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Donepezil improves obstructive sleep apnea in Alzheimer's disease: a double-blind placebo-controlled study

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Disclosure statement

All the authors have read and approved the manuscript, and have nothing to disclose.

Abstract

Background: There is an association between Alzheimer's disease and sleep disordered breathing. Donepezil is the drug most frequently used to treat cognitive symptoms in Alzheimer's disease. This study evaluates the effects of donepezil on obstructive sleep apnea in patients with Alzheimer's disease.

Methods: Randomized, double-blind, placebo-controlled design. Twenty-three patients with mild to moderate Alzheimer's disease and AHI >5 were allocated to two groups, donepezil-treated (n=11) and placebo-treated (n=12). Polysomnography and cognitive evaluation using ADAS-cog subscale were performed at baseline and after 3 months. Cognitive and sleep data were analyzed using ANOVA.

Results: AHI and oxygen saturation improved significantly after donepezil treatment compared to baseline and placebo ($p<0.05$). REM sleep duration increased after donepezil treatment ($p<0.05$). ADAS-cog scores improved after donepezil treatment although did not correlate with REM sleep increase and sleep apnea improvement ($p<0.01$).

Conclusions: Donepezil treatment improved AHI and oxygen saturation in patients with Alzheimer's disease. Treatment also increased REM sleep duration and reduced ADAS-cog scores.

Trial Registration Number: ClinicalTrials.gov NCT00480870

Key words: sleep apnea, oxygen saturation, Alzheimer, donepezil, REM sleep, polysomnography

Abbreviations

AASM	American academy of sleep medicine
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AHI	Apnea-hypopnea index
AHI imp	Apnea-hypopnea index improvement ratio
ANOVA	Variance analysis
APOE-4	Apolipoprotein E epsilon 4
BMI	Body mass index
CDR	Clinical dementia rating
EEG	Electroencephalogram
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
OSA	Obstructive sleep apnea
OSA-AD	Obstructive sleep apnea and Alzheimer's disease
PSG	Polysomnography
REM	Rapid eye movement
Non-REM	Non- rapid eye movement
WASO	Wake after sleep onset

1. Introduction

The association between Alzheimer's disease and sleep-disordered breathing has been frequently studied.[1,2,3,4,5] The presence of APOE-4 seems to be linked to the occurrence of both conditions suggesting a genetic basis.[3,6] Central acting cholinesterase inhibitors are the first primary pharmacological treatments approved for Alzheimer's disease, of which donepezil is the most frequently used.[7] Multicenter studies have found little toxicity, and its side effects (diarrhea, nausea, vomiting, nightmares, among others) are mild and transient.[7,8,9,10] Donepezil is a reversible inhibitor of the acetyl-cholinesterase enzyme, thus enhancing cholinergic transmission.[11] Its half-life is approximately 70 hours.[11] It is excreted intact in the urine and metabolized into four major metabolites, two of which are known to be active.[11]

Cholinergic activity also influences the upper airway opening via central and peripheral mechanisms.[12,13,,14,15] Decreased thalamic pontine cholinergic projections may affect respiratory drive leading to both central and obstructive apnea at least in certain degenerative conditions.[14,15] Since impairment of cholinergic transmission is a putative pathophysiological mechanism for Alzheimer's disease, it is expected that cholinergic-related respiratory disturbances may occur.[7,8,16] However, donepezil has been shown to augment REM sleep in patients with Alzheimer's disease, a sleep stage during which sleep apnea events are more frequent.[7,17,18,19] Such conflicting effects make it difficult to know *a priori* whether improvement of sleep apnea is likely to occur during donepezil treatment.[14,15]

Mindful of the above, the authors hypothesized that (A) donepezil may influence respiratory variables during sleep in patients with OSA-AD, and (B) there is a correlation between cognitive improvement and sleep respiratory changes.

2. Methods

2.1. Population

Forty patients diagnosed with mild to moderate Alzheimer's disease were consecutively recruited from geriatric and neurologic clinics at the University Hospital of the Universidade Federal de São Paulo. Thirty of them had obstructive sleep apnea and presented AHI higher than 5 according to AASM criteria.[20] They were not previously diagnosed or treated for OSA. There were technical problems in the PSG recordings of 7 patients due to frequent patients' movement artifacts. The final sample consisted of the remaining 23 patients who were randomly allocated to two groups, donepezil-treated (n=11) and placebo-treated (n=12).

