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

nighttime sleep disorders before the onset of dementia.

3. Other medical disorders with potential consequences for sleep patterns (e.g., periodic limb movement disorder and obstructive sleep apnea syndrome) were clinically assessed and did not account for the primary symptoms.

4. The sleep disturbance could not be characterized as parasomnia.

Other inclusion criteria included the following: presence of sleep disorders causing emotional distress to caregivers (score ≥2 on the NPI); use of stable medications for at least 4 weeks prior to the screening visit; possibility of attaching an actigraph to a mobile upper limb; residence with a responsible spouse, family member, or professional caregiver who was present during the night and who would agree to assume the role of the principal caregiver for the 3-week protocol; computed tomography or magnetic resonance imaging since the onset of memory problems showing no more than one lacunar infarct in a nonstrategic area and no clinical events suggestive of stroke or other intracranial disease. Exclusion criteria included the following: sleep disorders associated with an acute illness, delirium, or psychiatric disease; clinically significant movement disorders; severe agitation; unstable medical conditions; and prior use of trazodone for the treatment of sleep disorders. Current intake of antipsychotics and hypnotics were allowed if prescribed at least 30 days prior to the screening visit and remained stable during the study.

Outcome Measures

The outcome measures included comparisons between both treatment arms (placebo or trazodone) expressed as changes from baseline in the variables described below obtained using an actigraphic algorithm. For analysis purposes, the nocturnal period was defined as the continuous 12-hour time epoch from 8:00 P.M. to 08:00 A.M., whereas the daytime period was the 12-hour diurnal epoch from 8:00 A.M. to 08:00 P.M. The total sleep duration (in minutes) during the nocturnal period (NTST) was the primary outcome measure. Other outcomes included the following:

1. Nighttime waking after sleep onset (WASO) (in minutes) during the nocturnal and prior to final waking.

2. Number of nighttime awakenings (Awakenings) during the nocturnal period, after sleep onset, and prior to the awakening.

3. Daytime total sleep time (DTST), in minutes, during the daytime period.

4. Number of daytime naps (NAPS) during the daytime period. A nap was defined as a (daytime) sleep period greater than 10 minutes.

5. Nighttime percent sleep (%Sleep) during the nocturnal period, after sleep onset until the final awakening.

6. Gain of greater than 30 minutes, measured as the proportion of subjects who gained at least 30 minutes in NTST.

7. Change from baseline in functional assessments in the Katz Index of Independence in Activities of Daily Living.[20]

8. Change from baseline in cognitive assessments using the MMSE, Paired Associate Learning Test–Form I (short-term memory), and Paired Associate Learning Test–Form II (long-term memory) of the Wechsler Memory Scale,[21] Digit Span Test (DST), Arithmetic, Letter-Number Sequencing, Digit Symbol-Coding and Symbol Search of the Wechsler Adult Intelligence Scale (third edition, WAIS-III).[22]

9. Tolerability and side effects of trazodone, which were collected via spontaneous report.

10. Subjective analysis of sleep improvement by caregiver (equal or worse and better or much better).

Intervention

The interventions consisted of 50 mg of trazodone or matching placebo for 2 weeks. After consent forms had been signed, a brief neurological examination was performed. The scores on the MMSE, Cornell Depression Scale,[23] Clinical Dementia Rating (CDR),[24] Katz Index of Independence in Activities of Daily Living, NPI (Nighttime Behavior item), and Hachinski Ischemic Score were obtained by a trained neuropsychologist. Each patient's medical record was reviewed to confirm the diagnosis of probable AD. Prior to the intervention, participants wore the actigraphs uninterruptedly throughout the 7- to 9-day screening period and further wore them for the 14-day protocol period. The actigraphic data for each subject were downloaded after the screening period, and sleep quality and variables of sleep were analyzed. Subsequently, patients were investigated

for the inclusion and exclusion criteria. Additionally, their medication prescriptions were reviewed, they received usage recommendations, and the study medication was dispensed by an experienced pharmacist. Actigraphic data collection was performed for 2 weeks. During the study period, patients were not allowed to change medications, and they were instructed to maintain caffeine abstinence after 2:00 P.M. and to limit the use of alcohol up to 2 doses per day, with only one dose allowed after 6:00 P.M. The same scales were administered after intervention, except the Cornell Depression Scale.

