The Effect of Donepezil on Sleep and REM Sleep EEG in Patients with Alzheimer Disease: A Double-Blind Placebo-Controlled Study

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Study Objective: Examine the effects of donepezil on sleep and rapid eye movement (REM) sleep electroencephalogram (EEG) in patients with Alzheimer disease, using polysomnography, and the correlation between REM sleep EEG parameters and cognitive scores.

Design: Randomized, double-blind, placebo-controlled design.

Settings: Two sleep research centers, University Hospital.

Participants: Thirty-five patients with mild to moderate Alzheimer disease, allocated to 2 groups: donepezil treated (n=17) and placebo treated (n=18).

Intervention: Patients were administered donepezil or placebo.

Outcome Measures: Polysomnography with REM sleep EEG spectral analysis and cognitive evaluation using the Alzheimer Disease Assessment Scale, cognitive subscale, were performed at baseline and after 3 and 6 months. Slowing ratio was the ratio between slow and fast EEG frequency bands. Cognitive and sleep data were analyzed using analysis of variance. Correlations between cognitive improvement and REM sleep EEG were also calculated.

Results: REM sleep increased significantly after 3 and 6 months of donepezil treatment compared with baseline and placebo ($p < .01$). Overall theta ($p = .04$), frontal theta ($p < .01$) and frontal delta ($p = .03$) absolute power during REM sleep decreased after 6 months of donepezil treatment. The occipital slowing ratio decreased during treatment ($p = .04$). REM sleep overall and frontal and centroparietal alpha absolute power significantly correlated with the cognitive improvement rate on the Alzheimer Disease Assessment Scale, cognitive subscale ($r = 0.75$, $r = 0.71$, $r = 0.78$); $p < .01$).

Conclusions: Donepezil treatment enhanced REM sleep and reduced slow frequencies of REM sleep EEG, suggesting a possible action upon REM sleep-related cholinergic neurons in patients with Alzheimer disease. Furthermore, REM sleep alpha power may predict the cognitive response to donepezil.

Keywords: Cognitive function, Alzheimer, donepezil, REM sleep EEG, polysomnography

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INTRODUCTION

CENTRALLY ACTING CHOLINESTERASE INHIBITORS (TACRINE, DONEPEZIL, RIVASTIGMINE, AND GALANTAMINE) ARE THE FIRST PRIMARY pharmacologic treatments approved for patients with Alzheimer disease.[1-4] Of these, donepezil is the most frequently used. Multicenter studies have found little toxicity, and its side effects (diarrhea, nausea, vomiting and nightmares, among others) are mild and transient.[5-8] Donepezil is a reversible inhibitor of the acetyl-cholinesterase enzyme, with an enhancing cholinergic function. Its half-life is approximately 70 hours, and it is excreted intact in the urine and metabolized to 4 major metabolites, 2 of which are known to be active.[9]

Studies have highlighted that cholinergic-active drugs may be expected to affect rapid eye movement (REM) sleep.[10-12] Research has studied the effects of many cholinergic agents on sleep in normal and pathologic situations.[10,12-21] Studies with galantamine and rivastigmine have reported increased REM sleep in normal, alcohol-dependent, and depressed patients.[10,11,13-15,20] Polysomnographic studies in which donepezil was administered to normal elderly and young healthy subjects consistently reported increases in REM sleep percentage and REM density, with reduced REM latency after a single 5-mg dose.[16,21] These findings correlate with findings on memory performance, although the studies were not double blind or placebo controlled. REM sleep enhancement has also been observed in depressed patients treated with donepezil.[17] Very few studies have examined the effects of cholinergic treatments on sleep in patients with Alzheimer disease.[5,8,18,22] A study on the effects of tacrine on REM sleep was not conclusive, probably because doses higher than 100 mg per day could not be used due to liver toxicity.[18]

Spectral analysis of the REM sleep electroencephalogram (EEG) is potentially an important tool to study the effects on the treatment of Alzheimer disease. Most studies have reported an increase of slow frequencies, with a decrease of fast frequencies, during wakefulness in Alzheimer-type dementia, which was correlated with the severity of the disease.[23-31] However, the discriminatory power of REM sleep EEG slowing is higher than the EEG recorded for wakefulness, even in less-impaired patients.[18,28,32] Moreover, the most pronounced EEG slowing during REM sleep occurred in the centroparietal and temporal regions.[27] Mindful of the above, the REM sleep EEG may be more sensitive to changes occurring in Alzheimer disease because of the greater involvement of acetylcholine in cortical desynchronization during this state. In addition to the cholinergic pathway, several other neurotransmitter systems are involved in cortical activation during

