Article
Arq Neuropsiquiatr 2011;69(1):44-49

Trazodone for the treatment of sleep disorders in dementia

An open-label, observational and review study

Einstein Francisco Camargos [1], Marcela Basso Pandolfi[1], Marco Polo Dias Freitas[1,2], Juliana Lima Quintas[3], Juliana de Oliveira Lima[4], Leandra Camapum Miranda[4], Luciano Wanderley Pimentel[4], Patricia Medeiros-Souza[5]

ABSTRACT

Sleep disorders (SD) in patients with dementia are very common in clinical practice. The use of antidepressants with hypnotic actions, such as trazodone, plays an important role in these cases. The aim of this study is to present a profile of the use of trazodone in demented patients with SD, as well as a review of trazodone hydrochloride in SD. We evaluated 178 elderly patients with Alzheimer's disease and other dementias, clinically presenting SD and treated with hypnosedative medications. In the one-year period comprising the study, 68 (38.2%) of the 178 had sleep disorders. Most patients (114; 64%) had a diagnosis of Alzheimer's disease. Approximately 85% of patients with SD used hypnosedative drugs. Trazodone was the most commonly used drug among patients (N = 35), with an effectiveness of 65.7%. Trazodone has been shown to be a good option for treatment of the elderly with dementia and associated SD.

Key words: sleep, dementia, Alzheimer's disease, trazodone, antidepressant.

Trazodona para o tratamento de distúrbios do sono em demência: um estudo aberto, observacional e de revisão

RESUMO

Distúrbios do sono (DS) em pacientes com demência são muito comuns na prática clínica. O uso de antidepressivos com ação hipnótica, como a trazodona, tem um papel importante nesses casos. O objetivo desse estudo é apresentar um perfil do uso da trazodona em pacientes com demência e com DS, bem como revisar o cloridrato de trazodona no DS. Nós avaliamos 178 idosos com doença de Alzheimer (DA) e outras demências, clinicamente apresentando DS e que foram tratados com medicações hipnossedativas. No período de um ano de estudo, 68 (38,2%) tiveram DS. A maioria (114; 64%) tinham diagnóstico de DA. Aproximadamente 85% usaram fármacos hipnossedativos. A trazodona foi a mais utilizada (N=35), com evidência de melhora de 65,7%. A trazodona mostrou-se ser uma boa opção no tratamento de idosos com demência e DS associado.

Palavras-chave: sono, demência, doença de Alzheimer, trazodona, antidepressivos.

Sleep disorders are one of the major complications related to dementia and cause significant impacts on functionality and quality of life in elderly patients[1]. These sleep disorders often contributes to institutionalization[2].

The origin of sleep disorders in dementia is usually multifactorial, resulting from

Correspondence
Einstein F. Camargos
SGAN 605 Av. L2 Norte - Asa Norte
70840-901 Brasilia DF - Brasil
E-mail: einstein@unb.br

Received 8 July 2010
Received in final form 30 September 2010
Accepted 07 October 2010

[1]Assistent Geriatrician, Geriatric Medical Centre (CMI), University Hospital (HuB), Brasilia University (UnB), Brasilia DF, Brazil; [2]Public Health and Aging Research Group, Oswaldo Cruz Foundation René Rachou Institute, Belo Horizonte MG, Brazil; [3]Neuropsychologist,CMI/HUB/UnB; [4]Pharmacists specializing in Clinical Pharmacy (UnB); [5]Professor of Pharmacy, Department of Health Sciences (UnB).

pathophysiological changes associated with the disease itself, sensory deprivations such as a reduction in auditory and visual acuity, and changes in environmental stimuli such as light. Some studies have shown that damage to cholinergic neurons may contribute to changes in the sleep of patients with Alzheimer's disease (AD)[1].

Epidemiological surveys conducted in patients with AD have identified a prevalence of sleep disorders in up to 40% of patients with any stage of the disease[3].