Diagnosis of Alzheimer's disease was based on the probability criteria of the Alzheimer's Disease and Related Disorders Association.[21] Patients were rated 1 and 2 (mild to moderate level) on the Brazilian version of the CDR and the more severe cases were excluded.[22] Potential subjects were evaluated by history, physical exam, MMSE, ADAS-cog[23], brain MRI and laboratory tests (hematological evaluation, renal and liver functions, vitamin B12, folic acid, thyroid hormones, fasting glycemia, venereal disease research test and urine sediment). Exclusion criteria were the presence of other causes of dementia, MRI compatible with other etiology of dementia, pulmonary, cardiac, and other current severe medical or psychiatric diseases. No psychoactive drugs, other than the experimental drug, were taken during the trial or the preceding one-month period. Alcohol and sleep medications were not permitted during the trial and the preceding one-month period. Caregivers were instructed to take note of the use of any non-psychoactive drugs in daily

sleep diaries.

2.2. Drugs and administration

Tablets containing placebo were prepared and packed in the same fashion as those with 5 mg donepezil. Donepezil and placebo were administered in a single dose, at bedtime. Dosage was 1 tablet/day in the first month and 2 tablets/day for the next two months. After completion of the protocol patients were referred to our Sleep Clinic to have OSA treated.

2.3. **Randomization**

Each medication-containing box was packed by a standard pharmacy service. Boxes were coded as A or B, indicating placebo or donepezil (the signification of the codes was kept in a closed envelope). A random number list with uniform distribution from 0 to 1 was generated by Statsoft Statistica® software. Patients were consecutively allocated to two treatment groups according to the random number list, being numbers ≤0.5 to group A and >0.5 to group B. Researchers were blind to patients' condition when recording and scoring their parameters. Codes were opened and assigned to each patient when statistical analyses were performed.

2.4. Polysomnographic recording and scoring

Patients were submitted to 2 nights of PSG recording for habituation purposes, followed by a baseline recording before the onset of treatment and a second recording after 3 months of treatment. The minimum duration of PSG monitoring was 7 hours.

PSG recordings were performed in the sleep laboratory of the Psychobiology

Department at Universidade Federal de São Paulo using 32-channel Meditron™ Sonolab® equipment (Sao Paulo, Brazil), resolution 256 Hz: 22 EEG, 2 electro-oculogram, 1 chin electromyogram, 1 leg electromyogram, 1 electrocardiogram, 1 tracheal microphone, 1 oronasal thermistor, 1 nasal pressure transducer (Protech®), 2 chest and abdominal effort sensors and 1 pulse oximeter (Nellcor™ Pleasanton-CA, USA).

Two researchers scored the recordings visually using Rechtshaffen and Kales and AASM criteria for respiratory parameters and microarousals.[24,,25,26]

Apneas and hypopneas were scored according to AASM criteria.[20] Variables analyzed were total sleep time, sleep efficiency (sleep time/recording time x 100), sleep latency (time from lights-off to sleep onset), REM sleep latency (time from sleep onset to REM sleep onset), WASO, REM and non-REM sleep percentage, microarousal index (microarousals/hour), overall AHI (apnea + hypopnea events per hour of sleep), obstructive AHI, central AHI, mixed AHI, REM AHI, non-REM AHI, average oxygen saturation and percentage of sleep time with oxygen saturation below 90%. Apnea-hypopnea improvement ratio was calculated was calculated by the formula: AHI imp = initial AHI – final AHI / initial AHI.

Caregivers answered a Portuguese language modified version of Stanford Sleep Disorders Questionnaire after polysomnography to rule out other major sleep disorders.[27]

2.5. Psychometric testing

The Alzheimer's disease assessment scale – cognitive subscale evaluates multiple cognitive functions including word evocation, verbal fluency, understanding of simple commands, constructive praxis, ideational praxis, temporo-spatial orientation, word

recognition, verbal fluency, vocabulary and understanding. Scores range from 0 to 70, higher scores indicating more cognitive deterioration. The Brazilian version of ADAS-cog.[22] was applied before donepezil treatment and again after 3 months.

2.6. Ethics

Subjects or caregivers signed informed consent forms that explained possible side effects of donepezil and assured they could leave the trial at any moment. Clinical treatment was assured to all subjects. The Ethics Committee at Universidade Federal de São Paulo authorized the study.

2.7. Statistical analysis

One-way ANOVA was used to compare all variables for donepezil and placebo groups during baseline recording night. Polysomnographic and cognitive data at baseline, and after 3 months of treatment were analyzed using two-way ANOVA for repeated measures with treatment-group and treatment-time as the main factors and time/treatment interaction effect followed by Bonferroni test, with p-level ≤ 0.01 comparing data. The Spearman correlation test was used to assess possible correlations between cognitive, BMI and sleep respiratory parameters in the donepezil-treated group.