Apparatus

Actigraphy was used to assess the effects of the drug interventions in AD patients with sleep disorders.[6] The actigraphs used in this study were made by Actiwatch Respironics, Inc. (Mini-Mitter, Bend, OR) and were analyzed with its software (Actiware, version 5.59.0015, 2010). Actigraphs were worn on participants' non-dominant wrist, and we analyzed the following parameters: 1) wake threshold selection = medium; 2) wake threshold value = 40; and 3) sleep interval detection algorithm = 10 immobile minutes for sleep onset and sleep end.

Randomization and Masking

Randomization was performed by the co-investigator using the True Random Number Service developed by the School of Computer Science and Statistics in Dublin, Ireland, and is available at www.random.org. The co-investigator, who did not participate in any clinical phase of the study, used the string generator mode to produce 40 random, alphanumeric, three-digit codes. The codes were handed to an external pharmacist, who prepared an individual pill pack for each patient labeled with only the identifying code. The external pharmacist was not involved in the outcome assessment. Then, all those bottles were handed in a scrambled order to a clinical pharmacist who assisted the geriatricians by reviewing the medication prescription and providing usage recommendations to each patient. Both the medication pills and the equivalent placebos were received in bulk from the sole manufacturer of trazodone in Brazil (Apsen Laboratory Espírito Santo, São Paulo, Brazil), and the placebos were prepared to be indistinguishable in appearance with trazodone

prepared as 50 mg pills. The bottles of trazodone or placebo were the same size. All patients and geriatricians were blinded to the treatment assignment, and the final randomization list was not accessed until the clinical database was completed. Therefore, only the co-investigator had access to the blinded assignment throughout the intervention. The results of actigraphic analyses were completed before the randomization code was broken at the end of the completed trial.

### Tolerability and Adherence Assessments

The tolerability and side effects of trazodone were collected by spontaneous reporting. One pharmacist handed out the study medication to the patients, assessed adverse events (AEs), and gave information regarding the study, including time of administration, how to fill in the sleep log, and tips about caffeine and alcohol use. AEs were classified by the investigator as mild, moderate, or severe. Medication adherence was assessed using a manual pill count. At the end of treatment, family members/caregivers were asked to return the pill box, and the number of pills was counted again. Adherence was defined as suitable when the drug intake was 85% or higher, based on pill counting.

Statistical Analyses

Baseline measures in the two groups were compared using the χ^2 test (or Fisher's exact test in case of expected frequencies <1) for categorical variables, and using the t test for continuous variables with normal distribution or the Mann-Whitney U test for discrete non-Gaussian distributed variables.

The post-treatment values of the variables were compared between groups using an analysis of covariance (ANCOVA). These values were considered dependent variables whereas the treatment type was the independent variable, and the baseline values of the variables were the co-variables. To indicate the net difference between treatment arms, the values of the absolute mean change of each arm were added. To test whether the intercorrelated nature of some dependent variables affected the parametric analyses outputs, multivariate analysis of covariance (MANCOVA) were run to compare post-treatment values across groups with adjustment for baseline recordings. The null hypothesis was rejected in each statistical test when p was less than 0.05.