A longitudinal study conducted with 76 elderly demented patients over two years revealed that 24% of study participants used a hypnosedative drug chronically, increasing from 3 to 17% in the first year, and remaining high at 13% in the second year[4]. In the study of Grace and colleagues, in which the use of hypnosedative drugs was recorded in less than 30% of patients with sleep disorders, the authors argued that there was reluctance by doctors to use hypnotic drugs in demented patients with sleep disorders[5]. Appropriate treatment of sleep disorders may benefit both patients and their caregivers.

Antidepressants with hypnotic action, such as trazodone, have played important roles in treating the elderly with sleep disorders, particularly in patients with dementia[1]. The therapeutic dose to induce sleep using these drugs is much smaller than that used for depression, showing effectiveness in inducing sleep and little mood alteration effects.

Trazodone has proved to be effective in the treatment of sleep disorders in depressed patients (not always older)[6-8], in secondary sleep disorders when compared to other substances[9,10] and in healthy individuals[11].

Assessments of the clinical response to trazodone hydrochloride for the treatment of sleep disorders in demented patients may contribute to the pool of therapeutic options for these patients.

The objective of this analysis was to establish a profile of the use of hypnosedative drugs in demented patients with sleep disorders, with an emphasis on trazodone hydrochloride and its effectiveness. This is an open-label, uncontrolled, observational study. General data and specific analysis of sleep disorders have been the aims of another publication.

METHOD

This is a retrospective study that was previously approved by the Ethics Research Committee of the University of Brasilia. To be included, patients had to be diagnosed with dementia and followed for at least 12 months, during which time they were examined periodically every two months. The visits of each patient during 2008 and their records from visits in previous years since their first consultation were considered for selection and analysis. Among the 250 patients followed in the Geriatric Medical Centre of the University's General Hospital in 2008 (Cognitive Geriatric Unit), 128 were excluded: follow-up of less than one year (n=39), mild cognitive impairment (n=20), other possible causes of cognitive impairment cognitive (depression, hypothyroidism, syphilis, use of medication and alcohol intake) (n=13). Sleep disorders were present in 31.4% (56/178) of patients at the time of admission and in 38.2% (68/178) at end of follow-up. Baseline characteristics for the patients are summarized in Table 1. The Centre is accredited by the Ministry of Health as a reference center for patients with Alzheimer's disease in the Brazilian Federal District.

Demographic and clinical data collected by interview and evaluation consisted of: gender, age, educational level, functionality, co-morbidities, aggressiveness, type of dementia and clinical data was gathered using the Objective Geriatric Assessment, a screening instrument developed for teaching and research in the Centre. Patients had complete physical examinations, laboratory tests [thyroid-stimulating hormone (TSH), vitamin B12, VDRL, biochemistry screen, and blood count] and imaging examinations [magnetic resonance imaging (MRI) and/or skull tomography].

The DSM-IV criteria[12] were used for the diagnosis of dementia and those of NINCDS-ADRDA[13] for AD (probable). Functionality was established using the Assessment of Instrumental Activities of Daily Life[14]. Mini Mental State Examination[15] and Clinical Dementia Rating (CDR)[16] were used in the cognitive assessment and in the characterization of the dementia stage, respectively.

The NPI (Nighttime Behavior) scale includes eight items that are rated as to how often they occurred during the past month[17]. Were considered to have a sleep disorder when all the following criteria: [1] Complaint of sleep disorder from patient or caregiver (NPI items - nighttime behavior); [2] Exhaustion of caregiver (score ≥2; scale from 0 to 5, with 2 indicating mild distress).

Polysomnography and actigraphy were not performed, and structured sleep diaries were not requested because of the low educational level of patients and caregivers and the high proportion of patients with advanced degrees of dementia.

The presence of all of the items below (1 and 2) was the criterion for effectiveness in the treatment of sleep disorders: 1. Improvement of the sleep disorder complaint. 2. Reduction in the exhaustion of the caregiver in the item of NPI that deals with night behavior disorders for 1 (minimum) or 0 (absent).