3. Results

3.1. General

Table 1 shows that there were no significant differences in age, gender, BMI, MMSE and CDR scores between the donepezil and placebo groups before treatment. There was no significant correlation between AHI improvement ratio and BMI. MRI scan showed brain atrophy. Results of other laboratory tests were within normal range.

3.2. Adverse effects

Mild and transitory side effects involving nausea and headache occurred in 3 patients receiving donepezil. There were no reports of nightmares or worsening of sleep when caregivers were questioned.

3.3. Sleep Polysomnographic Variables

REM sleep percentage increased after 3-month donepezil treatment, as seen in Table 2. There was a significant improvement in the following respiratory parameters after 3 months of donepezil treatment: AHI, obstructive AHI, mixed AHI, lowest oxygen saturation and time spent with oxygen saturation below 90 % (table 2). Central AHI did not improve significantly after donepezil treatment. (table 2, figure 1) There was also a significant reduction in non-REM AHI after donepezil treatment (interaction factor $F(1,21)=5.39$ $p=0.03$). (table 2) Although there was a trend toward reduction of REM AHI, it was not significant (interaction factor $F(1,21)=3.47$ $p=0.07$) (table 2) Microarousal index decreased significantly after donepezil treatment due to a reduction in respiratory-related

microarousals (table 2). Nine donepezil-treated patients (81%) had improvement of the AHI (figure 1). Six patients (54%) spent >1% sleep time below saturation of 90% before donepezil treatment (figure 1). Five of these patients (83%) improved after donepezil treatment.(figure 1). There were no significant differences between donepezil and placebo groups in the following polysomnographic parameters: total sleep time, sleep efficiency, sleep latency, REM sleep latency, WASO, and percentage of non-REM sleep stages. There was no significant difference in percentage of time spent in supine position within and between groups. (table 2)

3.5. Psychometric variables

ADAS-cog scores significantly decreased after 3-month donepezil treatment (table 2). Correlations between ADAS-cog scores, AHI, average oxygen saturation, time of oxygen saturation spent below 90%, microarousal index and other polysomnographic variables did not reach statistical significance in the donepezil-treated group, before and after therapy.

4. Discussion

The main finding of the present study was the significant improvement in AHI and oxygen saturation of OSA-AD patients treated with donepezil. No previous polysomnographic studies on the effect of donepezil on sleep apnea in Alzheimer's disease have been undertaken. As expected, donepezil was well tolerated and no major side effects occurred.[10,11] No evidence of worsening of sleep or nightmares was found in this study. This is in accordance with the findings of other authors, who have studied larger samples in general practice.[11] Acetylcholinesterase inhibitors elevate central and peripheral acetylcholine levels. However the distribution of donepezil varies between different brain and peripheral tissues.[28] An increase in REM sleep proportion after donepezil treatment was an expected finding. [7]

In contrast to the prolific literature on physical and surgical treatments for sleep apnea there is a dearth of effective pharmacological approaches.[29,30,31,32] Most drugs previously tested for this purpose acted upon monoaminergic and adenosinergic systems and showed unsuccessful or ambiguous results.[29,30,31,32] Hedner and colleagues published the only previous report on a cholinergic pharmacological treatment in humans using an intravenous infusion of the anticholinesterase drug physostigmine in sleep-disordered breathing patients, improving both obstructive and central respiratory events mostly during REM sleep.[12] However that study focused on the acute effect of a drug that does not sustain plasma levels during the entire night.[12] We have selected a cholinergic drug which had already been approved by many regulatory agencies for the treatment of Alzheimer's disease, that has been extensively studied and shown to be safe and pharmacologically stable.[10] Taking advantage of the characteristics of this drug we were able to show that the

beneficial respiratory effect is maintained after long-term use possibly adding to its therapeutic spectrum. In contrast to this previous report, we found that overall AHI improvement was due to a reduction in obstructive and mixed respiratory events.[12] In addition, we did not find a significant improvement in AHI during REM sleep although there was a non-significant trend toward reduction. These results suggest that AHI improvement after donepezil treatment is related to cholinergic mechanisms involved in obstructive and mixed apnea and is not specifically dependent on REM AHI reduction. OSA-AD patients showed different individual responses to donepezil. We found no parameter that could predict individual treatment outcome. Future studies are needed to explain individual differences in response to cholinergic drugs for OSA treatment. As expected, there was a high degree of variability in respiratory parameters of the control group and no clear tendency to worsening.[33,34] Besides respiratory effects, donepezil increased REM sleep, and decreased microarousal index and ADAS-cog scores after 3-month donepezil treatment, confirming findings of previous research.[7,17,18] Hedner et al. reported a similar finding in non-Alzheimer OSA patients in abstract form. [35]

