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## **Innovation in cholinergic enhancement for Alzheimer's Disease**

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# **Acute response to cholinergic challenge predicts long-term response to galantamine treatment in patients with Alzheimer's Disease**

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## ABSTRACT

**BACKGROUND** Cholinesterase inhibitors (CEIs) have been shown to improve cognitive functioning in Alzheimer's Disease (AD) patients, but are associated with multiple side effects and only 20-40% of the patients clinically improve. In this study, we aimed to investigate the acute pharmacodynamic (PD) effects of a single dose administration of galantamine on central nervous system (CNS) functioning in mild to moderate AD patients and its potential to predict long-term treatment response.

**METHODS** This study consisted of a challenge and treatment phase. In the challenge phase, a single dose of 16 mg galantamine was administered to 50 mild to moderate AD patients in a double-blind, placebo-controlled cross-over fashion. Acute PD effects were monitored up to 5 hours after administration with use of the NeuroCart CNS test battery and safety and pharmacokinetics were assessed. In the treatment phase, patients were treated with open-label galantamine according to regular clinical care. After 6 months of galantamine treatment, patients were categorized as either responder or as non-responder based on their MMSE, NPI and DAD scores. An analysis of covariance was performed to study the difference in acute PD effects during the challenge phase between responders and non-responders.

**RESULTS** A single dose of galantamine significantly reduced saccadic reaction time ( $-0.0099$ ; 95%CI= $-0.0195, -0.0003$ ;  $p=.0430$ ), absolute frontal EEG parameters in alpha ( $-14.9$ ; 95%CI= $-21.0, -8.3$ ;  $p=.0002$ ), beta ( $-12.6$ ; 95%CI= $-19.4, -5.3$ ;  $p=.0019$ ) and theta ( $-17.9$ ; 95%CI= $-25.0, -10.0$ ;  $p=.0001$ ) frequencies. Relative frontal ( $-1.669$ ; 95%CI= $-2.999, -0.339$ ;  $p=.0156$ ) and occipital ( $-1.856$ ; 95%CI= $-3.339, -0.372$ ;  $p=.0166$ ) EEG power in theta frequency and relative occipital EEG power in the gamma frequency ( $1.316$ ; 95%CI= $0.158, 2.475$ ;  $p=.0273$ ), also increased significantly compared to placebo. Acute decreases of absolute frontal alpha ( $-20.4$ ; 95%CI= $-31.6, -7.47$ ;  $p=.0046$ ), beta ( $-15.7$ ; 95%CI= $-28.3, -0.93$ ;  $p=.0390$ ) and theta ( $-25.9$ ; 95%CI= $-38.4, -10.9$ ;  $p=.0024$ ) EEG parameters and of relative frontal theta power ( $-3.27\%$ ; 95%CI= $-5.96, -0.58$ ;  $p=.0187$ ) on EEG significantly distinguished responders ( $n=11$ ) from non-responders ( $n=32$ ) after 6 months.

**CONCLUSIONS** This study demonstrates that acute PD effects after single dose of galantamine are correlated with long-term treatment effects and that patients who demonstrate a reduction in EEG power in the alpha and theta frequency after a single administration of galantamine 16 mg will most likely respond to treatment.

## INTRODUCTION

Alzheimer's Disease (AD) is the major cause of dementia worldwide.<sup>1</sup> This neurodegenerative disorder is characterized by a profound loss of cholinergic innervation and cholinergic deficiency.<sup>2-4</sup> As the disease progresses, cognitive functions deteriorate in parallel with loss of cholinergic neurons, which correlates with disease severity.<sup>5</sup> Despite huge efforts, no curative therapy has been found yet, and current therapies mainly focus on the loss of cholinergic function. Cholinesterase inhibitors (CEIs) fall under the class of cholinergic treatments currently in use for the symptomatic treatment of dementia.<sup>6-8</sup> CEIs attempt to restore the loss of acetylcholine occurring after the neurodegeneration of the cholinergic system by increasing the acetylcholine (ACh) levels in the synaptic cleft of the remaining cholinergic neurons.<sup>6-8</sup> Galantamine is an example of a specific, competitive and reversible CEI, which, however, may also have a more direct modulating effect on the nicotinic acetylcholine receptor (AChR).<sup>6</sup> CEIs have shown to improve cognitive function in AD, Lewy Body Dementia and Parkinson's Disease Dementia.<sup>7,8</sup>

Unfortunately, CEIs lead to a clinical improvement in only 20-40% of the AD patients, depending on the definition of treatment response.<sup>9,10</sup> Since it is difficult to distinguish who will clinically improve in response to treatment and who will not at an early stage of disease<sup>10,11</sup> many patients are unnecessarily exposed to drug treatment and potentially experience adverse effects. It would be favourable to determine responsiveness to treatment before long-term drug exposure. In daily clinical practice, a favourable response to CEI treatment is defined by the postponement of progression of symptoms of AD. This can only be determined at a point in time when clinical progression is expected. Usually, patients are treated for at least 6 months before treatment response is assessed, using clinical scales for cognitive domains, functioning in daily life and behaviour. However, based on the mechanism of action, CEIs are expected to increase the level of ACh in the synaptic cleft immediately after dosing. We argue that acute pharmacodynamic (PD) effects of CEIs can be measured when sensitive methods are used at multiple time points in the hours after dosing, especially in comparison to placebo in a cross-over study design.

Acute PD effects of galantamine in AD patients have been reported previously,<sup>12</sup> but only in pharmacological magnetic resonance imaging studies at one timepoint after dosing.<sup>12-14</sup> One study showed an effect on paired associate learning after the administration of donepezil 5 mg,<sup>15</sup> however this study had no placebo-controlled cross-over design and measurements were performed at one fixed time point after

dosing. None of these studies reported a longer follow-up period or associated correlation parameters. Other studies attempted to link long term treatment effects of rivastigmine to the pharmacokinetics (PK) in plasma and cerebrospinal fluid at steady state<sup>16</sup> or measured electroencephalography (EEG) changes after one week of treatment.<sup>17</sup> However, neither performed PD measurements in the first hours after single dosing. Conceptually, acute PD effects, when accurately measured, are expected to be correlated with treatment response, if the clinical effect is related to the pharmacological activity of the compound. By inference, a single administration of a CEI could be used in clinical practice to decide which patient to treat and which patient not to expose to unnecessary side effects.

Based on the pharmacological properties of CEIs and evidence from previous studies, we hypothesized that reactivity to an acute cholinergic challenge will predict the long-term response to cholinergic treatment.<sup>12,17</sup> In the present study, we therefore aimed to investigate the acute PK and PD effects of a single dose administration of galantamine on central nervous system (CNS) functioning in mild to moderate AD patients in a placebo-controlled, cross-over fashion. Subsequently, patients were treated with galantamine for 6 months and clinical response to treatment was evaluated. Finally, the relationship between the reactivity to the acute cholinergic challenge and clinical response to long term cholinergic treatment was assessed.

## METHODS

### Study design and subjects

This was a multicentre, double-blind, placebo controlled, randomized cross-over study with galantamine compared to placebo, followed by a 6 months open label treatment phase in patients with AD. Fifty patients with mild to moderate AD were included in the study. Inclusion was based on a clinical diagnosis of AD, Mini Mental State Examination (MMSE) score ranging from 18 to 26 and a Clinical Dementia Rating (CDR)<sup>18</sup> score between 0.5 and 2.0. Main exclusion criteria were the previous or current use of CEIs, anti-cholinergic drugs or neuroleptics, contraindications for the use of CEIs, use of benzodiazepines 48 hours prior to the study days or any history of psychiatric disorders.

Before entering the study, all patients were screened for eligibility, including evaluation of diagnosis, use of medication, presence of contraindications for the use of galantamine, electrocardiogram (ECG) and laboratory investigations. Also, a training session for the pharmacodynamic measurements performed with the NeuroCart® CNS test battery was planned. This test battery includes 10 different computerized tasks and EEG on a wide range of CNS domains<sup>19,22</sup> and is

also sensitive to cholinergic effects.<sup>23,24</sup> All eligible patients entered the challenge phase, consisting of two study days, during which the effects of galantamine or placebo were measured according to a predefined time schedule, with a one week wash-out period in between. Directly after the second challenge occasion, patients entered the open-label treatment phase. During this phase, patients were treated with galantamine according to standard care for 6 months and visited the clinic after two months and 6 months of treatment for the assessment of clinical outcome measures. This study was performed in collaboration with the vu University Medical Center (Amsterdam, The Netherlands), and the University Hospital of Bucharest (Romania). Subjects were also recruited via the memory clinic of the Spaarne Gasthuis Hospital (Haarlem, The Netherlands). All subjects gave written informed consent for participation in the study. The study was approved by the Medical Ethics Committee of the vu University Medical Center and the Medical Ethics Committee of the Clinicii de neurologie a Spitalului Universitar de Urgenta and it was carried out according to the ICH Good Clinical Practice.