The effectiveness percentile was calculated using the number of patients who showed evidence of improvement in their sleep disorder by the total number of patients treated with this drug. Adverse events were collected by spontaneous (unsolicited) reporting.

Table 1. Baseline characteristics of subjects.

Characteristics	N=178 (%)	With SD (n=68) (%)	Without SD (n=110) (%)
Educational level in years			
Illiterate	33 (18.5)	15 (22.1)	18 (16.4)
Less than 4 years	80 (44.9)	33 (48.5)	47 (42.7)
Between 4 and 8 years	33 (18.5)	10 (14.7)	23 (20.9)
More than 8 years	32 (18.1)	10 (14.7)	22 (20)
Most frequent co-morbidities			
Systemic blood hypertension	105 (59)	38 (55.9)	67 (60.9)
Dyslipidemia	38 (21.6)	13 (19.1)	25 (22.7)
Diabetes mellitus	35 (19.7)	16 (23.5)	19 (17.3)
Smoking	35 (19.7)	15 (22.1)	20 (18.2)
Hypothyroidism	25 (14)	10 (14.7)	15 (13.6)
Previous stroke	22 (12.4)	8 (11.8)	14 (12.7)
Coronary artery disease	12 (6.7)	3 (4.4)	9 (8.2)
Functionality (IADL instrument)			
Dependent	137 (77)	52 (76.5)	85 (77.3)
Independent	41 (23)	16 (23.5)	25 (22.7)
Types of dementias			
AD	114 (64)	43 (63.2)	71 (64.5)
Mixed	24 (13.5)	9 (13.2)	15 (13.7)
VD	13 (7.3)	7 (10.2)	6 (5.5)
FTD	9 (5)	5 (7.4)	4 (3.6)
LBD	7 (4)	2 (3)	5 (4.5)
Others	11 (6.2)	2 (3)	9 (8.2)
CDR			
1	77 (43.2)	27 (39.7)	50 (45.5)
2	85 (47.8)	35 (51.5)	50 (45.5)
3	16 (9)	6 (8.8)	10 (9.1)
Report of aggressiveness			
Yes	109 (61.2)	46 (67.6)	63 (57.3)
No	69 (38.8)	22 (32.4)	47 (42.7)

SD: sleep disorder; VD: vascular disease; FTD: frontotemporal dementia; LBD: Lewy body dementia; CDR: clinical dementia rating.

Table 2. Most commonly used drugs for the treatment of sleep disorders in patients with dementia in follow-up.

Drugs	N	Evidence of improvement N (%)	Dose (mg/day)
Trazodone	35	23 (65.7)	50-100
Clonazepam	23	16 (69.5)	0.5-2
Mirtazapine	20	17 (85)	15-30
Mianserin	16	10 (62.5)	30
Others	13	9 (69.2)	–

Table 3. Polysomnographic sleep variables with the use of trazodone in chosen studies.

Studies	Mouret et al.[6]	Scharf e Sachais[7]	Bemmel et al.[8]	Montgomery et al.[28]	Haffmans e Vos[9]	Suzuki et al.[11]	Kaynak et al.[10]	Ware e Joe[29]
Mean age (year)		30.1	43.5	61	44	23.9	42	24
Sleep onset latency	↓	↓	→	→	→	→	→	→
% stage 2	↑	→	→	↑	↑	↓	→	→
% stage 3, 4	↑	↑	→	↑	↑	↑	↑	↑
REM latency	↑	↑	↑	↑	→	→	→	↑ *
% REM		→	↓	↓	↓	→	→	→
Total sleep time	↑	↑	→	→	→	→	↑	→
Nº of awakenings	↓	↓	→	↓	↓	‡	↓	↓ *
Dose used (mg/day)	400-600	150-400	300-400	150	50	50-100	100	200
Special caracteristics	depressed patients	depressed patients	major depressive disorder	poor sleepers	SD induced by brofaromine	healthy volunteers	treated with stimulant antidepressants	healthy young adults

*not statistically significant; ↓ decreased; ↑ increased; → not change; ‡ not evaluated; SD: sleep disorder.

