MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 3887-3899
DOI: 10.12659/MSM.896327

Received: 2015.10.18
Accepted: 2015.11.30
Published: 2015.12.14

Cognitive Results of CANTAB Tests and Their Change Due to the First Dose of Donepezil May Predict Treatment Efficacy in Alzheimer Disease

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Jurgita Kuzmickienė
ABCDEF Gintaras Kaubrys

Clinic of Neurology and Neurosurgery, Faculty of Medicine, Vilnius University; Center of Neurology, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania

Corresponding Author: Gintaras Kaubrys, e-mail: gintaras.kaubrys@santa.lt
Source of support: Departmental sources

Background: Ability to predict the efficacy of treatment in Alzheimer disease (AD) may be very useful in clinical practice. Cognitive predictors should be investigated alongside with the demographic, genetic, and other predictors of treatment efficacy. The aim of this study was to establish whether the baseline measures of CANTAB tests and their changes due to the first donepezil dose are able to predict the efficacy of treatment after 4 months of therapy. We also compared the predictive value of cognitive, clinical, and demographic predictors of treatment efficacy in AD.

Material/Methods: Seventy-two AD patients (62 treatment-naïve and 10 donepezil-treated) and 30 controls were enrolled in this prospective, randomized, rater-blinded, follow-up study. Treatment-naïve AD patients were randomized to 2 groups to take the first donepezil dose after the first or second CANTAB testing, separated by 4 hours. Follow-up Test 3 was performed 4 months after the initial assessment.

Results: The groups were similar in age, education, gender, Hachinski index, and depression. General Regression Models (GRM) have shown that cognitive changes after the first dose of donepezil in PAL (t-values for regression coefficients from 3.43 to 6.44), PRMd (t=4.33), SWM (t=5.85) test scores, and baseline results of PAL (t=2.57–2.86), PRM (t=3.08), and CRT (t=3.42) tests were significant predictors of long-term donepezil efficacy in AD ($p<0.05$).

Conclusions: The cognitive changes produced by the first donepezil dose in CANTAB PAL, PRM, and SWM test measures are able to predict the long-term efficacy of donepezil in AD. Baseline PAL, PRM, and CRT test results were significant predictors.

MeSH Keywords: Alzheimer Disease • Cholinesterase Inhibitors • Neuropsychological Tests • Paired-Associate Learning • Prognosis • Treatment Outcome

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/896327

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Background

Alzheimer disease (AD) is a chronic progressive neurodegenerative disorder accompanied by atrophy of the cerebral cortex and the deep structures in the brain, which are related to memory encoding (nucleus of Meynert and others). During its course AD also affects most of the other cognitive functions, such as language, visuospatial perception, constructive and ideational praxis, and executive functions. AD is the most common cause of dementia worldwide, accounting for two-thirds of dementia cases in adults over the age of 65 years [1–3]. Alzheimer disease affects approximately 5.3 million people in the United States alone, and the annual number of new cases of AD and other dementias is projected to double by 2050 [1–3]. Between 2000 and 2013, deaths attributed to AD increased by 71%, while those attributed to the number one cause of death (heart disease) decreased by 14% in the US [2]. It is established that the degeneration of cholinergic system in the brain and the deficiency of acetylcholine in synapses plays a major role in pathogenesis of AD cognitive symptoms [4–6]. Symptomatic therapies are the only treatments approved for AD at this time. Cholinesterase (ChE) inhibitors interfere with the breakdown of acetylcholine in the synaptic cleft and promote its accumulation in the synapse, thereby enhancing cholinergic neurotransmission and cognitive function in AD patients [7,8]. Donepezil is a centrally acting selective acetylcholinesterase inhibitor (AChEI), and is the most commonly used cholinergic medication in AD treatment. Pivotal clinical trials demonstrated that approximately 3 months of stable-dose donepezil treatment leads to the highest possible improvement, followed by a plateau lasting several months, and then a cognitive decline in line with the natural course of AD, but with the MMSE score remaining 2–3 point above those with placebo [7–10]. The long-term efficacy of DZP treatment and the magnitude of the treatment effects are highly variable among individual AD patients [11].