FIGURE 1. Patient flow.
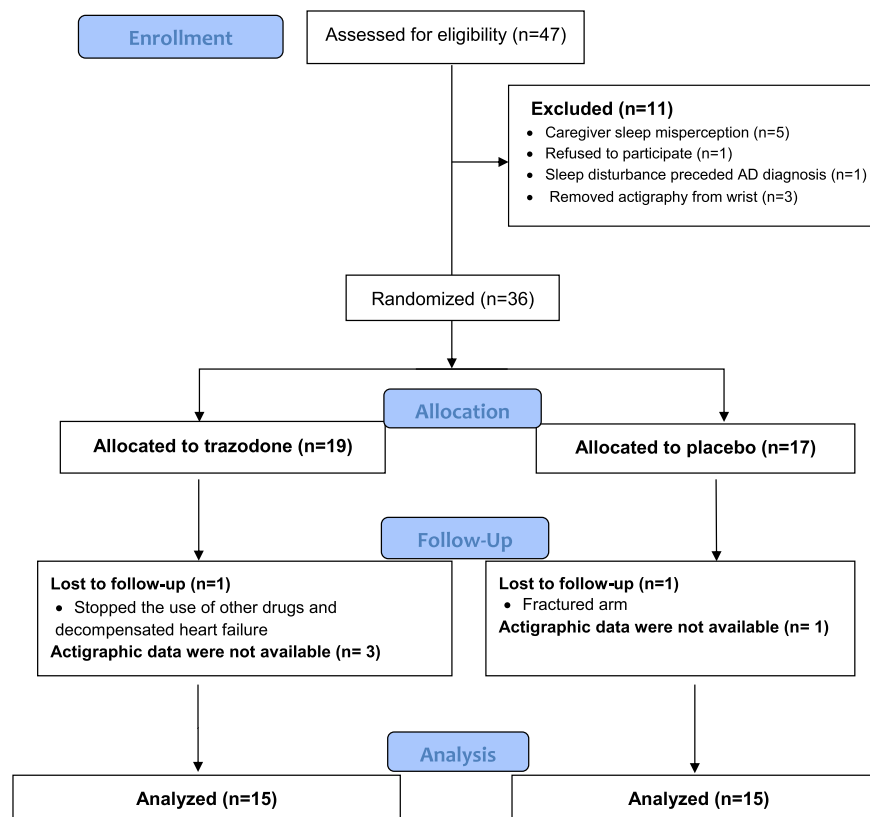
Analysis was performed using SAS v.9.2 Software (SAS Institute, Inc., Cary, NC, 1999).

RESULTS

Patients

Forty-seven subjects diagnosed with AD and sleep disorders were enrolled in the study. Thirty-six of these participants met the inclusion criteria and were randomized to either the active treatment group (N = 19) or the placebo counterpart (N = 17). Figure 1 shows the CONSORT flow chart. After allocation and randomization, one subject from the trazodone group was excluded because of failure in using anti-hypertensive and antiarrhythmic drugs and, thus, evolving into heart failure. One patient of the placebo group was also excluded because of an episode of agitation and consequent arm fracture. Unfortunately,

the actigraphic data from four participants failed to be accurately registered during intervention (3 from the trazodone group and 1 from the placebo group) due to a technical failure or decalibration that resulted in wrong signals, mostly showing movements above the threshold all night long. The analyses of actigraphic output of these four excluded patients showed an abnormal rhythmicity pattern, which was not compatible with either sleep or agitation (regular activity counts all night long throughout all recording period). The complete analysis comprised 30 patients in either the active treatment group (N = 15) or the placebo group (N = 15).

Baseline Measures and Adherence to Trial

The mean age of the subjects was 81.0 ± 7.5 years, with women constituting 66.7% of the sample. The mean MMSE score of 11.2 ± 6.2 and the frequent CDR scores of 2 and 3 were compatible with moderate to

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TABLE 1. Baseline Characteristics

