A Review of the Evidence for the Efficacy and Safety of Trazodone in Insomnia

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Received March 26, 2004; accepted Sept. 23, 2004. From the University of Chicago, Chicago, Ill.

Sepracor Inc. assisted in the preparation of this manuscript, and Dr. Mendelson received compensation from Sepracor Inc. for the services he provided in support of the development of this manuscript.

Dr. Mendelson has served as a consultant for VivoMetrics Inc., Sepracor, Sanofi, Neurocrine, Aventis, Merck, King, and Elan.

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Objective: Trazodone, a triazolopyridine antidepressant, is currently the second most commonly prescribed agent for the treatment of insomnia due to its sedating qualities. Given trazodone's widespread use, a careful review of the literature was conducted to assess its efficacy and side effects when given for treatment of insomnia.

Data Sources: In April 2003, a MEDLINE search was conducted using the search terms *trazodone and insomnia* and *trazodone and sleep* and restricted to 1980–2003, human subjects, and English language. As trazodone has been implicated in cardiac disorders, a further search was conducted using the term *cardiac and trazodone*.

Study Selection: All clinical trials that measured any endpoint for insomnia efficacy were included in the assessment. A total of 18 studies were identified from the literature search. In addition, commonly used texts were consulted for information regarding adverse effects related to trazodone.

Data Extraction: Because so few studies were identified by the literature search, all were evaluated and described.

Data Synthesis: Evidence for the efficacy of trazodone in treating insomnia is very limited; most studies are small, conducted in populations of depressed patients, raise issues of design, and often lack objective efficacy measures. Side effects associated with trazodone are not inconsequential, with a high incidence of discontinuation due to side effects, such as sedation, dizziness, and psychomotor impairment, which raise particular concern regarding its use in the elderly. There is also some evidence of tolerance related to use of trazodone.

Conclusion: Given the relative absence of efficacy data in patients with insomnia and the adverse events associated with trazodone's use in general, it is uncertain whether the risk/benefit ratio warrants trazodone's use in nondepressed patients with insomnia.

(J Clin Psychiatry 2005;66:469–476)

Trazodone was approved in 1982 for the treatment of depression. It is currently the second most commonly prescribed medication for the treatment of insomnia.[1] Prescription utilization records from 1987 through 1996 indicate that prescribing trazodone for depression decreased throughout this decade, while off-label use of the drug for insomnia increased steadily until it was the most frequently prescribed insomnia agent.[2] By 2001, zolpidem had taken over as the leading medication used in insomnia.[1] Trazodone's popularity for managing insomnia may be related to a number of factors, including its *perceived* absence of risk, its availability as a generic agent, its unscheduled status, and the lack of restrictions on prescription duration.

Trazodone is a triazolopyridine derivative, chemically and pharmacologically distinct from other antidepressants.[3] Although the precise mechanisms of action are not fully understood, trazodone is thought to be a weak but specific inhibitor of synaptosomal reuptake of serotonin (5-HT). It also has antagonistic action at the 5-HT_{1A}, 5-HT_{1C}, and 5-HT_2 receptors,[3] as well as at α_1-adrenoceptors and to a lesser extent α_2-adrenoceptors. The alpha-blocking properties may be associated with the side effects of orthostatic hypotension and priapism.

Due to its sedating qualities, trazodone has increasingly been prescribed off-label for insomnia at subtherapeutic antidepressant doses of 100 mg or less.[2,4] One dose-finding study[5] conducted in 75 depressed patients found effects on sleep disorders at doses of 50 to 100 mg/day, with 100 mg/day being the most effective dose. The dose in nondepressed patients with sleep disorders has not been established. Trazodone's half-life is approximately 6.4 hours in younger adults and 11.6 hours in the elderly.[6,7] In view of trazodone's widespread use in treating insomnia, it seems worthwhile to carefully review what is known of its efficacy and side effects.

To that end, a MEDLINE search was conducted using the search terms *trazodone and insomnia* and *trazodone and sleep* and restricted to English-language articles describing studies published from 1980 through April 2003 in human subjects. Commonly used texts were consulted for information regarding adverse effects related to trazodone. A further search was conducted using the search string *cardiac and trazodone*, as trazodone has been implicated in cardiac disorders.

