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Off-Label Drug Uses

Trazodone: Insomnia (Adults)

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts,* a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Insomnia is a deficient quality or quantity of sleep that negatively affects an individual's ability to perform daytime activities. Primary chronic insomnia may present as an organic illness in which sleep disturbances last longer than 1 month and all other causes of sleeplessness have been ruled out. Secondary insomnia may be precipitated by medical or psychiatric disorders, medication use, environmental factors, or changes in circadian rhythm.

Effective treatment of insomnia requires appropriate diagnosis, as well as pharmacological and behavioral therapy. Traditionally, short-acting hypnotics have been preferred for the treatment of primary and secondary insomnia; however, abuse potential, dependence, adverse effects, and withdrawal symptoms are associated with their use. To avoid such risks, alternative agents with sedative properties have been investigated, including trazodone.[1]

PATIENT POPULATION

Adult patients with primary or secondary insomnia.

DOSAGE AND DURATION

50 mg to 100 mg at bedtime.[1,2]

RESULTS

Primary Insomnia

The use of trazodone in treatment of primary insomnia is limited to 2 controlled trials evaluating short-term use (1 to 2 weeks); objective sleep measurements were assessed in only one trial and subjective measurements were assessed in both trials.[2,3]

Controlled Trials

In a multicenter, double-blind, randomized, parallel-group, placebo-controlled trial, 306 adult patients (21 to 65 years) were randomized to receive placebo (n = 104), zolpidem 10 mg (n = 102), or trazodone 50 mg (n = 100) for 14 days. A total of 278 patients completed the study (97 vs 91 vs 90 patients, respectively). Inclusion criteria consisted of a 1-month history of disturbed sleep (ie, at least 30 minutes of self-reported sleep latency [SSL] and a 4- to 6-hour self-reported sleep duration [SSD] at least 3 nights a week). During week 1, trazodone decreased SSL significantly more than placebo, and zolpidem decreased SSL significantly more than either trazodone or placebo. SSD was also significantly longer in patients treated with either trazodone or zolpidem during week 1. During week 2, SSL was still significantly shorter in patients receiving zolpidem; however, the effects of trazodone on SSL were comparable with placebo. Only patients receiving zolpidem continued to experience significantly longer SSD in week 2. Progressive lengthening of SSD with placebo was noted in weeks 1 and 2, potentially lessening the treatment effects of both zolpidem and trazodone in week 2.[3]

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The hypnotic efficacy and daytime effects of trazodone was examined in a double-blind, placebo-controlled crossover study enrolling 16 adult patients with sleep lab–confirmed primary insomnia (sleep efficiency ≤85%). Trazodone (50 mg) or placebo was administered 30 minutes before bedtime for 1 week with a 1-week washout between treatment periods. Patients took medications under sleep lab conditions on nights 1 and 7 of the treatment periods. Sleep efficiency parameters were measured on nights 1 and 7 of the treatment periods and daytime impairment effects (eg, equilibrium, short term-memory, simulated driving) were measured on the morning after nights 1 and 7. When compared to placebo, trazodone significantly reduced total awakenings, total time (minutes) spent in stage 1 sleep, and percentage time spent in stage 1 sleep. On day 7, trazodone treatment was associated with a significant increase in slow wave sleep (SWS) time. There was no difference between the groups for sleep latency, rapid eye movement (REM) latency, wake after sleep onset (WASO), stage 2 sleep (time or percentage), REM sleep (time or percentage), SWS%, or sleep efficiency. Small but significant impairments were noted with trazodone for short-term memory, verbal learning, equilibrium, and arm muscle endurance tests. There were no differences between the 2 groups for driving errors in simulated driving tasks. The authors concluded that trazodone is efficacious for sleep maintenance but may be associated with cognitive and motor impairment.[2]

Secondary Insomnia

Trazodone has been evaluated in several controlled trials for the management of secondary insomnia (eg, associated with depression, medication use, or mood disorders), measuring subjective and objective measurements with use up to 6 weeks.[4-8]

