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REVIEW

# Outpatient treatment of sleep disorders in Alzheimer patients

## Tratamento ambulatorial dos transtornos do sono em pacientes com doença de Alzheimer

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## ABSTRACT

Sleep disorders are common in patients with Alzheimer dementia and affect the quality of life of patients and of their caregivers. Despite the rising number of studies in the area, almost all of them are about non-pharmacological treatment. Our objective was to review the literature concerning pharmacological and non-pharmacological approaches to treat sleep disorders of elderly patients with Alzheimer dementia in the ambulatory setting. The treatments revised consisted of sleep hygiene and/or use of intense light coupled or not with use of melatonin, cholinesterase inhibitors, antipsychotics, hypnotics or antidepressants. In addition to the non-pharmacological measures, there is evidence that the use of trazodone may aid the treatment of sleep disorders of older individuals with Alzheimer dementia. More studies are necessary to examine the non-pharmacological and pharmacological treatments revised herein.


**Keywords:** Sleep disorders/therapy; Insomnia/therapy; Alzheimer disease; Ambulatory care


## RESUMO

Os transtornos do sono são comuns nos pacientes com doença de Alzheimer e interferem na qualidade de vida do paciente e de seu cuidador. Apesar da alta prevalência desses transtornos, existe pouca evidência em relação ao seu tratamento. Nosso objetivo foi revisar a literatura em relação ao tratamento não farmacológico e farmacológico dos transtornos do sono nos idosos com doença de Alzheimer em comunidade. Os tratamentos incluídos consistiram na higiene do sono e/ou no uso da luz intensa, combinados ou não com o uso da melatonina, nos inibidores de acetilcolinesterases, antipsicóticos, hipnóticos ou antidepressivos. Para além das medidas não farmacológicas, há evidência de que o uso da trazodona é efetivo no tratamento dos transtornos do sono de pacientes com doença de Alzheimer. Mais estudos sobre as estratégias farmacológicas e não farmacológicas aqui revisadas ou outras são desejáveis.


**Descritores:** Transtornos do sono/terapia; Insônia/terapia; Doença de Alzheimer; Assistência ambulatorial

## INTRODUCTION

Sleep disorders (SD) in patients with Alzheimer's disease (AD) are among the behavioral disorders that most interfere in the quality of life of the patient and of the caregiver. Besides the increased risk of institutionalization, SD have negative repercussions on cognition, functionality, and behavior of these patients.[1,2] Up to 40% of the patients with AD present some SD along the clinical course of the disease.[3]

The factors that contribute towards SD in the elderly with dementia come from the neuropathological alterations observed in AD, such as neuronal loss and atrophy of the suprachiasmatic nucleus of the hypothalamus, which interfere in the organization of the sleep-wake cycle and in reduction of cholinergic activity, since acetylcholine participates in REM sleep.[4,5] Additionally, less exposure to light, lower light capture and difficulty in comprehending temporal references throughout the day also influence the sleep of elderly with AD.[6]

In AD, the most common symptoms related to SD are perambulation, confusion, and nocturnal awakening, besides sleepiness during the day and inversion of the sleep-wake cycle, with reports of night waking being the most stressful aspect for caregivers, and daytime somnolence the most frequent observation.[5,7,8]

Scientific literature on SD has been growing over the last decades. However, most studies are related to non-pharmacological interventions and a few focuses on pharmacological treatment. In the elderly, besides the small number of studies, most are carried out in homes for the aged. The circumscribed routine and standardized care given in these environments are limitations that interfere in the conduction of a

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study and can impede extrapolation of findings to the community.[9]

## OBJECTIVE

To evaluate the effectiveness of drug and non-drug treatment of sleep disorders in community-dwelling elderly individuals with Alzheimer's disease.

## METHODS

The search for articles was carried out using PubMed, LILACS, SciELO, and the Cochrane databases up until January 2014. Observational studies and clinical trials in Portuguese and English were included. The terms used were "sleep disorder", "insomnia", "Alzheimer disease", "outpatient", "dwelling patient", "community patient", and "treatment". Excluded were studies performed exclusively in homes for the aged, those that covered SD of AD patient caregivers, those that analyzed treatment of secondary causes of SD, those that included only patients with mild cognitive impairment, and those that did not address SD treatment.