As previously mentioned, it was expected that the REM sleep increase would be associated to the worsening of OSA, because respiratory events are more frequent during this sleep stage.[12,19] However, cholinergic drugs display more complex effects on respiration. Available evidence demonstrates that cholinergic stimulation has potent excitatory effects on medullary respiratory neurons, and respiratory motoneurones.[14] It also affects the central chemosensitive drive of the respiratory control system.[14] Upper airway dilating muscle activity is characterized by an early-peaking pattern which serves to dilate the upper airway at the time when the greatest negative intraluminal pressure is generated by contraction of the chest wall muscles and diaphragm.[36] An experimental study showed

an increase in hypoglossus nerve activity with consequent opening of the upper airway following carbachol pontine injection in cats.[36] Physostigmine administered to cholinergic neurons located in the rostral ventrolateral medulla of anesthetized vagotomized and artificially ventilated cats resulted in elongation of the hypoglossal-to-phrenic nerve firing interval resulting in improved oxygenation.[37] It also antagonizes respiratory depression induced by fentanyl in rats.[38] Furthermore, physostigmine stimulates saliva production, resulting in reduced superficial tension that increases upper airway stability, that may represent another mechanism for improving OSA.[39, 40] Cholinergic stimulation of the respiratory center and the carotid body increases sensitivity to hypoxia improving the chemoreflex response.[12,14,15,41] Such effects may contribute to the cholinergic-induced improvement of the peripheral and central components of respiratory regulation during sleep.[12,14,15,37,38,39,40,41,42] In our study most of the reduction of the microarousal index in the donepezil group was attributable to a significant decrease in respiratory-related microarousals, even though cholinergic drugs may elicit arousal. [43,44]

Donepezil-related cognitive improvement measured by ADAS-cog scale did not correlate with respiratory parameters suggesting independence between cognition and sleep respiratory symptoms in patients with Alzheimer's disease.[1] However, further clarification is required as to whether or not OSA contributes to cognitive deterioration in Alzheimer's disease.[3,4,5]

In summary our results support the concept that cholinergic transmission is involved in the pathogenesis of OSA in Alzheimer's disease, suggesting a possible target for pharmacological intervention. Larger placebo-controlled studies are needed to confirm these results.

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Table 1 Socio-demographic data

	Donepezil group n=11	Placebo group n=12	p
Age (years)	76.8±6.2 (68 to 86)	72.6±11.0 (62 to 87)	0.27
Gender	3 male, 8 female	5 male, 7 female	0.49
Body mass index (kg/m2)	26.3±4.8 (17.2 to 32.0)	26.6±4.1 (17.0 to 32.1)	0.85
MMSE	19±3.6 (13 to26)	17.2±7.8 (6 to 27)	0.50
CDR	1.3±0.5	1.3±0.5	0.76

One-way ANOVA (mean±standard deviation) significant $p<0.05$

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Table 2. Cognitive and polysomnographic data