EFFICACY

Overview

There is a paucity of clinical trial data that examine trazodone's effect on insomnia. Eighteen studies[5,10–26] were identified that evaluate trazodone's effect on sleep endpoints (Table 1). Studies are grouped in the table according to similarities in research objectives and study populations. Two additional studies,[8,9] published after the completion of the MEDLINE search, were included in this article for completeness. The majority of these studies were small; only 5 trials enrolled more than 30 patients in trazodone arms.[5,10–13] The studies were also of limited duration. Half of the trials employed an active treatment period of 3 weeks or less[13–19,23,24]; no trials exceeded 6 weeks of active treatment. Only 3 trials were of randomized, double-blinded, and placebo-controlled design.[13–15] Of these 3 trials, only 1 employed objective measures[14]; it was conducted in 7 depressed patients with brofaromine-induced insomnia and had an active treatment duration of only 1 week. Fourteen of the studies were performed in depressed populations in which insomnia was either secondary to depression or induced by antidepressants,[5,10–12,14,15,19–26] and 2 studies assessed trazodone's effect on sleep in healthy subjects.[16,17] Only 2 studies were identified that examined trazodone's effect in nondepressed subjects with sleep disorders.[13,18]

Efficacy in Primary Insomnia

In the only placebo-controlled trial of trazodone conducted to date in primary insomnia, Walsh et al.[13] compared the hypnotic efficacy of trazodone and zolpidem with placebo in 306 adults (aged 21–65 years). Subjects were randomly assigned to receive trazodone 50 mg, zolpidem 10 mg, or placebo nightly for 2 weeks. Sleep parameters were assessed using a subjective sleep questionnaire that patients completed each morning and at weekly office visits. There were no objective measurements. Self-reported endpoints included sleep latency, sleep duration, number of awakenings (NAW), and wake time after sleep onset (WASO) (the last 2 being measurements of sleep maintenance). Relative to placebo, patients reported significant improvement in subjective sleep latency, sleep duration, WASO, and sleep quality with trazodone and zolpidem during week 1 ($p < .02$), and sleep latency for zolpidem was significantly shorter than that for trazodone ($p < .037$). During week 2, the trazodone group did not differ significantly from the placebo group. However, the zolpidem group demonstrated significant improvement compared with placebo for sleep latency ($p = .037$) and sleep duration ($p < .02$) even though the placebo group demonstrated increases in sleep duration over the 2-week period (25 minutes above baseline during week 1 and 37 minutes during week 2).[13]

The other study that evaluated the effect of trazodone on sleep in nondepressed subjects enrolled 9 self-described "poor sleepers" (aged 50–70 years)[18]; no criteria were used to establish a diagnosis of primary insomnia or depression. This study used both subjective and objective measures. Sleep quality was subjectively rated through visual analogue scales (VAS). Other sleep endpoints, including analysis of sleep stages, were evaluated objectively by polysomnography (PSG) conducted in a sleep laboratory environment. In the subjective ratings, sleep quality improved significantly during weeks 1 and 2 ($p < .001$) but not during week 3. In terms of objective measures, trazodone had no effect on sleep duration (as measured by total sleep time [TST]) or sleep latency, but WASO was reduced over 3 weeks of treatment relative to baseline.[18]

Efficacy in Secondary Insomnia

As indicated in Table 1, 14 studies enrolled depressed or dysthymic patients and analyzed insomnia as a correlate of depression.[5,10–12,14,15,19–26] Five of these studies, all conducted in the 1980s, focused primarily on the antidepressant activity of trazodone and included subjective measures of sleep endpoints as a secondary analysis.[10–12,19,20] Ather et al.[10] used a VAS to subjectively assess how well patients slept. Patients ($N = 51$) treated with trazodone 100 to 300 mg demonstrated improved subjective reports of sleep, but there was no statistical significance or dose differentiation reported.[10] A quarter of the subjects in the trazodone arm discontinued the study; 9 of these 13 patients withdrew due to side effects, with dizziness being the most frequently reported event leading to discontinuation. In terms of overall side effects reported during the trial, drowsiness was the most common side effect in the trazodone cohort (25% of 36 events reported).[10] Botros et al.[19] measured sleep quality and duration through a subjective sleep questionnaire. Sleep quality was statistically improved ($p < .001$) in the 112 patients treated with trazodone 150 mg, but there was no effect on sleep duration.[19]

