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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 small 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 (AHI) by modulating the ArTh or loop gain.

Methods: In this randomized, double-blind cross-over trial, Forty one OSA subjects underwent two polysomnograms with ArTh and loop gain evaluated, during which 10 mg of donepezil or placebo were administered.

Measurements and Main Results: Compared to placebo, sleep efficiency (77.2 vs 71.9%; $P=0.015$) and total sleep time decreased with donepezil (372 vs 351min; $P=0.004$). No differences were found in AHI (51.8 vs 50.0 events/hr; $P=0.576$), or nadir SpO₂ (80.3 vs 81.1%; $P=0.241$) between placebo and donepezil, respectively. ArTh was not significantly changed (-18.9 vs -18.0 cmH₂O; $P=0.394$) with donepezil. As a whole group, loop gain (LG1, ventilatory response to a 1 cycle/min disturbance) did not change significantly ($P=0.089$).

Conclusions: A single dose of donepezil does 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 clinicaltrials.gov (NCT02264353)

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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 is the first line treatment for OSA, but it only has an adherence rate of 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 non-anatomical contributors in a substantial proportion of patients with OSA³. Respiratory events terminated with cortical arousals are associated with increased risk of secondary respiratory events compared to 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 ⁶. 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 ⁵. Therefore, pharmacologically increasing arousal threshold (ArTh) and/or decreasing loop gain may be beneficial for some OSA patients 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 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 10mg 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-lab overnight polysomnograms (PSGs) at least 12 days apart based on the pharmacological half-life of donepezil ($t_{1/2} = 70$ hours). Subjects were administered either 10 mg of donepezil or an indistinguishable placebo (in blinded, arbitrary order) two 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 apnea-hypopnea index (AHI) seen in a prior study of donepezil¹². With a 90% power to reject the null hypothesis and $\alpha = 0.05$, the estimated sample size was 38 subjects. Based on 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/h according to American Academy of Sleep Medicine Task Force criteria¹⁴. Exclusion criteria were presence of pulmonary, cardiac, neurological or other active severe medical or psychiatric diseases; current use of continuous positive airway pressure therapy. No drugs that might interact with the investigational medication or known to affect sleep were taken during the trial or one month before the study. We also excluded patients with known allergy to donepezil, currently smoking, or taking alcohol >3 oz per 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, University of California San Diego.

Polysomnography

Electroencephalograms, electrooculograms, and surface electromyograms were applied to score arousals, leg movements, and sleep stage. Abdominal and chest movements, pulse oxygen saturation, oral and nasal flow were recorded to detect respiratory events. Participants were instructed to sleep supine 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 of American Academy of Sleep Medicine Task Force criteria¹⁹.

Arousal Threshold Measurements

Respiratory ArTh was measured using 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 prior to cortical arousal (>3 sec of high-frequency activity on the EEG) from 20 randomly selected respiratory events. To evaluate the impact of epiglottic pressure monitoring on the assessment of the change of sleep parameters with donepezil, ArTh was assessed in 21 of the 41 subjects (i.e. about the half 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 OSA²¹. Loop gain is reflected in the size of the ventilatory overshoot following a ventilatory perturbation (hypopnea/apnea), where loop gain = response/disturbance. Ventilatory fluctuations are estimated using the square-root transformed nasal pressure waveform. Loop gain was reported as the ventilatory response to a 1 cycle/min disturbance (LG1); a value of LGn>1 yields periodic central apnea. Calculations were performed using MATLAB (MathWorks, Natick, MA, USA).

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, Illinois). Sleep parameters with placebo or donepezil were compared using the Wilcoxon signed ranks test. Obstructive sleep apnea severity and loop gain with placebo or donepezil were compared using

t test. The respiratory arousal thresholds with placebo and donepezil were compared using 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 lab after taking placebo; one reported "heartburn" and decided to quit after taking placebo; one was excluded due to a pulmonary embolism detected 10 days after placebo administration and prior to 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. BMI did not change between placebo visit to donepezil visit ($p=0.349$). There were no significant statistical differences in anthropometric or the baseline sleep apnea severity in the patients with or without epiglottic pressure assessment ($p > 0.05$, see supplementary material for details).

