The Use of Trazodone as a Hypnotic: A Critical Review

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Background: The last few years have seen a remarkable rise in the off-label use of trazodone for inducing sleep in nondepressed patients, to a degree that it is prescribed for this purpose as commonly as the leading hypnotic. In view of this widespread popularity, it seems prudent to review what is known of the safety and efficacy of trazodone when used in this context.

Data Sources and Selection: A MEDLINE search of the literature published in English between 1975 and 2003 that included the keywords *sleep, trazodone, Desyrel, depression, sleeping pill,* and *sedative-hypnotics* was conducted.

Data Synthesis: From this review, it is concluded that there are very few data to suggest that trazodone improves sleep in patients without mood disorder, though it does increase total sleep in patients with major depressive disorder. There are virtually no dose-response data for trazodone vis-à-vis sleep and, similarly, no available data on tolerance to its possible hypnotic effects. Areas of concern with its use include reports of significant dropout rates and induction of arrhythmias, primarily in patients with histories of cardiac disease, as well as the development of priapism.

Conclusion: In summary, there are few data to support the use of trazodone in nondepressed subjects. When the risk-benefit ratio of trazodone is assessed, its side effect profile, which is much more significant than that of conventional hypnotics, should be considered.

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In recent years, the number of prescriptions for drugs given for the purpose of aiding sleep has declined, and the types of drugs used have changed dramatically. Perhaps the most notable shift has been the rise of the use of low-dose antidepressants, notably trazodone, for insomnia. Although the number of mentions of trazodone in the National Disease and Therapeutic Index has been relatively constant, prescriptions for use of the drug as an antidepressant have declined, while those for sleep have increased.[1] Indeed, a survey of over 3000 office-based physicians found that trazodone was given for sleep more commonly than the leading hypnotic, zolpidem.[2] Although people with insomnia also self-medicate to a considerable degree with alcohol and over-the-counter sleep aids,[3] the widespread use of trazodone merits a review of what is known of its efficacy and safety for sleep disturbance. A MEDLINE search of the literature published in English between 1975 and 2003 that included the keywords *sleep, trazodone, Desyrel, depression, sleeping pill,* and *sedative-hypnotics* was therefore conducted.

DESCRIPTION OF TRAZODONE

Trazodone is a heterocyclic antidepressant, a triazolopyridine, that inhibits serotonin reuptake. In addition, it acts as a blocker of 5-HT_2 and alpha-1 adrenergic receptors. At least part of its antidepressant effect is thought to be due to its active metabolite metachlorophenylpiperazine (*m*-CPP). In normal subjects, trazodone decreases stages 1 and 2 sleep while increasing slow-wave sleep, with relatively little effect on REM sleep.[4] In patients with major depression, trazodone 100 mg has been reported to increase total sleep, sleep efficiency, and slow-wave sleep, again with minimal effects on REM sleep.[5] Electroencephalographic power spectral studies, however, have not shown an increase in power in the delta band.[6] In addition to the data for depression, there are some data to suggest its usefulness in posttraumatic stress disorder (PTSD)[7] and discontinuation of long-term benzodiazepine administration.[8]

EFFICACY

There are remarkably few data available on the use of trazodone in nondepressed patients. In a 14-day study of

trazodone 50 mg, zolpidem 10 mg, and placebo, Walsh et al.[9] reported that in the first week both active drugs reduced patient-reported sleep latency, though trazodone was significantly less effective than zolpidem. By the second week, only zolpidem was significantly better than placebo. Neither drug altered patient-reported total amounts of sleep. In a sleep laboratory study of dysthymic patients with insomnia, 1 night of treatment with trazodone 100 mg was reported to increase slow-wave sleep, but without altering traditional measures of hypnotic efficacy, such as total sleep time, sleep latency, and awakenings.[10] A later study from the same laboratory reported that trazodone 100 mg increased total sleep and sleep efficiency, but not sleep latency, in patients with major depression.[5] There are 2 reports of improved subjective measures of sleep in PTSD patients.[7,11] In the Warner et al.[11] study, during an 8-week trial with doses primarily in the range of 50 to 200 mg nightly, 92% of PTSD patients indicated that trazodone improved sleep onset, while 78% described improvement in sleep maintenance. There was a strong correlation between the rate of decrease in nightmares and improvement of sleep, so it is not clear to what degree sleep would be aided independent of the reduction in nightmares.

TRADITIONAL CONCERNS WITH HYPNOTICS: DAYTIME RESIDUAL EFFECTS, TOLERANCE, AND WITHDRAWAL SLEEP DISTURBANCE

In patients with major depression, 100 mg of trazodone given at night compared with placebo reduces critical flicker fusion[5] the following morning, revealing continued impairment in visual discrimination that persists beyond sleep. When trazodone 50 mg was given at bedtime in a study of erectile dysfunction in patients with a mean age of 65 years, 31% reported daytime drowsiness and 19% described fatigue.[12] As far as the present authors can determine, there are no other data to address the issue of daytime residual effects following bedtime administration, nor are there available data on whether sleep is disturbed following cessation of trazodone given to aid sleep. There is no information on tolerance when trazodone is given for sleep. In a study of depressed inpatients given 150 to 450 mg of trazodone per day, patients appeared to develop tolerance to daytime somnolence after 2 weeks.[13]