### Dosing rationale

**CHALLENGE PHASE** Previous studies have shown measurable changes in functional magnetic resonance imaging 3 hours post-administration, and no serious side effects as a consequence of the administration of a single dose of 8 mg galantamine.<sup>12-14</sup> Therefore, this study started with a challenge dose of 8 mg. An interim analysis was planned and performed when the first 11 patients completed the challenge phase to assess whether this dose induced any measurable acute PD effects compared to placebo. There were no significant differences in pharmacodynamic effects between galantamine 8 mg and placebo and side effects at this dose were minimal. A recently performed study by Klaassens and colleagues also found no pharmacodynamic effects after a single dose of galantamine 8 mg.<sup>14</sup> Based on this, it was decided to increase the challenge dose to 16 mg galantamine. Study drug was administered orally as one or two capsules, each containing 8 mg of galantamine hydrobromide or a placebo. During the challenge phase, an immediate release formulation of Reminyl® was used.

**TREATMENT PHASE** Directly after completing the challenge phase, patients entered the treatment phase. Patients were treated with extended release galantamine (Reminyl® or equivalent) capsules, according to the guidelines used in daily clinical practice: to prevent side effects caused by fast accumulation due to the long half-life of galantamine, the starting dose was 8 mg once daily for four weeks. The dose was then increased to 16 mg once daily for the remaining months.

## Pharmacokinetic assessments

Venous blood samples were obtained via an indwelling catheter at baseline and at 0, 25, 0.5, 1, 1.5, 2, 2.5, 3.5 and 5 hours following drug administration. Plasma galantamine concentrations were determined at the department of Clinical Pharmacy and Pharmacology at the VU University Medical Centre by a validated method using high-performance liquid chromatography coupled to a tandem-mass spectrometry.

## Pharmacodynamic assessments

To evaluate the acute PD effects of galantamine, the NeuroCart® was used, including 10 different computerized tasks and EEG. The NeuroCart test battery has previously shown sensitivity to drug effects on a wide range of CNS domains<sup>19-22</sup> and is also sensitive to (anti)cholinergic effects.<sup>23,24</sup> The N-back tests evaluated working memory,<sup>25,26,27</sup> adaptive tracking measured sustained attention and eye-hand coordination,<sup>28,29,32</sup> and the Simple Reaction Time task measured the attention and speed of information processing.<sup>29</sup> The visual analogue scale according to Bond and Lader assessed changes in subjective states,<sup>13</sup> the facial encoding and recognition task episodic memory,<sup>12,21</sup> and the visual verbal learning test (VVL) covered the scope of learning behaviour (i.e., acquisition, consolidation, storage and retrieval).<sup>30</sup> Pharmacoelectroencephalography, eye movements, and pupil size were used to determine drug effects on neurophysiological and autonomous system function.<sup>10,31,34</sup> Pupil size, eye movements, adaptive tracking, simple reaction time, visual analogue scales and N-back tests were performed twice at baseline, and at 1, 2, 4, and 5 hours following galantamine or placebo administration. The VVL was executed 1.5 hours after drug-administration (immediate recall) and 3.0 hours following drug-administration (delayed recall and recognition). The facial recognition task was performed at baseline and 2.5 hours after dosage. Pharmacoelectro-EEG measurements were performed at baseline and 0.5, 1, 1.5, 2, 4 and 5 hours post galantamine administration. Measurements were performed in a quiet room with ambient illumination with only one subject per session in the same room.

## Clinical outcome assessments

The Alzheimer's Disease Assessment (ADAS)-cog subscale was used to evaluate the severity of cognitive and non-cognitive behavioral dysfunction characteristic for AD patients.<sup>35</sup> This subscale comprises 11 items that have been allocated to represent

3 key cognitive domains: language, memory, and praxis.<sup>36-38</sup> Positive changes on the ADAS-cog scale (0-70) imply worsening of cognition. Cognitive performance of subjects was assessed by the Clinical Dementia Rating Scale (CDR) in which statements related to the following 6 domains are scored: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.<sup>18</sup> The global CDR score is derived from a synthesis of the individual ratings in each domain in accordance with established clinical scoring rules and represents a 5-point ordinal scale, where CDR 0 indicates no dementia, and CDR 0.5, 1, 2, and 3 indicate questionable, mild, moderate, and severe dementia. The Disability Assessment in Dementia (DAD) scale was used to evaluate basic and instrumental activities of daily living (ADL).<sup>39</sup> Items from this 46-item questionnaire can be divided into basic ADL and instrumental ADL. Higher scores represent fewer disabilities and lower scores indicate increased disabilities.<sup>40</sup> The Mini Mental State Examination (MMSE) is a brief 30-point questionnaire test which was used to screen for cognitive impairment.<sup>41,42</sup> With the Neuropsychiatric Inventory (NPI) diverse behavioural and psychological symptoms of dementia were measured.<sup>43</sup> The ADAS-cog, CDR, DAD, MMSE and NPI were carried out after two and 6 months of treatment.

## Safety assessments

Before participation in the study, all subjects underwent medical screening, including medical history, physical examination, vital signs measurements, 12-lead ECG, urinalysis, urinary drug screen, haematology and biochemistry blood sampling. During study days, vital signs measurements, 12-lead ECG, urinalysis, urinary drug screen, haematology and biochemistry blood sampling were performed at baseline. ECG and vital signs were additionally performed at 0.5, 1.5 and 5.0 hours post-drug administration in order to monitor possible adverse effects of the drug and assess safety.

**SAMPLE SIZE CALCULATION** The study aimed to enrol 50 patients with mild to moderate AD. This number was based on a sample size calculation that hypothesized an effect size comparable to the reduction in theta power on EEG examination (-27.3%) after onset of treatment with rivastigmine in patients who clinically improved in another.<sup>17</sup> Of the 20 patients with mild to moderate AD who participated in that study, 8 patients (40%) clinically improved in response to treatment, defined as an improvement of short-term memory after 6 months. A logistic regression analysis revealed that 50% of the observed variance in clinical improvement as a result of treatment could be explained by the decrease in

theta power, one week after onset of treatment.<sup>17</sup> With an estimated correlation coefficient of  $r^2=0.50$ , a sample size calculation determined that with an alpha of 0.05 and a power (1-beta) of 0.8, at least 30 patients were needed to observe a significant correlation between the acute response to the galantamine challenge and clinical improvement after 26 weeks. With an estimated drop-out rate of 35%,<sup>11</sup> the total number of patients needed was calculated to be 46, which is why 50 patients were targeted.

**INTERIM ANALYSIS** After the challenge phase, data of the first 11 subjects were collected and a pre-defined interim analysis was performed. For the interim analysis, the PD variables were analysed by mixed model of analysis with treatment, time, and treatment by time as fixed factors, subject, subject by treatment, and subject by time as random factors and the average pre-value as covariate. The results were presented as a result table of the analysis with the p-value of the contrast between placebo and galantamine, the least square means of the treatments, the estimate of the difference and the 95% confidence interval around the difference. No individual data were reported to avoid unblinding.

**PHARMACODYNAMIC ANALYSIS** Acute effects on different PD variables were analysed as described for the interim analysis. Log transformation was used to correct for log-normal distribution of the data. Calculation of time and treatment by time effects were for graphical presentation purposes only; only contrasts within the overall treatment effect were estimated and reported, along with 95% confidence intervals. Log-transformed parameters were back-transformed after analysis where the results may be interpreted as percentage change. Due to the exploratory nature of this study, no formal adjustment for multiple testing was used.

**CORRELATION ANALYSIS** To investigate whether the acute PD effects were correlated with the MMSE, NPI and DAD scores at 6 months independently, change from baseline AUC for galantamine and placebo were calculated and Pearson (or Spearman) correlation coefficients were calculated. According to Chan et al., correlation was defined as poor (0.1 – 0.2), fair (0.3 – 0.5), moderate (0.6 – 0.7), very strong (0.8 – 0.9) or perfect (1).<sup>44</sup>

The group of patients was subsequently divided in responders and non-responders. If MMSE and NPI and DAD at month 6 were  $\geq$  MMSE and NPI and DAD at baseline, a patient was a responder. If not all three measurements improved or at least stayed the same, the patient was a non-responder. The challenge effects of the PD variables were analysed comparing the responders with the non-responders. The challenge variables were analysed with a mixed model analysis of

variance with fixed factor group (responder/non-responder), treatment, period, time, treatment by time, treatment by group and treatment by group by time as fixed factor, subject, subject by time and subject by treatment as random factor and the average pre-value as covariate. The contrast of interest was responders (galantamine-placebo) versus non-responders (galantamine-placebo). The difference of the change from baseline galantamine AUC and the placebo AUC was graphically analysed for the responders and the non-responders. The percentage of responders and non-responders outside the range of the non-responders and responders respectively, was calculated.

**PHARMACOKINETIC ANALYSIS** The following PK parameters were estimated using compartmental analysis: maximum plasma concentrations ( $C_{max}$ ), time of maximum plasma concentrations ( $T_{max}$ ), area under the concentration versus time curve from time zero to the time of the last quantifiable concentration and to infinity ( $AUC_{\infty}$ ), terminal elimination rate constant ( $\lambda_z$ ), terminal elimination half-life ( $T_{1/2}$ ), and clearance ( $CL/F$ ).