## RESULTS

Of the 73 studies identified (having already excluded repeated studies in different databases), 18 articles were selected. In all, 930 patients with AD and SD who lived in the community were evaluated. Five studies assessed non-drug treatment (sleep hygiene and phototherapy with intense light);[10-14] as to pharmacological treatment, three studies evaluated the effectiveness of melatonin,[15-17] two of antipsychotics,[18,19] five of acetyl cholinesterase inhibitors (IAch),[20-24] and three of antidepressant agents.[25-27]

### Non-pharmacological therapy

In 2003, the first results of the Nighttime Insomnia Treatment and Education for Alzheimer's Disease (NITEAD) project were published.[10] This was a randomized controlled study that evaluated compliance with non-drug treatment when the caregiver was trained to apply sleep hygiene and daily physical exercise for 30 minutes. The control group received general orientation on sleep. The trained caregivers were more effective in changing the habits of AD patients ($p<0.01$). One year later, NITEAD measurements were made in three patients along with an actigraph evaluation. After 2 months, an improvement was seen both in effectiveness of sleep (with a mean gain of 8%) and in reduction of nocturnal awakening and daytime somnolence.[11]

In 2005, McCurry et al. published the results of a randomized controlled study to investigate the impact of non-drug interventions of NITEAD added to intense light exposure.[12] Patients from the intervention group were submitted to light therapy at 2,500lux potency (equivalent to eight 55-watt lamps) for a period of 1 hour, applied 2 hours before start of sleep, besides having received six home visits from a gerontologist (psychologist) with experience in behavioral therapy for SD treatment. According to the actigraph assessment, those who received the intervention awoke fewer times at night and stayed awake for a smaller period ($p<0.05$). Six years later, McCurry et al. compared the interventions in an isolated form in a randomized clinical trial: in one group, daily physical exercise for 30 minutes, in the other light therapy (2,500lux) for 1 hour (2 hours before sleep), and in the third group, a combination of the two measures. All three groups remained awake less time at night (mean of 37 minutes) and obtained a 5% mean improvement in effectiveness of sleep after six months of intervention.[13]

Colenda et al. did not obtain the same results as McCurry et al. when applying intense light phototherapy (at 2,000lux) in five patients with AD and SD for 2 hours in the morning for 10 consecutive days. No change was noted in any sleep parameter.[14]

### Pharmacological therapy

#### Melatonin

Three studies covered the use of melatonin for SD treatment in elderly patients with AD.[15-17] The first, a retrospective study, evaluated the use of 9mg of melatonin for 22 to 35 months in 14 patients and showed improved quality of sleep by means of a sleep diary and a structured interview.[15] The second, a randomized clinical trial, compared the effect of using 6mg of melatonin for 7 weeks to the use of placebo, and evaluated sleep parameters by means of actigraphy. In this study, four patients with vascular dementia and ten institutionalized patients were included. No benefit from the use of melatonin was confirmed, having compared the mean time awake at night ($p=0.18$), the number of nocturnal awakenings ($p=0.75$), and the efficacy of sleep ($p=0.24$).[16] The same result was found by the randomized placebo-controlled study done by Singer et al. that used melatonin at doses of 2.5mg, 5mg, and 10mg for 8 weeks and did not show significant differences ($p>0.05$) in any of the sleep parameters evaluated by means of actigraphy.[17] In this third study, institutionalized elderly individuals were also included.