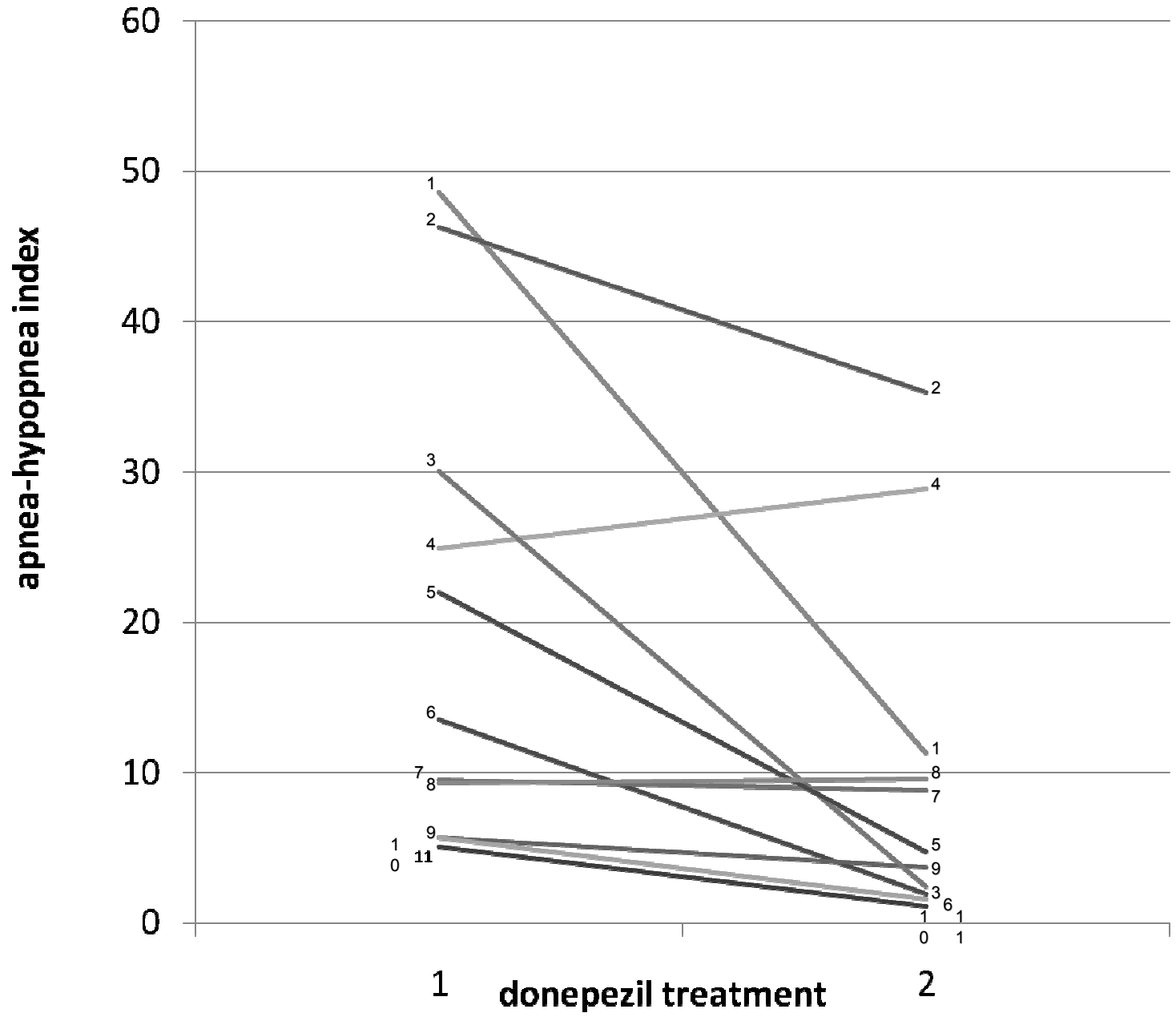
	Donepezil group n=11		Placebo group n=12		
Polysomnogram	Baseline	3rd month	Baseline	3rd month	Interaction p
Total sleep time(minutes)	307.7±90.9	312.9±106.8	296.9±61.6	295.6±81.3	0.81
Sleep efficiency %	76.6±18.0	73.4±23.4	74.2±12.7	74.0±17.0	0.56
Sleep latency	35.6±86.6	41.9±86.0	14.5±21.5	16.9±19.1	0.63
REM sleep latency	125.7±80.7	138.7±136.4	129.5±79.4	133.7±89.4	0.87
WASO	91.9±74.4	114.8±111.1	104.4±56.7	100.9±64.9	0.23
Stage 1%	9.0±7.7	9.1±11.2	14.4±11.3	14.8±13.0	0.90
Stage 2%	54.2±16.7	49.0±14.8	54.5±13.5	52.7±12.8	0.53
Slow wave sleep%	30.3±16.6	30.5±14.8	22.0±15.3	21.8±10.5	0.95
REM sleep %	7.2±4.3	15.9±11.1	11.8±6.6	9.7±5.9	**0.022***
Time spent in supine position %	42.7±17.1	41.7±17.2	39.2±24.7	36.1±26.4	0.63
Microarousal index	26.3±12.6	15.7±8.3	23.9±19.7	23.8±21.0	**0.021***
NResp microarousal index	15.5±14.8	10.9±4.7	12.3±10.8	11.8±8.8	**0.33**
Resp microarousal index	11.0±10.4	5.1±7.1	11.6±15.9	12.0±8.2	**0.001***
Apnea-Hypopnea Index	20.0±15.9	9.9±11.5	23.2±26.4	22.9±28.8	**0.035***
REM Apnea-Hypopnea Index	24.7±19.4	7.6±7.9	35.4±31.5	39.0±25.6	**0.077**
Obstructive Apnea-Hypopnea Index	19.4±15.4	9.2±10.3	22.7±25.8	21.3±26.7	**0.047***
Central Apnea-Hypopnea Index	0.1±0.2	0.6±1.9	0.1±0.4	0.3±0.6	**0.56**
Mixed Apnea-Hypopnea Index	0.4±0.8	0.1±0.2	0.3±0.8	1.3±2.3	**0.033***
Average oxygen saturation	91.5±6.1	94.0±2.0	94.0±2.5	93.5±3.1	0.12
Lowest oxygen saturation	80.8±8.3	85.7±6.3	83.0±11.1	81.9±10.9	**0.002***
Desaturation events	15.4±18.2	5.8±8.7	31.7±44.3	30.4±61.3	0.36
Time oxygen saturation <90%	13,4±17.4	3.7±4.8	8.5±14.7	11.0±20.1	**0.017***
ADAS-cog score	34.5±15.8	29.7±15.7	29.3±17.3	31.8±18.5	**0.004***