## RESULTS

In total, 50 patients with mild to moderate AD were included in our study. Of these patients, 39 were enrolled via the Centre for Human Drug Research and the vu medical center in the Netherlands (of whom 5 were recruited via the Spaarne Gasthuis in Haarlem) and 11 patients were enrolled at the Tangent data research unit at University hospital of Bucharest in Romania. Patients had a mean age of 66.8 years (range 49 - 90) and a mean weight of 75.8 kg (range 50 - 122). The first 11 patients (all tested in the Netherlands) received 8 mg of galantamine. Following the predefined interim analysis, it was decided to escalate the dose to 16 mg of galantamine for the remaining 39 patients. Two patients prematurely dropped out of the study during the challenge phase due to practical issues (lack of time or hospitalization for unrelated reasons). Therefore, 48 patients could be analyzed in the challenge phase of the study. During the treatment phase, three additional patients cancelled study appointments (one patient experienced side effects, two patients lacked time or were hospitalized for other reasons). Two patients had incomplete follow-up data. A total of 43 patients could therefore be analyzed in the treatment phase.

## Challenge phase

**INTERIM ANALYSIS** An interim analysis after the first 11 subjects revealed no clear differences between 8 mg galantamine treatment and placebo on most of the PD measurements. Differences were observed between galantamine and placebo treatment for the second immediate recall of the vVLT (-1.8; 95% CI=-2.7,-0.9;  $p=0.0084$ ). However, since no differences were found for all other parameters (see supplementary material online), the measured PD effects of 8 mg galantamine were considered insufficient and it was decided to increase the dose of galantamine to 16 mg for the remaining 39 subjects. No interim analysis could be performed for the pupil size, N-back average reaction time 2 back and recognition of the vVLT, since too few subjects were able to perform these tests, due to the complexity of the computer interface. The computer interface was subsequently simplified based on this observation.

**PHARMACODYNAMICS** Acute PD effects of a single dose of galantamine in comparison to placebo in mild to moderate AD patients are displayed in table 1. A single dose of galantamine significantly reduced saccadic reaction time (-0.0099; 95%CI=-0.0195,-0.0003;  $p=0.0430$ ) when compared to placebo condition. Peak effects on saccadic eye movements were observed around the  $T_{max}$  of galantamine. An improvement in performance on the adaptive tracker was observed after administration of galantamine, but the difference was not significant. Notably, galantamine appeared to increase performance on adaptive tracking at 1, 4 and 5 hours post drug administration, but not around 2 hours following administration (Table 1).

In addition, galantamine administration acutely reduced absolute alpha (-14.9; 95%CI=-21.0,-8.3;  $p=0.0002$ ), beta (-12.6; 95%CI=-19.4,-5.3;  $p=0.0019$ ) and theta power (-17.9; 95%CI=-25.0,-10.0;  $p=0.0001$ ) and relative frontal (-1.669; 95%CI=-2.999,-0.339;  $p=0.0156$ ) and occipital (-1.856; 95%CI=-3.339,-0.372;  $p=0.0166$ ) EEG power in theta frequency and increased relative occipital EEG power in the gamma frequency (1.316; 95%CI=0.158,2.475;  $p=0.0273$ ) on the pharmacoelectroencephalography in comparison to placebo. For all EEG spectra, except for the delta range, a significant decrease in power was observed compared to placebo, with strongest reductions around the  $T_{max}$  of galantamine. For the delta range a reduction of absolute power was observed following galantamine administration, but the difference was not significant. Reductions in delta power were strongest around 2 hours post-drug administration and continued to be equally reduced over time. VAS scores on nausea significantly increased after galantamine compared to placebo (0.2908 log mm; 95%CI=0.0968,0.4848;  $p=0.0043$ ). All other PD parameters were not significantly affected by galantamine.

**PHARMACOKINETICS** Mean  $T_{max}$  was 2.42 h (range 1.00 - 4.58) for 8 mg and 1.38 h (range 0.45 - 4.60) for 16 mg of galantamine with a  $C_{max}$  of respectively 43.17 ng mL<sup>-1</sup> (range 23.90 - 57.30) and 79.00 (range 43.30 - 139.00). Graphs and other PK parameters can be found in the supplemental material.

## Treatment Phase

After 6 months, 11 (26%) patients were defined as responder to galantamine treatment and 32 (74%) patients were defined as non-responder, based on the a priori definition of response of no decline on MMSE, DAD and NPI. Table 2 describes the differences between responders and non-responders in their reactivity to the acute cholinergic challenge compared to placebo. Differences between responders and non-responders in their reactivity to the cholinergic challenge compared to placebo were statistically significant for absolute frontal alpha (-20.4; 95%CI=-31.6,-7.47;  $p=0.0046$ ), beta (-15.7; 95%CI=-28.3,-0.93;  $p=0.0390$ ) and theta power (-25.9; 95%CI=-38.4,-10.9;  $p=0.0024$ ) and for relative frontal theta power (-3.27%; 95%CI=-5.96,-0.58;  $p=0.0187$ ) on EEG. It is interesting to note that on visual inspection, long-term responders showed an acute increase after placebo on absolute frontal EEG parameters and on relative frontal theta power compared to baseline on the placebo occasion and a decrease compared to baseline on the galantamine occasion, whereas non-responders hardly showed any change from baseline on either the placebo nor galantamine occasion (figure 1). On the scatter plots, both absolute frontal alpha and frontal theta power distinguished responders from non-responders well, with minimal overlap between responders and non-responders (figure 2). For frontal alpha power, no responders were in the overlapping range. For frontal theta power, 2 responders (22,2%) and 3 non-responders (12,5%) were in the overlapping range. For relative frontal theta power on the EEG, 4 responders (80%) and 9 non-responders (64,3 %) were in the overlapping range. Acute improvements in saccadic eye movements that were observed after single dose galantamine, did not clearly predict long-term clinical improvement: saccadic peak velocity increased on average in responders but not in non-responders, but this failed to reach statistical significance (Table 2).

Correlations between the acute PD effects and MMSE, NPI and DAD scores at 6 months independently, are shown in the supplementary material (online available). Supplemental Table 2 shows that the majority of the coefficients of correlation reached a value under (-)0.50, which can be considered as fair.<sup>44</sup> Coefficients reaching levels over (-)0.50 showed a moderate correlation between acute effects on smooth pursuit ( $r=0.58$ ), alertness ( $r=0.54$ ), N-back ( $r=0.63$ ) and relative frontal alpha power on EEG ( $r=-0.59$ ) and treatment response according to the DAD only.

TABLE 1 Acute pharmacodynamic effects of a single dose of galantamine in mild to moderate Alzheimer patients.