Three of these 5 trials employed the Leeds Sleep Evaluation Questionnaire, which evaluates 4 sleep factors: "ease of getting to sleep," "quality of sleep," "ease of awakening," and "feelings on and after awakening."[11,12,20] All 3 trials, which administered 150 mg of trazodone either as a single nightly dose or as a 50-mg dose 3 times a day, reported improvements throughout the

Table 1. Trazodone Clinical Trials With Effects on Sleep Endpoints

Reference (Year)	Study Design	Study Population (N)	Trazodone Dosage, mg/d (N)	Active Treatment Duration	Objective Sleep Assessment	Subjective Sleep Assessment
Primary insomnia						
Walsh et al[13] (1998)	Randomized, double-blind, parallel-group, placebo-controlled	DSM-III-R–defined primary insomniacs (N = 306)	50 (N = 100)	2 weeks	none	Sleep questionnaire
Montgomery et al[18] (1983)	Nonrandomized, noncontrolled	Middle-aged self-described "poor sleepers" (N = 9)	150 (N = 9)	3 weeks	PSG	VAS
Depression with secondary assessment of sleep function						
Ather et al[10] (1985)	Randomized, double-blind, parallel-group	Elderly depressed inpatients and outpatients (N = 149)	100–300 (N = 51)	6 weeks	none	VAS
Blacker et al[11] (1988)	Randomized, double-blind, parallel-group	Depressed outpatients (N = 227)	150 (N = 112)	6 weeks	none	Leeds Sleep Evaluation Questionnaire
Botros et al[19] (1989)	Randomized, double-blind, parallel-group	Depressed patients (N = 20)	50 (N = 10)	3 weeks	none	St. Mary's Hospital Sleep Questionnaire
Davey[12] (1988)	Randomized, double-blind, parallel-group	Depressed patients (N = 183)	50 tid (N = 87) or 150 nightly (N = 95)	6 weeks	none	Leeds Sleep Evaluation Questionnaire
Moon and Davey[20] (1988)	Randomized, double-blind, parallel-group	Depressed outpatients (N = 39)	150 (N = 19)	6 weeks	none	Leeds Sleep Evaluation Questionnaire
Secondary insomnia (depression-associated or antidepressant-induced)						
Haffmans and Vos[14] (1999)	Randomized, double-blind, crossover, placebo-controlled	Depressed patients with brofaromine-induced insomnia (N = 7)	50 (N = 7)	1 week	PSG	HAM-D
Mashiko et al[5] (1999)	Dose-finding study; randomized, noncontrolled	Depressed patients with sleep disorders (N = 75)	50, 75, or 100 (N = 75)	6 weeks	none	HAM-D; HAM-A; Self-Rating Depression Scale; Self-Rating for Sleep
Mouret et al[21] (1988)	Nonrandomized, noncontrolled	Depressed inpatients (N = 10)	400–600 (N = 10)	5 weeks	PSG	Spiegel and Norris sleep scales
Nierenberg et al[15] (1994)	Randomized, double-blind, crossover, placebo-controlled	Depressed patients with fluoxetine- or bupropion-induced insomnia (N = 17)	50–100 (N = 17)	6.5 days (mean)	none	Pittsburgh Sleep Quality Index; Yale-New Haven Hospital Depressive Symptom Inventory
Parrino et al[22] (1994)	Nonrandomized, noncontrolled, single-blind	Dysthymic patients with chronic insomnia (N = 6)	50–100 (N = 6)	6 weeks	PSG	VAS
Saletu-Zyhlarz et al[23] (2001)	Single-blind, crossover, placebo-controlled	Dysthymic patients with insomnia and healthy controls (N = 22)	100 (N = 11)	1 night	PSG	Self-Assessment of Sleep and Awakening Quality Scale
Saletu-Zyhlarz et al[24] (2002)	Single-blind, crossover, placebo-controlled	Depressed patients with insomnia and healthy controls (N = 22)	100 (N = 11)	1 night	PSG	Self-Assessment of Sleep and Awakening Quality Scale
Scharf and Sachais[25] (1990)	Nonrandomized, noncontrolled, single-blind	Depressed patients with significant sleep disturbances (N = 6)	150–400 (N = 6)	5 weeks	PSG	none
van Bemmel et al[26] (1992)	Nonrandomized, noncontrolled, single-blind	Depressed outpatients (N = 8)	300–400 (N = 8)	5 weeks	PSG	none
Sleep in healthy subjects						
Ware and Pittard[16] (1990)	Double-blind, crossover, placebo-controlled	Healthy males (N = 6)	50–200 (N = 6)	4 nights	PSG	none
Yamadera et al[17] (1999)	Nonrandomized, noncontrolled	Healthy males (N = 12)	50–100 (N = 12)	2 nights	PSG	none

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, PSG = polysomnographic, VAS = visual analogue scale.

