Impact of nighttime donepezil administration on sleep in the older adult population: A retrospective study

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ABSTRACT

Introduction. Although not definite, studies are finding Alzheimer's disease may be related to loss of cholinergic innervation. In order to impact this loss of function, therapeutic agents have been developed to reduce the breakdown of acetylcholine, a neurotransmitter vital in cognitive processes. Donepezil has been used in Alzheimer's disease for improving cognition. Although the package insert suggests nighttime administration to reduce the instance of daytime side effects, some patients report sleep disturbances.
Methods. Patient charts at the Tallahassee Memorial Healthcare Neuroscience Center (TMH-NSC) were reviewed. Charts of those patients who met the inclusion criteria were used to determine the correlation between night time administration of donepezil and sleep disturbances.
Results. A total of 186 patient charts were analyzed. Of those 186, 103 of the patients were taking donepezil as directed in the package labeling, at night time. Nearly half (47.6%) of the patients taking donepezil at night reported night time disturbances (NTD) and only 21 of the 83 patients taking donepezil in the morning reported NTD.
Conclusion. This retrospective study showed that taking donepezil at night may be associated with sleep disturbances. Although labeling suggests administration in the evening, should NTDs occur, changing the medication administration to the morning should be explored before switching therapeutic agents.

KEYWORDS

Alzheimer's disease, donepezil, sleep, night time disturbance

INTRODUCTION

The pathogenesis of Alzheimer's disease is not fully understood, but may be related to the loss of central cholinergic innervations. Some available therapeutic agents aim to enhance neurotransmission of acetylcholine in order to improve cognitive processes. Donepezil HCl is a reversible acetylcholinesterase inhibitor.[1] It is highly selective for centrally acting acetylcholinesterase, and is associated with a decrease in the incidence of cholinergic side effects.[2] It is a preferred agent for the management of the symptoms of Alzheimer's disease since it has been shown to be of benefit in mild, moderate and severe stages of the disease. It has also shown benefit in the management of vascular dementia and dementia associated with Parkinson's disease.[3]

Donepezil (Aricept®; Eisai Inc., Woodcliff Lake, NJ) tablets are used as once-daily doses ranging from 5 to 23

mg. The drug is also available in 5 mg and 10 mg orally disintegrating tablets. The package insert recommends that donepezil be administered in the evening just before retiring.[4] Nighttime administration was suggested to prevent the patient from experiencing the side effects during the day. In clinical trials, the most common adverse effects included nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia.[4]

Vivid dreams and sleep disturbances are adverse effects that can also occur with the use of donepezil as directed.[5] In placebo-controlled clinical trials in adults with mild to moderate Alzheimer's disease, abnormal dreams were reported in 3% of patients who received donepezil once daily.[4] Changing the administration time of donepezil to the morning may decrease the incidence of sleep disturbances. This study aims to determine whether there is a relationship between nighttime administration of donepezil and sleep disturbances.

METHODS

This was a retrospective study. All data were collected from pharmacy consults at Tallahassee Memorial Healthcare Neuroscience Center (TMH-NSC). TMH-NSC Patients are referred to pharmacy clinic by neurologist or psychologist for medication review when there are multiple cognitively impairing medications on profile or in cases of polypharmacy. Upon approval from Florida A & M University Institutional Review Board, the data was collected from selected records.

Inclusion criteria included: age 55 or older, participation in a pharmacy consult interview at TMH-NSC outpatient memory disorder clinic between January 1, 2001 and August 1, 2011, and reported donepezil use (morning or nighttime administration). Exclusion criteria included: diagnosis of post-traumatic stress disorder, sleep apnea or restless leg syndrome, or coinciding (within 2 weeks) initiation or dose change of any opioid or psychotropic agent other than donepezil, and noontime donepezil administration. The study was not funded by any organizational or institutional entity.

The following information was gathered and recorded from the pharmacy consult interview transcripts: patients' gender, race, prescribed donepezil dose, dosing schedule, length of therapy, and report of sleep disturbances (vivid dreams, nightmares, insomnia, sleep-walking, sleep-talking, night time psychosis etc.). Sleep disturbances may have been reported by the patient or caregiver and recorded during interview. It is important to note that the interview is not standardized and the encounters were conducted by several different pharmacists over the 10 years. Chi-square tests were utilized to determine whether there is a relationship between nighttime administration of donepezil and sleep disturbances in the patients of TMH-NSC.