Parameter	LS Means			LS Means change from baseline			Contrasts	
	Placebo	Galantamine	Placebo	Placebo	Galantamine	Placebo	Treatment effect (95% CI)	Treatment p-value
Smooth Pursuit (%)	27.9	28.1	-1.95	-1.78			0.16 (-1.26,1.59)	0.8147
Saccadic Inaccuracy (%)	7.3	6.6	-0.27	-0.95			-0.69 (-1.38,0.01)	0.0516
Saccadic Peak Velocity (deg/s)	489.6	496.8	-12.28	-5.08			7.20 (-4.62,19.02)	0.2173
Saccadic Reaction Time (sec)	0.253	0.243	0.0061	-0.0038			-0.0099 (-0.0195,0.0003)	0.0430
Simple reaction time task (sec)	392.99	393.15	1.4%	1.5%			0.0%	0.9911
Adaptive tracking (%)	17.76	18.54	0.084	0.863			0.779 (-0.247,1.805)	0.1320
vas Alertness (mm)	61.5	56.7	-0.98	-5.83			-4.85 (-9.83,0.13)	0.0560
vas Calmness (mm)	63.0	59.5	1.89	-1.62			-3.51 (-9.71,2.70)	0.2541
vas Mood (mm)	64.4	62.5	0.17	-1.75			-1.92 (-6.37,2.53)	0.3813
vas Nausea log(mm)	0.633	0.924	-0.0341	0.2567			0.2908 (0.0968,0.4848)	0.0043
N-back mean RT 0 back (msec)	512	524	5.7	17.9			12.2 (-21.6,46.1)	0.4631
N-back mean RT 1 back (msec)	651	627	-13.0	-37.1			-24.1 (-80.8,32.5)	0.3754
N-back mean RT 2 back (msec)	743	726	-26.6	-43.8			-17.2 (-102.9,68.4)	0.6797
N-back corr-incorr/total 0	5.93	5.97	-0.054	-0.007			0.047 (-0.070,0.163)	0.4081
N-back corr-incorr/total 1	5.28	5.33	0.202	0.248			0.046 (-0.357,0.448)	0.8158
N-back corr-incorr/total 2	3.43	3.37	-0.449	-0.513			-0.064 (-0.584,0.456)	0.8014
EEG Alpha Fz-Cz (uV)	2.17	1.86	10.8%	-5.3%			-14.9% (-21.0%,8.3%)	0.0002
EEG Alpha Pz-Oz (uV)	3.26	3.22	-0.7%	-2.0%			-1.3% (-10.8%,9.2%)	0.7953
EEG Beta Fz-Cz (uV)	1.88	1.66	10.2%	-3.0%			-12.0% (-18.7%,4.7%)	0.0026
EEG Beta Pz-Oz (uV)	1.87	1.92	1.2%	3.9%			2.6% (-6.0%,12.0%)	0.5505
EEG Delta Fz-Cz (uV)	1.48	1.35	12.5%	2.9%			-8.3% (-19.9%,4.9%)	0.2033
EEG Delta Pz-Oz (uV)	1.60	1.49	2.2%	-4.6%			-6.7% (-18.6%,7.0%)	0.3111
EEG Gamma Fz-Cz (uV)	0.56	0.53	7.7%	2.2%			-5.10%	0.2763
EEG Gamma Pz-Oz (uV)	0.63	0.72	-1.4%	12.3%			(-13.8%,4.5%)	0.0923
EEG Theta Fz-Cz (uV)	2.03	1.67	16.9%	-3.9%			14.0% (-2.3%,33.0%)	0.0001
EEG Theta Pz-Oz (uV)	2.26	2.05	2.2%	-7.5%			-17.9% (-25.0%,10.1%)	0.1403
EEG Relative Alpha Fz-Cz (%)	26.48	25.93	-0.398	-0.950			-9.5% (-20.9%,3.5%)	0.2427
EEG Relative Alpha Pz-Oz (%)	33.43	33.87	-0.745	-0.307			-0.552 (-1.497,0.393)	0.633
EEG Relative Beta Fz-Cz (%)	23.12	23.01	-0.447	-0.552			0.438 (-1.442,2.318)	0.7628
EEG Relative Beta Pz-Oz (%)	19.09	19.9	-0.082	0.727			-0.106 (-0.814,0.603)	0.099
EEG Relative Delta Fz-Cz (%)	18.26	19.5	0.121	1.359			0.809 (-0.162,1.781)	0.1213
EEG Relative Delta Pz-Oz (%)	17.09	16.21	0.717	-0.168			1238 (-0.347,2.823)	0.1811
EEG Relative Gamma Fz-Cz (%)	7.22	8.08	-0.225	0.643			-0.885 (-2.207,0.437)	0.0544
EEG Relative Gamma Pz-Oz (%)	7.04	8.35	-0.226	1.091			0.868 (-0.018,1.753)	0.0273
EEG Relative Theta Fz-Cz (%)	25.07	23.4	1.098	-0.571			1.316 (0.158,2.475)	0.0156
EEG Relative Theta Pz-Oz (%)	23.54	21.68	0.524	-1.332			-1.856 (-3.339,0.372)	0.0166
Left Pupil/Iris ratio	0.3486	0.3537	-0.01204	-0.00690			0.00513 (-0.01380,0.02406)	0.5846
Right Pupil/Iris ratio	0.3485	0.3557	-0.00350	0.00367			0.00717 (-0.01071,0.02506)	0.4219
Face: number correct	14.8	14.7	-0.46	-0.60			-0.14 (-1.68,1.39)	0.8506
Face: avg RT correct (msec)	1807	1733	117.6	44.2			-73.4 (-332.9,186.1)	0.5574
Word recall 1 correct	2.4	2.5		0.14			0.14 (-0.31,0.60)	0.5242
Word recall 2 correct	4.1	4.1		-0.00			-0.00 (-0.68,0.67)	0.9946
Word recall 3 correct	4.7	5.0		0.30			0.30 (-0.46,1.05)	0.4319
Delayed word recall correct	0.9	0.7		-0.21			-0.21 (-0.63,0.21)	0.3138
Delayed word recognition correct	11.2	10.4		-0.89			-0.89 (-2.72,0.94)	0.3301
Delayed word recog RT correct (msec)	5285.3	4111.3		-1174.07			-1174.07 (-2602.93,254.80)	0.1038
IGF_BF3 serum (mg/L)	2.54	2.62	1.1%	4.6%			3.5% (-1.0%,8.2%)	0.1297
IGF_I serum (nmol/L)	19.06	19.42	2.2%	4.1%			1.9% (-1.4%,5.2%)	0.2502

**SAFETY** Of all patients in the challenge phase, 39 reported at least one treatment emergent adverse event. Nausea was the most frequent reported adverse event, with 6 (54.5%) patients receiving 8 mg and 25 (64.1%) patients receiving 16 mg of galantamine and 2 (4%) patients receiving placebo. Diarrhoea was reported in 5 (12.8%) patients on galantamine 16 mg and 1 (2.6%) patient on placebo. Vomiting was reported in 2 (18.2%) patients on galantamine 8 mg and 14 (35.9%) patients on galantamine 16 mg. Dizziness was reported in 2 (18.2%) patients on galantamine 8 mg, 15 (38.5%) patients on galantamine 16 mg and 2 (4%) patients on placebo. Malaise and somnolence were reported in 4 (10.3%) patients on galantamine 16 mg and somnolence was reported in 1 (2.6%) patient on placebo. None of the

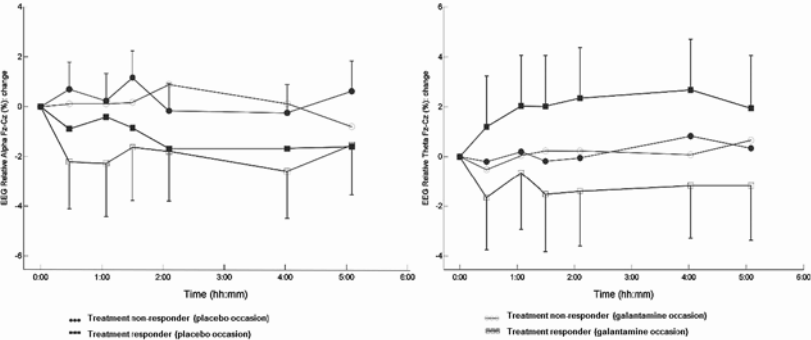
**TABLE 2 Differences between responders and non-responders in their reactivity to the cholinergic challenge compared to placebo.** PD variables were analysed by mixed model of analysis with treatment, time, and treatment by time as fixed factors, subject, subject by treatment, and subject by time as random factors and the average pre-value as covariate. Subjects were responders if MMSE, NPI and DAD at 6 months ≥ MMSE, NPI and DAD at baseline.

Parameter	LS Means		Contrast	
	Resp.	Non-Resp.	Resp. (Gal-Plac) vs Non-Resp. (Gal-Plac)	P-value
	(Gal-Plac)	(Gal-Plac)		
			Treatment effect (95% CI)	
Smooth Pursuit (%)	0.80	-0.40	1.21 (-1.63, 4.05)	0.3882
Saccadic Inaccuracy (%)	-0.90	-0.50	-0.43 (-1.80, 0.94)	0.5218
Saccadic Peak Velocity (deg/s)	18.20	-3.80	22.09 (-1.38, 45.57)	0.0636
Saccadic Reaction Time (sec)	-0.008	-0.012	0.0043 (-0.01, 0.02)	0.6498
Simple reaction time task (sec)	1.04%	0.96%	7.80% (-6.40%, 24.10%)	0.2841
Adaptive tracking (%)	0.71	0.85	-0.14 (-2.19, 1.92)	0.8948
VAS Alertness (mm)	-6.50	-3.20	-3.35 (-13.31, 6.61)	0.4968
VAS Calmness (mm)	-2.80	-4.20	1.43 (-10.9, 13.85)	0.8135
VAS Mood (mm)	-2.90	-0.90	-2.03 (-10.87, 6.82)	0.6398
VAS Nausea log(mm)	0.20	0.379	-0.17 (-0.56, 0.21)	0.3595
N-back mean RT 0 back (msec)	9	15	-6.10 (-73.40, 61.10)	0.8518
N-back mean RT 1 back (msec)	-21	-27	5.40 (-106.80, 117.60)	0.9187
N-back mean RT 2 back (msec)	0	-34	33.60 (-142.30, 209.50)	0.6948
N-back corr-incorr/total 0	-0.05	0.14	-0.19 (-0.42, 0.04)	0.1028
N-back corr-incorr/total 1	-0.11	0.21	-0.32 (-1.12, 0.48)	0.4126
N-back corr-incorr/total 2	0.00	-0.13	0.14 (-0.90, 1.17)	0.7873
EEG Alpha Fz-Cz (uV)	0.77%	0.95%	-18.4% (-29.6%, -5.5%)	0.0086

