The Effect of Donepezil on Arousal Threshold and Apnea–Hypopnea Index

A Randomized, Double-Blind, Cross-Over Study

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Abstract

Rationale: Obstructive sleep apnea (OSA) has multiple pathophysiological causes. A low respiratory arousal threshold (ArTh) and a high loop gain (unstable ventilatory control) can contribute to recurrent respiratory events in patients with OSA. Prior studies have shown that donepezil, an acetylcholinesterase inhibitor, might improve OSA, but the mechanism is unknown.

Objectives: To determine whether a single dose of donepezil lowers the apnea–hypopnea index by modulating the ArTh or loop gain.

Methods: In this randomized, double-blind, crossover trial, 41 subjects with OSA underwent two polysomnograms with ArTh and loop gain evaluated, during which 10 mg of donepezil or placebo was administered.

Measurements and Main Results: Compared with placebo, sleep efficiency (77.2 vs. 71.9%; $P = 0.015$) and total sleep time

decreased with donepezil (372 vs. 351 min; $P = 0.004$). No differences were found in apnea–hypopnea index (51.8 vs. 50.0 events/h; $P = 0.576$) or nadir oxygen saturation as determined by pulse oximetry (80.3 vs. 81.1%; $P = 0.241$) between placebo and donepezil, respectively. ArTh was not significantly changed (−18.9 vs. −18.0 cm H₂O; $P = 0.394$) with donepezil. As a whole group, loop gain (ventilatory response to a 1-cycle/min disturbance) did not change significantly ($P = 0.089$).

Conclusions: A single dose of donepezil did not appear to affect the overall severity of OSA in this patient group, and no consistent effects on ArTh or loop gain were observed. Donepezil may have minor effects on sleep architecture.

Clinical trial registered with www.clinicaltrials.gov (NCT02264353).

Keywords: obstructive sleep apnea; donepezil; arousal threshold; loop gain; treatment

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Obstructive sleep apnea (OSA), which is characterized by repetitive narrowing or collapse of the upper airway during sleep, is an increasing public health issue (1). Continuous positive airway pressure (CPAP) is the first-line treatment for OSA, but it has an adherence rate of only about 50–75% (2). Thus, alternative therapies targeting OSA pathogenesis are needed.

A low respiratory arousal threshold (awakening easily to respiratory stimuli) and a high loop gain (exaggerated response to ventilatory perturbations) are important nonanatomical contributors in a substantial proportion of patients with OSA (3). Respiratory events terminated with cortical arousals are associated with increased risk of secondary respiratory events compared with events without arousals (4). Moreover, premature arousals may disrupt accumulation of respiratory stimuli, which could activate upper airway dilator muscles and help achieve stable breathing (5). A high loop gain, which is associated with enhanced ventilation responses and sequential excessive blood gas fluctuations, may lead to instability of ventilation during sleep, resulting in an increase in respiratory events (6). Therefore, pharmacologically increasing the arousal threshold (ArTh) and/or decreasing the loop gain may be beneficial for some patients with OSA (7–9). Some sedative medications have been reported to increase the ArTh and eliminate sleep apnea in patients with low ArTh (7–9); decreasing loop gain by medication or supplemental oxygen might improve sleep apnea severity (10, 11).

Donepezil is a reversible acetylcholinesterase inhibitor commonly used to treat Alzheimer's disease (AD). Prior small studies have shown that donepezil improved OSA in both patients with AD and without AD over a period of weeks (12, 13). Acetylcholine plays an important role in the sleep process and modulation of ventilatory control (14–16). Moreover, we have previously identified an important medullary region with heavy cholinergic staining, which we believe is crucial for pharyngeal patency (17, 18). Thus, pharmacological manipulation of acetylcholine might improve sleep apnea via augmenting pharyngeal protective reflexes. However, the mechanism of potential improvement in OSA with donepezil is unknown. The hypothesis

of this study is that a single dose of donepezil (10 mg) will reduce the apnea–hypopnea index (AHI) by modulating the ArTh.