Statistical analysis was performed using SPSS version 14.0 for Windows (SPSS, Chicago, USA). The data frequency was examined using the chi-squared test and t-tests were used to investigate baseline differences between genders. Statistical significance was set at $p<0.05$.

RESULTS

Approximately 2/3 of patients (64.6%) were women and the mean age of the sample cohort was 79.1+7.4 years. There was no difference between genders ($p>0.05$) with regards to average age. Most patients (114; 64%) had the diagnosis of AD.

The primary sleep disorder found among the elderly participants was difficulty in maintaining sleep at night (staying asleep). Difficulty in falling asleep, frequent arousals from sleep and early morning awakenings were observed. Although caregivers of our patients frequently complained about difficulties in sleep maintenance, the patients' sleep disorders could not be classified. Table 2 shows the most commonly used drugs for the treatment of sleep disorders in patients with dementia (some used more than one medication).

The other drugs (N=13) were combined into a single group known as "others", represented by benzodiazepines (triazolam, estazolam, and midazolam), antipsychotics (olanzapine and thioridazine) and non-benzodiazepine inducers (zolpidem).

The average time of use of antidepressants in months for the treatment of sleep disorders was 8.1 (±4) for trazodone, 18.6 (±10.1) for mirtazapine and 19.3 (±6.8) for mianserin.

Trazodone was used at a dose of 50 mg/day (at bedtime) in most patients (34) and 100 mg/day in one patient. No adverse effects were reported (spontaneously). In the cases where non-effectiveness of treatment was experienced (12), such non-effectiveness was observed from the first days of treatment, except for one case in which non-effectiveness began after 5 months of drug use.

DISCUSSION

Trazodone is among the antidepressants used with good tolerability in this sample, showing effectiveness in 2/3 of patients.

Antidepressants are a suitable option for the treatment of sleep disorders in the elderly[18]. Tricyclic antidepressants such as amitriptyline, imipramine and cloimipramine, have been used to induce sleep in patients without dementia, especially when the sleep disorder is associated with depression[19]. However, their anticholinergic action may lead to impaired cognition and risk of mental confusion.

Trazodone offers a dual action on serotonin receptors by blocking serotonergic receptor 2A (5HT2A) and inhibiting serotonin reuptake. Phenylpiperazines are differentiated from tricyclic antidepressants since they show greater selectivity for 5HT2A receptors. With regard to the blocking of serotonin reuptake, trazodone is less potent than tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs), and also blocks alpha 1 receptors. There is also a blockade of histaminergic receptors, thus differing from nefazodone; this blocking of histaminergic receptors may be responsible for the extreme sedative effect of this drug. As a result of sleepiness induced as a side-effect, even with off-label use, trazodone has been used in various circumstances in which the main goal is sleep induction[20], but not in dements patients. Trazodone has also been used as an adjuvant to other antidepressants because it increases the tolerabili-

ty of these antidepressant by working to reduce their induced adverse effects via the blocking of 5HT2A receptors (stimulated by SSRI)[21].

The classic indication of trazodone is for depression, particularly when anxiety and insomnia are also present. The usual daily dose for improvement of the sleep disorder complaint varies between 150 and 200 mg/day. Extreme doses of 50 and 600 mg/day may be used in specific cases. Lower doses, between 25 and 100 mg/day, have been prescribed as a hypnosedative for patients with insomnia and to correct the adverse effects of insomnia caused by SSRIs[22]. Due to its relative safety and its low inhibition of cholinergic receptors, trazodone has been used in the treatment of depression in elderly patients with cardiovascular disease. Reduced anticholinergic effect allows its use in elderly patients with cardiovascular impairments and delirium.