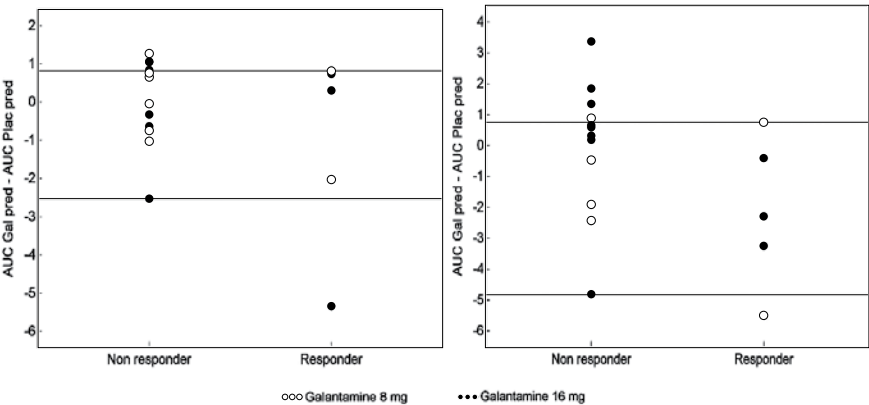
**CONTINUATION TABLE 2**

Parameter	LS Means		Contrast	
	Resp.	Non-Resp.	Resp. (Gal-Plac) vs Non-Resp. (Gal-Plac)	P-value
	(Gal-Plac)	(Gal-Plac)		
			Treatment effect (95% CI)	
EEG Alpha Pz-Oz (uV)	0.93%	1.05%	-11.2% (-27.5%, 8.9%)	0.2440
EEG Beta Fz-Cz (uV)	0.82%	0.95%	-14.0% (-26.6%, 0.9%)	0.0629
EEG Beta Pz-Oz (uV)	0.99%	1.07%	-7.7% (-22.6%, 10.1%)	0.3605
EEG Delta Fz-Cz (uV)	0.86%	0.98%	-11.6% (-32.8%, 16.2%)	0.3644
EEG Delta Pz-Oz (uV)	0.91%	0.96%	-5.3% (-32.8%, 16.2%)	0.6889
EEG Gamma Fz-Cz (uV)	0.93%	0.97%	-3.7% (-20.7%, 16.9%)	0.6924
EEG Gamma Pz-Oz (uV)	1.13%	1.15%	-2.0% (-20.7%, 16.9%)	0.8970
EEG Theta Fz-Cz (uV)	0.71%	0.95%	-25.3% (-37.8%, -10.4%)	0.0027
EEG Theta Pz-Oz (uV)	0.81%	1.02%	-20.7% (-39.5%, 4.0%)	0.0903
EEG Relative Alpha Fz-Cz (%)	-0.82	-0.28	-0.538 (-2.441, 1.364)	0.5679
EEG Relative Alpha Pz-Oz (%)	0.73	0.14	0.590 (-3.184, 4.365)	0.7481
EEG Relative Beta Fz-Cz (%)	0.04	-0.25	0.282 (-1.147, 1.711)	0.6898
EEG Relative Beta Pz-Oz (%)	1.19	0.43	0.767 (-1.178, 2.711)	0.4258
EEG Relative Delta Fz-Cz (%)	2.06	0.42	1.644 (-1.556, 4.845)	0.3029
EEG Relative Delta Pz-Oz (%)	-0.50	-1.27	0.771 (-1.874, 3.415)	0.5548
EEG Relative Gamma Fz-Cz (%)	1.54	0.20	1.341 (-0.456, 3.137)	0.1375
EEG Relative Gamma Pz-Oz (%)	1.60	1.04	0.561 (-1.765, 2.886)	0.6256
EEG Relative Theta Fz-Cz (%)	-3.30	-0.03	-3.271 (-5.958, -0.584)	0.0187
EEG Relative Theta Pz-Oz (%)	-3.18	-0.53	-2.651 (-5.631, 0.328)	0.0785
Left Pupil/Iris ratio	0.0037	0.0065	-0.00282 (-0.04087, 0.03524)	0.8811
Right Pupil/Iris ratio	0.0083	0.0060	0.00232 (-0.03353, 0.03817)	0.8966
Face: number correct	-1.1	0.8	-1.86 (-4.90, 1.19)	0.2226
Face: avg RT correct (msec)	-72	-75	2.3 (-513.3, 518.0)	0.9924
Word recall 1 correct	0.1	0.2	-0.06 (-0.97, 0.85)	0.8962
Word recall 2 correct	-0.7	0.7	-1.34 (-2.68, 0.01)	0.0517
Word recall 3 correct	0.3	0.3	-0.08 (-1.59, 1.43)	0.9129
Delayed word recall correct	-0.3	-0.1	-0.21 (-1.05, 0.62)	0.6072
Delayed word recognition correct	-0.7	-1.1	0.41 (-3.23, 4.05)	0.8207
Delayed word recog RT correct (msec)	-1885.8	-462.4	-1423.38 (-4257.69, 1410.93)	0.3135
IGF_BP3 serum (mg/L)	1.04%	1.03%	1.0% (-7.6%, 10.4%)	0.8265
IGF_I serum (nmol/L)	1.01%	1.03%	-1.8% (-8.0%, 4.8%)	0.5649

**FIGURE 1** Changes in relative frontal EEG alpha and theta parameters of responders and non-responders. Figure 1 shows the changes in relative frontal EEG alpha (A) and theta (B) parameters of responders and non-responders compared to baseline on either the placebo or galantamine occasion. Long-term responders showed an acute increase after placebo on absolute frontal EEG parameters and on relative frontal theta power compared to baseline on the placebo occasion and a decrease compared to baseline on the galantamine occasion, whereas non-responders hardly showed any change from baseline on either the placebo nor galantamine occasion.



**FIGURE 2** Delta AUC in relative frontal EEG alpha and theta parameters of responders and non-responders. Figure 2 shows a plot of delta AUC in relative frontal EEG alpha (A) and theta (B) power parameters of responders and non-responders. On the scatter plots, both absolute frontal alpha and frontal theta power distinguished responders from non-responders, with minimal overlap between responders and non-responders. For frontal alpha power, no responders were in the overlapping range. For frontal theta power, 2 responders (22,2%) and 3 non-responders (12,5%) were in the overlapping range.



other reported AEs occurred in more than 10% of patients. All adverse events were considered mild or moderate and spontaneously disappeared after a few hours.

During the treatment phase, one patient experienced moderate nausea during the first week of treatment and decided to discontinue the study and stop using galantamine. Two patients experienced mild nausea in the first two months of treatment. This subsided spontaneously and patients continued the use of galantamine. One patient reported moderate hyperhidrosis at the 6 month visit. In hindsight, this has been present the whole period. This patient decided to stop using galantamine.

# DISCUSSION

In this study, we investigated the acute pharmacodynamic effects of a single dose administration of the galantamine on CNS functioning in mild to moderate AD patients and its role as a potential predictor of long-term treatment response. The results show improvements of saccadic eye movements and reductions of frontal EEG parameters in alpha, beta and theta frequencies after the challenge phase. Acute decreases of absolute frontal alpha, beta and theta power on EEG and an acute decrease in relative theta power significantly correlated with long-term response to galantamine treatment. In addition, a highly significant effect on the nausea VAS score was found, which may have particularly had an impact on tests that required sustained attention or active participation.

Reductions in saccadic inaccuracy and reaction time during the challenge phase might reflect an improvement in visual attentional function.<sup>45</sup> The cholinergic neuronal system plays a well-known role in the maintenance of attention through projections of neurons in the basal forebrain complex to broad areas of the neocortex. Moreover, slowing of saccadic eye movements is considered as a biomarker of declining alertness, particularly caused by benzodiazepines,<sup>46-50</sup> and eye movements are also sensitive to anticholinergic drugs. In this context it is interesting to note that patients demonstrated a clear and anticipated improvement in attentional function, without a statistically significant improvement in mean adaptive tracker performance. The adaptive tracker is known for its sensitivity to disturbances and enhancement of central cholinergic neuronal functioning and can be regarded as a test of sustained attention.<sup>21,23,47</sup> It might be that a reduced eye-hand coordination in this population of elderly patients has played a role in this discrepancy. The occurrence of adverse events (e.g. nausea) during the challenge phase of the study, as well as the highly significant effect on the nausea VAS score may also have played a role in obscuring

some of the beneficial effects of galantamine on CNS test performance, as some patients were not able to perform all tests, and particularly the adaptive tracking test which requires sustained attention.

In addition to the acute improvement in attentional function, the results show decreases of frontal alpha, beta and theta EEG parameters after dosing in the challenge phase. Slow wave activity, such as theta and delta waves, are associated with a lower cognitive function in AD patients.<sup>51,52</sup> Previous studies have already reported reductions in theta power following chronic CEI treatment.<sup>17,53</sup> In this study we demonstrate that galantamine administration also acutely reduces theta power in AD patients. Previous, an increase in frontal theta power was observed in a condition of mental exhaustion.<sup>54</sup> This might explain the observed increase in theta power during the day on the placebo occasion among patients classified as responders. This might also explain the increase of theta power in responders after the administration of placebo in the challenge phase. Interestingly, our results indicate that a single dose of galantamine is already able to reduce theta power. It is surprising that galantamine administration also reduced alpha and beta power in our study, while faster wave lengths are associated with improved cognition.<sup>51,52,55,56</sup> However, the absolute values for alpha and beta power reduction were relatively small and there was no reduction in relative alpha or beta power. Also, studies involving the anti-cholinergic and cognitive impairing drug scopolamine have reported conflicting results regarding the effects on alpha and beta power.<sup>21,57</sup>

Overall, there is a serious need for predictive markers of treatment response following CEI treatment in AD patients. So far it has been impossible to predict who will respond to CEI treatment and only 20-40% of the patients clinically improve. Most of the attempts to predict clinical response to long term treatment included pre-dose characteristics, for example sex,<sup>58-61</sup> age,<sup>62,63</sup> severity of cognitive impairment and impaired performance on baseline neuropsychological test scores at baseline,<sup>11,64-67</sup> pre-treatment progression rate,<sup>68-71</sup> cerebrospinal fluid levels of A $\beta$ 42, T-tau and P-tau at baseline,<sup>68,72</sup> carotid intima media thickness,<sup>73</sup> regional cerebral blood flow of the lateral and medial frontal lobes,<sup>74</sup> substantia innominata atrophy,<sup>75,76</sup> performance on baseline alertness tests,<sup>9</sup> baseline behavioural<sup>77</sup> and SPECT profile,<sup>78</sup> pre-treatment blood pressure drop,<sup>62,79</sup> and APOE genotype.<sup>58-61,80-83</sup> Some of these factors showed a positive correlation with treatment response. Our findings suggest that patients demonstrating a reduction in EEG alpha and theta power and saccadic eye movements after a single administration of galantamine 16 mg are more likely to respond to treatment. Nevertheless, it remains to be investigated how the addition of a galantamine challenge adds value on top of the above-mentioned correlations found in previous studies in predicting treatment response.