Two-way ANOVA (mean ± standard deviation) * significant, p<0.05 NResp = non-respiratory-related Resp = respiratory-related WASO =wake after sleep on

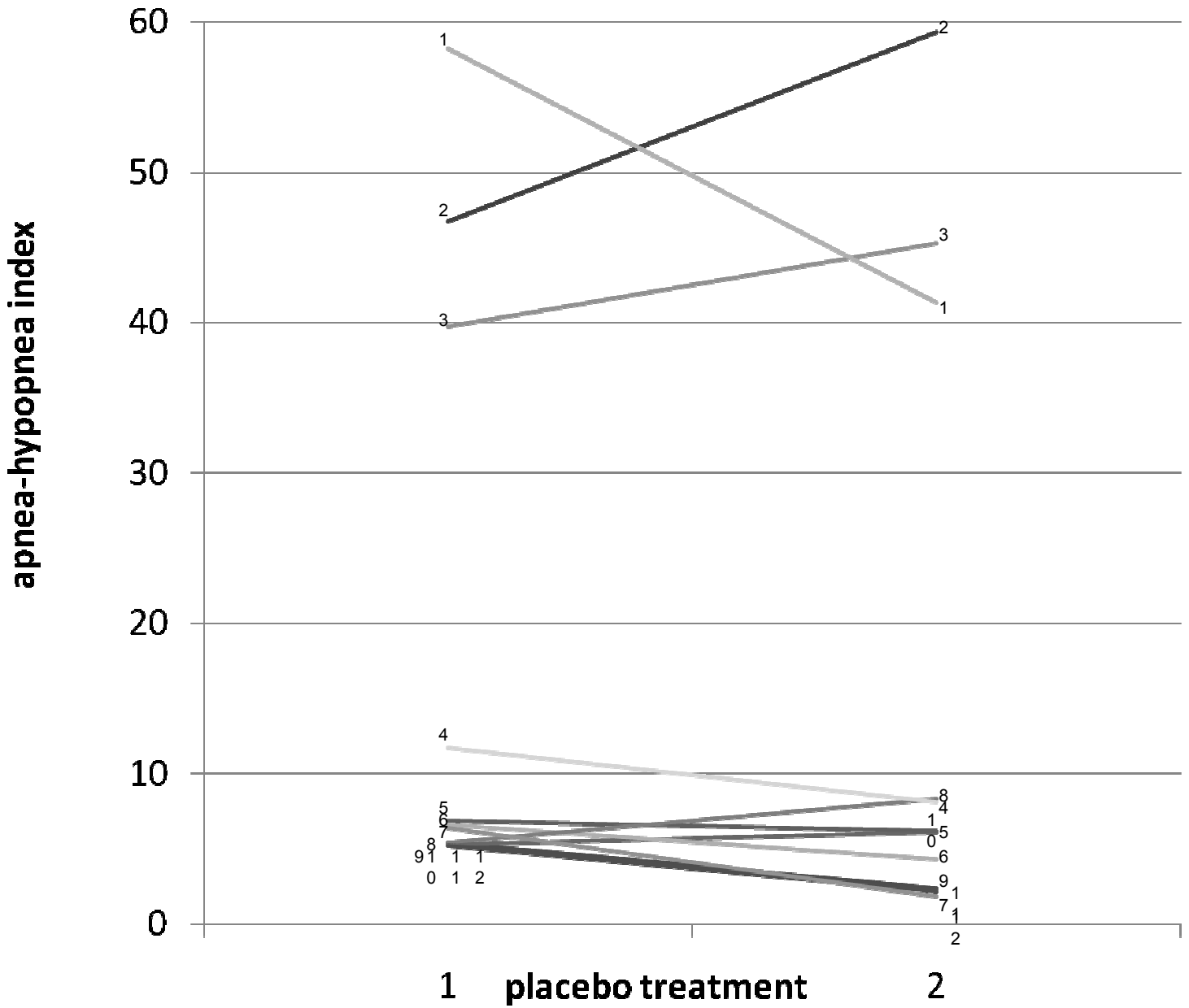
Figure 1 Apnea-hypopnea index before (1) and after (2) donepezil (A) or placebo (B) treatment.