Effect of Donepezil on Obstructive Sleep Apnea Severity and Sleep Parameters

Sleep apnea severity was not different between donepezil and placebo (Table 2). Although the group means showed little difference, there was wide intra-subject variability. Changes of AHI and NREM supine AHI with donepezil compared with placebo varied from -29.2 to 35.3

events/hr and -31.67 to 35.8 events/hr, respectively.

In 25 (61.0%) of the study population, the AHI difference between the two nights of the recording was greater than 5 events/hr. Reduction in AHI $\geq 10\%$ and $\geq 15\%$ with donepezil were observed in 15 (36.6%) and 9 (22.0%) patients; increase of AHI $\geq 10\%$ and $\geq 15\%$ with donepezil were found in 9 (22.0%) and 6 (14.6%) subjects.

There were two people who had substantially increased AHI (>30 events/h) with donepezil compared with 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 AHI in the remaining participants, but we view such analyses as exploratory and require further study.

Figure 1 shows individual AHI change with placebo and donepezil. Compared with the placebo visit, decreased total sleep time and sleep efficiency were observed in 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] cmH₂O, $Z=-0.852$, $p=0.394$) between placebo and donepezil in the 21 patients with epiglottic pressure assessment. Even when focused on patients with a low arousal threshold (defined as <-15 cm of water, $n=8$), there was no significant change in ArTh (-12.2 [-13.8, -10.3] vs. -11.3 [-14.2, -8.5] cmH₂O, $Z=-0.059$, $P=0.953$). Individual ArTh changes with placebo and donepezil are shown in Figure 2.

Effect of Donepezil on Loop Gain

As a whole group, loop gain at a disturbance of frequency 1 cycle /minute (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 subject with a relatively high LG1 (LG1>0.5, n=26), LG1 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.

The Relationships between the Changes in Physiological Traits and the 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 the changes of AHI and the change of ArTh ($r=0.331$, $P=0.143$, Figure 4). There was a positive association between the changes of AHI and the changes of LG1 ($r=0.325$, $p=0.038$, Figure 5).

Discussion

We identify 3 major findings of this study. First, we did not find a consistent change in sleep apnea severity with a single dose of 10mg 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 vs.

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 (ESS) score in patients with or without dementia^{12 13}. The major findings of the present study are different from the previous one¹², who observed improvement in OSA severity from 42.2 events/hour 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 two weeks and 10 mg/day for the last two weeks for non-dementia OSA patients. Given the medication may have some beneficial effects on the long-term facilitation of upper airway dilatory 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 vitro²². Because donepezil has a long elimination half-time of ~70 hours²³, longer duration of medication administration might generate a more robust effect.

In addition, the current study population covered a larger range of baseline AHI (with a range of 6.1-101.3 events/h) compared to the previous studies. None of the previous studies included subjects with a baseline AHI >70 events/h while eleven were included in our study. Among these subjects, two had substantially increased AHI (>30 events/h) with donepezil compared with 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 of over 15 events/h or more in AHI under 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 persons²⁶. 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 monitoring²⁹. 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 severity³⁰. In the present study, the changes of sleep apnea severity or sleep architecture with donepezil were not significantly different in the group with epiglottic pressure catheter from the group without catheter (*see supplement results*).

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-lab 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 vs placebo administration in our study (*see supplement results*).

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 the severity of OSA decreased about 25% with long-term donepezil administration in prior studies¹², one could consider pharmacological treatment of OSA as a short term alternative i.e. applied when patients are short term 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 of OSA severity with a single dose of donepezil. Thus it is unlikely that donepezil could be used as a short-term alternative treatment for OSA patients. 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 studies¹⁷. 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 beneficial effect of longer administration of donepezil in patients with OSA previously reported, a single dose of 10mg 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 only be effective in a subset of OSA patients. However, whether there is a readily identifiable subset of OSA patients who may respond well to donepezil remains unclear.

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Figure Legends

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

Figure 2: Arousal threshold (ArTh, cm of water) during the placebo and donepezil condition.

Figure 3: Loop gain (the ventilatory response to a 1 cycle/min disturbance, LG1) during the placebo and the donepezil condition for each patient.

Figure 4: Change in AHI during the placebo/donepezil condition and the change of the respiratory arousal threshold. There was no significant association between the changes of AHI and the change of ArTh ($r=0.331$, $P=0.143$).

Figure 5: Change in AHI during the placebo/donepezil condition and the change of loop gain (the ventilatory response to a 1 cycle/min disturbance, LG1) There was a positive association between the changes of AHI and the changes of LG1 ($r=0.325$, $p=0.038$).