Most studies evaluating trazodone in the treatment of sleep disorders were conducted in patients with depression. Saletu-Zyhlarz and collaborators, using polysomnography, evaluated 11 individuals with depression and sleep disorders and compared them to 11 healthy subjects. The authors observed an improvement in sleep parameters with the use of 100 mg/day of trazodone[23]. There was an increase in sleep total time, as we well as a reduction in nighttime and early awakenings. This study also reported improvements in the subjective quality of sleep, sleep efficiency, numerical memory and somatic complaints. This improvement in memory may be welcomed in cases of patients with dementia. In our study, the patients did not use trazodone at doses higher than 100 mg/day, which may have contributed to a lower effectiveness when compared to mirtazapine. There appears to be some improvement in sleep parameters with increasing doses of trazodone[6,7,10].

Nierenberg and colleagues reported good in subjective sleep parameters (PSQI - Pittsburgh Index) with the use of 50 mg/day of trazodone while evaluating patients with secondary insomnia with the use of antidepressants[24]. Similar findings were observed by Kaynak using trazodone at a dose of 100 mg/day, with subjective and objective improvement of quality of sleep after one week of treatment[10].

Despite the improvement in sleep parameters reported in most studies, polysomnographic findings vary among studies, probably due to differences in the dose used and age of the participants (Table 3).

Trazodone has been shown to be effective in the elderly population mainly due to associated reduced anticholinergic effects and undetectable electrocardiographic changes. Another important aspect of this drug is its good tolerability as a treatment for depression in elderly patients. In the current study, 1/3 terminated treatment with trazodone due to a lack of effectiveness but not due to adverse effects. The study of Lebert and colleagues showed no increase in adverse effects of trazodone in patients with dementia[25].

The mechanism involved in the sedative effect of some antidepressants, among them trazodone, remains unclear. It is not known whether there is an improvement in sleep due to an improvement in depression or whether the improved sleep is due to the direct action of the medication[11]. Kaynak and collaborators suggest that the therapeutic effect of trazodone on sleep is independent of its antidepressant effect[10].

Trazodone and other antidepressants with strong antagonism of 5-HT2 receptors have properties that increase the slow-wave sleep in healthy volunteers and in depressed patients with insomnia[26].

The risk of priapism and trazodone-related cardiac arrhythmia is low and is only associated with high doses. The alpha-adrenergic blockade caused by trazodone is thought to the mechanism responsible for priapism[22].

Limitations of this study include: absence of an instrument to ensure that all patients met diagnostic criteria for sleep disorders; the lack of a double-blind design; drugs eligibility was determined on the basis of physician's clinical judgment, because this study sought to reflect the manner in which physicians treat SD in dement elderly; information regarding the effectiveness of these drugs cannot be so clearly, since different drugs might be selected for different purposes. For example, a highly effective drug might look ineffective since doctors might tend to use it only in the most refractory patients; absence of a placebo control group, it is not possible to draw definitive conclusions as one might with a randomized, blinded trial; under-reporting is a recognized limitation of studies based upon spontaneous adverse event reporting.

Nonetheless, the results of this study, in an apparently representative cohort of demented elderly, provide useful and clinically relevant information. This study was intended to show the effectiveness of drugs (trazodone, specially) to SD in demented elderly under 'real world' conditions and make a review. References are cited spanning at least three decades of research.

According to Erman, the lack of studies on the chronic use of trazodone is a reflection of the lack of interest by health authorities and pharmaceutical industries to develop controlled studies with placebo and double-blind groups to assess the effectiveness and safety of the drug in these patients, since the drug has no more patent reserves[27]. The literature reveals the need for controlled, prospective, double-blind and randomized studies to evaluate the benefits of trazodone in this particular segment of the population with dementia[20,28,29].

ACKNOWLEDGMENTS – We thank Prof. Pedro Tauil, MD, PhD, for assistance in method construction and data analysis.