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wakefulness.[33] This is arguably why some studies have posited that altered REM sleep EEG activity is a good marker for Alzheimer disease.[28,32,34,35]

The cholinergic system plays a crucial role in memory function and REM sleep generation.[2,36] Based on these findings, our initial hypothesis was that donepezil treatment for patients with Alzheimer disease might increase REM sleep percentage and alter the REM sleep EEG power spectrum by increasing cholinergic transmission. Furthermore, REM sleep parameters might correlate with donepezil-related cognitive improvement, since both depend on the cholinergic system.

METHODS

Population

Forty-seven patients from geriatric and neurologic clinics at the University Hospital, Universidade Federal de São Paulo, were recruited for the study. Four were excluded due to severe sleep disorders. A further 8 patients left the study due to technical difficulties in polysomnography recordings. The final sample consisted of 35 patients with mild to moderate Alzheimer disease, randomly allocated to 2 groups, donepezil treated (n=17) and placebo treated (n=18).

Diagnosis of Alzheimer disease was based on the probability criteria of the Alzheimer's Disease and Related Disorders Association.[37] Patients were rated 1 and 2 (mild to moderate level) on the Brazilian version of the Clinical Dementia Rating (CDR), and the more severe cases were excluded.[38] Potential subjects were evaluated by history, physical exam, validated Brazilian version of Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog),[38,39] brain magnetic resonance imaging, and laboratory tests (hematologic evaluation, creatinine, vitamin B_{12}-folic acid, thyroid hormones, glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, gamma-glutamyl transpeptidase, bilirubin, fasting glycemia, venereal disease research test, and urine sediment). Exclusion criteria were the presence of other causes of dementia, other current severe medical or psychiatric disease, and evidence of moderate to severe sleep disorders, based on medical, sleep, and psychiatric interviews. Patients with an apnea-hypopnea index > 10 per hour and periodic leg movement index > 5 per hour at baseline polysomnographic recording were also excluded. No psychoactive drugs, other than the experimental drug, were taken during the trial or the 1-month period preceding the project.

Randomization

Wyeth-Whitehall laboratories produced tablets containing placebo or 5 mg of donepezil, packed into boxes labeled with a numeric code corresponding to placebo or donepezil (open codes were kept in a closed envelope). The individual responsible for random allocation of patients to the 2 treatment groups and their monthly supply of tablets was blind to the treatment code, and the researchers were blind to patients' conditions when recording and scoring the sleep parameters. On performing statistical analysis, the codes were opened and assigned to each patient.

Drugs and Administration

Donepezil, 5 mg, or placebo tablets were administered in a single dose at bedtime. Dosage was 1 tablet per day in the first month and 2 tablets per day from the second month on.

Polysomnographic Recording and Scoring

Patients underwent 2 nights of recording for habituation purposes, followed by a baseline recording before the onset of treatment, a second recording after 3 months of treatment, and a third recording after 6 months of treatment. The minimum duration was 7 hours.

Recordings took place 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 leads, 2 electrooculogram, 1 chin electromyogram, 1 leg electromyogram, 1 electrocardiogram, 1 tracheal microphone, 1 oronasal thermistor, 2 chest and abdominal effort sensors, and 1 pulse oximeter (Nellcor™ Pleasanton, CA). Two researchers scored the recordings visually using Rechtschaffen and Kales and American Academy of Sleep Medicine criteria.[40-43]

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), REM density (number of ocular movements per minute during REM sleep), REM and non-REM sleep percentage, apnea-hypopnea index ([AHI] number of apnea + hypopnea events per hour), arousals per hour, periodic leg movements per hour, and mean oxygen saturation.