Table 1. Baseline demographics and sleep parameters of the participants

	Subject Characteristics (n=41)
Gender (Male/Female)	27/14
Race	33 Caucasians, 6 Asians and 2 more than one races
Age (years)	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 (days)	14[13,16] †

*Normally distributed parameters were showed as mean ± Std. deviation; † parameters were showed as median [25 percentage, 75 percentage]

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

	Placebo	Donepezil	<i>p</i> Value
AHI(events/hr)	51.8±27.4	50.0±23.4	0.576
Supine NREM AHI (events/hr)	51.7±26.6	51.8±31.0	0.954
Supine REM AHI (events/hr)	49.8±22.1	47.8±26.3	0.291
Hypopnea Index (events/hr)	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/hr)	49.1±19.6	48.7±21.7	0.824
Nadir O ₂ saturation (%)	80.3±6.4	81.1±7.1	0.241

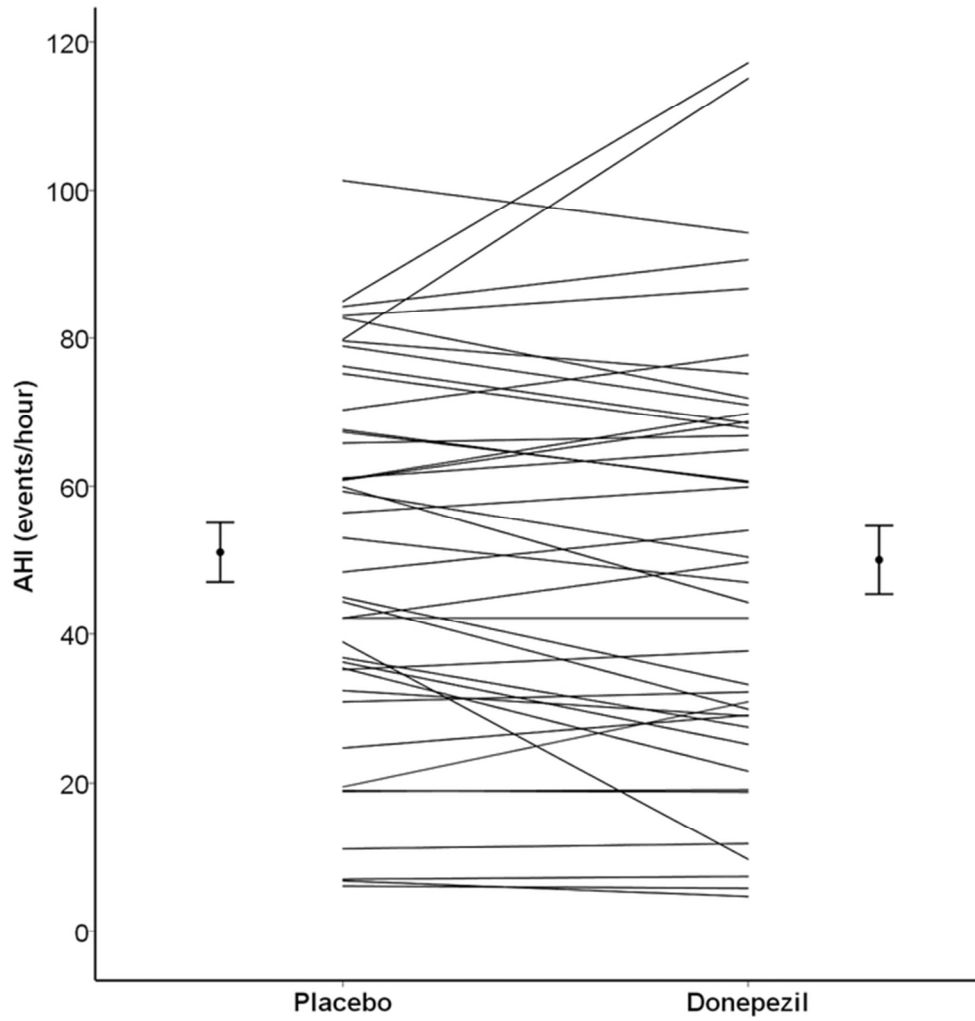
Data were showed as mean ± Std. deviation. Abbreviations: NREM, Non rapid eye movement sleep; REM, Rapid eye movement sleep; AHI, apnea hypopnea index.