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Table 2. Objective Measures of Changes in Sleep Architecture and Significant Improvement in Sleep Endpoints[a]

Reference (Year)	Trazodone Dose mg/day (N)	Active Treatment Duration	Sleep Stage (S)				Sleep Endpoints (Improvement Direction)				
			S1	S2	S3/4	REM	SL	TST	WASO	NAW	SE
Haffmans and Vos[14] (1999)	50 (N = 7)	1 week							NR	✓	NR
Mouret et al[21] (1988)	400–600 (N = 10)	5 weeks		↑	↑		✓	✓	NR	✓	NR
Parrino et al[22] (1994)	50–100 (N = 6)	6 weeks		↓	↑					NR	
Saletu-Zyhlarz et al[23] (2001)	100 (N = 11)	1 night			↑				NR		
Saletu-Zyhlarz et al[24] (2002)	100 (N = 11)	1 night			↑	↑	NR	✓	NR	✓	✓
Van Bemmel et al[26] (1992)	300–400 (N = 8)	5 weeks				↓			NR	NR	
Montgomery et al[18] (1983)	150 (N = 9)	3 weeks	↓		↑	↓	×		✓	NR	NR
Scharf and Sachais[25] (1990)	150–400 (N = 6)[b]	5 weeks			↑		✓	✓	NR	✓	✓
Ware and Pittard[16] (1990)	50–200 (N = 6)	15 nights			↑		NR		NR		NR
Yamadera et al[17] (1999)	50–100 (N = 12)	2 nights	NR	NR	↑	NR	NR	NR	NR	NR	NR

[a]Change measured from baseline or placebo baseline. Significance reported at $p \leq .05$. Empty cells indicate no change or not significantly different.
[b]Five evaluated.
Abbreviations: NAW = number of awakenings, NR = not reported, REM = rapid-eye movement, SE = sleep efficiency, SL = sleep latency, TST = total sleep time, WASO = wake time after sleep onset.
Symbols: ✓ = improvement, ↑ = increased minutes in sleep stage, ↓ = decreased minutes in sleep stage, × = significant decrease.

6-week treatment period for "ease of getting to sleep" and "quality of sleep." However, all 3 trials also reported impairments in "ease of awakening" and "feelings on/after awakening," although scores improved after 2 to 3 weeks of treatment.[11,12,20] This suggests that the therapeutic benefits of trazodone 150 mg for the treatment of insomnia may be limited by impaired next-day function. However, because lower doses were not assessed, it is impossible to know if lower doses will provide the desired outcome, sleep onset, and sleep maintenance without next-day impaired function.

The remaining 9 studies conducted with depressed or dysthymic patients focused on the effects of trazodone in treating depression-associated or antidepressant-induced insomnia (see Table 1 and references 5,14,15,21–26). Aside from the Mashiko et al. study,[5] which enrolled 75 patients, the trials had small trazodone study populations of 6 to 17 subjects. The Mashiko et al. study was primarily concerned with dose finding, and it compared the efficacy of 50-, 75-, and 100-mg/day trazodone doses. All doses improved sleep symptoms as rated by sleep items on the Hamilton Rating Scale for Depression (HAM-D) and Hamilton Rating Scale for Anxiety, with optimal results achieved with trazodone 100-mg/day dosage. The HAM-D items included premature morning awakening, lack of sound sleep, and difficulty of initiating sleep. However, 42 (56%) of the 75 patients failed to complete the 6-week study. The researchers attributed this high discontinuation rate to strict protocol requirements and not to adverse effects or lack of efficacy.[5]

The small sample sizes, unconventional methodology, and weak descriptive statistics render the findings from the other 8 studies difficult to interpret. For example, 1 study of 6 patients included no p values or interquartile ranges and reported standard deviations.[25] Consequently, this study was excluded from this analysis. Moreover, while subjective assessment tools were used in many of these studies, inconsistent reporting hampered any comparison of results.