REM Sleep EEG Spectral Analysis

We used fast Fourier transform to process EEG-channel data. Frequency-band definitions were delta, 0.8 to 3.8 Hz; theta, 4 to 7.8 Hz; alpha, 8 to 12.8 Hz; and beta, 13 to 20.3 Hz. Scalp EEG areas were as follows: overall (average of all electrodes), frontal (F3, F4, F7, F8, Fz), temporal (T3, T4, T5, T6), centroparietal (P3, P4, Pz, C3, C4, Cz), and occipital (O1, O2, Oz). Fast Fourier transforms were applied to all REM sleep episodes at 4-second intervals. Artifacts were visually excluded from the analysis. The REM sleep EEG slowing ratio for each area was calculated as previously described.[32]

REM sleep EEG slowing ratio = delta absolute power + theta absolute power/alpha absolute power + beta absolute power

Psychometric Testing

The cognitive performance was assessed with the validated Brazilian version of the ADAS-cog.[39] The ADAS-cog examines selected aspects of cognitive performance, including elements of memory, orientation, attention, reasoning, language, and praxis. The ADAS-cog scoring range is from 0 to 70, with higher scores indicating greater cognitive impairment.[37,39]

The Brazilian version of ADAS-cog[39] was applied before donepezil treatment and again after 3 months and after 6 months. Relative reduction in ADAS-cog scores was expressed as a cognitive improvement rate calculated as follows: Cognitive improvement rate = baseline ADAS-cog – 6-month treatment ADAS-cog/baseline ADAS-cog.

Ethics

Subjects or caregivers signed informed consent forms, and the Ethics Committee at the Universidade Federal de São Paulo authorized the study.

Statistical Analysis

Data from 10 patients were initially analyzed for sample-size estimation. Based on the information of this subsample, the calculated sample size was 15 subjects in each group, to set out a difference of 8 percentage points in REM sleep percentage, fixing the significance level at 1% and a power goal of 95%. To assess the interaction term in the analysis of variance (ANOVA) model, 27 subjects were required in each group. However, it was feasible to obtain a power of 80% with the sample size analyzed.

One-way ANOVA was used to ensure that all variables were not significantly different for donepezil and placebo groups during the baseline recording night. Polysomnographic and cognitive data were analyzed using 2-way ANOVA for repeated measures with treatment group and treatment time as the main factors and time/treatment interaction effect. A posthoc Duncan multiple range test was performed, with the p level set at ≤ .01, comparing data at baseline and after 3 and 6 months of treatment. We used the Spearman test to assess the correlation between cognitive improvement rate and REM sleep and sleep EEG parameters. Significant correlations were taken when $|R| > 0.70$.

Table 1—Sociodemographic Data

	Group		P value
	Donepezil	Placebo	
No.	17	18	
Age, y	77.4 ± 6.6	74.5 ± 9.8	.32
Men/women, no.	4/13	7/11	.34
BMI, kg/m^2	26.0 ± 4.8	24.9 ± 4.5	.48
Years of education	4.4 ± 3.6	6.0 ± 5.2	.30
Clinical dementia rating, score	1.2 ± 0.4	1.5 ± 0.5	.11

Data are presented as mean ± SD unless otherwise indicated. One-way analysis of variance. BMI refers to body mass index.

RESULTS

General

Table 1 shows that there were no significant differences in sociodemographic data between the donepezil and placebo groups. Brain magnetic resonance images showed some degree of brain atrophy and occasionally small ischemic areas. Results of other laboratory tests were normal.

Adverse Effects

Mild and transitory side effects involving nausea and headache occurred in 3 patients receiving donepezil. No patients complained of nightmares or worsening of sleep throughout the entire treatment period.