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 (minutes)	5.6[2.9,34.7]	8.75[4.4,20.2]	0.422
NREM Stage1 sleep (%TST)	28.8[21.8,51.0]	27.5[18.1,48.5]	0.502
NREM Stage2 sleep (%TST)	54.7[34.8,60.7]	48.8[41.7,56.8]	0.547
NREM Stage3 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 (minutes)	372[304,407]	351[278,379]	0.004†

Abbreviations: NREM, Non rapid eye movement sleep; REM, Rapid eye movement sleep; TST,

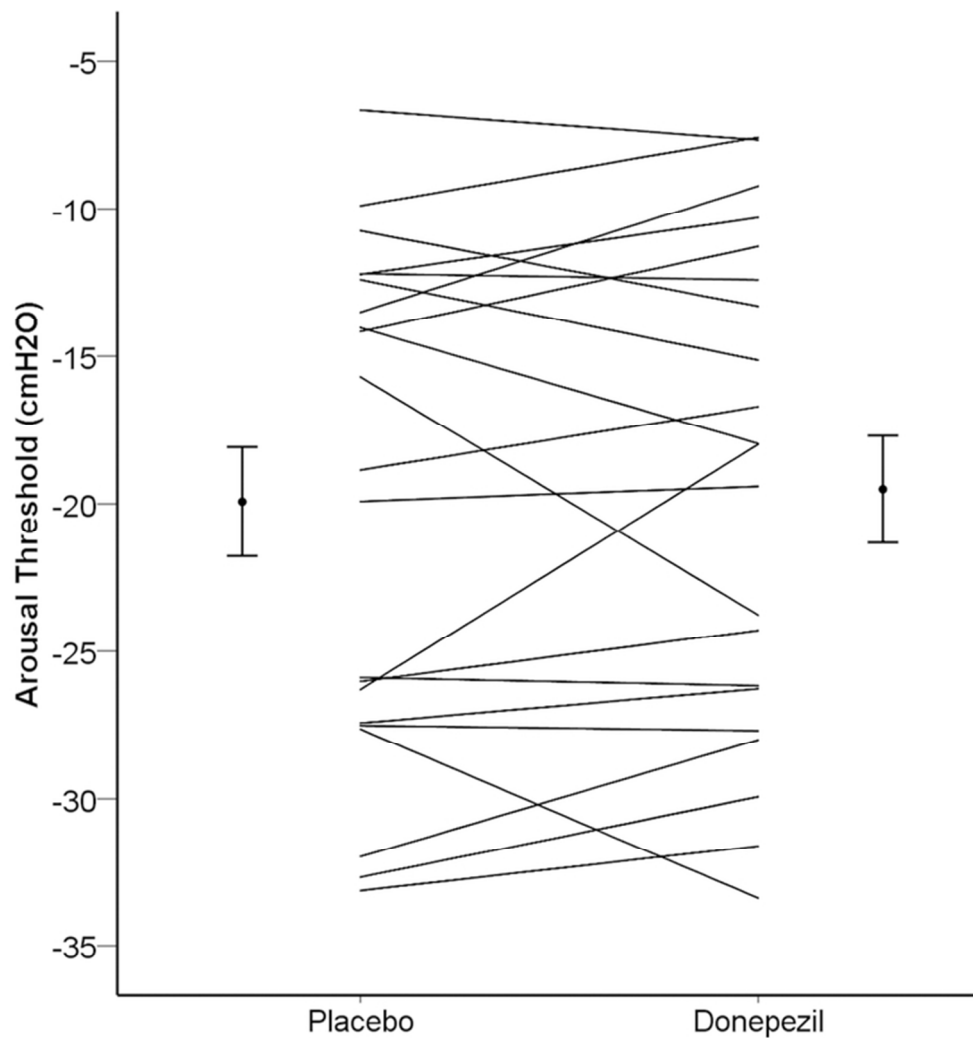
Total sleep time. Median [25 percentage,75 percentage]. * $p < 0.05$; † $p < 0.01$.



