Trazodone Improves Sleep Parameters in Alzheimer Disease Patients: A Randomized, Double-Blind, and Placebo-Controlled Study

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Objectives: *There are no randomized clinical trials regarding efficacy of trazodone in the treatment of sleep disturbances (SD) in patients with Alzheimer disease (AD). We tested the efficacy and safety of trazodone to treat SD in patients with AD.* **Design:** *We conducted a double-blind, randomized and controlled trial during periods of 7−9 days at baseline and 2 weeks of treatment.* **Setting:** *Geriatric medical center of the university's general hospital.* **Participants:** *Individuals with probable AD and SD. The complete analysis comprised 30 patients assigned to either the active treatment group (N = 15) or the placebo group (N = 15).* **Intervention:** *Patients received 50 mg of trazodone once daily at 10:00 P.M. or placebo in a 1:1 ratio for 2 weeks.* **Measurements:** *Patients were evaluated using actigraphy and structured scales before and after intervention.* **Results:** *Compared with the placebo group, trazodone users slept 42.5 more minutes per night and had their nighttime percent sleep increased 8.5 percentage points according to actigraphic data post-treatment. Neither trazodone nor placebo induced significant daytime sleepiness or naps. The treatments with trazodone or placebo did not show any effects either on cognition (Mini-Mental State Examination, forward/backward digit span task, letter-number sequencing, arithmetic, digit symbol-coding, and symbol search) or functionality (Katz index). There were no differences in frequency or severity rating of adverse events between the groups.* **Conclusions:** *This study shows significant therapeutic effects of trazodone 50 mg in community-dwelling AD patients with SD.* (Am J Geriatr Psychiatry 2014; ■:■−■)

Key Words: Sleep disorders, insomnia, Alzheimer disease, trazodone, treatment, intervention

Sleep disorders in patients with Alzheimer disease (AD) are common and challenging in clinical practice because these disorders have negative effects on the patient's cognition and functionality and increase the caregivers' burden.[1] Nearly half of all patients with AD have sleep disorders that reduce their quality of life and represent a challenge in hospital, institutional, and community settings. Sleep disorders can often contribute to institutionalization.[2]

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Among the many types of sleep disorders in patients with AD, nighttime wandering, difficulty with sleep onset and/or maintenance, fragmented sleep, and circadian rhythm abnormalities are the greatest concerns.[3]

Behavioral interventions have been efficient in resolving those disturbances. McCurry et al. showed that walking, light exposure, or their combination may be effective treatments for improving sleep in community-dwelling persons with AD.[4] Other research teams have established that behavioral and environmental interventions can contribute to improved sleep quality in demented patients, in both institutionalized and community-dwelling elderly with dementia.[5] Other studies, however, have failed to show improvements.[6]

Pharmacological intervention, despite its usefulness, can only be recommended with great caution to this group of elderly patients. Sedative-hypnotic agents, including benzodiazepines, are extensively used in clinical practice; however, meta-analysis has shown an increased risk of adverse events in older people, especially a risk of falls and cognitive impairment.[7]

Based on nonrandomized controlled studies, outcome studies, and observational studies, antidepressants with hypnotic action, such as mianserin and trazodone, have long been considered candidates for treating older adults with sleep disorders, particularly in the context of dementia.[8,9] Trazodone in particular is used off-label for insomnia, though the 2005 U.S. National Institutes of Health State-of-the-Science conference on insomnia did not recommend the use of trazodone or other antidepressants for the treatment of insomnia.[10] Few randomized clinical trials have been conducted to evaluate the efficacy of trazodone in the treatment of sleep disturbances.[11,12]

Our primary objective was to examine the efficacy of trazodone 50 mg in patients with AD and sleep disorders. This dose was chosen because we used it in a previous study and because it is commonly prescribed for sedative/hypnotic purposes.[9]

METHODS

Trial Design

This trial incorporated two phases over a period of 7–9 days at baseline and for 2 weeks during treatment, when the patients were randomized to study drug. Patients received 50 mg of trazodone once daily at 10:00 P.M., contrasted with placebo in a 1:1 ratio. Based on a previous observational study, our primary hypothesis was that trazodone would improve sleep parameters in patients with AD who were diagnosed with sleep disturbance.[9] Our secondary hypotheses were that trazodone would be safe and would not result in cognitive or functional impairment. Sleep parameters were assessed by actigraphy, which is often used to assess the effects of cognitive/behavioral therapy and drug interventions in patients with AD and sleep disorders.[6] In patients with dementia, the correlation between actigraphy and polysomnography ranged from 0.81 to 0.91 for the total sleep time and from 0.61 to 0.78 for the percentage of sleep time in the total rest period.[13] The American Academy of Sleep Medicine suggests the use of actigraphy for the management of community-dwelling older adults under treatment, allied with other measures such as sleep diaries and/or caregiver observations.[14]

Standard Protocol Approvals, Registrations, and Patient Consent

The study was previously approved by the ethics research committee of the University of Brasilia. Written informed consent was obtained from all participants (clinicaltrials.gov; NCT01142258).

Participants

Individuals with probable AD[15] were recruited from among the outpatients of the geriatric medical center of the university's general hospital from February 2010 to July 2012.

The inclusion criteria were as follows: age 60 years or older; caregiver or family member able to provide informed consent, ability to comply with the protocol, Mini-Mental State Examination (MMSE)[16] score 24 or less, and Hachinski Ischemic Score[17] 4 or less. Sleep disorders were assessed by a trained researcher using the following items from the Neuropsychiatric Inventory (NPI) Nighttime Behavior[18] and the criteria recommended by Yesavage et al.[19] (with modifications):

1. The patient complained of nighttime insomnia with or without excessive daytime sleepiness, or the caregiver observed these symptoms.
2. Sleep complaints were reported after the diagnosis of AD, with no prior clinical history of