Table 2 summarizes findings from the 10 studies that employed objective (PSG) measures of sleep endpoints and/or sleep stages either alone or in combination with subjective measures.[14,16–18,21–26] All but 1 of these studies examined the effect of trazodone on depression-associated or antidepressant-induced secondary insomnia. The Montgomery et al. study of primary insomnia has also been included, as it recorded similar endpoints, although the study population of self-described "poor sleepers" was seemingly nondepressed.[18]

The 10 studies included in Table 2 encompassed a total of 86 patients (approximately 9 patients per study) and a wide variety of active treatment durations (1 night–6 weeks) and dosage amounts (50–600 mg/day). However the limited number of patients per study, limited number of parameters to compare between studies, and lack of consistent efficacy across studies preclude definitive conclusions of trazodone's objective efficacy.

It is unclear from the studies if improvement in TST was related to sleep maintenance and/or sleep onset efficacy. While effects on sleep maintenance may be indicated by reduced NAW, WASO is increasingly being explored as a more informative measure of sleep maintenance. NAW was reduced in all studies that reported this endpoint[14,21,23,24]; however, WASO was recorded in only 2 of the studies.[18,22] The lack of WASO reporting deters an assessment of trazodone's objective effect on sleep maintenance. Furthermore, no objective studies have been conducted in DSM-defined primary insomnia, and thus there are no objective data to support the efficacy of trazodone for the treatment of primary insomnia.

In a multicenter open-label study of 549 depressed patients with insomnia symptoms,[9] patients were treated with 50 to 300 mg of trazodone controlled release. Patients reported significant improvement on HAM-D across

the 6-week study. Although the 3 insomnia-related items (early, middle, and late insomnia) of the 21-item HAM-D were determined to be among the 5 most improved items (suicide and loss of weight were second and fourth, respectively), sleep efficacy was not directly assessed. Further, this study lacked placebo control and was designed to assess the antidepressant effect of trazodone; thus, the dosages and dose scheduling were not consistent with trazodone's use as an insomnia treatment.

In a double-blind, placebo-controlled study of 12 depressed females with insomnia caused by selective serotonin reuptake inhibitor therapy,[8] 100 mg of trazodone taken 1 hour before bedtime was shown to reduce objective measures of insomnia, but not subjective measures. After 15 days of treatment, Pittsburgh Sleep Quality Index improvements were similar for the placebo and trazodone groups, while statistically significant PSG improvements were seen for TST, NAW, Sleep Efficiency Index, and Sleep Continuity Index ($p < .01$ first night and $p < .05$ last night for all parameters).

Effects on Sleep Architecture

The sleep laboratory environment also afforded an opportunity to assess trazodone's effect on sleep architecture. Ten of the 18 studies in Table 1 used PSG recordings to objectively evaluate the effect of trazodone on sleep stages.[14,16–18,21–26] Seven of these studies were conducted with depressed or dysthymic patients with sleep disorders,[14,21–26] 1 study used nondepressed poor sleepers,[18] and 2 studies enrolled healthy young males.[16,17] The main consistent finding was an increase in stage 3/4 (slow-wave) sleep (Table 2). However, although various theories have been postulated, there is no consensus on how this finding is applicable to the clinical management of insomnia and whether this actually contributes to improved sleep and outcomes.

SAFETY

Overview

Trazodone's most common (≥ 10%) adverse events seen at doses of 75 mg/day to 500 mg/day include drowsiness, dizziness, dry mouth, nausea/vomiting, constipation, headache, hypotension, and blurred vision.[27] According to an analysis of pooled data from adult populations, average percentages and percentage ranges were 29.1% for drowsiness (20%–50%), 21.9% for dizziness (10%–30%), and 17.7% for dry mouth (2%–33.8%).[27] In terms of overall side effects, an overview of controlled trials of trazodone use for clinical depression found that as many as 25% to 30% of patients experience some difficulty tolerating trazodone.[28] Several clinical trials report discontinuation due to such adverse events as drowsiness, dizziness, hypotension, confusion, edema, and pruritus.[10,29–32] It should be noted that dropout rates in trazodone studies, when reported, are high. Reported discontinuation rates range from 25% to 60%.[5,10,11,29–32] In these studies, approximately 25% to 50% of discontinuations were due to adverse events. Although lower doses are typically used to treat insomnia, it is unclear what trazodone's adverse effect profile is at these dosage amounts, as so few studies have been conducted in nondepressed, insomnia populations. As trazodone use has not been systematically explored in patients with insomnia, who often receive lower-than-antidepressant doses, conclusions regarding risks associated with use in these patients cannot be made.