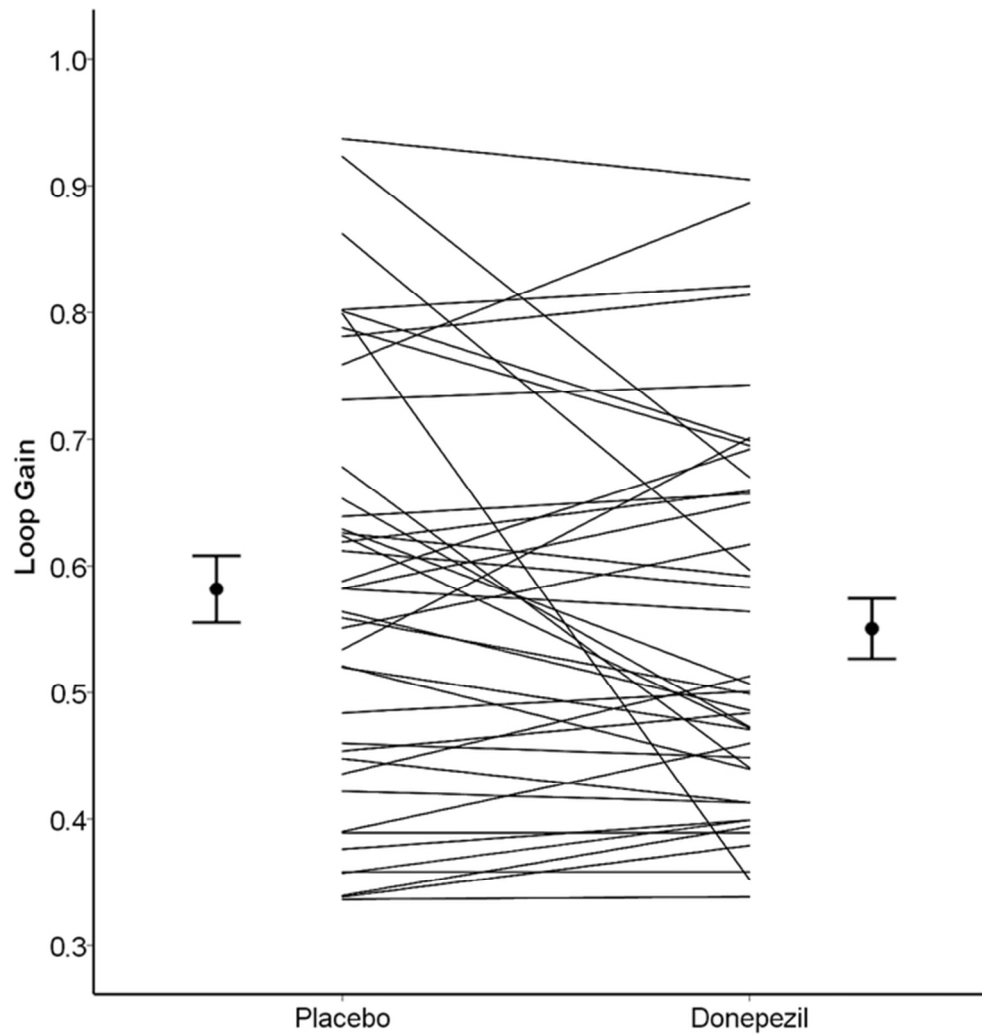
Sleep apnea severity as measured by apnea hypopnea index (AHI, events/hr) under each condition.

figure 1

62x64mm (300 x 300 DPI)