Lancot and colleagues reviewed studies focusing on methods to predict the response to anticholinesterase therapy and markers for treatment response.<sup>84</sup> They were able to demonstrate the predictive value of qEEG profile after a test dose of the CEI tacrine, based on four clinical trials. Alhainen et al<sup>85</sup> firstly demonstrated that an increased alpha-theta ratio 90 minutes after a 50 mg test dose of tacrine led to higher MMSE scores four weeks post-treatment in 14 patients with probable AD. Alhainen and Riekkinen confirmed these findings on a longer term and showed that responders after seven weeks demonstrated a significant increase in mean absolute alpha power and alpha/theta ratio 90 minutes after a 50 mg test dose of tacrine.<sup>86</sup> Knott et al observed an increase of relative alpha and delta power waves in responders at 12 weeks, only 2 hours after an oral dose of 30 mg tacrine.<sup>87</sup> Almkvist et al suggested the validity of baseline EEG profiles as predictors of response to CEI therapy in 24 mildly to very mildly demented AD patients.<sup>88</sup> Except for the trial of Almkvist, these trials had an open-label design and all of them included only small numbers of patients, thus replication of these findings under double-blind conditions with larger patient samples was in our view necessary before conclusions can be drawn. Adler et al. further showed that treatment with rivastigmine 3 mg/day for one week led to a significant decrease in theta power on EEG which significantly correlated with responder status. When theta power and a baseline score for short term memory were both included as independent variables in a logistic regression model, treatment response could be accurately predicted.<sup>17</sup> Interestingly, the decrease in absolute alpha and theta power on EEG also predicted treatment response in our study. If we would have selected patients to be treated with galantamine based on either absolute frontal alpha power or absolute frontal theta power, *and* would also treat patients in the overlapping range, all patients defined as treatment responder would receive treatment. If this selection would be based on absolute alpha power, no non-responders would be treated. A selection based on absolute frontal theta power would result in the treatment of 3 non-responders. When selecting based on relative frontal theta power, 9 non-responders would be treated. Several combinations of these parameters have been investigated, but do not lead to a better prediction of treatment response. Moreover, all these explorations were *post hoc* and they would obviously require prospective validation.

While the studies of Adler, the Lancot trials and our study show some inconsistencies, i.e. none of the other studies investigated the effects of galantamine and all of them used different definitions for 'acute response' (ranging from 90 minutes to one week), the predictive role of theta power on EEG seems consistent and is also confirmed in the current study. The Lancot trials interestingly report on the increased alpha/theta ratio as a discriminator between

responders and non-responders, and not on absolute power EEG bands. Previous studies have shown that high/low band frequency ratios, e.g. alpha/theta ratios, can easily differentiate between AD patients and controls.<sup>89-91</sup> In our study, alpha/theta ratio was not a pre-defined outcome measure.

The sizeable group, the placebo controlled cross-over design and frequently repeated measures after dosing in the challenge phase and the combination with a follow-up study are strong aspects of the current study. Although the predefined response criteria of improvement on all three clinical scales may seem strict, this definition is based on not only improvement in cognition, but also activities of daily living and behavioural aspects, and it is closer therefore to a true clinical improvement than a responder criterion based on only one of these tests. If a patient declines in one dimension, e.g. ADL functioning, but not in another, e.g. cognitive functioning, both patient and doctor are likely to still regard this as an unsatisfactory non-response to treatment. Also, the correlations between the individual challenge tests and clinical follow-up measures did not show any consistent correlations and the number of responders (11 (25%)), which was consistent with expectations based on previous studies.<sup>10,17,83</sup> The difference between responders and non-responders could not be attributed to differences in levels of drug exposure, since there was no difference in average plasma concentrations of galantamine after two months of treatment between responders and non-responders.

It should be noted that sample size calculations were based on the observed variance in clinical improvement correlated with the decrease in theta power in a comparable study,<sup>17</sup> while we mainly draw conclusions about dichotomized treatment response (responder and non-responder) at 6 months in relation with acute challenge effects of PD variables. As data from that study was most comparable to data in the current study at that time, we believe this as the most appropriate method. Also, a responder score based on MMSE, NPI and DAD instead of independent scores, seemed more representative for real-world clinical improvement in AD patients. Other weaknesses of this study include the occurrence of side effects due to a pharmacological challenge, which were such that in the challenge phase some patients were not able to perform all tests due to nausea or had to decline the last round of tests due to fatigue. Also, especially the 2-back condition of the N-back turned out to be too difficult for AD patients.

This study is the first placebo controlled study with cross-over design that links typical PD effects in an early phase clinical drug trial to the clinically relevant outcome measures used for phase III registration studies in the field of AD. Furthermore, this study generates a well-defined time-profile of the effects of galantamine in the target population of patients with mild to moderate AD, with an observed

$T_{max}$  of galantamine around 2 hours after administration, which is consistent with previously reported findings of a  $T_{max}$  of approximately 1.5 hours after a single oral dose of 10 mg galantamine with immediate release formulation.<sup>92</sup> Reductions in both absolute and relative theta power were obviously most pronounced around 2 hours after the administration of galantamine and continued to be equally reduced over time. Cut-off criteria seem arbitrary, however we believe that cut-off criteria based on multiple tests are more representative for the actual patient condition, compared to cut-off criteria based on one test.

## Conclusion and future perspectives

This study demonstrates that acute PD effects after single dose of galantamine are correlated with long-term treatment effects and that patients demonstrating a reduction in EEG alpha and theta power and saccadic eye movements after a single administration of galantamine 16 mg are more likely to respond to treatment. Further confirmation of these findings is needed from prospective trials. This study takes a first step towards finding predictive biomarkers of treatment response to CEIs. In the future, these biomarkers might prevent the redundant exposure of AD patients to drug treatment and its related side effects.