Methods

Study Design

A double-blind, randomized, crossover study design was used. All participants underwent two in-laboratory overnight polysomnograms (PSGs) at least 12 days apart, based on the pharmacological half-life of donepezil ($t_{1/2} = 70$ h). Subjects were administered either 10 mg of donepezil or an indistinguishable placebo (in blinded, arbitrary order) 2 hours before sleep. When they returned for a second PSG, they received a placebo or donepezil (10 mg) based on initial randomization.

Power Calculation

The number of observations needed was estimated according to the values of the standard deviation of the difference in AHI seen in a prior study of donepezil (12). With 90% power to reject the null hypothesis and $\alpha = 0.05$, the estimated sample size was 38 subjects. On the basis of a 10% dropout rate we recruited 44 subjects.

Participants

Patients were eligible for the study if they were 18–70 years of age. All subjects had a history of untreated OSA with an AHI greater than 5 events/hour according to American Academy of Sleep Medicine Task Force criteria (19). Exclusion criteria included the presence of pulmonary, cardiac, neurological, or other active severe medical or psychiatric diseases; and the current use of CPAP therapy. No drugs

that might interact with the investigational medication or that are known to affect sleep were taken during the trial or in the 1 month preceding the study. We also excluded patients with known allergy to donepezil, currently smoking, or taking alcohol at a rate exceeding 3 oz/day. Written informed consent was signed by the subject before participation in the study, and the study protocol was approved by the Human Research Committee of the University of California, San Diego (La Jolla, CA).

Polysomnography

Electroencephalograms, electro-oculograms, and surface electromyograms were applied to score arousals, leg movements, and sleep stage. Abdominal and chest movements, pulse oximetry–determined oxygen saturation, oral and nasal flow were recorded to detect respiratory events. Participants were instructed to sleep in the supine position as much as possible throughout the duration of the night. PSGs were analyzed by experienced technicians who were blinded to both the order of medication/placebo and the ArTh measurement according to the scoring guidelines described in the American Academy of Sleep Medicine Task Force criteria (19).

Arousal Threshold Measurements

Respiratory ArTh was measured according to previously reported methods (7–9, 20). Briefly, subjects were instrumented overnight with an epiglottic pressure catheter (model MCP-500; Millar, Houston, TX). ArTh was defined as the average nadir epiglottic pressure immediately before cortical arousal (>3 s of high-frequency activity on the EEG) from 20 randomly selected respiratory events. To evaluate the

Table 1. Baseline demographics and sleep parameters of participants

Characteristic (<i>n</i> = 41)	Value
Sex, male/female	27/14
Race	33 white, 6 Asian, and 2 of more than one race
Age, yr	51.6 ± 11.1*
Epworth Sleepiness Scale	8 (4.5, 12) [†]
Body mass index, kg/m ²	29.2 ± 5.4*
Apnea–hypopnea index, events/h	51.8 ± 27.4*
Nadir oxygen saturation during sleep, %	80.3 ± 6.4*
Time between studies, d	14 (13, 16) [†]

*Normally distributed parameters are shown as means ± SD.

[†]Parameters are shown as median (25th percentile, 75th percentile).

impact of epiglottic pressure monitoring on the assessment of the change in sleep parameters with donepezil, ArTh was assessed in 21 of the 41 subjects (i.e., about one-half of the subjects slept without a catheter in place).

Loop Gain Analyses

The sensitivity of the ventilatory control system (loop gain) was quantified by fitting a simplified mathematical model to the spontaneous ventilatory pattern of OSA (21). Loop gain is reflected in the size of the ventilatory overshoot after a ventilatory perturbation (hypopnea/apnea), where loop gain = response/disturbance. Ventilatory fluctuations are estimated on the basis of the square-root-transformed nasal pressure waveform. Loop gain was reported as the ventilatory response to a 1-cycle/minute disturbance (LG1); an LG1 value greater than 1 yields periodic central apnea. Calculations were performed with MATLAB (MathWorks, Natick, MA).

Statistical Analysis

Statistical analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL). Sleep parameters with placebo or donepezil were compared by Wilcoxon signed ranks test. Obstructive sleep apnea severity and loop gain with placebo or donepezil were compared by *t* test. The respiratory arousal thresholds with placebo and donepezil were compared by Mann-Whitney *U* test. Spearman's correlation coefficient was used to identify significant associations. Statistical significance was set at $P < 0.05$.