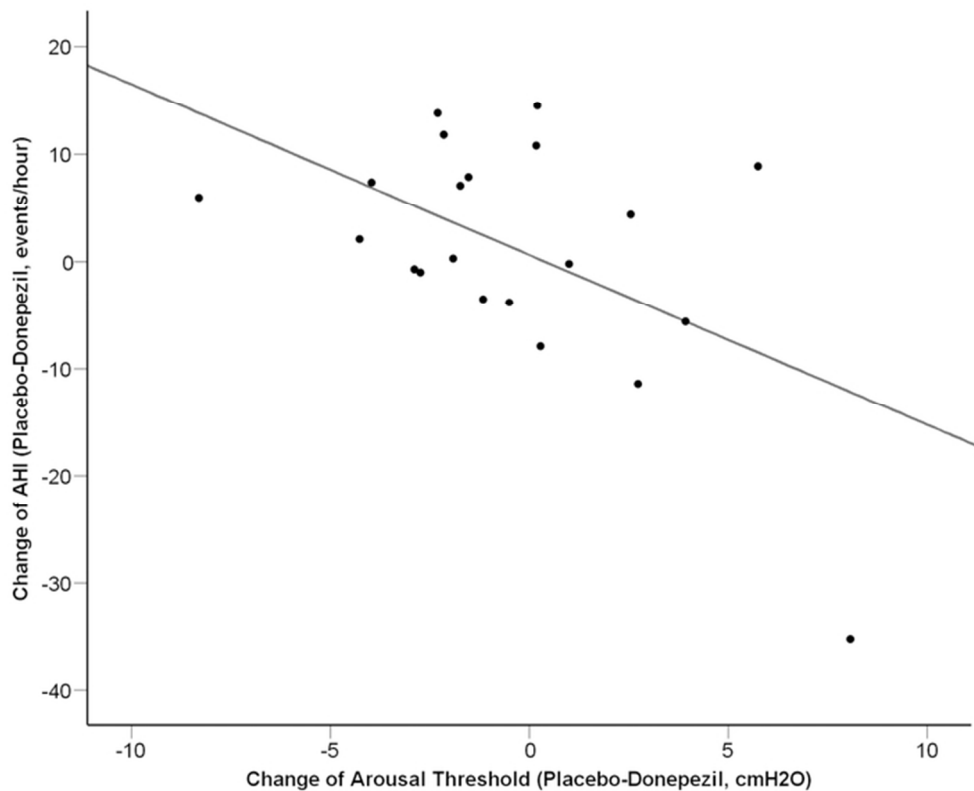
Arousal threshold (ArTh, cm of water) during the placebo and donepezil condition.
figure 2
67x71mm (300 x 300 DPI)



Loop gain (the ventilatory response to a 1 cycle/min disturbance, LG1) during the placebo and the donepezil condition for each patient.

figure 3

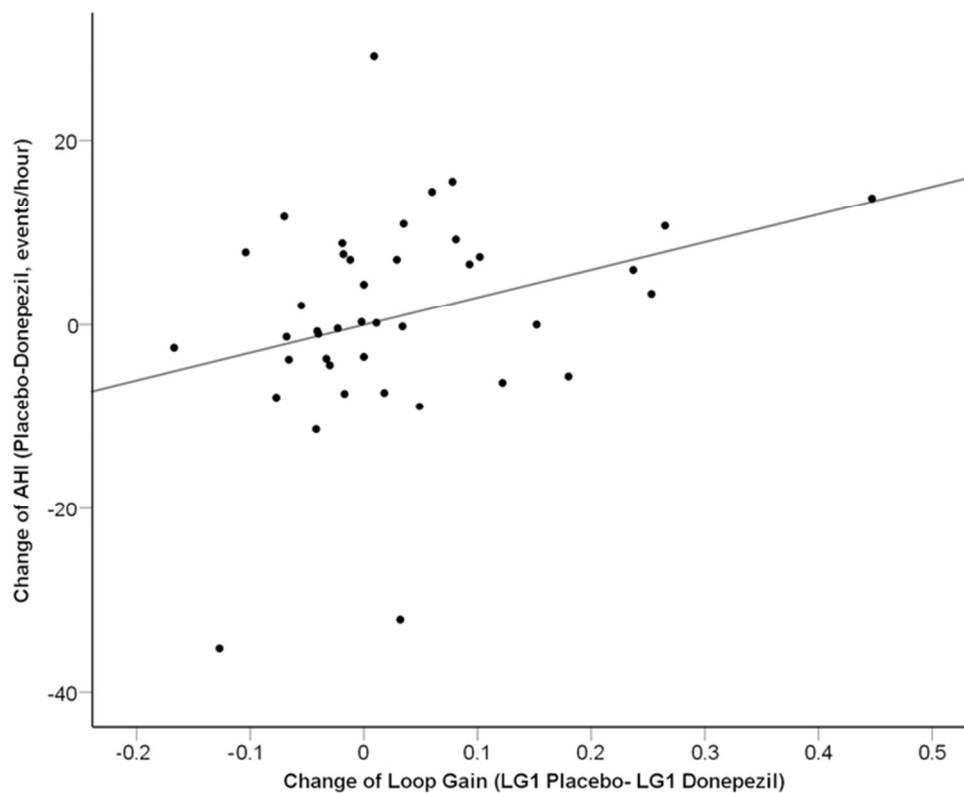
60x65mm (300 x 300 DPI)



Change in AHI during the placebo/donepezil condition and the change of the respiratory arousal threshold. There was no significant association between the changes of AHI and the change of ArTh ($r=0.331$, $P=0.143$).