## REFERENCES

- 1 Wortmann M. Dementia: a global health priority-highlights from an ADI and World Health Organization report. *Alzheimer's research & therapy*. 2012;4(5):40.
- 2 Mesulam M. The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learning & memory* (Cold Spring Harbor, NY). 2004; doi:10.1101/lm.69204.
- 3 Mesulam MM, Geula C. Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: observations based on the distribution of acetylcholinesterase and choline acetyltransferase. *The Journal of comparative neurology*. 1988; doi:10.1002/cne.902750205.
- 4 Drachman DA, Leavitt J. Human memory and the cholinergic system. A relationship to aging? *Archives of neurology*. 1974;30(2):113-21.
- 5 Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *British medical journal*. 1978;2(6150):1457-9.
- 6 Birks J. Cholinesterase inhibitors for Alzheimer's disease. *The Cochrane database of systematic reviews*. 2006; doi:10.1002/14651858.cd005593.
- 7 Maidment I, Fox C, Boustani M. Cholinesterase inhibitors for Parkinson's disease dementia. *The Cochrane database of systematic reviews*. 2006; doi:10.1002/14651858.cd004747.pub2.
- 8 Graepe J, Daniel S, Stevens T, Shankar KK, Walker Z, Byrne EJ, et al. Long-Term use of rivastigmine in patients with dementia with Lewy bodies: an open-label trial. *International psychogeriatrics*. 2001;13(2):199-205.
- 9 Connelly PJ, Prentice NP, Fowler KG. Predicting the outcome of cholinesterase inhibitor treatment in Alzheimer's disease. *Journal of neurology, neurosurgery, and psychiatry*. 2005; doi:10.1136/jnnp.2004.043559.
- 10 Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. *The Galantamine USA-1 Study Group*. *Neurology*. 2000;54(12):2261-8.
- 11 Lemstra AW, Kuiper RB, Schmand B, van Gool WA. Identification of responders to rivastigmine: a prospective cohort study. *Dementia and geriatric cognitive disorders*. 2008; doi:10.1159/00011549.
- 12 Goekoop R, Scheltens P, Barkhof F, Rombouts SA. Cholinergic challenge in Alzheimer patients and mild cognitive impairment differentially affects hippocampal activation—a pharmacological fMRI study. *Brain : a journal of neurology*. 2006; doi:10.1093/brain/awh671.
- 13 Goekoop R, Rombouts SA, Jonker C, Hibbel A, Knol DL, Truyen L, et al. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. *NeuroImage*. 2004; doi:10.1016/j.neuroimage.2004.08.006.
- 14 Klaassens BL, van Gerven JM, Klaassen ES, van der Grond J, Rombouts SA. Cholinergic and serotonergic modulation of resting state functional brain connectivity in Alzheimer's disease. *NeuroImage*. 2019;199:145-52.
- 15 Kuzmickienė J, Kaubrys G. Cognitive results of CANTAB tests and their change due to the first dose of donepezil may predict treatment efficacy in Alzheimer disease. *Medical science monitor: international medical journal of experimental and clinical research*. 2015;21:3887.
- 16 Gobburu JV, Tammara V, Lesko L, Jhee SS, Sramek JJ, Cutler NR, et al. Pharmacokinetic-pharmacodynamic modeling of rivastigmine, a cholinesterase inhibitor, in patients with Alzheimer's disease. *Journal of clinical pharmacology*. 2001;41(10):1082-90.
- 17 Adler G, Brassen S, Chwalek K, Dieter B, Teufel M. Prediction of treatment response to rivastigmine in Alzheimer's dementia. *Journal of neurology, neurosurgery, and psychiatry*. 2004;75(2):292-4.
- 18 Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *International psychogeriatrics*. 1997;9 Suppl 1:173-6; discussion 7-8.
- 19 Liem-Moolenaar M, Zoethout RW, de Boer P, Schmidt M, de Kam ML, Cohen AF, et al. The effects of a glycine reuptake inhibitor R231857 on the central nervous system and on scopolamine-induced impairments in cognitive and psychomotor function in healthy subjects. *Journal of psychopharmacology* (Oxford, England). 2010; doi:10.1177/0269881109105573.
- 20 Liem-Moolenaar M, Zoethout RW, de Boer P, Schmidt M, de Kam ML, Cohen AF, et al. The effects of the glycine reuptake inhibitor R23129 on the central nervous system and on scopolamine-induced impairments in psychomotor and cognitive function in healthy subjects. *Journal of psychopharmacology* (Oxford, England). 2010; doi:10.1177/0269881109106942.
- 21 Liem-Moolenaar M, de Boer P, Timmers M, Schoemaker RC, van Hasselt JG, Schmidt S, et al. Pharmacokinetic-pharmacodynamic relationships of central nervous system effects of scopolamine in healthy subjects. *British journal of clinical pharmacology*. 2011; doi:10.1111/j.1365-2125.2011.03936.x.
- 22 de Haas SL, de Visser SJ, van der Post JP, Schoemaker RC, van Dyck K, Murphy MG, et al. Pharmacodynamic and pharmacokinetic effects of MK-0343, a GABA(A)  $\alpha 2, \gamma$  subtype selective agonist, compared to lorazepam and placebo in healthy male volunteers. *Journal of psychopharmacology* (Oxford, England). 2008; doi:10.1177/0269881107082108.
- 23 Baakman AC, t Hart E, Kay DG, Stevens J, Klaassen ES, Maelicke A, et al. First in human study with a prodrug of galantamine: Improved benefit-risk ratio? *Alzheimer's & Dementia: TRCI*. 2016;2(1):13-22.
- 24 Baakman AC, Alvarez-Jimenez R, Rissmann R, Klaassen ES, Stevens J, Gouloze SC, et al. An anti-nicotinic cognitive challenge model using mecamylamine in comparison with the anti-muscarinic cognitive challenge using scopolamine. *British journal of clinical pharmacology*. 2017;83(8):1676-87.
- 25 Lim HK, Juh R, Pae CU, Lee BT, Yoo SS, Ryu SH, et al. Altered verbal working memory process in patients with Alzheimer's disease: an fMRI investigation. *Neuropsychobiology*. 2008; doi:10.1159/000147471.
- 26 Rombouts SA, Barkhof F, Van Meel CS, Scheltens P. Alterations in brain activation during cholinergic enhancement with rivastigmine in Alzheimer's disease. *Journal of neurology, neurosurgery, and psychiatry*. 2002;73(6):665-71.
- 27 Sweet LH, Rao SM, Primeau M, Durgierian S, Cohen RA. Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. *Human brain mapping*. 2006; doi:10.1002/hbm.20163.
- 28 Borland RG, Nicholson AN. Immediate effects on human performance of a 1,5-genzodiazepine (clobazam) compared with the 1,4-benzodiazepines, chlorthalidopoxide hydrochloride and diazepam. *British journal of clinical pharmacology*. 1975;2(3):215-21.
- 29 van Steveninck AL, Gieschke R, Schoemaker HC, Pieters MS, Kroon JM, Breimer DD, et al. Pharmacodynamic interactions of diazepam and intravenous alcohol at pseudo steady state. *Psychopharmacology*. 1993;110(4):471-8.
- 30 van Steveninck AL, Schoemaker HC, Pieters MS, Kroon R, Breimer DD, Cohen AF. A comparison of the sensitivities of adaptive tracking, eye movement analysis and visual analog lines to the effects of incremental doses of temazepam in healthy volunteers. *Clinical pharmacology and therapeutics*. 1991;50(2):172-80.
- 31 van Steveninck AL, van Berckel BN, Schoemaker RC, Breimer DD, van Gerven JM, Cohen AF. The sensitivity of pharmacodynamic tests for the central nervous system effects of drugs on the effects of sleep deprivation. *Journal of psychopharmacology* (Oxford, England). 1999; doi:10.1177/026988119901300102.
- 32 Gijssman HJ, Van Gerven JM, Tieleman MC, Schoemaker RC, Pieters MS, Ferrari MD, et al. Pharmacokinetic and pharmacodynamic profile of oral and intravenous methachlorophenylpiperazine in healthy volunteers. *Journal of clinical psychopharmacology*. 1998;18(4):289-95.
- 33 Bond A, Lader M. The use of analogue scales in rating subjective feelings. *British Journal of Medical Psychology*. 1974; doi:10.1111/j.2044-8341.1974.tb02285.x.
- 34 Baloh RW, Sills AW, Kumley WE, Honrubia V. Quantitative measurement of saccade amplitude, duration, and velocity. *Neurology*. 1975;25(11):1065-70.
- 35 Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *The American journal of psychiatry*. 1984; doi:10.1176/ajp.141.11.1356.
- 36 Mohs RC, Knopman D, Petersen RC, Ferris SH, Ernesto C, Grundman M, et al. Development of cognitive instruments for use in clinical trials of anti-dementia drugs: additions to the Alzheimer's Disease Assessment Scale that broaden its scope. *The Alzheimer's Disease Cooperative Study*. *Alzheimer disease and associated disorders*. 1997;11 Suppl 2:S13-21.
- 37 Winblad B, Brodaty H, Gauthier S, Morris JC, Orgogozo JM, Rockwood K, et al. Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success? *International journal of geriatric psychiatry*. 2001;16(7):653-66.
- 38 Weyer G, Erzigkeit H, Kanowski S, Ihl R, Hadler D. Alzheimer's Disease Assessment Scale: reliability and validity in a multicenter clinical trial. *International psychogeriatrics*. 1997;9(2):123-38.
- 39 Teunisse S, Derix MM. The interview for deterioration in daily living activities in dementia: agreement between primary and secondary caregivers. *International psychogeriatrics*. 1997;9 Suppl 1:155-62.
- 40 Gelinas I, Gauthier L, McIntyre M, Gauthier S. Development of a functional measure for persons with Alzheimer's disease: the disability assessment for dementia. *The American journal of occupational therapy : official publication of the American Occupational Therapy Association*. 1999;53(5):471-81.
- 41 Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state': A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 1975;12(3):189-98.
- 42 Cockrell JR, Folstein MF. Mini-Mental State Examination (MMSE). *Psychopharmacology bulletin*. 1988;24(4):689-92.
- 43 de Medeiros K, Robert P, Gauthier S, Stella F, Politis A, Leoutsakos J, et al. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. *International psychogeriatrics*. 2010; doi:10.1017/s1041610210000876.
- 44 Chan Y. *Biostatistics 104: correlational analysis*. Singapore Med J. 2003;44(12):614-9.
- 45 Mesulam MM. Cholinergic circuitry of the human nucleus basalis and its fate in Alzheimer's disease. *The Journal of comparative neurology*. 2013;521(18):4124-44.
- 46 de Visser SJ, van der Post JP, de Waal PP, Cornet F, Cohen AF, van Gerven JM. Biomarkers for the effects of benzodiazepines in healthy volunteers. *British journal of clinical pharmacology*. 2003;55(1):39-50.
- 47 Alvarez-Jimenez R, Groeneveld GJ, van Gerven JM, Gouloze SC, Baakman AC, Hay JL, et al. Model-based exposure-response analysis to quantify age related differences in the response to scopolamine in healthy subjects. *Br J Clin Pharmacol*. 2016;82(4):1011-21.
- 48 Sparks DL. The brainstem control of saccadic eye movements. *Nature Reviews Neuroscience*. 2002;3(12):952.
- 49 Kobayashi RM, Palkovits M, Hruska RE, Rothschild R, Yamamura HI. Regional distribution of muscarinic cholinergic receptors in rat brain. *Brain research*. 1978;154(1):13-23.
- 50 Flynn DJ, Reeve CM, Ferrari-DiLeo G. Pharmacological strategies to selectively label and localize muscarinic receptor subtypes. *Drug development research*. 1997;40(2):104-16.
- 51 Roca-Stappung M, Fernandez T, Becerra J, Mendoza-Montoya O, Espino M, Harmony T. Healthy aging: relationship between quantitative electroencephalogram and cognition. *Neuroscience letters*. 2012;510(2):115-20.
- 52 Riekkinen P, Buzsaki G, Riekkinen P, Soininen H, Partanen J. The cholinergic system and EEG slow waves. *Electroencephalography and clinical neurophysiology*. 1991;78(2):89-96.
- 53 Brassen S, Adler G. Short-term effects of acetylcholinesterase inhibitor treatment on EEG and memory performance in Alzheimer patients: an open, controlled trial. *Pharmacopsychiatry*. 2003;36(6):304-8.
- 54 Wascher E, Rasch B, Sängler J, Hoffmann S, Schneider D, Rinkenauer G, et al. Frontal theta activity reflects distinct aspects of mental fatigue. *Biological psychology*. 2014;96:57-65.
- 55 Klimesch W. EEG alpha and theta oscillations reflect cognitive and memory performance: a review and analysis. *Brain Res Rev*. 1999;29(2):169-95.
- 56 Ray WJ, Cole HW. EEG alpha activity reflects attentional demands, and beta activity reflects emotional and cognitive processes. *Science (New York, NY)*. 1985;228(4700):750-2.
- 57 Ebert U, Grossmann M, Oertel R, Gramatte T, Kirch W. Pharmacokinetic-pharmacodynamic modeling of the electroencephalogram effects of scopolamine in healthy volunteers. *Journal of clinical pharmacology*. 2001;41(1):51-60.
- 58 Farlow MR, Lahiri DK, Poirier J, Davignon J, Schneider L, Hui SL. Treatment outcome of tacrine therapy depends on apolipoprotein genotype and gender of the subjects with Alzheimer's disease. *Neurology*. 1998;50(3):669-77.
- 59 MacGowan SH, Wilcock GK, Scott M. Effect of gender and apolipoprotein E genotype on response to anticholinesterase therapy in Alzheimer's disease. *International journal of geriatric psychiatry*. 1998;13(9):625-30.
- 60 Rigaud AS, Traykov L, Latour F, Couderc R, Moulin F, Forette F. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response to donepezil treatment in Alzheimer's disease. *Pharmacogenetics*. 2002;12(5):415-20.
- 61 Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology*. 2001;57(5):489-95.
- 62 Schneider LS, Lyness SA, Pawluczyk S, Gleason RP, Sloane RB. Do blood pressure and age predict response to tacrine (THA) in Alzheimer's disease? A preliminary report. *Psychopharmacology bulletin*. 1991;27(3):309-14.
- 63 Evans M, Ellis A, Watson D, Chowdhury T. Sustained cognitive improvement following treatment of Alzheimer's disease with donepezil. *International journal of geriatric psychiatry*. 2000;15(1):50-3.
- 64 Pakrasi S, Muketova-Ladinska EB, McKeith IG, O'Brien JT. Clinical predictors of response to Acetyl Cholinesterase Inhibitors: experience from routine clinical use in Newcastle. *International journal of geriatric psychiatry*. 2003; doi:10.1002/gps.928.
- 65 Van Der Putt R, Dineen C, Janes D, Series H, McShane R. Effectiveness of acetylcholinesterase inhibitors: diagnosis and severity as predictors of response in routine practice. *International journal of geriatric psychiatry*. 2006; doi:10.1002/gps.1557.
- 66 Saumier D, Murtha S, Bergman H, Phillips N, Whitehead V, Chertkow H. Cognitive predictors of donepezil therapy response in Alzheimer disease. *Dementia and geriatric cognitive disorders*. 2007; doi:10.1159/000102569.
- 67 Rota E, Ferrero P, Ursone R, Migliaretti G. Short term response is predictive of long term response to acetylcholinesterase inhibitors in Alzheimer's disease: a starting point to explore Bayesian approximation in clinical practice. *Bioinformation*. 2007;2(2):43-9.

