement tools that are available and used in research studies, which complicates the literature and makes it difficult to examine treatment efficacy across studies. As the types of scales and assessments used were not uniform, there is an inherent challenge that arises when trying to systematically compare results of multiple studies. Last, there was no evidence from equipment-based measurements in confirming the effect of trazodone on insomnia and patient-reported outcomes among different psychiatric disorders.

CONCLUSION

The findings in this review show that trazodone is a generally safe therapeutic that has been repeatedly validated as an efficacious treatment for insomnia, particularly for patients with comorbid depression. Trazodone has been effective for insomnia across many different populations. While it is not currently a drug indicated for insomnia, it is among the most common off-label choices for treating insomnia. This review article has found that trazodone can be an effective option when treating insomnia with little to no risk in most cases. Of note, trazodone produces a low risk for habit-formation and addiction. In addition, trazodone also produces few adverse reactions, with select exceptions (e.g., drug interactions). Most of the studies included in this review reported minimal to no side effects with trazodone. While the initial onset of insomnia is typically habituated by patients' responses, as earlier stated, trazodone might be able to negate those responses while patients go through recommended courses of cognitive behavioral therapy. Findings from the current study are especially promising for the treatment of comorbid conditions. While the current findings are encouraging, larger randomized clinical trials using objective measures are still needed in order to better understand the effectiveness of trazodone in treating insomnia. Future researchers should focus on the long-term benefits of insomnia treatment with trazodone, investigate its safety and efficacy in pediatric populations or other patient populations with secondary insomnia (e.g., sleep apnea, chronic pain, fibromyalgia, psychotic disorders), and explore and investigate the role that remission from insomnia might possibly play in contributing to the prognosis of other psychiatric conditions.

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