Results

Of the 44 subjects recruited, one quit the study because of difficulty in falling asleep in the laboratory after taking placebo; one reported "heart burn" and decided to quit after taking placebo; one was excluded because of a pulmonary embolism detected 10 days after placebo administration and before the second study night. The final sample consisted of the remaining 41 patients. One subject reported mild nausea after completing the study; however, no unanticipated problems related to donepezil were observed during the study.

The characteristics of the participants are listed in Table 1. Body mass index did not change between placebo visit

Table 2. Sleep apnea severity with placebo or donepezil: $n = 41$

	Placebo	Donepezil	<i>P</i> Value
AHI, events/h	51.8 ± 27.4	50.0 ± 23.4	0.576
Supine NREM AHI, events/h	51.7 ± 26.6	51.8 ± 31.0	0.954
Supine REM AHI, events/h	49.8 ± 22.1	47.8 ± 26.3	0.291
Hypopnea index, events/h	31.5 ± 18.1	30.3 ± 18.7	0.472
Event duration, s	26.0 ± 4.9	24.9 ± 5.3	0.055
Arousal index, events/h	49.1 ± 19.6	48.7 ± 21.7	0.824
Nadir O ₂ saturation, %	80.3 ± 6.4	81.1 ± 7.1	0.241

Definition of abbreviations: AHI = apnea-hypopnea index; NREM = non-rapid eye movement sleep. Data are shown as means ± SD.

and donepezil visit ($P = 0.349$). There were no statistically significant differences in anthropometric measurements or baseline sleep apnea severity in patients with or without epiglottic pressure assessment ($P > 0.05$; see the online supplement for details).

Effect of Donepezil on Obstructive Sleep Apnea Severity and Sleep Parameters

Sleep apnea severity was not different between patients receiving donepezil and placebo (Table 2). Although the group means showed little difference, there was wide intrasubject variability (Figure 1). Changes in AHI and NREM supine AHI with donepezil compared to placebo varied from -29.2 to 35.3 events/hour and from -31.67 to 35.8 events/hour, respectively.

In 25 (61.0%) of the study population, the AHI difference between the two nights of the recording was greater than 5 events/hour. Reductions in AHI of at least 10 and 15% with donepezil were observed in 15 patients (36.6%) and 9 patients (22.0%), respectively; an increase in AHI of at least 10 and 15% with donepezil was found in 9 subjects (22.0%) and 6 subjects (14.6%), respectively.

There were two people who had substantially increased AHI (>30 events/h) with donepezil compared with the placebo condition (subject 2, AHI = 85 events/h at baseline and 117.2 events/h with donepezil; subject 41, AHI = 79.8 events/h at baseline and 115.1 events/h with donepezil). If we remove these two outliers, we do see a significant improvement in

Figure 1. Sleep apnea severity as measured by apnea-hypopnea index (AHI, events/h) under each condition.

Table 3. Sleep parameters with placebo or donepezil: $n = 41$

	Placebo	Donepezil	P Value
Sleep efficiency, %	77.2 (63.7, 85.2)	71.9 (65.1, 80.0)	0.015*
Sleep onset latency, min	5.6 (2.9, 34.7)	8.75 (4.4, 20.2)	0.422
NREM stage 1 sleep, % TST	28.8 (21.8, 51.0)	27.5 (18.1, 48.5)	0.502
NREM stage 2 sleep, % TST	54.7 (34.8, 60.7)	48.8 (41.7, 56.8)	0.547
NREM stage 3 sleep, % TST	0.34 (0, 3.26)	0.42 (0, 7.57)	0.642
REM sleep, % TST	13.5 (8.6, 16.1)	15.0 (8.8, 23.7)	0.014*
Total sleep time, min	372 (304, 407)	351 (278, 379)	0.004†

Definition of abbreviations: NREM = non-rapid eye movement sleep; TST = total sleep time.

Data are shown as median (25th percentile, 75th percentile).

* $P < 0.05$.

† $P < 0.01$.

AHI in the remaining participants, but we view such analyses as exploratory and requiring further study.

Compared with the placebo visit, decreased total sleep time and sleep efficiency were observed during the donepezil visit (Table 3).