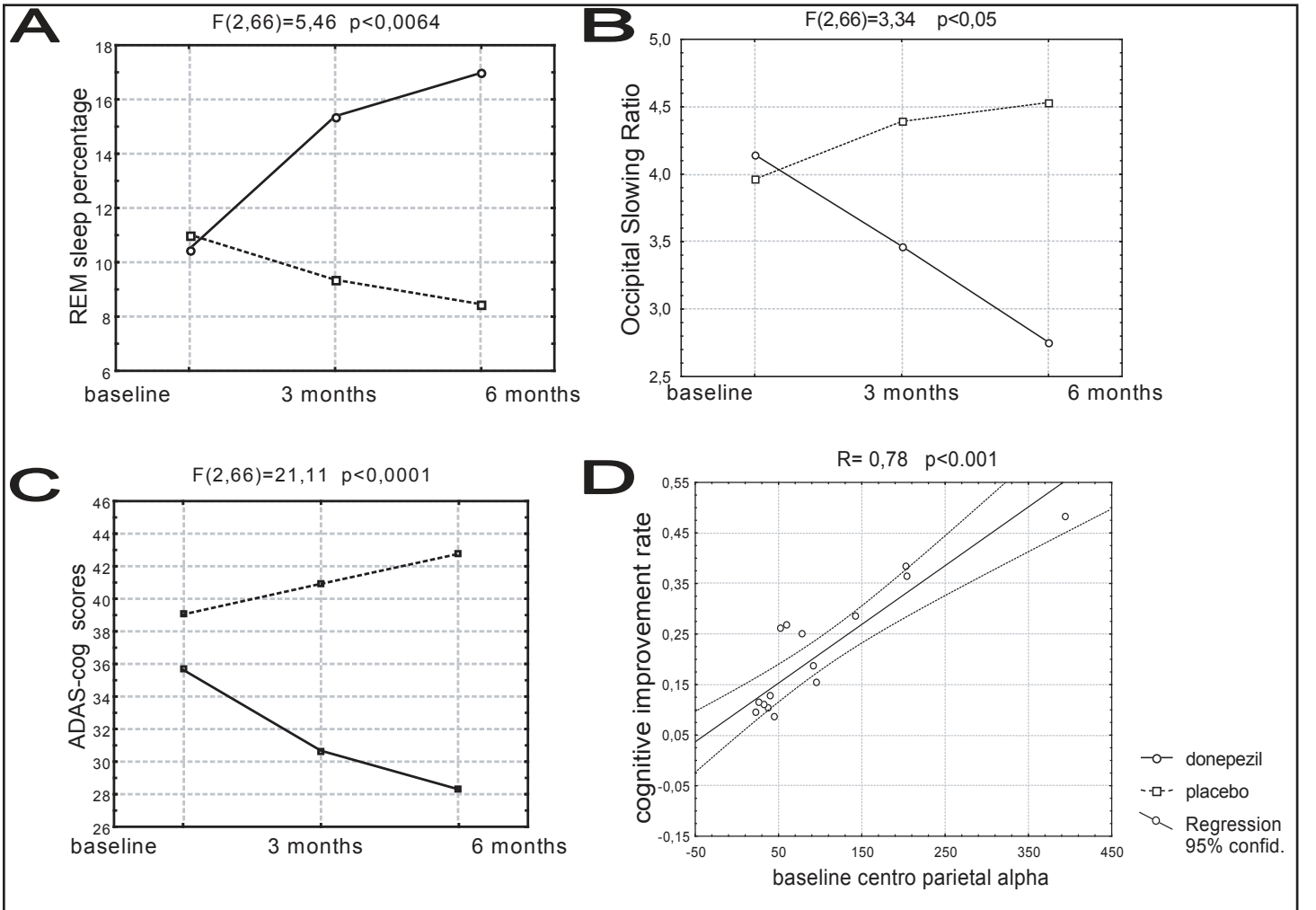

Figure 1—Donepezil and placebo groups: (A) rapid eye movement (REM) sleep percentage. (B) Occipital slowing ratio. (C) ADAS-cog scores. (D) Cognitive improvement rate and baseline centroparietal alpha linear regression.