Sedation

Drowsiness has been consistently reported as an adverse effect in numerous trials of trazodone for the treatment of depression at doses ranging from 50 to 600 mg.[7,10,11,20,30,32–34] Next-day sedation can be a problem with trazodone, even when the drug is administered to depressed patients as a hypnotic at doses between 25 mg and 100 mg before bedtime. Next-day sedation at doses of 25 to 75 mg resulted in a discontinuation rate of 31% of patients (5/16) taking fluoxetine for depression in combination with trazodone for insomnia.[35] In a double-blind, placebo-controlled crossover study of 12 women with depression who took 100 mg of trazodone nightly for 7 days, 17% reported mild next-day sedation.[8] However, the study lacked a structured assessment of adverse effects, which may have reduced reporting.

Because there is only 1 placebo-controlled study of trazodone use in primary insomnia,[13] it is unclear what trazodone's adverse effect profile is in this population. However, the limited data available suggest that even at doses as low as 50 mg, somnolence remains a problem with trazodone. In the Walsh et al. study,[13] 23% of the patients who took 50 mg of trazodone nightly for 2 weeks reported problems with daytime somnolence, compared with 8% of the placebo group and 16% of the zolpidem group.

Cardiac Safety

Based on older studies published in the 1980s, trazodone is often thought to have a relatively benign cardiovascular risk profile compared with tricyclic antidepressants.[36,37] However, in a comprehensive literature review of trazodone treatment, Haria et al.[3] cite numerous studies and case reports illustrating trazodone's cardiovascular adverse effect profile, including hypotension, orthostatic hypotension with syncope, ventricular arrhythmias, cardiac conduction disturbances, and exacerbation of ischemic attacks. While most of these reports involved trazodone at antidepressant doses (100–600 mg/day), orthostatic hypotension has been observed in elderly patients receiving lower doses of trazodone (50–175 mg/day) and concomitant antihypertensive ther-

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apy.[38,39] Cardiac arrhythmias were also seen with trazodone dosages ranging from 200 mg/day to 300 mg/day.[40,41]

In addition, torsades de pointes, which is characterized by prolongation of QTc, and other arrhythmias have been observed in patients receiving trazodone.[42,43] Inhibition of the cardiac potassium current I_{Kr} is the most common cause of QT-interval prolongation by noncardiac drugs. A preclinical study[44] that compared trazodone's effects on human ether-a-go-go–related gene (hERG) channel current in stably transfected HEK293 cells to those of astemizole, cisapride, and terfenadine found that all 4 agents inhibited hERG channel current in a concentration-dependent manner. The effect with trazodone was with doses as low as 50 mg, yet trazodone can be prescribed at doses as high as 600 mg, resulting in increased plasma concentrations and an increased risk for QT prolongation and torsades de pointes.[44] However, the majority of studies, which include longer treatment durations with higher dosages, found that trazodone did not have a significant or lasting effect on the QT interval.[45] Drug-drug interactions have also been reported with digoxin and antihypertensives.[3]

Priapism

As cited in a literature review by Haria et al.,[3] the incidence of trazodone-induced priapism has been reported to be between 1 in 1000 and 1 in 10,000. In 1987, Warner et al.[46] reviewed adverse report data submitted to the U.S. Food and Drug Administration and found that the majority of cases occurred with doses of 50 to 150 mg/day (amounts typically used to treat insomnia). Onset usually occurred within the first 28 days of treatment.[46] In a review of psychotropic-associated priapism, Thompson et al.[47] observed that 207 (79%) of 261 reported cases were associated with trazodone, and the remainder with antipsychotics. Medication-associated priapism is notoriously difficult to treat, and surgical intervention has been required in trazodone cases.[48] It has been theorized that trazodone's α-adrenergic–blocking properties contribute to the induction of priapism.[47,48]

TOLERANCE

Tolerance associated with trazodone use has not been systematically evaluated. The few trazodone studies that refer to tolerance cite a 1987 review of sleep and depression by Jones et al.[49] However, this article simply states that little or no tolerance develops to antidepressant drugs as compared with barbiturates; no studies or corroborating evidence are provided. In a 2-week study of tolerance to daytime somnolence using daytime administered doses,[34] patients did not show differing levels of sedation when rated 2 hours post-dosing on day 1 compared with day 14. The authors theorized that nighttime dosing could have a clinically beneficial sustained sedative effect.