Significant efforts have been devoted to the identification of factors that may influence the response of AD to ChEIs, and can be used as predictors of treatment response in individual patients [12]. A wide variety of predictors have been investigated, ranging from genetic polymorphisms in AD risk genes, to neuroimaging predictors, demographic factors, clinical and cognitive features, and more. Many genetic polymorphisms were explored: Apolipoprotein E (ApoE) gene [13,14], CYP2D6 gene [15,16], Butyrylcholinesterase K Variant [17], ChAT gene [18], FOXO1 gene [19], and CHRNA7 gene encoding the α7 nicotinic acetylcholine receptor subunit [20] have been reported to be useful in predicting clinical response to donepezil. ApoE ε4 allele is by far the most studied genetic risk factor that may influence the response to donepezil. However, due to the complex network of genetic and environmental interactions, the search for reliable predictors of treatment response cannot be limited to a single special indicator (genetic or not), but should rather analyze a wide variety of predictors. Some researchers reported that APOE ε4/ε4 carriers are the worst responders to conventional treatments [13], while other reports showed that AD patients carrying at least 1 ε4 allele may respond better to donepezil therapy [14]. Other, non-genetic, predictors of the response of AD patients to donepezil include: measures of hippocampal volume [21], atrophy of the substantia innominata on MRI [22], and FDG-PET studies [23]. The effect of genetic and neuroimaging predictors of response to treatment is usually influenced by other genetic polymorphisms and demographic factors, such as age. Because of frequently contradictory reports on the same predictors, unsuccessful efforts to reproduce the results, and quite limited direct quantitative evidence about interaction of factors related to response, it might be suggested that a complex network of interacting factors of very different natures influences the response to AD treatment. It has been demonstrated that demographic and clinical factors, such as dementia severity and age of the AD patients, significantly influence the response to donepezil [24,25]. Some results indicated that lower cognitive ability and older age predicted better cognitive response but worse functional response [26]. Comorbidity also has been found to influence the response to ChEI treatment: improvement is more likely to occur only in AD patients without concomitant diseases and only for those who had demonstrated a positive response at 3 months of treatment [27]. Cognitive predictors of response to donepezil therapy in AD have also been studied, leading to conclusions that the domains of visual-spatial motor abilities and lexical-semantic functioning are the most reliable predictors of response to donepezil in AD [28]. Quite substantial information is available about the predictive value of baseline cognitive, clinical, and demographic characteristics in relation to long-term donepezil treatment efficacy. However, there has been very limited research focussed on establishing the value of the initial cognitive response to the first single dose of donepezil as a predictor of long-term efficacy. Therefore, we investigated whether the cognitive changes produced by the first single DPZ dose in Cambridge Neuropsychological Test Automated Battery (CANTAB) test measures and the baseline scores of the same test measures are able to predict the long-term efficacy of DPZ in AD. The CANTAB is a validated, automated, neuropsychological battery [29], with vast possibilities to assess various cognitive functions, such as attention, learning, memory, problem solving, and executive function [30]. We tried to determine this in a systematic way, and our analysis included not only cognitive data, but also a wide variety of clinical and demographic characteristics that could affect the efficacy of long-term administration of donepezil, such as age, gender, general dementia severity (MMSE), depression level (GDS), and vascular comorbidity (Hachinski Ischemic Index). Baseline cognitive measures of CANTAB tests and their changes due to the first single dose of donepezil were included in

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

our analysis as separate predictors. GRM models were built for various CANTAB battery tests and different measures provided by these tests. Computerized tests have many advantages over "paper and pencil" cognitive tests: their administration is simple, most computerized tests have multiple alternate versions, and they usually do not exhibit floor or ceiling effects. A computerized test battery may provide more objective results in the individual test than the classical "paper and pencil" tests [31–34]. While it was reported that the CANTAB battery, especially the Paired Associates Learning (PAL) test, may be very informative in early prognosis of the development of AD, there has been virtually no research using computerized tests with the aim of establishing a value of the first single-dose response (the change in cognition after the first dose of donepezil) for prediction of a long-term treatment response [35–38]. Having a reliable, simple, and inexpensive cognitive function-based tool for prediction of long-term responders and non-responders might aid in selecting the optimal medication or a combination of medications when more symptomatic treatment options become available. Personalization of the treatment of AD may be achieved through various approaches and using various methods from genomics and advanced neuroimaging to perform detailed, in-depth cognitive assessment [39]. Therefore, there is an increased need for simple and inexpensive diagnostic markers to reliably predict treatment response in AD. One promising strategy is to search for these markers in the same field in which AD exhibits its main symptoms – cognitive functions and their changes.

The objectives of this study were to establish the ability of the response to the first single dose of donepezil and the baseline scores, measured by means of the CANTAB battery tests, to predict the long-term efficacy of donepezil in AD and to compare the significance of CANTAB-based cognitive predictors with other clinical and demographic predictors of the long-term efficacy of donepezil in treatment of AD.