Effect of Donepezil on Respiratory Arousal Threshold

ArTh was not significantly different (-18.9 [$-27.5, -12.3$] vs. -18.0 [$-27.0, -11.8$] cm H₂O; z -score = -0.852 ; $P = 0.394$) between placebo and donepezil in the 21 patients with epiglottic pressure assessment. Even when focused on patients with a low arousal threshold (defined as less than -15 cm H₂O; $n = 8$), there was no significant change in ArTh (-12.2 [$-13.8, -10.3$] vs. -11.3 [$-14.2, -8.5$] cm H₂O; z -score = -0.059 ; $P = 0.953$). Individual ArTh changes with placebo and donepezil are shown in Figure 2.

Effect of Donepezil on Loop Gain

For the whole group, loop gain at a 1-cycle/minute disturbance of frequency (LG1) did not change significantly with placebo and donepezil (0.58 ± 0.16 vs. 0.55 ± 0.15 ; $t = 1.744$; $P = 0.089$). In the subjects with a relatively high LG1 (LG1 > 0.5 ; $n = 26$), LG1 values were slightly lower with donepezil (0.67 ± 0.13 vs. 0.62 ± 0.14 ; $t = 2.093$; $P = 0.046$). Figure 3 shows individual LG1 change with placebo and donepezil in subjects.

Relationships between Changes in Physiological Traits and Treatment Responses

Given the wide range of responses in OSA severity to donepezil and the underlying physiological traits, we sought to understand the relationship between changes in AHI

and the underlying traits. In the 21 patients with epiglottic pressure measurement, there was no significant association between changes in AHI and changes in ArTh ($r = 0.331$; $P = 0.143$; Figure 4). There was a positive association between changes in AHI and changes in LG1 ($r = 0.325$; $P = 0.038$; Figure 5).

Discussion

We identify three major findings of this study. First, we did not find a consistent change in sleep apnea severity with a single dose of 10 mg of donepezil. Moreover,

some individuals with severe OSA even showed significant increases in AHI with donepezil, raising potential safety concerns. Second, donepezil may be associated with decreased sleep efficiency compared with placebo. Third, there were no significant changes in respiratory ArTh and loop gain for the donepezil versus placebo night. However, loop gain might decrease with donepezil in the select subjects with relatively high loop gains.

To our knowledge, no previous studies have examined the acute effect of donepezil on OSA. To date, there are two studies supporting the beneficial impact of donepezil on AHI, nadir oxygen saturation, as well as Epworth Sleepiness Scale score in patients with or without dementia (12, 13). The major findings of the present study are different from the previous one (12), the authors of which observed improvement in OSA severity from 42.2 to 32.8 events/hour with 2–4 weeks of daily donepezil. There are several potential reasons for the inconsistency across studies. First, in one prior study, donepezil was given at a dosage of 5 mg/day for the first 2 weeks and at 10 mg/day for the last 2 weeks for nondementia patients with OSA. Given the medication may have some beneficial effects on the long-term facilitation of upper airway dilatory

Figure 2. Arousal threshold (cm H₂O) under placebo and donepezil conditions.

Figure 3. Loop gain (the ventilatory response to a 1-cycle/min disturbance) under the placebo and donepezil conditions for each patient.

muscle activity and ventilatory control, a single night of therapy may be insufficient to see potential benefits.

Moreover, donepezil inhibits acetylcholinesterase dose-dependently in the human brain *in vitro* (22). Because donepezil has a long elimination half-time of approximately 70 hours (23), longer duration of medication administration might generate a more robust effect.

In addition, the current study population covered a larger range of baseline AHI (range, 6.1–101.3 events/h) compared with the previous studies. None of the previous studies included subjects with a baseline AHI greater than 70 events/hour, whereas 11 were included in our study. Among these subjects, two had substantially increased AHI (>30 events/h) with donepezil compared with the placebo

condition (subject 2, AHI = 85 events/h at baseline and 117.2 events/h with donepezil; subject 41, AHI = 79.8 events/h at baseline and 115.1 events/h with donepezil). In contrast, no increase exceeding 15 events/hour or more in AHI under the donepezil condition was observed in the prior studies.