In a randomized, open-label, 6-week study, the effective dose of trazodone was evaluated in patients with nonorganic insomnia secondary to a depressive disorder. Seventy-five patients were given trazodone 50 mg/day for 2 weeks and then randomized to receive 50, 75, or 100 mg/day for the remaining 4 weeks. Symptoms were assessed at baseline and 2, 4, and 6 weeks after treatment initiation. The Hamilton Depression Rating Scale (HDRS), Hamilton Anxiety Scale (HAS), Self-Rating Depression Scale (SDS), and self-rating for sleep were used. Imipramine was the only concomitant medication allowed. Of the initial study population, 33 patients completed the study. Depressive symptoms were significantly improved at 2, 4, and 6 weeks, with symptom improvement similar among the doses. Sleep disturbances, premature morning awakening, difficulty initiating sleep, and lack of sound sleep were significantly improved at 2, 4, and 6 weeks at all doses, with trazodone 100 mg as the most effective dose in improving measures of sleep.[4]

In a double-blind, placebo-controlled crossover study, effects of trazodone were examined on serotonin reuptake inhibitor–induced insomnia. During study night 1 (adaptation), 12 female patients' sleep was evaluated, followed by baseline polysomnography (PSM) on night 2. Patients were then randomized to treatment phases with trazodone 100 mg or placebo for 7 days separated by 7-day washout period. PSM recordings were repeated on nights 3, 9, 17, and 23 of the study. At baseline and at end point, HDRS was used to evaluate depression, and sleep was assessed by patient rating using the Pittsburgh Sleep Quality Index (PSQI). The HDRS score at endpoint was significantly decreased in all patients; however, no significant difference existed between placebo and trazodone scores. Compared with baseline, the PSQI score was significantly reduced in all patients, with no significantly greater effects of trazodone observed. Total sleep time, percentage of stage 3 and 4 sleep, stage shifts, awakenings, sleep efficiency index, and sleep continuity index were acutely improved after 1 night of treatment with trazodone compared with baseline. In comparison with the first night of trazodone treatment, total sleep time, sleep efficacy index, and sleep continuity index were decreased at trazodone therapy conclusion, yet were still significantly higher than at baseline. Decreases in awakenings and stage shifts, as well as increases in stage 3 and 4 sleep, were further improved at the conclusion of trazodone therapy compared with 1 night of treatment.[5]

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Trazodone labeling has a black box warning regarding a possible increased risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults with major depressive disorders and other psychiatric disorders. The most common adverse reactions noted in reviewed trials included daytime sedation, nausea, headache, and dizziness.[2-7]

THERAPY CONSIDERATIONS

Results from short-term controlled trials indicate trazodone's effectiveness for the treatment of primary or secondary insomnia (eg, associated with depression, medication use, or mood disorders). Daytime sedation and motor impairment should be considered.

REFERENCES

1. Mendelson WH. A review of the evidence for the efficacy and safety of trazodone in insomnia. *J Clin Psych*. 2005;66:469-476.

2. Roth AJ, Mc Call WV, Liguori A. Cognitive, psychomotor and polysomnographic effects of trazodone in primary insomniacs. *J Sleep Res*. 2011;20:552-558.

3. Walsh J, Erman M, Erwin C, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSM-III-R primary insomnia. *Hum Psychopharmacol*. 1998;13(3):191-198.

4. Mashiko H, Niwa S, Kumashiro H, et al. Effect of trazodone in a single dose before bedtime for sleep disorders accompanied by a depressive state: Dose-finding study with no concomitant use of hypnotic agent. *Psychiatry Clin Neurosci*. 1999;53(2):193-194.

5. Kaynak H, Kaynak D, Gozukirmizi E, Guilleminault C. The effects of trazodone on sleep in patients treated with stimulant antidepressants. *Sleep Med*. 2004;5(1):15-20.

6. Haffmans PM, Vos MS. The effects of trazodone on sleep disturbances induced by brofaromine. *Eur Psychiatry*. 1999;14(3):167-171.

7. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. Insomnia in depression: Differences in objective and subjective sleep and awakening quality to normal controls and acute effects of trazodone. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(2):249-260.

8. Saletu-Zyhlarz GM, Abu-Bakr MH, Anderer P, et al. Insomnia related to dysthymia: Polysomnographic and psychometric comparison with normal controls and acute therapeutic trials with trazodone. *Neuropsychobiology*. 2001;44(3):139-149. ■