Material and Methods

Participants

This prospective, randomized, rater-blind follow-up study was performed at the Memory Disorders Unit of the Neurology Center, Vilnius University Hospital Santariskiu Klinikos, and 102 subjects were enrolled in the study. We recruited 62 consecutive, *de novo*-diagnosed, treatment-naïve AD patients: 10 patients taking the stable Donepezil dose of 10 mg/day for at least 3 months (Treatment group, TG), and 30 healthy controls (Control group, CG) matched according to age, education, and gender. All patients were diagnosed with AD in standard clinical practice settings by a neurologist not involved in this study. Patients started their treatment with donepezil when the medication was prescribed by the neurologist of the Memory Disorders Unit. After the day of the first assessment, the patients continued their treatment with donepezil as per usual clinical practice rules according to the treatment guidelines established by the Lithuanian Ministry of Health. No modifications to the patient treatment were made due to this research.

Study design

Informed consent was obtained, screening evaluation (MMSE, GDS, and others) performed, Inclusion/Exclusion criteria verified, and both assessments 1 and 2 (CANTAB test 1and 2) were performed on the same day (baseline day of the study), when the *de novo* patients took their first dose of donepezil. Newly diagnosed AD patients were randomly assigned to 1 of 2 research groups with the ratio 1: 1 using the sequence of random numbers 1 or 2, produced by the on-line Research Randomizer at http: //www.randomizer.org/. Thirty AD patients were assigned to the New AD+DPZ group and 32 patients were assigned to the New AD-DPZ group. Ten patients taking the stable dose of donepezil for no less than 3 months were enrolled into the Treated AD group; they took donepezil after Test 1 and Test 2 (i.e., there was no donepezil usage in this group between Test 1 and Test 2). Patients allocated to the New AD+DPZ group received a 5-mg donepezil tablet immediately after the CANTAB Test 1. Test 2 was performed 4 hours after the New AD+DPZ group patients took donepezil. The 4-hour period was selected because this is consistent with the pharmacokinetic profile of a single-dose oral administration of donepezil. The peak plasma concentration is observed at 4.1 hours [40]. Patients in the New AD-DPZ group underwent both Test 1 and Test 2 without taking donepezil between these tests (i.e., the New AD+DPZ group and the New AD-DPZ group completed the CANTAB Test 1 while treatment-naïve). CANTAB Test 2 was completed by New AD+DPZ group 4 hours after the first single 5 mg dose of donepezil. The New AD-DPZ group completed the CANTAB Test 2 after the same period of 4 hours after Test 1, but still being treatment-naïve. The New AD+DPZ, New AD-DPZ, and Treated AD groups did not differ by age, education, or gender, as was verified after the completion of the recruitment period. The neurologist performing CANTAB testing was blinded to the participant's assignment to a specific group. Global severity of dementia was assessed by the Mini-Mental State Examination (MMSE) [41], the Geriatric Depression Scale (GDS) was used for the assessment of depression [42], and the Hachinski Ischemic Index was used to evaluate vascular comorbidity [43]. MMSE, GDS, and Hachinski Ischemic Index were assessed and donepezil usage instructions were provided by another neurologist. Control group participants were recruited from a group of older adults with no medical history of AD or other dementia. No significant differences were found between the study groups according to education, age, and gender. For each group, the

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

study required 2 testing days. On Day 1 all participants completed the CANTAB Test 1 (Baseline assessment) and Test 2 at 4 hours post-baseline. Day 2 occurred 4 months later. The participants then completed the CANTAB Test 3. The results of CANTAB Test 3 were the primary endpoint of the study.

Approval by ethics committee

The study Protocol and Informed Consent Form were approved and permission was granted by the Vilnius Regional Biomedical Research Ethics Committee. Written Informed consent was obtained from all of the participants.

Inclusion/exclusion criteria and the schedule of assessments

Detailed and strict inclusion and exclusion criteria were applied for enrollment in the study. Inclusion and exclusion criteria for all study groups are shown in Table 1. The Inclusion /Exclusion criteria were created with the aim to include only the AD patients with typical sporadic late-onset mild and mild-to-moderate AD and to exclude all mixed dementia cases, AD patients with significant comorbidities, and atypical AD cases, because in the heterogeneous samples it is difficult to achieve unequivocal results due to confounding of AD by the different types of pathologic processes. Randomization to New AD+DPZ or New AD-DPZ groups were performed after enrollment, but before Test 1.

The Schedule of Assessments or the "Study Flow Chart" is provided in Table 2.