Variables	Trazodone group (N = 15)	Placebo group (N = 15)	t, χ^2, Fisher's Exact, Mann-Whitney (df)	p value
Age, years	81.5 ± 9.4	80.5 ± 5.5	0.38 (28)	0.707[a]
Sex			2.40 (1)	0.121[c]
Female	8 (53.3)	12 (80.0)		
Male	7 (46.7)	3 (20.0)		
Marital status				0.795[d]
Married	8 (53.3)	6 (40.0)		
Widower/Widow	5 (33.3)	6 (40.0)		
Other	2 (13.4)	3 (20.0)		
Educational level				0.334[d]
Illiterate	3 (20.0)	4 (26.7)		
<4 years	7 (46.7)	3 (20.0)		
≥4 years	5 (33.3)	8 (53.3)		
CDR				0.342[d]
1	8 (53.3)	4 (26.7)		
2	4 (26.7)	7 (46.7)		
3	3 (20.0)	4 (26.6)		
Cornell Depression Scale	9.3 ± 4.0	9.2 ± 6.1	0.04 (28)	0.971[a]
Treatments for AD				
Anticholinesterase	6 (40.0)	10 (66.6)	2.14 (1)	0.143[c]
Memantine	3 (20.0)	4 (26.6)		0.666[d]
Antipsychotics				
Yes	1 (6.7)	2 (13.3)		0.542[d]
Another hypnotic				
Yes	1 (6.7)	1 (6.7)		1.000[d]
Actigraphic measures				
NTST (min)	292.7 ± 86.5	282.9 ± 91.4	0.30 (28)	0.765[a]
WASO (min)	224.0 ± 76.0	196.3 ± 84.6	0.95 (28)	0.353[a]
Awakenings (n°)	27.5 ± 8.3	22.6 ± 6.2	1.84 (28)	0.076[a]
%Sleep	54.5 ± 14.6	53.6 ± 15.7	0.15 (28)	0.881[a]
DTST (min)	175.3 ± 117.1	121.6 ± 89.5	1.41 (28)	0.169[a]
Naps (n°)	30.7 ± 16.5	27.7 ± 15.7	0.51 (28)	0.612[a]
Other outcomes				
Katz Index	6.3 ± 5.6	7.7 ± 4.4	−0.72 (28)	0.475[a]
MMSE	11.4 ± 6.7	11.0 ± 5.9	0.17 (28)	0.864[a]
FBDS	5.0 ± 3.4	5.7 ± 3.3	0.08 (1)	0.863[b]
Letter-Number	1.4 ± 1.2	0.8 ± 1.0	1.23 (1)	0.282[b]
Sequencing	3.9 ± 2.5	3.5 ± 2.3	0.394 (1)	0.550[b]
Arithmetic	1.6 ± 4.0	2.4 ± 3.7	0.440 (1)	0.530[b]
Digit-Symbol Coding Symbol Search	1.1 ± 2.5	2.6 ± 3.5	0.762 (1)	0.402[b]

Notes: Data are expressed as the mean ± SD or absolute number and proportion in parenthesis for each group of patients. AD: Alzheimer disease; CDR: Clinical Dementia Rating; min: minutes; n°: number; NTST: Total sleep duration during the nocturnal period; WASO: Nighttime waking after sleep onset; %Sleep: Nighttime percent sleep; DTST: Daytime total sleep time; MMSE: mini-mental state exam; FBDS: forward/backward digit span (sum).
[a]t test.
[b]Mann-Whitney test.
[c]χ^2 test.
[d]Fisher's exact test.

severe dementia being the most frequent phenotypes in total group. Because the demographic and descriptive variables were similar between both intervention groups at baseline (Table 1), none of these variables were reexamined at the endpoint stage. The actigraphic measures and other outcomes were also similar between groups at baseline (Table 1).

The adherence was high; all of the subjects included in the analyses reported an adherence rate of 85% or more throughout the trial. Pill counts indicated that four patients (half under trazodone therapy) did not take one dose, and three patients (two under trazodone therapy) missed two doses.

There were no differences in the frequency or severity ratings of spontaneously reported AEs between groups (p = 1.000, Fisher's exact test). No reported AE was rated as moderate or severe, with mild AEs observed in four subjects using trazodone

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TABLE 2. Sleep Outcomes Measured after Treatment Using an Actigraph