Interestingly, if the two outliers who experienced deterioration are removed, we do see a small but significant improvement in AHI in the remaining participants, but we recognize such subgroup analyses are underpowered and therefore exploratory. Thus, the discrepancy of the results between various studies might be due to subject characteristics as well. Moreover, physiological characteristics could be used in subsequent studies to determine who may be good candidates for pharmacological intervention. To our knowledge, no previous study examining the effect of donepezil on arousal threshold or loop gain in patients with OSA has been reported. We found no change in either arousal threshold or loop gain with acute administration of donepezil.

Breathing control is relatively stable in slow-wave sleep, and the upper airway is considered to be more vulnerable to collapse during REM (24, 25). Thus, change in sleep architecture may also be related to the severity of sleep apnea. Our results were consistent with one previous study showing decreases in REM latency and increases in REM percentage in the first donepezil night in healthy persons (26). Although REM sleep percentage increased from 13.5 to 15% with donepezil, REM AHI and NREM AHI were not changed by donepezil. Furthermore, slow-wave sleep percentage was not changed by donepezil (27, 28). Therefore, it is unlikely that acute donepezil has a major impact on AHI through sleep stage migration.

One consideration when we designed the experiment was the impact of epiglottic pressure monitoring on the assessment of sleep parameters. In an early report, there was a statistically insignificant trend for reduced sleep quality and oxygen saturation with esophageal pressure monitoring (29). A more recent study reported that an epiglottic catheter was well tolerated and also found no statistically significant impact on sleep quality parameters or sleep apnea severity (30). In the present study, the changes in sleep apnea severity or sleep architecture with donepezil were not significantly different in the group with epiglottic pressure catheter

Figure 4. Change in apnea-hypopnea index (AHI) under the placebo and donepezil conditions and the change in respiratory arousal threshold (ArTh). There was no significant association between changes in AHI and change in ArTh ($r = 0.331$, $P = 0.143$).

Figure 5. Change in apnea-hypopnea index (AHI) under placebo and donepezil conditions and the change in loop gain (the ventilatory response to a 1-cycle/min disturbance, LG1). There was a positive association between the change in AHI and the change in LG1 ($r = 0.325$, $P = 0.038$).

compared with the group without a catheter (see the online supplement).

A different order of donepezil and placebo administration may alter the effects of donepezil by the “first night effect” (31), which refers to lower sleep efficiency and less REM sleep during the first in-laboratory polysomnographic study in a series of polysomnograms. In theory, this effect should be minimized by a randomized study design. With further analyses, we also confirmed no significant impact of order of medication versus placebo administration in our study (see the online supplement).

Limitations

We performed an acute experimental study and thus we did not test the long-term effect

of donepezil on OSA severity and the physiological traits.

Considering that the severity of OSA decreased about 25% with long-term donepezil administration in prior studies (12), one could consider pharmacological treatment of OSA as a short-term alternative, for example, when patients are temporarily off CPAP. In theory, a subset of patients with particular physiological features may respond well to the medication. Our study results did not show an improvement in OSA severity with a single dose of donepezil. Thus it is unlikely that donepezil could be used as a short-term alternative treatment for patients with OSA. We call for more research to determine the short-term and

long-term effects of various potential pharmacotherapies in OSA.

The one sleep apnea phenotypic trait we did not measure was upper airway muscle effectiveness (so-called upper airway gain). Cholinergically mediated neurons have been reported to promote upper airway negative pressure reflexes in animal studies (17). Thus, we would advocate for future studies to assess the impact of donepezil on upper airway motor control and perhaps to identify patients likely to respond to donepezil by measuring upper airway mechanics.

Summary

Overall, in contrast with the previously reported beneficial effect of longer administration of donepezil in patients with OSA, a single 10-mg dose of donepezil does not appear to affect the severity of OSA, and no consistent effects on arousal threshold were observed. As some individuals with severe OSA showed significant increases in AHI with donepezil, the potential risk of donepezil in worsening sleep apnea should be considered in certain patients. In addition, the underlying mechanism(s) of sleep apnea is likely to vary across individuals such that one might predict that an intervention may be effective only in a subset of patients with OSA. However, whether there is a readily identifiable subset of patients with OSA who may respond well to donepezil remains unclear. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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