Table 2—Cognitive and Polysomnographic Data

Polysomnogram	Group: Donepezil Baseline n=17	Donepezil Month 3 n=17	Donepezil Month 6 n=17	Placebo Baseline n=18	Placebo Month 3 n=18	Placebo Month 6 n=18	p **
TST, min	298.3±107.5	304.5±81.9	265.8±76.1	301.1±76.5	299.0±83.7	310.6±56.5	0.30
Sleep efficiency, %	80.1±16.5	71.3±18.8	69.1±19.7	74.3±12.5	71.3±17.0	70.4±11.0	0.39
AHI, no./h	4.3±4.0	3.4±5.8	4.5±6.6	3.7±6.1	3.3±5.4	3.1±3.2	0.18
Mean SaO_2, %	94.0±4.0	94.5±3.3	94.6±4.7	95.2±2.6	96.0±1.6	95.1±2.3	0.96
PLM/h, no.	0.3±1.1	0.2±.0.7	0.3±1.2	0.8±1.7	0.7±1.6	0.8±1.7	0.99
Sleep latency, min	24.9±70.5	19.7±19.4	24.9±35.5	16.7±13.4	15.4±24.8	29.4±30.9	0.66
REM latency, min	112.9±94.5	123.3±83.7	127.2±113.7	124.3±81.8	143.1±54.0	152.4±98.1	0.93
Sleep stage, %							
1	5.1±6.9	6.0±6.1	8.1±9.1	7.4±6.5	9.4±8.7	7.8±5.9	0.28
2	52.7±15.8	46.8±15.3	46.0±10.5	54.7±13.9	57.3±16.8	54.9±18.2	0.26
3+4	31.6±15.6	31.2±18.5	29.0±16.4	26.8±18.2	24.0±17.6	28.8±19.2	0.37
REM	10.5±6.1	15.4±9.5	17.0±9.9	11.0±7.4	9.3±5.8	8.4±5.4	**<0.01 ***
REM density, REM/min	4.7±2.2	6.4±3.3	5.7±2.1	4.1±1.5	5.2±2.8	5.0±3.2	0.86
ADAS-cog score	35.6±13.7	30.7±13.9	28.3±12.3	39.0±18.5	40.9±19.4	42.8±18.7	**<0.01 ***

Two-way analysis of variance. Data are presented as mean ± SD unless otherwise indicated. TST refers to total sleep time; AHI, apnea-hypopnea index; PLM, periodic limb movements; REM, rapid eye movement; ADAS-cog, Alzheimer Disease Assessment Scale, cognitive subscale.
*p < .05
**Interaction factor

Table 3—Sleep Electroencephalographic Frequency Bands[a]

Frequency Band	Donepezil Baseline n=17	Donepezil Month 3 n=17	Donepezil Month 6 n=17	Placebo Baseline n=18	Placebo Month 3 n=18	Placebo Month 6 n=18	p **
Overall							
Delta	456.5±202.0	425.1±181.3	395.0±148.6	409.9±214.6	429.8±201.8	425.8±263.5	0.30
Theta	354.5±231.9	317.4±122.1	269.1±117.0	299.9±137.1	344.1±174.1	354.3±266.6	**0.04 ***
Alpha	218.7±218.1	178.2±104.1	162.7±104.2	147.9±102.2	146.7±60.8	139.0+53.0	0.41
Beta	85.9±61.0	85.6±48.4	137.0±177.9	92.6±110.7	73.5±44.2	75.3±41.8	0.27
Frontal							
Delta	151.1±96.6	122.6±54.5	118.0±39.3	119.7±66.3	135.1±66.9	133.6±78.9	**0.03 ***
Theta	102.7±67.6	83.8+27.4	76.0±23.6	82.3±36.7	102.2±49.8	103.5±67.6	**<0.01 ***
Alpha	47.2±48.1	35.5±15.4	35.9±20.4	35.8±27.5	37.1±14.9	34.1±10.9	0.38
Beta	22.2±17.7	20.2±10.5	32.3±40.1	20.2±17.4	18.3±10.2	19.1±10.8	0.38
Temporal							
Delta	63.2±28.1	64.3±31.1	55.4±24.2	62.8±40.3	63.1±38.5	65.4±43.7	0.37
Theta	49.3±36.1	49.5±24.2	37.0±21.7	45.3±26.9	48.0±33.2	60.2±73.1	0.10
Alpha	32.7±35.1	30.7±21.7	23.2±15.0	23.4±15.3	20.5±7.5	22.5±10.2	0.23
Beta	14.3±12.4	15.8±12.0	23.1±37.0	17.4±28.8	10.0±5.5	11.7±6.1	0.35

Two-way analysis of variance. Data are presented as mean ± SD unless otherwise indicated.
*p < .05
**Interaction factor
[a]Absolute power in μV^2

Polysomnographic Variables

REM sleep percentage increased gradually after 3 and 6 months of donepezil treatment compared with the placebo group (group factor $F_{1,33} = 5.75$, p = .02, interaction factor $F_{2,66} = 5.46$, p < .01) (Table 2, Figure 1A).