Variable	Trazodone Mean [95% CI]		Placebo Mean [95% CI]		Trazodone versus placebo difference [95% CI]	F-value (df)	p value[a]
	Baseline	Post-treatment	Baseline	Post-treatment			
NTST (min)	292.7 [244.8, 340.6]	324.4 [266.3, 382.5]**	282.9 [232.3, 333.5]	281.9 [225.3, 338.6]	42.46 [0.9, 84.0]	5.09 (1;27)	0.045
WASO (min)	224.0 [181.9, 266.1]	183.0 [127.0, 239.0]*	196.3 [149.4, 243.1]	203.4 [149.2, 257.6]	−20.41 [−60.4, 19.6]	1.87 (1;27)	0.302
Awakenings (n°)	27.5 [22.9, 32.1]	22.3 [16.1, 28.4]**	22.6 [19.2, 26.1]	26.0 [19.9, 32.0]	−3.71 [−8.2, 0.8]	4.06 (1;27)	0.106
%Sleep	54.4 [46.4, 62.5]	59.1 [49.8, 68.3]**	53.6 [44.9, 62.3]	50.6 [41.5, 59.6]	8.53 [1.9, 15.1]	8.05 (1;27)	0.013
DTST (min)	175.3 [110.4, 240.2]	149.8 [104.1, 195.5]	121.6 [72.0, 171.2]	144.7 [100.2, 189.3]	5.12 [−28.2, 38.4]	0.17 (1;27)	0.753
Naps (n°)	30.7 [21.6, 39.8]	29.6 [24.7, 34.4]	27.7 [19.0, 36.3]	28.7 [24.0, 33.5]	0.84 [−2.6, 4.3]	0.75 (1;27)	0.623

Notes: min: minutes; n°: number; CI: confidence interval; NTST: Total sleep duration during the nocturnal period; WASO: Nighttime waking after sleep onset; %Sleep: Nighttime percent sleep; DTST: Daytime total sleep time; Baseline mean = mean over the 7- to 9-day screening period; Post-treatment mean = averaged over 14 days of treatment. Comparisons within group: *p <0.05; **p <0.01.
[a]Comparisons made using an analysis of covariance between groups (adjusted).

and in six subjects using placebo. In the trazodone group, one patient had dyspepsia and diarrhea, one had coryza, one had irritability, and another had swollen lower limbs. In the placebo group, one subject had itching, one had a memory worsening complaint, two had anxiety, one had dyspepsia, and one had agitation.

Sleep Outcome Measures

The primary symptoms among the elderly participants according to NPI were as follows: got up during the night (N = 28; 93.3%), awakened caregivers during the night (N = 23; 76.6%), showed nighttime wandering (N = 20; 66.6%), awakened too early in the morning (N = 18; 60%), had difficulty falling asleep (N = 17; 56%), slept excessively during the day (N = 16; 53%), and woke up at night, got dressed, and planned to go out (N = 15; 50%).

Patients who used trazodone for 2 weeks showed significant improvements in several sleep parameters. The ANCOVA showed that trazodone users slept 42.5 more minutes per night and had their nighttime sleep increased by 8.5 percentage points post-treatment, compared with the placebo group (Table 2). Moreover, neither trazodone nor placebo induced significant daytime sleepiness or naps. Despite a trend towards a reduction in the time spent awake after sleep onset and number of awakenings, these differences were not statistically significant when the net change was compared between treatment arms. The trazodone group had nine (60%) subjects with gains of at least 30 minutes of NTST, compared with five (33%) patients in the placebo group (χ^2 = 2.143, df = 1, p = 0.143). The MANCOVA for NTST, WASO, Awakenings, and Nighttime percent sleep as dependent variables, baseline recording as covariate yielded similar significant differences for these variables (Hotelling's Trace (4,21) = 0.546, F = 2.87, p = 0.048). In parallel, MANCOVA for DTST and Naps as dependent variables, baseline recording as covariate remained nonsignificant (Hotelling's Trace (2,25) = 0.031, F = 0.39, p = 0.679).

Other Outcome Measures

Table 3 shows that neither treatment with trazodone nor placebo had any effect on cognition (MMSE, forward/backward digit span task, letter-number sequencing, arithmetic, digit-symbol coding, and

TABLE 3.   Other Outcomes (Cognitive and Functional Assessments)