**Antipsychotics**

As to antipsychotics, one study evaluated the use of ziprasidone[18] and the other of risperidone, olanzapine, and quetiapine[19] in elderly patients with AD and behavioral disturbances. The first, carried out in Brazil, consisted of an open-label trial with ziprasidone (at 40 to 160mg), having observed improvement of sleep by means of the Neuropsychiatric Inventory (NPI), with p=0.01. Half of the sample was made up of institutionalized elderly individuals.[18] The other was a retrospective study of risperidone, olanzapine, and quetiapine in which sleep assessment consisted of a secondary outcome. The three groups, that used risperidone, olanzapine, and quetiapine, obtained improvement in the NPI score, with no differences among them (p=0.002).[19]

**Acetyl cholinesterase inhibitors**

Five studies with IAch were conducted in non-institutionalized elderly patients with SD and AD.[20-24] Galantamine was evaluated in two randomized clinical trials.[20,21] The first consisted of a randomized placebo-controlled clinical study and did not show benefit from its use in SD, according to the NPI evaluation (p=0.51).[20] In the second, galantamine was compared to donepezil by actigraphy and no association was found with improved sleep measurements.[21] A third study, which was cross-sectional, compared the use of galantamine, rivastigmine, and donepezil by means of polysomnography, showing that all increased REM sleep, reduced stage I of NREM sleep (p=0.01), and increased stage 2 of NREM sleep (p=0.03). However, the group of patients treated with donepezil presented reduced stage 1 of NREM sleep when compared to the group treated with galantamine (p=0.01), while stage 2 of NREM sleep was increased (p=0.04) when compared to the group that did not use the IAch, suggesting a benefit from using donepezil.[22] Moraes et al., in a randomized placebo-controlled study on the use of donepezil in patients with AD and SD, showed an increase in duration of REM sleep in the group treated with donepezil, by means of polysomnography (p<0.05), confirming the result of the previous study.[23] Mizuno et al., in an open-label study with 5mg of donepezil, also found benefits in using donepezil in these patients. The administration of donepezil increased the percentage of REM sleep (p<0.01), improved efficacy of sleep (p<0.01), and reduced latency of sleep (p<0.01).[24]

**Antidepressants**

Camargos et al., in a retrospective study, evinced good effectiveness and tolerability in using trazodone at 50 to 100mg in two-thirds of the patients with AD and SD seen at a geriatric ambulatory. The use of 15 to 30mg of mirtazapine also demonstrated effectiveness in 85% of the patients who used this drug.[25] To confirm the findings of observational studies, the same group conducted a randomized placebo-controlled, double-blind study using trazodone 50mg in treating SD in AD patients. By means of actimetric analyses, it was noted that the patients who used trazodone showed improvement in sleep parameters compared to the group treated with placebo, with a mean gain of 40 minutes of nocturnal sleep (p=0.045) and with an 8.5% higher percentage of night sleep on average (p=0.013). The use of trazodone or placebo did not cause increased daytime sleep (p=0.623).[26] The use of mirtazapine was described in a report of three cases of ambulatory patients with SD and AD, in which an improvement was seen in SD symptoms with the dose of 15 to 30mg by means of subjective evaluation.[27]

**Hypnotics**

No evidence was found for the use of benzodiazepines or other hypnotics in elderly individuals with AD and SD.

## DISCUSSION

Studies on SD treatment in non-institutionalized AD patients are still scarce, despite the various consequences generated by these disorders and their high prevalence in this population.

Sleep hygiene is a behavioral therapy and evidence suggests that success depends on the individual experience of the one who is implementing it, as well as good compliance with the treatment.[20] In the elderly with dementia, the application of these measures depends on the caregiver, and in clinical practice, we note low compliance of caregivers regarding sleep hygiene measures. Also frequent is the poor perception of sleep by caregivers.[8] McCurry et al. observed good compliance with sleep hygiene when the caregiver received active assistance for implementing the program and not only written instructions as is habitually done.[12] Sleep hygiene, associated with intense light, proved to improve symptoms in only one clinical trial performed in patients at home.[13] Considering that non-drug measures are usually low risk and low cost measures, it is advisable that they be applied in patients with AD and SD. Therapy with intense light, when it was performed, was to be applied for 1 hour at 2,500lux per hour, 2 hours before sleep. In homes for the aged, various clinical studies assessed therapy with intense

light, but showed contradictory results and insufficient evidence for its recommendation.[28]