Neuropsychological assessment instruments

The Mini-Mental State Examination (MMSE) was used as a global measure of dementia severity. Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition Ltd., United Kingdom) tests were used as a primary investigative instrument. CANTAB is a computer-based test battery using a touch-tone screen and press-pad with 2 buttons. Results of the CANTAB Battery Test 1 were used as the Baseline. Test 2 was performed at the time of peak concentration of donepezil after taking the first donepezil dose. Test 3 was performed at the time of cognitive stabilization and the peak improvement of cognitive function when using 10 mg/day of Donepezil daily for at least for 3 months. During all CANTAB Battery testing sessions, indicated for brevity as Test 1, Test 2, and Test 3, the selection of separate CANTAB tests was performed (specified below). The order of these pre-selected tests remained the same in all 3 Testing sessions, but parallel versions were used where available.

All study participants were provided with the initial explanation, then they were asked to perform the following CANTAB tests in order, remaining identical during all 3 testing sessions:

- Choice reaction time (CRT) is a 2-stimuli visual discrimination and category achievement test. Choice Reaction Time (CRT) test measures speed of response in a simple 2-choice paradigm using a 2-button press pad [45].
- Stockings of Cambridge (SOC) is a task that assesses the subject's ability to engage in spatial problem solving. This test makes substantial demands on executive function, spatial planning, working memory, and motor control. SOC gives a measure of frontal lobe function [45].
- Paired associate learning (PAL) is a test for the assessment of simple visual pattern and visuospatial associative learning, which contains aspects of both a delayed response procedure and a conditional learning task. Paired Associates Learning (PAL) test assesses episodic visual recall memory and new learning [45]. PAL is sensitive to changes in medial temporal lobe functioning.
- Pattern recognition memory (PRM) immediate (PRMi) is a test of visual recognition memory in a 2-choice forced discrimination paradigm. Recognition task was performed immediately after a series of stimulus presentation.
- Spatial working memory (SWM) is a test for the assessment of the subject's ability to retain spatial information and to manipulate remembered items in working memory. SWM assesses working memory and strategy use and is a sensitive measure of working memory, as well as frontal lobe and executive dysfunction [45].
- Pattern Recognition Memory (PRM) delayed (PRMd) test assesses delayed visual recognition memory. PRM is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. Recognition task was performed in our study 30 minutes after the initial stimulus presentation.

Parallel versions of most CANTAB tests were used (where available) at Test 1 (Testing session 1), Test 2, and Test 3.

Statistical analysis

Comparisons between groups were performed using Student's t-test or analysis of variance (ANOVA) for continuous variables, where appropriate. Bonferroni post-hoc test was used for multiple comparisons. The chi-square test was used for categorical variables. Normal distribution of data was verified by means of the Shapiro-Wilk test. Levene's test was used to assess the homogeneity of variances across the participant groups. The statistical significance value was set at $p<0.05$.

A Comprehensive initial General Regression Model (GRM) (Whole GRM), which included the cognitive, demographic, and clinical variables, was built to evaluate the predictive value of variables under investigation. The backward removal method

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 1. Inclusion and exclusion criteria for all participant groups.

Inclusion criteria			
New AD+DPZ group (N=30)	**New AD-DPZ group (N=32)**	**Treated AD group (N=10)**	**Control group (N=30)**
The participant has sporadic late onset probable Alzheimer's disease diagnosed based on NINCDS-ADRDA criteria [44]			Normal cognition (MMSE score 27–30)
The participant has MMSE score from 18 to 23 inclusive			
The participant has a newly diagnosed AD and is treatment-naïve		The participant has been treated with the stable daily donepezil dose of 10 mg/day for 3 months or more prior to assessment	
The participant **has taken** the first DPZ dose between Test 1 and Test 2	The participant **has not taken** the first DPZ dose between Test 1 and Test 2	The participant **has not taken** the DPZ dose between Test 1 and Test 2	
The participant has had a CT or MRI less than 12 months before the assessment with results consistent with the diagnosis of probable AD			
The participant is aged at least 65 years			
The participant's sight and hearing are sufficient to complete the study assessment			
The participant is proficient in the Lithuanian language			
The participant has Hachinski Ischemic Index equal or less than 4			
The participant has Geriatric Depression Scale (GDS) score equal or less than 19			
The participant's Education is equal or more than 8 years			
Exclusion criteria			
The participant has been treated with any other medication for AD available on the market or any investigational product for AD			
The participant has evidence of any neurodegenerative disease, or other serious neurological disorders other than AD including, but not limited to Lewy body dementia, fronto-temporal dementia, Parkinson's disease, Huntington's disease, major stroke, major head trauma, cerebral neoplasia that are likely to affect cognition			
The participant has a history of seizures			
The participant has findings that fulfil the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherché et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for vascular dementia			
The participant has been tested positive for HBsAg, anti-HCV, or human immunodeficiency virus (HIV)			
The participant a DSM-IV-TR Axis I disorder other than AD including delirium, amnestic disorders, bipolar disorder, schizophrenia, psychosis, current major depressive episode			
The participant has CT or MRI evidence of space-occupying lesion, a stroke, or any clinically significant brain disease other than AD			
The participant has evidence of clinically significant comorbidities including but not limited to gastrointestinal, pulmonary, hepatic, renal, cardiovascular system, endocrine disease, or vitamin B12 deficiency which could influence cognition			
The participant has taken any other cognitive enhancing drug within 6 months prior to the first assessment			