There were no significant differences between donepezil and placebo groups on the following polysomnographic parameters: total sleep time, sleep efficiency, AHI, mean SaO_2, periodic leg movements per hour, sleep latency, REM sleep latency, non-REM sleep-stage percentages, and REM density (Table 2). We found no difference between CDR groups among donepezil-treated patients for these parameters.

Sleep EEG Variables

All REM sleep EEG frequency bands were comparable during baseline recording for both groups (p > .2). The overall theta band power during REM sleep was reduced after 6 months of donepezil treatment compared with the placebo group (interaction $F_{2,66} = 3.36$, p = .04) (Table 3). There was a significant decrease in frontal delta and theta band after 6 months of donepezil treatment compared with the placebo group (interaction $F_{2,66} = 3.82$, p = .03 and $F_{2,66} = 5.63$, p < .01), respectively (Table 3).

The occipital slowing ratio decreased gradually during donepezil treatment (interaction $F_{2,66} = 3.34$, p = .04) (Table 4, Figure

Table 4—Sleep Electroencephalographic Frequency Bands[a]

Frequency Band	Donepezil			Placebo			p **
	Baseline n=17	Month 3 n=17	Month 6 n=17	Baseline n=18	Month 3 n=18	Month 6 n=18	
Centroparietal							
Delta	171.7 ±66.5	165.8 ±74.1	158.7 ±78.0	161.7 ±87.7	161.9 ±78.5	163.5 ±108.4	0.80
Theta	148.6 ±92.6	130.9 ±52.1	111.8 ±60.8	129.8±58.4	136.0 ±69.9	137.1 ±87.2	0.10
Alpha	98.6 ±94.5	77.2 ±47.4	73.1 ±51.2	65.3 ±45.3	62.3 ±30.2	59.8 ±24.5	0.43
Beta	36.7 ±22.6	36.6 ±20.2	54.1 ±63.0	37.6 ±37.4	33.8 ±25.4	34.3 ±21.3	0.33
Occipital							
Delta	71.8 ±29.4	71.9 ±31.8	63.1 ±25.0	61.8 ±30.8	66.7 ±33.1	64.9 ±39.5	0.48
Theta	54.0 ±43.5	52.8 ±27.6	44.2 ±26.6	47.3 ±22.2	54.3 ±32.9	54.2 ±43.7	0.25
Alpha	40.3 ±46.1	34.7 ±29.1	30.6 ±24.2	25.1 ±15.7	24.8 ±13.0	23.1 ±10.3	0.52
Beta	12.7 ±10.0	12.6 ±7.9	27.5 ±44.4	17.7 ±29.7	10.7 ±7.1	10.4 ±6.1	0.12
Slowing ratio							
Overall	3.9 ±2.6	3.4 ±1.9	3.0 ±1.5	4.2 ±2.9	4.2 ±3.0	4.2 ±3.1	0.17
Frontal	4.9 ±3.0	4.1 ±1.7	3.7 ±1.7	4.7 ±2.9	4.8 ±3.0	4.9 ±3.3	0.11
Temporal	3.7 ±2.7	3.2 ±2.2	3.0 ±2.0	3.9 ±2.8	4.0 ±2.8	4.1 ±3.1	0.34
Centroparietal	3.5 ±2.3	3.1 ±1.8	2.8 ±1.7	3.8 ±2.8	3.9 ±2.9	3.9 ±3.0	0.32
Occipital	4.1 ±3.1	3.5 ±3.6	2.7 ±3.6	4.0 ±3.1	4.4 ±3.6	4.5 ±3.6	**0.04 ***

Two-way analysis of variance. Data are presented as mean ± SD unless otherwise indicated.
*p < .05
**Interaction factor
[a]Absolute power in μV^2

1B). Where CDR levels are concerned, CDR 2 (moderate severity) showed a more pronounced reduction than CDR 1 patients on REM sleep frontal delta and theta power during donepezil treatment (interaction $F_{2,30}$= 6,4867, p =. 00456 and $F_{2,30}$ = 6.2640, p = .005, respectively). No difference between donepezil-treated CDR groups was found in other sleep EEG variables.

