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Editorial

Trazodone as a hypnotic in major depression

Kaynak and associates report in this issue of *Sleep Medicine* that trazodone 100 mg is superior therapy than placebo in 12 younger, depressed female outpatients with insomnia [1]. Clinical practice often advances therapeutic methods that have insufficient scientific evidence to support their broad usage. Trazodone is increasingly used as a hypnotic even though the scientific evidence offers limited support of the clinical practice. In the United States, the usage of trazodone as a hypnotic has doubled during the last decade [2]. The usage has primarily increased due to the perception of primary care physicians that trazodone is an adequate hypnotic that carries little risk and is non-addictive. It is certainly lower in cost than new generation hypnotics. Case–control studies have suggested a role of trazodone to treat the insomnia that accompanies major depressive and other mood disorders.

Insomnia is a hallmark symptom of depressive illness. Seventy to 80% of patients with major depressive disorder will have difficulties of sleep onset, sleep maintenance, and early morning awakening [3]. With the advent of new, safer antidepressant medication, the treatment-emergent sleep disturbance has become more common, being seen in 15–33% of patients who are treated with Selective Serotonin Reuptake Inhibitors. Whether related to the process of illness or to the therapeutic intervention, early management of insomnia offers functional improvements for depressed patients.

Kaynak and associates studied 12 depressed women that were recruited from the University of Istanbul Psychiatry Outpatient Clinic and underwent polysomnography in the University's Sleep Disorders Unit. They were treated with trazodone 100 mg and placebo, according to a double blind, crossover design. It supports a study by Saletu-Zyhlarz et al. that demonstrated objective and subjective response to trazodone in 11 patients with insomnia and major depressive disorder [4]. The women in Kaynak's study were between 30 and 59 years of age and had mild to moderate severity of depression according to the Hamilton Depression Rating Scale. Low and potentially sub-therapeutic dosages of paroxetine, sertraline, citalopram, and venlafaxine had been taken for one to three prior months and had not resolved the sleep disturbance. Although the improvements in depression scores remained the same whether the patients received 7 days of trazodone or placebo, sleep quality was improved more significantly by trazodone. Trazodone increased the mean total sleep time by nearly 50 min throughout the 7 days of therapy while placebo demonstrated no significant change in sleep time. Trazodone also reduced stage 1 and increased stages 3/4 sleep while reducing wake time and stage shifts. Subjective improvements in sleep quality showed similar responses of trazodone over placebo according to the Pittsburgh sleep quality index.

The primary limitation of trazodone in patients with depression-related insomnia is the side effect of carryover sedation. The authors indicate that only two patients had mild daytime sedation in the morning from the bedtime dosing of trazodone 100 mg. This finding is in contrast to a report by Metz and Shader from 1990 that 31% of 16 fluoxetine-treated patients who took trazodone at 25–75 mg nightly discontinued therapy due to carryover sedation [5]. The difference between the two papers may have to do with the severity of depression, different patient mix by age and sex, and the various antidepressant agents that were taken. Kaynak and associates did not complete a systematic assessment of side effects and this could have resulted in a reduced reporting of adverse events.

Other studies with various limitations offer similar assessments of the benefit of trazodone for the insomnia of depressed patients. Jacobsen reported that 96% of his 48 consecutively treated depressed patients gained fair to good subjective response for insomnia when titrated in an open design between 25 and 150 mg of nightly trazodone [6]. Although other studies have not documented this high response rate, the objective and subjective assessments of various studies of 6–21 depressed patients support therapeutic benefit of trazodone in the management of depression-related insomnia [7–11].

Traditional sedative hypnotic agents have also demonstrated benefit in the treatment of insomnia related to depressive illness. Alprazolam and lorazepam have been reported to produce a more significant reduction of depressive symptoms during the first weeks of antidepressant therapy [12,13]. Zolpidem has been shown to improve the insomnia of depressed patients who are on SSRIs [14]. Although patients generally arrive at a similar final therapeutic response, whether they have received an antidepressant with or without a sedative hypnotic, the improvement of energy, attention, and focus after sleeping

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better is much appreciated by patients during the first weeks of antidepressant therapy.

Work to date shows limitations of sample size and design, but the message seems consistent—trazodone improves sleep in patients with depressive disorders. It improves sleep continuity and increases slow wave sleep. Although carryover sedation may limit its utility in some patients, low dosages usually produced limited side effects according to the findings of current studies. There remains no evidence that trazodone is addictive. Continuous observation for orthostatic hypotension, constipation, and priapism is required even at the low dosages of 25–150 mg.

There is only one published paper that compares the hypnotic efficacy of trazodone to zolpidem [15]. Although the results showed trends towards zolpidem, both trazodone 50 mg and zolpidem 10 mg proved superior to placebo in reducing subjective sleep latency. There remains insufficient evidence to determine whether trazodone should be the fastest growing, non-benzodiazepine receptor agonist for the treatment of primary insomnia or other sleep disturbance in the general population.

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