figure 4

60x48mm (300 x 300 DPI)



Change in AHI during the placebo/donepezil condition and the change of loop gain (the ventilatory response to a 1 cycle/min disturbance, LG1) There was a positive association between the changes of AHI and the changes of LG1 ($r=0.325$, $p=0.038$).

figure 5

60x48mm (300 x 300 DPI)

Online Data Supplement

The Effect of Donepezil on Arousal Threshold and Apnea Hypopnea Index: A Randomized, Double-blind Cross-over Study

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SUPPLEMENT RESULTS

The impact of epiglottic pressure measurements on the assessment of sleep parameters

Forty-one subjects completed the study. There were no statistically significant differences in mean age, baseline AHI, nadir oxygen desaturation during (LSAT) or the BMI in the patients with or without epiglottic pressure assessment for arousal threshold (Table S1)

The changes of sleep apnea severity or sleep architecture with donepezil were not significantly different in the group with epiglottic pressure catheter from the group without catheter (Table S2).

The impact of the order of donepezil and placebo administration on the study results

The impact of order of medication vs placebo administration on sleep parameters and sleep apnea severity was assessed by comparing the changes of sleep and physiological traits in patients with different medication/placebo administration orders (Table S3). No difference was found between the patients with different medication/placebo administration orders.

TABLES

Table S1. Baseline anthropometric and sleep characteristics in patients with or without epiglottic pressure measurements.

	Subjects with epiglottic pressure measurements (<i>n</i> = 21)	Subjects without epiglottic pressure measurements (<i>n</i> = 20)	<i>p</i> Value
Age (years)	50.7±13.1	52.6±8.9	0.594
BMI (kg/m ²)	29.2±5.4	28.9±4.0	0.831
Gender (M/F)	14/7	13/7	0.910
AHI	51.8±27.4	50.0±23.4	0.814
LSAT (%)	80.3±7.3	80.3±5.6	0.986

Abbreviations: BMI, body mass index; AHI, apnea hypopnea index; LSAT, Nadir oxygen saturation during sleep. Normally distributed data were showed as mean ± Std. deviation

Table S2. Changes of sleep and physiological traits with donepezil in patients with and without epiglottic pressure measurement

	With Epiglottic catheter (n=21)	Without Epiglottic catheter (n=20)	<i>t</i> Value	<i>p</i> Value
ΔAHI (events/hr)	1.2±11.0	0.8±12.1	-0.123	0.903
ΔSleep Efficiency%	10.3±12.4	1.3±12.6	-2.316	0.026*
ΔSupine NREM AHI (events/hr)	0.4±10.9	-0.7±14.9	-0.263	0.794
ΔEvent duration (s)	1.7±3.0	0.5±4.2	-1.084	0.285
ΔLSAT (%)	-1.1±4.1	0.6±5.0	0.327	0.745
ΔLG1	0.0±0.1	0.0±0.1	-0.143	0.887

* $p < 0.05$. Abbreviations: NREM, Non rapid eye movement sleep; AHI, apnea hypopnea index; LSAT, Nadir oxygen saturation during sleep; LG1, Loop gain (at a disturbance of frequency 1 cycle /minute). Normally distributed data are shown as mean \pm Std. deviation

Table S3. Changes of sleep and physiological traits in patients with different medication/placebo administration orders

	Arm1 first night with placebo, second night with donepezil (n=16)	Arm2 first night with donepezil, second night with placebo (n=25)	t Value	p Value
ΔAHI (events/hr)	4.2±6.3	-1.1±13.4	1.463	0.151
ΔSleep Efficiency%	4.3±14.0	7.0±12.7	-0.644	0.523
ΔSupine NREM AHI (events/hr)	2.4±8.7	-1.7±14.9	0.988	0.329
ΔEvent duration (s)	0.7±3.6	1.4±3.7	-0.585	0.562
ΔLSAT (%)	-0.6±5.5	-1.0±3.9	0.240	0.812
ΔLG1	0.05±0.11	0.02±0.12	0.669	0.507

Abbreviations: NREM, Non rapid eye movement sleep; AHI, apnea hypopnea index; LSAT, Nadir oxygen saturation during sleep. (Normally distributed data were showed as mean ± Std. deviation) , LG1, Loop gain (at a disturbance of frequency 1 cycle /minute). * p<0.05