was used to reduce the whole model to the simplest submodel, which still adequately accounted for the whole model. A detailed list of variables included in the initial (whole) GRM model and Backward Removal Criteria are specified in the Results section, where detailed descriptions of GRM models are provided.

Results

Demographic, clinical, and cognitive characteristics in participant groups

One-way ANOVA was used to assess the differences between the participant groups. Bonferroni post-hoc test was used for

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

Table 2. Flowchart of study specific assessments.

Visit	Visit 1		Visit 2
Assessment (Test)	Test 1	Test 2 (4 hours after the Test 1)	Test 3
Informed consent	+		
Demographics	+		
Medical history, AD history	+		
Vital signs	+	+	+
Inclusion/exclusion criteria	+		
NINCDS-ADRDA	+		
MMSE	+		+
GDS	+		+
Hachinski Index	+		
Education (years)	+		
Concomitant medications	+	+	+
Adverse events	+	+	+
CANTAB battery tests (CRT, SOC, PAL, PRM immediate, SWM, PRM delayed)	+ Test 1	+ Test 2	+ Test 3

Table 3. Demographic characteristics, dementia severity (MMSE scores), and depression level (GDS) in all participant groups.

Variable	New AD+DPZ group	New AD-DPZ group	Treated AD group	Control group	Statistical method
Number of subjects, N	30	32	10	30	
Age (years), Mean ±SD	77.30±5.11	77.03±5.28	76,50±4,43	76.43±6.36	One-way ANOVA F(3, 98)=0.148; p=0.931 ns
Gender, Women/Men, N	17/13	17/15	4/6	17/13	Pearson Chi-square=0.970; p=0.809 ns
Education (years), Mean ±SD	13.17±4.79	13.47±4.02	11,10±3,73	13.20±3.61	One-way ANOVA F(3, 98)=0.875; p=0.457 ns
Depression (GDS score), Mean ±SD	7.670±4.93	6.84±3.91	7,50±4,33	6.77±4.34	One-way ANOVA F(3, 98)=.286; p=0.835 ns
MMSE score, Mean ±SD	21.57±1.57	21.25±1.48	21,80±1,14	29.47±0.57	One-way ANOVA F(3, 98)=277.1; p<0.001 Bonferroni post-hoc: newAD+DPZ=newAD-DPZ=treatedAD (p=1.0); Control >newAD+DPZ; newAD-DPZ; treatedAD (p<0.001)

ns – not significant.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

multiple comparisons. Study groups did not differ significantly according to age (p=0.931), years of education (p=0.457), gender (p=0.809), depression level (GDS score, p=0.835), or Hachinski Ischemic Index (p=0.186). MMSE did not differ among all 3 AD groups, but was significantly higher in the Control group. Demographic characteristics, depression level based on GDS, and MMSE scores of all participant groups are provided in Table 3.

General Regression Model (GRM) for the assessment of the categorical and independent continuous predictors of the change from Test 1 to Test 3 in CANTAB Test Measures

A Comprehensive initial General Regression Model (GRM), which included the variables specified below, was built to evaluate predictive value of available variables. The backward removal method was used to search for the simplest submodel that adequately accounts for the dependent variable under investigation. Were defined the following Removal Criteria: p1, enter: 0.05; p2, remove: 0.05; F1, enter: 1; F2, remove: 1; Maximum steps: 100; Sweep delta: 1.E-7; Inverse delta: 1.E-12.

Difference of Scores on the CANTAB test measure at Test 3 and Test 1 was entered in a GRM as a dependent variable.

As Categorical predictors were entered in the GRM model: 1) The participant group; 2) Disease status: Alzheimer's patient or healthy control subject; 3) Gender; 4) Was the participant using donepezil before the Test 1?; 5) Did the participant take the dose of DPZ between Test 1 and Test 2?

Subsequent independent continuous predictors were entered in the GRM model: 1) Difference of scores on the CANTAB test measure at Test 2 and Test 1 was entered into a GRM as a dependent variable; 2) The Baseline Test 1 score of the CANTAB test measure; 3) Age (in years); 4) Education (in years); 5) Geriatric Depression Scale (GDS) score on Day 1 (when the Test 1 and Test 2 were performed); 6) Hachinski Ischemic Index (HII) on Day 1 (Baseline day); 7) MMSE score at Day 1 (Baseline score of global dementia severity).