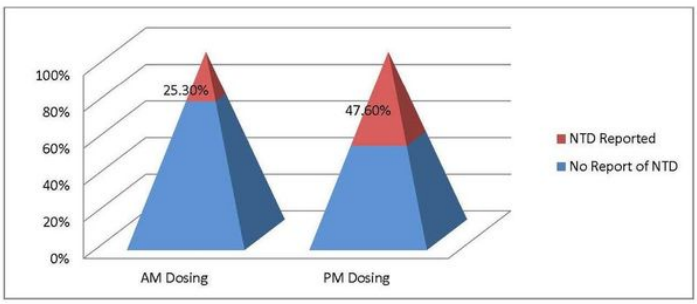
RESULTS

The data collected from 186 charts were included in the statistical analysis. Of those patients, 103 were taking donepezil at nighttime as directed by the drug package insert. The other patients (n=83) were taking the drug in the morning. Forty-nine (47.6%) of the patients taking donepezil at night reported night time disturbances (NTD) including insomnia, nightmares, and vivid dreams. Only 21 (25.3%) out of the 83 patients taking the drug in the morning reported NTD (Figure 1).

Specific times of administration were inquired about during the interview and self-reported by the participants. Seventy percent of all the patients who reported NTD administered the drug at night. Odds ratio analysis revealed that patients were 2.7 times more likely to report NTD if they were taking donepezil at night (p=0.002). Chi-square analysis demonstrated that the relationship between the donepezil dose (5 mg (36% of patients) or 10 mg (64% of patients)) and the occurrence of NTD was not statistically significant. Neither was the relationship between length of therapy and occurrence of NTD. The length of therapy varied between one week and six years.

In the consult reports of 98% of the patients who were taking donepezil at night and reported NTD, the clinician suggested that the time of administration be switched to the morning. A switch in the administration time from morning dosing to nighttime dosing was only recommended in two (2.4%) of the 83 patients taking the drug in the morning. One of those patients had reported NTD.

Figure 1: Night time disturbances reports vs. time of administration



DISCUSSION

The study showed that nighttime donepezil administration may be associated with the occurrence of

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NTD regardless of dosing and length of therapy. The drug package insert suggests that patients take donepezil right before retiring.[4] The manufacturers recommend a later time of administration to prevent patients from experiencing adverse effects (e.g., dizziness, nausea/vomiting, muscle cramps, fatigue, loss of appetite etc.) during the day. This precaution may be useful when trying to sleep through the gastrointestinal side effects. It should be noted that gastrointestinal side effects, muscle cramps, fatigue, and loss of appetite were found in clinical studies to often be mild in intensity and transient, resolving after continued donepezil treatment without the need for dose modification.[4] Also, many patients taking donepezil are older adults and tend to use the restroom during the night. The particular side effect of dizziness could prove to be even more dangerous in that population at night since they may be at a greater risk for falls when attempting to navigate in the dark.

Our study demonstrated that following the package insert instructions regarding time of administration proved to yield an increased risk of nighttime disturbances including insomnia, nightmares, and vivid dreams. Patients were almost 3 times more likely to report sleep disturbances if they were taking donepezil at night. Our results support the conclusion of a smaller study (N=8) conducted in Germany. In that particular study, a clear-cut relationship was observed between the occurrence of nightmares and an evening dose of donepezil.[6]

A study suggested that donepezil may act on REM sleep-related cholinergic neurons.[7] This may explain the sleep disturbances experienced by the patients, along with the fact that donepezil reaches its peak plasma concentration within 3 to 4 hours. If the dose is taken at night, high plasma concentrations are reached while the patient is asleep.[8] Our conclusions propose that if night time disturbances make donepezil intolerable for a patient who takes it at night, a switch in the administration time should be considered before a change in the pharmacological agent occurs. This supports a recommendation given in a published update on Alzheimer's drugs.[9] Another strategy could be to initially start donepezil with evening administration and switch to morning administration if tolerability develops for transient adverse effects.

The results of our study are limited by the small sample size and by the fact that the potential effects of concurrent medications or other medication administration time adjustments were not taken into consideration. Our study did not have a placebo or control group which is also a limitation since we would be unable to evaluate the incidence of NTD in the same patient population. We present reports of the clinicians' suggestions to switch the administration time to the morning when NTD were reported. However, because this was a retrospective study, it would have proven to be difficult to contact the patients and assess the impact of a change in the administration time of donepezil on quality of sleep. Our study also did not assess for increase of any other side effects (e.g., nausea/vomiting, diarrhea, muscle cramps, fatigue etc.) as related with time of administration. A larger study may take into consideration noontime donepezil administration and the 23 mg once-daily dose. Our study may serve as grounds for further research about time of administration of donepezil.

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