- 68 Wallin AK, Hansson O, Blennow K, Londo E, Minthon L. Can CSF biomarkers or pre-treatment progression rate predict response to cholinesterase inhibitor treatment in Alzheimer's disease? *International journal of geriatric psychiatry*. 2009; doi:10.1002/gps.2195.
- 69 Farlow MR, Hake A, Messina J, Hartman R, Veach J, Anand R. Response of patients with Alzheimer disease to rivastigmine treatment is predicted by the rate of disease progression. *Archives of neurology*. 2001;58(3):417-22.
- 70 Hanyu H, Asano T, Sakurai H, Tanaka Y, Takasaki M, Abe K. MR analysis of the substantia innominata in normal aging, Alzheimer disease, and other types of dementia. *AJNR American journal of neuroradiology*. 2002;23(1):27-32.
- 71 Wallin AK, Wattmo C, Minthon L. Galantamine treatment in Alzheimer's disease: response and long-term outcome in a routine clinical setting. *Neuropsychiatric disease and treatment*. 2011; doi:10.2147/ndt.s24196.
- 72 Sobow T, Flirski M, Liberski P, Kloszewska I. Plasma Abeta levels as predictors of response to rivastigmine treatment in Alzheimer's disease. *Acta neurobiologiae experimentalis*. 2007;67(2):131-9.
- 73 Modrego PJ, Rios C, Perez Trullen JM, Garcia-Gomara MJ, Errea JM. Carotid intima-media thickness as a predictor of response to cholinesterase inhibitors in Alzheimer's disease: an open-label trial. *CNS drugs*. 2009; doi:10.2165/00023210-200923030-00006.
- 74 Hanyu H, Shimizu T, Tanaka Y, Takasaki M, Koizumi K, Abe K. Regional cerebral blood flow patterns and response to donepezil treatment in patients with Alzheimer's disease. *Dementia and geriatric cognitive disorders*. 2003; doi:10.1159/000068785.
- 75 Kanetaka H, Hanyu H, Hirao K, Shimizu S, Sato T, Akai T, et al. Prediction of response to donepezil in Alzheimer's disease: combined MRI analysis of the substantia innominata and SPECT measurement of cerebral perfusion. *Nuclear medicine communications*. 2008; doi:10.1097/MNM.0b013e3282f5e5f4.
- 76 Bottini G, Berlingeri M, Basilio S, Passoni S, Danelli L, Colombo N, et al. GOOD or BAD responder? Behavioural and neuroanatomical markers of clinical response to donepezil in dementia. *Behavioural neurology*. 2012;25(2):61-72.
- 77 Mega MS, Masterman DM, O'Connor SM, Barclay TR, Cummings JL. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. *Archives of neurology*. 1999;56(11):1388-93.
- 78 Mega MS, Dinov ID, Lee L, O'Connor SM, Masterman DM, Wilen B, et al. Orbital and dorsolateral frontal perfusion defect associated with behavioral response to cholinesterase inhibitor therapy in Alzheimer's disease. *The Journal of neuropsychiatry and clinical neurosciences*. 2000; doi:10.1176/jnp.12.2.209.
- 79 Pomara N, Deptula D, Singh R. Pretreatment postural blood pressure drop as a possible predictor of response to the cholinesterase inhibitor velnacrine (HP 029) in Alzheimer's disease. *Psychopharmacology bulletin*. 1991;27(3):301-7.
- 80 Aerssens J, Raeymaekers P, Lilienfeld S, Geerts H, Konings F, Parys W. APOE genotype: no influence on galantamine treatment efficacy nor on rate of decline in Alzheimer's disease. *Dementia and geriatric cognitive disorders*. 2001; doi:10.1159/000051238.
- 81 Poirier J, Delisle MC, Quirion R, Aubert I, Farlow M, Lahiri D, et al. Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. *Proceedings of the National Academy of Sciences of the United States of America*. 1995;92(26):12260-4.
- 82 Farlow MR, Cyrus PA, Nadel A, Lahiri DK, Brashear A, Gulanski B. Metrifonate treatment of AD: influence of APOE genotype. *Neurology*. 1999;53(9):2010-6.
- 83 Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *Galantamine International-1 Study Group. BMJ (Clinical research ed)*. 2000;321(7274):1445-9.
- 84 Lancotot KL, Herrmann N, LouLou MM. Correlates of response to acetylcholinesterase inhibitor therapy in Alzheimer's disease. *Journal of psychiatry & neuroscience : JPN*. 2003;28(1):13-26.
- 85 Alhainen K, Partanen J, Reinikainen K, Laulumaa V, Soininen H, Airaksinen M, et al. Discrimination of tetrahydroaminoacridine responders by a single dose pharmac-EEG in patients with Alzheimer's disease. *Neuroscience letters*. 1991;127(1):113-6.
- 86 Alhainen K, Riekkinen PJ, Sr. Discrimination of Alzheimer patients responding to cholinesterase inhibitor therapy. *Acta neurologica Scandinavica Supplementum*. 1993;149:16-21.
- 87 Knott V, Mohr E, Mahoney C, Ilivitsky V. Pharmac-EEG test dose response predicts cholinesterase inhibitor treatment outcome in Alzheimer's disease. *Methods and findings in experimental and clinical pharmacology*. 2000;22(2):115-22.
- 88 Almkvist O, Jelic V, Amberla K, Hellstrom-Lindahl E, Meurling L, Nordberg A. Responder characteristics to a single oral dose of cholinesterase inhibitor: a double-blind placebo-controlled study with tacrine in Alzheimer patients. *Dementia and geriatric cognitive disorders*. 2001; doi:10.1159/000051232.
- 89 Bennys K, Rondouin G, Vergnes C, Touchon J. Diagnostic value of quantitative EEG in Alzheimer's disease. *Neurophysiologie clinique = Clinical neurophysiology*. 2001;31(3):153-60.
- 90 Schmidt MT, Kanda PA, Basile LF, da Silva Lopes HF, Baratho R, Demario JL, et al. Index of alpha/theta ratio of the electroencephalogram: a new marker for Alzheimer's disease. *Frontiers in aging neuroscience*. 2013; doi:10.3389/fnagi.2013.00060.
- 91 Jeong J. EEG dynamics in patients with Alzheimer's disease. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2004; doi:10.1016/j.clinph.2004.01.001.
- 92 Noetzi M, Eap CB. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clinical pharmacokinetics*. 2013;52(4):225-41.