Overall, 21 GRM models were built for different measures of 6 CANTAB tests (PRM in 2 modifications – immediate and delayed) used in this study. Thirteen GRM models stopped stepping during backward removal process, leaving from 3 to 5 predictors, which did not include the baseline result of CANTAB test or the cognitive change due to the first dose of donepezil. While results with the main predictors such as the age, gender, education, baseline dementia severity (MMSE score) and their interactions are interesting and worthy of further analysis, they are not in line with the main purpose of this study and are not analyzed further in this article. Two GRM models stopped stepping with no variable left at all, leaving only the Intercept. In this case further analysis of the predictive value of the corresponding test measure is meaningless. The results of 6 GRM models, which showed that corresponding CANTAB test measures or their change due to the first single dose of donepezil have a significant predictive value, are presented in Figure 1. For any of these models, the Regression coefficients and Pareto charts of t-values for the regression coefficients of significant predictors are presented along with the linear graphs of Means of CANTAB test scores for any of 4 participant groups in Test 1, Test 2, and Test 3 sessions.

While the cognitive change over a 4-month period from Test 1 to Test 3 represents donepezil treatment efficacy expressed only in 1 separate Test measure and most probably corresponds only to 1 cognitive domain or a part of it, we performed correlation analyses, trying to evaluate how improvements in 1 separate test measure correlate with the general measure of dementia severity. The results of correlation analysis are provided in Figure 2.

Discussion

Only 2 of 4 CANTAB PAL test measures, identified in our previous study as the tests that are able to detect significant cognitive change due to a single dose of donepezil, were found to be significant predictors of long-term donepezil treatment efficacy [46]. Both "PAL Mean trials to success" and "PAL Total trials (adjusted)" were able to detect significant cognitive change due to the first single dose and the long-term efficacy (4-month period) of donepezil in AD [46]. While "PAL Total errors (adjusted)" and "PAL Total errors (6 shapes, adjusted)" were able to detect significant cognitive change due to a single dose of donepezil, these 2 PAL measures did not significantly predict long-term efficacy of treatment [46]. On the other hand, "PAL Stages completed" detected significant differences of cognitive change due to a single dose of donepezil in groups with and without donepezil after the first test, but was not able to show the difference between the first and the second test results inside the New AD+DPZ group itself (insignificant within group effect) [46]. It seems that "PAL Stages completed" did not identify the change after taking the first single dose of donepezil in the New AD+DPZ group, but showed significant difference of change, mostly due to the worsening of the results, in the New AD-DPZ group. Despite that, "PAL Stages completed" was successful in predicting long-term treatment efficacy (Figure 1). According to the results of GRM models, "PAL Mean trials to success" and "PAL Stages completed" were similar in that both the cognitive change due to the first single dose of donepezil and the baseline results of these PAL test measures at Test 1 were significant predictors of long-term efficacy of donepezil, but for "PAL Total trials (adjusted)", the change, but not baseline score, was significantly predictive (Figure 1).