Variable (points)	Trazodone Mean [95% CI]		Placebo Mean [95% CI]		Trazodone versus placebo difference [95% CI]	F-value (df)	p value[a]
	Baseline	Post-treatment	Baseline	Post-treatment			
Katz Index	6.3 [3.2, 9.4]	6.9 [5.9, 7.8]	7.6 [5.2, 10.1]	6.4 [5.4, 7.3]	0.5 [−0.8, 1.8]	0.62 (1;27)	0.437
MMSE	11.4 [7.7, 15.1]	10.6 [9.9, 11.4]	11.0 [7.7, 14.2]	10.5 [9.8, 11.3]	0.1 [−0.9, 1.1]	0.03 (1;27)	0.866
FBDS	5.0 [3.0, 6.9]	6.1 [5.2, 7.0]	5.7 [3.5, 7.9]	5.1 [4.1, 6.1]	0.9 [−0.3, 2.3]	2.23 (1;27)	0.150
Letter−Number Sequencing	1.3 [0.6, 2.0]	1.2 [0.6, 1.8]	0.8 [0.0, 1.5]	1.1 [0.4, 1.9]	0.0 [−0.9, 0.9]	0.00 (1;27)	0.958
Arithmetic	3.9 [2.5, 5.3]	4.1 [3.7, 4.6]	3.5 [1.8, 5.1]	3.9 [3.4, 4.4]	0.2 [−0.4, 0.9]	0.58 (1;27)	0.453
Digit−Symbol Coding	1.6 [−0.6, 3.9]	2.2 [0.9, 3.4]	2.4 [−0.2, 5.0]	1.6 [0.1, 3.0]	0.6 [−1.3, 2.4]	0.41 (1;27)	0.528
Symbol Search	1.1 [−0.3, 2.6]	2.2 [1.3, 3.2]	2.6 [0.0, 5.1]	3.2 [2.1, 4.3]	−0.9 [−2.4, 0.5]	1.82 (1;27)	0.191

Notes: CI: confidence interval; MMSE: Mini-Mental State Exam; FBDS: forward/backward digit span (sum).
[a]Comparisons made using an analysis of covariance between groups (adjusted). No significant differences after treatment within groups were observed.

symbol search) or functionality (Katz index). The Paired Associate Learning Tests of the Wechsler Memory Scale could not be performed due to the severity of the demential status in most patients.

The subjective analysis of sleep provided by caregivers showed that 66.6% (N = 10) of the caregivers of the trazodone-treated patients rated the sleep pattern of their patients as better or much better. A similar proportion (60.0%; N = 9) of the caregivers of the placebo-treated group reported a similar response to the treatment (χ^2 test = 0.144, df = 1, p = 0.704).

DISCUSSION

This is the first double-blind, placebo-controlled study of trazodone in AD patients with sleep disorders. Our results suggest benefits for the use of trazodone 50 mg in these patients without any significant impact on daily sleepiness, cognitive performance, or AEs.

Trazodone is considered a multifunctional drug with dose-dependent pharmacologic actions.[25] It is a triazolopyridine derivative of a phenylpiperazine antidepressant that has a dual action on serotonin receptors, blocking serotonergic receptor 2A (5HT2A) and inhibiting serotonin reuptake. It exerts hypnotic actions at low doses (range: 25−150 mg) due to its blockade of 5HT2A receptors, H1 histamine receptors, and α1 adrenergic receptors.[25] Despite its approval by the U.S. Food and Drug Administration for the treatment of depression, sleep disorders are the most frequently prescribed (off-label) reason for trazodone prescription.[11]

Based on actigraphic analyses and the rigid inclusion and exclusion criteria used in this study, our sample was diagnosed at baseline with poor quality of sleep, characterized by a mean NTST of 287.8 ± 87.5 minutes, a mean nighttime percent sleep of 54% ± 14.9%, and a mean number of awake bouts of 25 ± 7.6. Singer et al. observed a high DTST (151 ± 96 minutes), similar to our finding (148 ± 106 minutes), demonstrating severe primary sleep disturbance in many AD patients in the diurnal distribution rather than decreased overall amount of sleep.[26]

There are only a few reports of the use of drugs for sleep disorders in these patients, with conflicting results. McCarten et al.,[27] in a placebo-controlled and crossover trial, did not find effects of triazolam 0.125 mg on the sleep of seven patients with AD. Savaskan et al.[28] studied quetiapine and haloperidol effects on the possible modification of the circadian sleep−wake cycle disturbances in 22 patients with AD (sleep as a secondary outcome). In a multicenter, placebo-controlled trial of melatonin for sleep disturbance in AD, Singer et al.[26] tested the administration of 8 weeks of melatonin (10 mg or 2.5 mg, sustained release formulations) in 157 individuals with AD. Monitored by actigraphy, neither melatonin nor placebo significantly improved the patients' sleep.