SIDE EFFECTS AND TOXICITY

Few data are available to assess the rate of discontinuation of trazodone when given to insomnia patients. In a study of trazodone administered for sleep in PTSD patients, approximately 20% were unable to tolerate a course of 8 weeks of treatment.[11] In a study in which 200 mg/day was given for 4 weeks for erectile dysfunction, an examination of serum drug concentrations indicated that half the patients were not compliant.[14] When trazodone is used for depression in elderly patients, anticholinergic effects are usually lower than with tricyclic antidepressants.[15] Priapism is the side effect usually associated with trazodone. The frequency is generally reported as 1 in 6000 patients[16]; one case series (N = 74) in which trazodone was administered to aid sleep and reduce nightmares in PTSD patients reported an incidence of 12%.[11] As with tricyclic antidepressants, orthostatic hypotension can develop, with one case series reporting the appearance of postural symptoms in 6% of depressed patients.[13] There has been 1 report of trazodone-induced parkinsonism in a hemodialysis patient, presumably as a result of the antidopaminergic effects of the drug.[17]

Trazodone has been reported to induce atrial and ventricular arrhythmias, primarily in persons with preexisting cardiac disease but occasionally in healthy subjects,[18–20] though some authors have questioned the degree to which this occurs.[21] Trazodone has been reported to induce QT prolongation and polymorphous ventricular tachycardia when given with amiodarone.[22] It thus seems likely that trazodone should not be given in combination with drugs that prolong the QT interval, in view of the risk of arrhythmias.

Trazodone appears more benign in acute overdose than tricyclic antidepressants.[15] Acute poisoning results in drowsiness, ataxia, nausea, and vomiting; rarely, deep coma may develop, especially if the medication is taken with alcohol.[23] Fatal outcomes following the development of arrhythmias, including torsades de pointes and complete atrioventricular block, have been recorded.[24] In summary, the side effect profile of trazodone is similar to, and perhaps slightly more benign than, that of tricyclic antidepressants. The question remains as to whether drugs with antidepressant-type profiles are indicated in insomnia patients without mood disorder.

INTERACTION WITH SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND MONOAMINE OXIDASE INHIBITORS

Fluoxetine increases the concentrations of both trazodone and its active metabolite *m*-CPP; some authors have speculated that desensitization of the 5-HT_2 receptor by *m*-CPP as well as fluoxetine may underlie the antidepressant effects when the 2 agents are given together.[25] Trazodone may improve sleep in patients with insomnia induced by the monoamine oxidase inhibitor antidepressant brofaromine.[26] It improves some scores on the Pittsburgh Sleep Quality Index and Yale-New Haven Hospital Depressive Symptom Inventory (though notably not difficulty falling asleep on the latter measure) in patients with sleep disturbance due to fluoxetine or bupropion treatment.[27] Speech dysfunction including dysarthria and speech blocking has been reported in a traumatic

brain injury patient given a combination of trazodone and fluoxetine.[28] Similarly, serotonin syndrome has been described when trazodone is given in combination with nefazodone.[29]

ABUSE LIABILITY

Acute daytime testing in volunteers with histories of alcohol and drug abuse demonstrates that trazodone may have less abuse liability (as measured on a "willing to take again" scale) than triazolam; scores for zolpidem were approximately equal to those for triazolam.[30] It should be noted, however, that the study had a small number of subjects, only male subjects, and no assessment of reinforcing effects. A similar study in healthy volunteers indicated that trazodone 100 to 300 mg had minimal subjective effects on daytime performance in common with triazolam and zolpidem.[31]

CONCLUSIONS

Trazodone appears to be one of several psychotropic compounds, including modafinil, gabapentin, and tiagabine, for which a large portion of use is for an off-label purpose. In recent years, the total number of prescriptions of trazodone have not appreciably changed, but the portion intended for antidepressant use has declined, while that for sleep has risen.[1] The reasons for this are not certain, but one can speculate about several. One consideration is that unlike benzodiazepines and the newer nonbenzodiazepine hypnotics, trazodone is not scheduled by the U.S. Drug Enforcement Administration. Another element may be the relatively low cost compared with the newer hypnotics.

On the other hand, these benefits may come with some associated costs. Although trazodone benefits some aspects of sleep in patients with major depressive disorder, there is little or no evidence from systematic studies that it aids sleep in insomnia patients. Systematic dose-response information is lacking, as are data on tolerance. The side effect profile is substantial when compared with nonbenzodiazepine hypnotics, including the potential for priapism in 1 in 6000 patients, orthostatic hypotension, and induction of cardiac arrhythmias in patients with preexisting heart disease. Some authors recommend a routine electrocardiogram prior to administration,[16] which if performed must be considered when determining the overall cost of treatment. One apparent benefit seems to be a lower likelihood of abuse in patients with a history of drug and alcohol dependence. Trazodone may also be appropriate to use in patients with major depressive disorder who complain of disturbed sleep and potentially may be helpful in PTSD and benzodiazepine dependence. With these exceptions, it seems wise to await further data and consider the various limitations of trazodone when making the choice of which medication to prescribe to aid sleep.

Drug names: amiodarone (Cordarone and others), bupropion (Wellbutrin and others), fluoxetine (Prozac and others), gabapentin (Neurontin), modafinil (Provigil), nefazodone (Serzone and others), tiagabine (Gabitril), trazodone (Desyrel and others), triazolam (Halcion and others), zolpidem (Ambien).

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