REFERENCES

1. Vitiello MV, Borson S. Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. CNS Drugs 2001;15:777-796.
2. Hope T, Keene J, Gedling K, Fairburn CG, Jacoby R. Predictors of institutionalization for people with dementia living at home with a carer. Int J Geriatr Psychiatry 1998;13:682-690.
3. McCurry SM, Logsdon RG, Teri L, et al. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J Geriatr Psychiatry Neurol 1999;12:53-59.
4. Elmstahl S, Stenberg I, Annerstedt L, Ingvad B. Behavioral disturbances and pharmacological treatment of patients with dementia in family caregiving: a 2-year follow-up. Int Psychogeriatr 1998;10:239-252.
5. Grace JB, Walker MP, McKeith IG. A comparison of sleep profiles in patients with dementia with lewy bodies and Alzheimer's disease. Int J Geriatr Psychiatry 2000;15:1028-1033.
6. Mouret J, Lemoine P, Minuit MP, Benkelfat C, Renardet M. Effects of trazodone on the sleep of depressed subjects: a polygraphic study. Psychopharmacology (Berl) 1988;95(Suppl):S37-S43.
7. Scharf MB, Sachais BA. Sleep laboratory evaluation of the effects and efficacy of trazodone in depressed insomniac patients. J Clin Psychiatry 1990;51 (Suppl):S13-S17.
8. van Bemmel AL, Havermans RG, van Diest R. Effects of trazodone on EEG sleep and clinical state in major depression. Psychopharmacology (Berl) 1992; 107:569-574.
9. Haffmans PM, Vos MS. The effects of trazodone on sleep disturbances induced by brofaromine. Eur Psychiatry 1999;14:167-171.
10. Kaynak H, Kaynak D, Gozukirmizi E, Guilleminault C. The effects of trazodone on sleep in patients treated with stimulant antidepressants. Sleep Med 2004;5:15-20.
11. Suzuki H, Yamadera H, Nakamura S, Endo S. Effects of trazodone and imipramine on the biological rhythm: an analysis of sleep EEG and body core temperature. J Nippon Med Sch 2002;69:333-341.
12. APA. Diagnostic and statistical manual of mental disorders. 4th edition ed. Washington, DC: American Psychiatric Association; 1994.
13. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939-944.
14. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179-186.
15. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-198.
16. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566-572.
17. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44: 2308-2314.
18. Doghramji K. Treatment strategies for sleep disturbance in patients with depression. J Clin Psychiatry 2003;64 (Suppl 14):S24-S29.
19. Wolkove N, Elkholy O, Baltzan M, Palayew M. Sleep and aging 2. Management of sleep disorders in older people. CMAJ 8 2007;176:1449-1454.
20. James SP, Mendelson WB. The use of trazodone as a hypnotic: a critical review. J Clin Psychiatry 2004;65:752-755.
21. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications. 3rd ed, Fully rev. and expanded. ed. Cambridge ; New York: Cambridge University Press; 2008.
22. Cantarelli MDG, Marcolin MA. Trazodona: farmacologia e interações medicamentosas. Rev Psiquiatr Clin 2006;33:329-336.
23. 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;26:249-260.
24. Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994;151:1069-1072.
25. Lebert F, Stekke W, Hasenbroekx C, Pasquier F. Frontotemporal dementia: a randomised, controlled trial with trazodone. Dement Geriatr Cogn Disord 2004;17:355-359.
26. Yamadera H, Suzuki H, Nakamura S, Endo S. Effects of trazodone on polysomnography, blood concentration and core body temperature in healthy volunteers. Psychiatry Clin Neurosci 1999;53:189-191.
27. Erman MK. Is it a sleeping pill? Primary Psychiatry 2000;15:34-36.
28. Montgomery I, Oswald I, Morgan K, Adam K. Trazodone enhances sleep in subjective quality but not in objective duration. Br J Clin Pharmacol 1983;16: 139-144.
29. Ware JC, Pittard JT. Increased deep sleep after trazodone use: a double-blind placebo-controlled study in healthy young adults. J Clin Psychiatry 1990;51(Suppl):S18-S22.