There are no controlled and randomized studies evaluating the effects of antidepressants on sleep disorders and AD. Conversely, the off-label prescription of antidepressants for the treatment of sleep disorders in patients with dementia is common practice.[11] A retrospective study using mianserin in 16 patients with dementia and sleep disturbance showed good tolerability and effectiveness in 62.5% of patients, resolving

sleep complaints and caregiver distress, as rated using the NPI Nighttime Behavior scale.[8] Despite one report describing trazodone use in a sample of demented patients with effectiveness in two thirds of patients, this was an open label study that did not use polysomnography or actigraphy to estimate sleep parameters either before or after intervention.[9]

Clinical trials with trazodone for different scenarios that used polysomnography as the recording method corroborate the observed benefits on sleep parameters, similar to those described in the present study, mainly in NTST and awakenings. Kaynak et al.[29] studied 20 female patients with insomnia associated with serotonin-specific reuptake inhibitors using a double-blind crossover design that used trazodone 100 mg and placebo for 7 days in each treatment arm. Trazodone improved sleep parameters, significantly increasing both total sleep time (382.1 ± 57.9 to 435.0 ± 34.0 minutes, p <0.01) and sleep efficiency and decreasing the number of awakenings (25.1 ± 11.0 to 13.0 ± 6.0, p <0.01) compared with the baseline. It seems that trazodone's effects on perceived sleep quality are related to reduction in nighttime awakenings.[30]

In general, trazodone was well tolerated, and AEs were transient and mild, which is in line with other studies.[29,31] Impaired next-day memory performance, equilibrium, and muscle endurance have been mentioned,[30] but our sample did not present impairments on cognitive tests after 2 weeks of trazodone use.

An interesting finding resulted from the subjective analysis of sleep by caregivers, who did not notice differences between trazodone and placebo treatment. Caregivers of placebo-treated patients reported improvement in the sleep pattern to the same extent as those treated with trazodone. In fact, sleep misperception is common in caregiver-reported evaluations.[32] Caregivers may have made some behavioral and environmental adaptations, however, because they believed that these patients were using active treatment. These results reinforce the use of cognitive behavior therapy (mainly sleep hygiene) as an effective treatment for sleep disturbances.[6] In addition, despite a discrete decrease in awakenings, this reduction was not sufficient to improve the subjective analysis of sleep by the caregivers.

Our study has some limitations. First, we did not perform a power calculation before starting the study. Second, the small sample size could be viewed as a limitation. Technical difficulties with equipment led three patients to remove the actigraph from their wrists, and actigraphic data were not available for four participants after intervention. Polysomnographic assessments were not conducted, so the possibility cannot be excluded that some participants may have had undiagnosed primary sleep disorders. However, actigraphy and polysomnography have been shown to have between 81% and 91% agreement for total sleep time,[13] and polysomnography could contribute to increased patient burden and research costs. Moreover, actigraphy can be used as an outcome measure in clinical trials that include sleep-disordered patients.[6] We had problems with daily diary recordings, which might have impaired the measurement of variables directly dependent upon the time spent in bed, such as sleep latency. Choosing a 12-hour nighttime epoch to define the nocturnal period can be questionable. As Singer et al.[26] commented in their study, to define arbitrarily nighttime and daytime sleep periods may bias the quantity of sleep occurred. Any potential improvement in NTST as a result of study medication occurring before 8:00 P.M. or after 8:00 A.M. would be interpreted as a negative outcome in this analysis, such as naps or daytime somnolence. Finally, there are limitations regarding spontaneous reported adverse event information, such as difficulties with adverse event recognition, underreporting, biases and report quality, mainly in demented patients.

In conclusion, this study provides preliminary evidence that community-dwelling AD patients with sleep disorders may benefit from treatment with trazodone 50 mg. Trazodone was safe and effective in our sample. More studies are required to further elucidate the impact of trazodone on cognition and to evaluate tolerance as related to aspects not included in the present study.

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