Considering that the effect of melatonin seems to control the sleep-wake cycle and also regulate the circadian rhythm in humans, its use has received much attention over the last 10 years as a therapeutic possibility for SD in elderly persons with AD.[29] However, systematic reviews and meta-analyses on the topic have shown heterogeneous results, even when only young adults without dementia were considered.[30] The same happened in the studies analyzed in this review, especially the study by Singer et al., which showed good methodological quality and negative results.[17] The absence of response with the use of melatonin may be explained, in part, by a deficiency in melatonin MT1 receptors in the central nervous system of patients with a neurodegenerative disease.[31] Another explanation would be the inclusion of both individuals with a normal profile for melatonin secretion and individuals with altered melatonin secretion, since only individuals with reduced levels of the hormone seem to benefit from replacement therapy.[32] The non-characterization of the baseline metabolic profile of the patients and the non-differentiation among community-dwelling elderly individuals and residents in institutions may have interfered in the analysis of the results of the three studies available.[15-17] In this way, there is insufficient evidence to indicate the use of melatonin in SD of patients with AD who live in the community.

Antipsychotics are indicated to treat behavioral disturbances of AD, and in consequence of the blockage of the H1 histamine receptor, they induce somnolence and sedation, an effect often used to induce sleep in patients with AD.[33] Neither of the two studies included in this review is robust enough from the methodological point of view.[18,19] One of them consisted of an open-label study that also included elderly from homes for the aged in their analyses, with no objective method to evaluate sleep.[18] The other had a retrospective design, which accentuates the possibility of biases and non-controlled aspects.[19] The chronic use of antipsychotics in the elderly is associated with adverse reactions (five times more than in younger people) and the risk of a cerebrovascular event and death.[34] Due to the adverse effects, this class of medications should be reserved only for patients with serious and limiting behavioral symptoms. There is no sufficient evidence for the use of antipsychotics in treating SD in the non-institutionalized elderly with AD.

IAch, along with memantine, are the only pharmacological options for the treatment of AD. Despite the modest effect that IAch exert on cognition and functionality of patients, this class may aid in the control of behavioral disturbances. Nevertheless, among the three IACh in use (donepezil, rivastigmine, and galantamine), only donepezil seems to modify the architecture of sleep and act favorably on the symptoms of SD.[20-24]

Despite the prescription of antidepressants with a hypnotic effect being frequent in clinical practice, there is only one placebo-controlled clinical study, on the use of trazodone, in SD. The use of trazodone, with the dose of 25 to 100mg, constitutes a therapeutic option for community-dwelling AD patients with SD. The action of trazodone as an antagonist of 5HT2 and histaminergic receptors promotes an increase in slow-wave sleep in depressed elderly patients with insomnia.[35] Mirtazapine may be another option of an antidepressant drug used in this population since it also has the effect of antagonist of 5HT2 and histaminergic receptors, albeit with no sufficient evidence for use in SD patients with AD.[36]

Benzodiazepines are frequently used in clinical practice, but they may increase the risk of falls, cause daytime sedation, contribute towards cognitive worsening and the altered architecture of sleep in elderly individuals.[37,38] These effects are associated primarily with those drugs with greater half-lives and with the presence of active metabolites. The new generation of non-benzodiazepine hypnotics, the so-called Z compounds, such as zolpidem and zopiclone, are also agonists of GABA receptors, but they act more selectively in the central nervous system. Various studies have shown the safety and effectiveness of the chronic use (up to 12 months) of these drugs in the elderly, but no study has been done in the aged with dementia.[38]

## CONCLUSION

Sleep disorders are common in patients with AD. Despite the high prevalence, there is little evidence as to the effectiveness of SD treatment in this population, particularly in community-dwelling elderly individuals. The application of sleep hygiene by training the caregivers and application of brilliant light therapy in patients are suggested, both approaches recommended due to the low risk when compared to pharmacological treatment. Among the drugs that can be used, trazodone stands out as the one that shows the best evidence of efficacy in treating SD in community-dwelling patients with AD. More studies on the pharmacological and non-pharmacological strategies revised here or others are needed, as long as they are based on a good design, relevant variables, and satisfactory analytical power.

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