In the clinical trials cited previously that exceeded 1 week in duration, there were indications of possible tolerance. Both trials assessed trazodone's effect in primary insomnia in nondepressed patients. In the 2-week study (N = 306) of trazodone 50 mg that used only subjective measures,[13] patients with insomnia reported significant improvements in subjective sleep quality at week 1 ($p < .004$), but not at week 2. However, the response in the placebo group is at least partially responsible for the lack of statistical significance. In the second study (N = 9),[18] which compared objective and subjective measures of sleep to baseline values for patients taking 150 mg of trazodone nightly for 3 weeks, patients self-defined as "poor sleepers" reported significant improvements ($p < .001$) in subjective sleep quality during the first 2 treatment weeks that were not sustained in the third week; objective TST, however, was significantly better than baseline only in week 3 ($p < .05$).

In longer-term trials that employed objective measures, van Bemmel et al.[26] reported a slight decline in TST during week 4 (389.4 minutes) and week 5 (396.4 minutes) from the peak improvement achieved at week 3 (401.8 minutes) (statistical significance not reported). Similarly, Moon and Davey's sleep quality scatter plot[20] indicates a peak improvement at day 28 and a subsequent steady decline through day 42. Neither of these declines descended to or below baseline levels. The Mouret et al. overall sleep score graph[21] shows a relative plateau from days 21 through 35. More research needs to be conducted to definitively determine if tolerance develops to trazodone.

ELDERLY PATIENTS

Trazodone's safety profile raises considerable concerns for elderly patients. It should be noted that the elderly suffer disproportionately from insomnia with extremely high estimated insomnia prevalence and incidence rates (57% and 5%, respectively).[50,51] Sleep disturbances among the elderly are associated with significant morbidity and mortality.[4]

Risk for falls is closely associated with insomnia[52]; subsequent fall-related injuries are an important factor for nursing home placement.[4] Side effects of trazodone, such as dizziness and orthostatic hypotension, may heighten the risk for falls and injuries. Psychomotor/cognitive dysfunction and memory impairment may have detrimental effects on quality of life and functional ability. Cardiac arrhythmias pose additional risks; priapism is a serious urological emergency. Sedation and confusion may prevent adequate dosage titration and lead to noncompliance.[3] These significant safety concerns should be carefully considered when prescribing medications in the elderly.

DISCUSSION

Although trazodone is currently the second most prescribed agent to aid with sleep,[1] the data to support such widespread use are minimal, as most of the studies supporting its use were conducted in depressed patients—only 1 study was conducted in nondepressed, DSM-defined primary insomnia. Furthermore, while many of these studies employed polysomnographic measures, interpretation is limited by the small sample sizes, inadequate or nonexistent control groups, and questionable statistical methodology.

Objective measures of the studies reviewed here indicated that, with the exception of NAW, there was no clear trend with regard to trazodone's effects on sleep latency, TST, or sleep efficiency.[14,18,21–24,26] Moreover, while the studies that assessed sleep architecture were unified in their reporting of increases in stage 3/4 sleep, more research is needed to determine how that information is applicable to the clinical management of insomnia.[8,14,16–18,21–26] Studies that used subjective measures to determine trazodone's efficacy in improving sleep did demonstrate improvements in sleep quality, though the improvements were often paired with reports of next-day sedation and worsening of "ease of awakening" and "feelings on or after awakening."[11,12,20] With elderly patients, trazodone's side effect profile, in particular drowsiness and dizziness, and its drug-drug interactions with cardiovascular medications, should be carefully considered.

Given the increasing off-label use of trazodone for insomnia and the relative absence of efficacy data for that indication, it is clear that more placebo-controlled studies of subjective and objective effects are needed to determine whether trazodone has efficacy in the treatment of insomnia without major depression.

Drug names: bupropion (Wellbutrin and others), digoxin (Lanoxicaps, Lanoxin, and others), fluoxetine (Prozac and others), trazodone (Desyrel and others), zolpidem (Ambien).

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