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

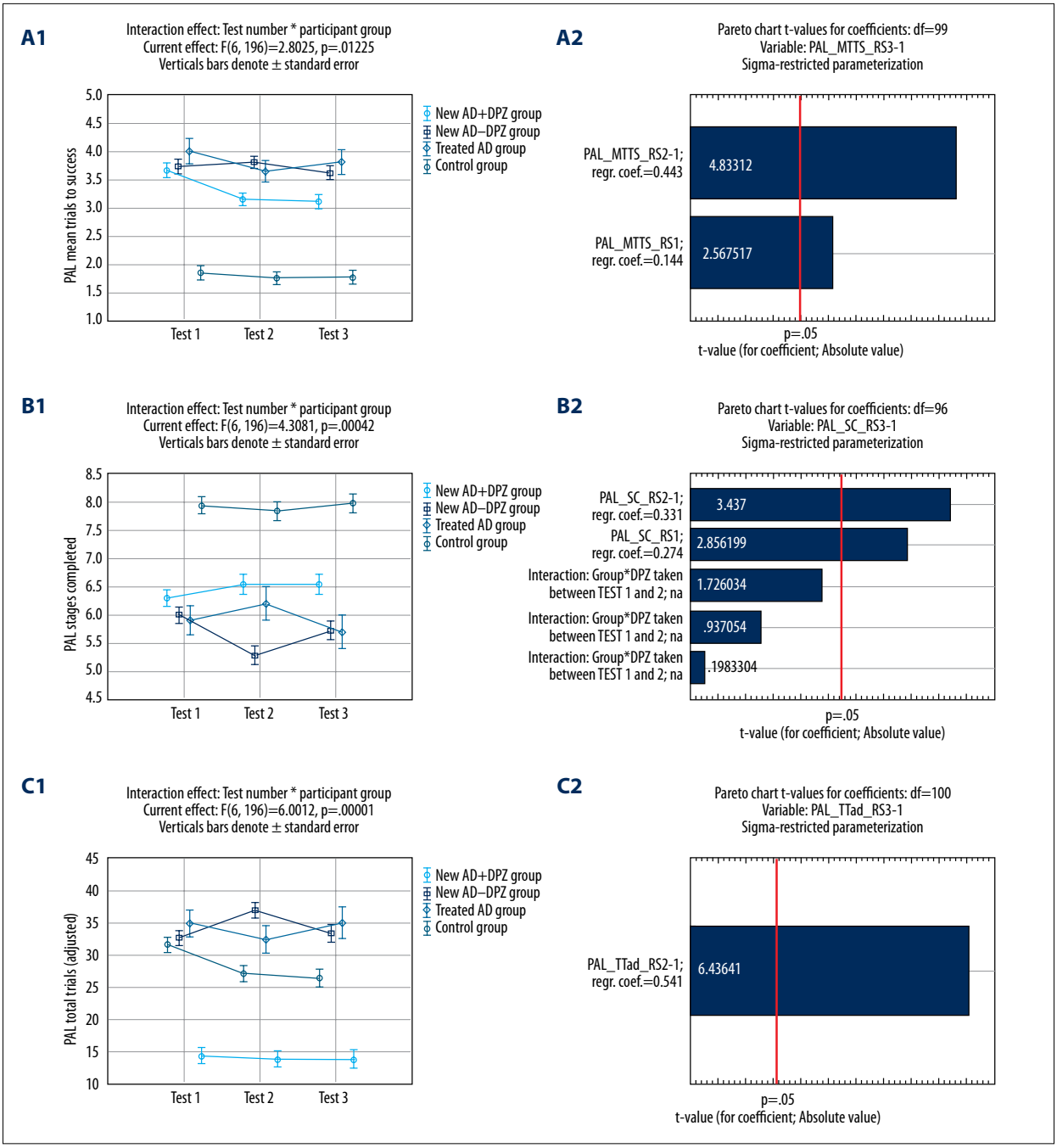

Figure 1 (A–C). Means, Regression coefficients, and Pareto charts for General Regression Models (backward removal method) of CANTAB test measures. (**A**) GRM Results for CANTAB PAL test "Mean Trials to Success" measure. (**A1**) Mean ±SD in participant groups at Test 1, Test 2, and Test 3. (**A2**) Pareto chart of t-values for coefficients with Regression coefficients provided in the chart. PAL_MTTS_RS2-1 is for the change of the PAL test "Mean Trials to Success" measure between Test 1 and Test 2. PAL_MTTS_RS1 is for PAL test "Mean Trials to Success" measure Baseline results in Test 1. (**B**) GRM Results for CANTAB PAL test "Stages completed" measure. (**B1**) Mean ±SD in participant groups at Test 1, Test 2, and Test 3. (**B2**) Pareto chart of t-values for coefficients with Regression coefficients provided in the chart. PAL_SC_RS2-1 is for the change of the PAL test "Stages completed" measure between Test 1 and Test 2. PAL_SC_RS1 is for PAL test "Stages completed" measure Baseline results in Test 1. (**C**) GRM Results for CANTAB PAL test "Total trials (adjusted)" measure. (**C1**) Mean ±SD in participant groups at Test 1, Test 2, and Test 3. (**C2**) Pareto chart of t-values for coefficients with Regression coefficients provided in the chart. PAL_TTad_RS2-1 is for the change of the PAL test "Total trials (adjusted)" measure between Test 1 and Test 2.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