Time spent with oxygen saturation below 90% before (1) and after (2) donepezil (C) or placebo (D) treatment.

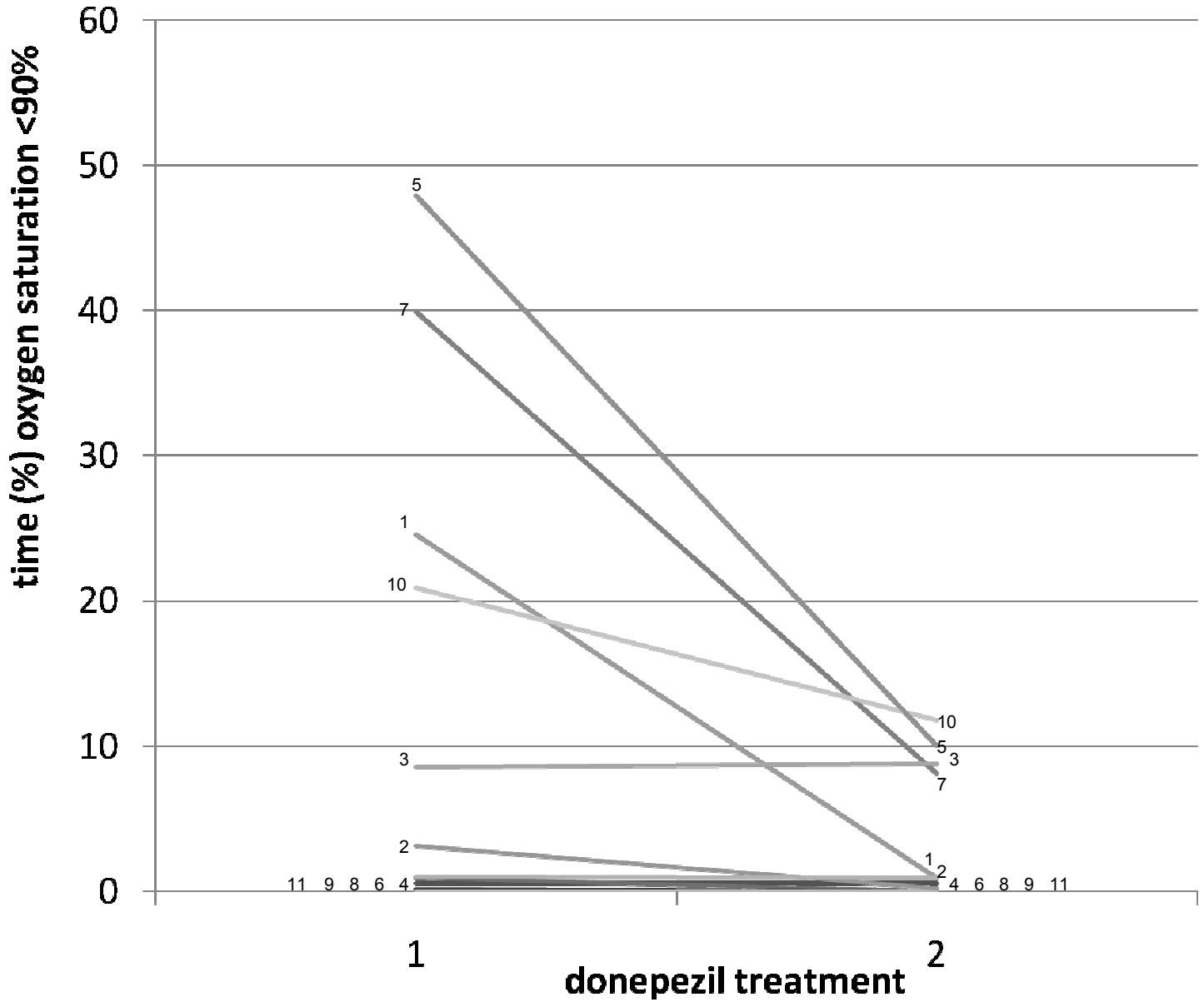
A


apnea-hypopnea index
60
50
40
30
20
10
0
1
2
donepezil treatment

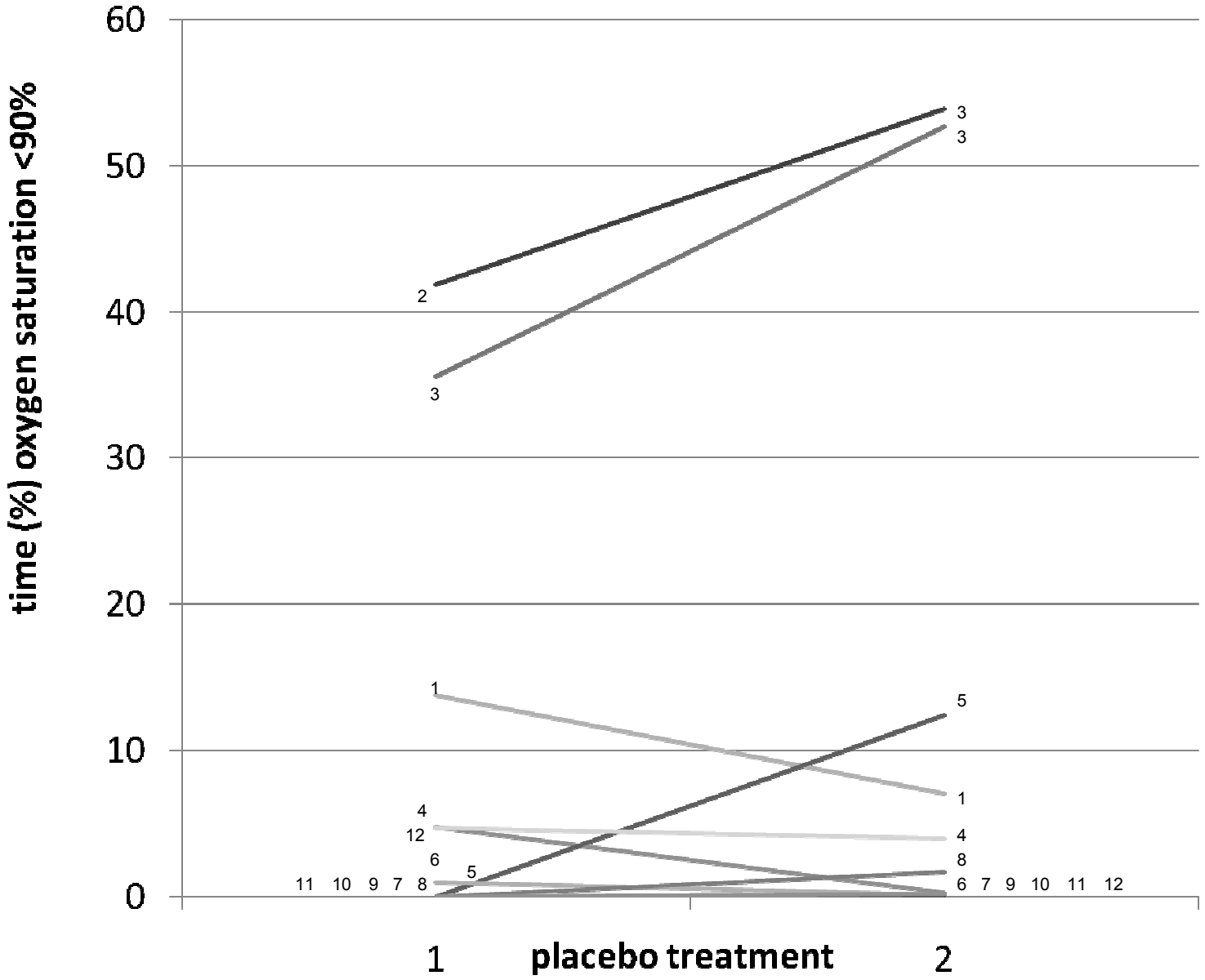
B



C


60
50
40
30
20
10
0
time (%) oxygen saturation <90%
5
7
1
10
3
2
11 9 8 6 4
10
5
3
7
1
2
4 6 8 9 11
1
2
donepezil treatment

D


60
50
40
30
20
10
0
time (%) oxygen saturation <90%
1
placebo treatment
2
3
3
2
3
1
5
1
4
12
4
6
8
5
11 10 9 7 8
6 7 9 10 11 12

Donepezil improves obstructive sleep apnea in Alzheimer's disease: a double-blind placebo-controlled study

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