Psychometric Analysis

ADAS-cog scores decreased gradually after 3 and after 6 months of donepezil treatment (interaction $F_{2,66}$=21.11, p < .01) (Table 2, Figure 1C). Baseline overall, frontal, and parietal alpha significantly correlated with cognitive improvement rate (R= 0.75, 0.71, 0.78 and p = .0005, .001, .0002, respectively)(Figure 1D). There was no significant difference between CDR groups in cognitive improvement rate (p = .35). We found no significant correlations between other REM sleep parameters and cognitive improvement.

DISCUSSION

There have been very few polysomnographic studies on the effect of cholinergic drugs on patients with Alzheimer disease, and this is particularly the case for donepezil. It was found to be well tolerated by our experimental subjects, and no major side effects have been previously reported in literature.[3,5,6,8] No evidence of sleep worsening or nightmares was found in this study, which corroborates the findings of other authors, who studied larger samples in general practice.[5]

The present study shows that donepezil treatment increases REM sleep percentage, whereas it decreases EEG slowing ratio and the REM sleep slow band power in specific brain areas in patients with Alzheimer disease, thus confirming our initial hypotheses.

Potentiation of cholinergic transmission might have induced a change in REM sleep EEG frequency bands.[22] We found a more pronounced reduction of REM sleep theta band absolute power in the frontal area, which is similar to what has been reported for long-term donepezil treatment in patients mild to moderate Alzheimer disease during wakefulness (similar population).[44,45] Moreover, we found that this effect was more pronounced in patients rated as having moderate disease. Steriade and collaborators have demonstrated that decreased cholinergic input is a requirement for the generation of EEG slow-wave delta and theta activity.[46] Thus, by increasing cholinergic transmission, we would expect a decrease in EEG theta activity.[46]

During wakefulness, theta reduction was not only found in frontal, but also in temporoparietal areas.[44] We did not find any significant change in REM sleep fast-frequency-band absolute power. The results for fast frequencies are controversial, since both increases and decreases have been reported.[22,44,45] Some previous studies have shown that EEG slowing results more from an increase in slow activity than from a decrease in fast activity.[22,44] Thus, the enhancement of the ratio between slow and fast frequencies after donepezil treatment in occipital leads may have followed a decrease in slow frequencies. The only previous study of REM sleep EEG spectral analysis in patients with Alzheimer disease treated with the anticholinesterase tacrine found no significant results, probably due to insufficient dosages.[18]

Another important finding is that cognitive improvement of patients with Alzheimer disease on donepezil treatment positively correlates with previous REM sleep overall, frontal, and centroparietal alpha power and, therefore, may be predicted by REM-sleep spectral analysis. According to this result, the more the patients showed increased alpha power at baseline REM sleep EEG, the higher the improvement rate after donepezil intake. In fact, we would expect better responses to donepezil by patients with less-deteriorated cholinergic systems. However, this result was independent of CDR in our sample.

In this context, we may assume that faster REM sleep EEG frequencies in centroparietal areas represent some degree of cholinergic-system preservation. Moreover, studies with positron emission tomographic scans and postmortem brain evaluations suggest that these brain areas are the most affected by Alzheimer's disease.[47-49] We believe that the predicting of treatment response through an objective marker may be of clinical interest and recommend further research on this issue.

A possible explanation for our findings is that donepezil increases central cholinergic transmission in areas related to different tasks, including cognitive function, REM sleep generation and REM sleep EEG desynchronization.[33,50] To some degree, anatomic structures affected by Alzheimer disease overlap with those related to the genesis and control of REM sleep. This has prompted some authors to speculate that there might be a functional relationship between REM sleep and the pathogenesis of Alzheimer disease.[51] Furthermore, there is an extensive but controversial number of studies relating REM sleep to cognitive function, which is impaired in Alzheimer's disease.[36,52-58] The relationship between REM sleep and cognition still requires complex interpretation.[52,58] The concurrent improvement of REM sleep and cognitive function of patients on donepezil treatment may suggest that REM sleep reduction is involved in the cognitive deterioration of patients with Alzheimer disease. The role played by REM sleep disturbances in the cognitive impairment of patients with Alzheimer disease continues to be a promising field, worthy of additional scrutiny.

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