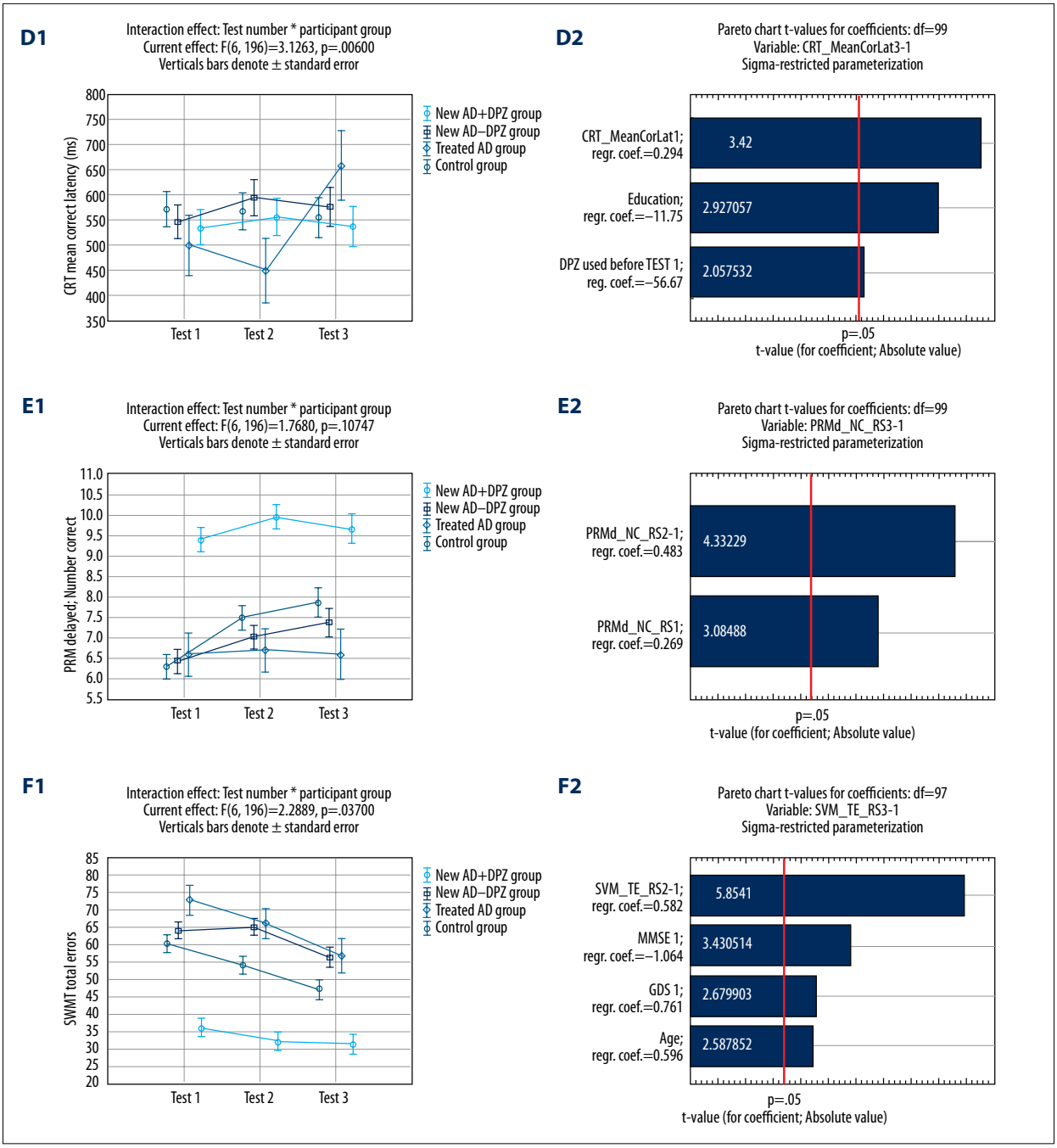

Figure 1 (D–F). Means, Regression coefficients, and Pareto charts for General Regression Models (backward removal method) of CANTAB test measures. (**D**) GRM Results for CANTAB CRT test "Mean correct latency (ms)" measure. (**D1**) Mean ±SD in participant groups at Test 1, Test 2, and Test 3. (**D2**) Pareto chart of t-values for coefficients with Regression coefficients provided in the chart. CRT_MeanCorLat1 is for CRT test "Mean correct latency (ms)" measure Baseline results in Test 1. (**E**) GRM Results for CANTAB PRM delayed test "Number correct" measure. (**E1**) Mean ±SD in participant groups at Test 1, Test 2, and Test 3. (**E2**) Pareto chart of t-values for coefficients with Regression coefficients provided in the chart. PRMd_NC_RS2-1 is for the change of the PRM delayed test "Number correct" measure between Test 1 and Test 2. PRMd_NC_RS1 is for PRM delayed test "Number correct" measure Baseline results in Test 1. (**F**) GRM Results for CANTAB SWM test "Total errors" measure. (**F1**) Mean ±SD in participant groups at Test 1, Test 2, and Test 3. (**F2**) Pareto chart of t-values for coefficients with Regression coefficients provided in the chart. SWM_TE_RS2-1 is for the change of the SWM test "Total errors" measure between Test 1 and Test 2.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

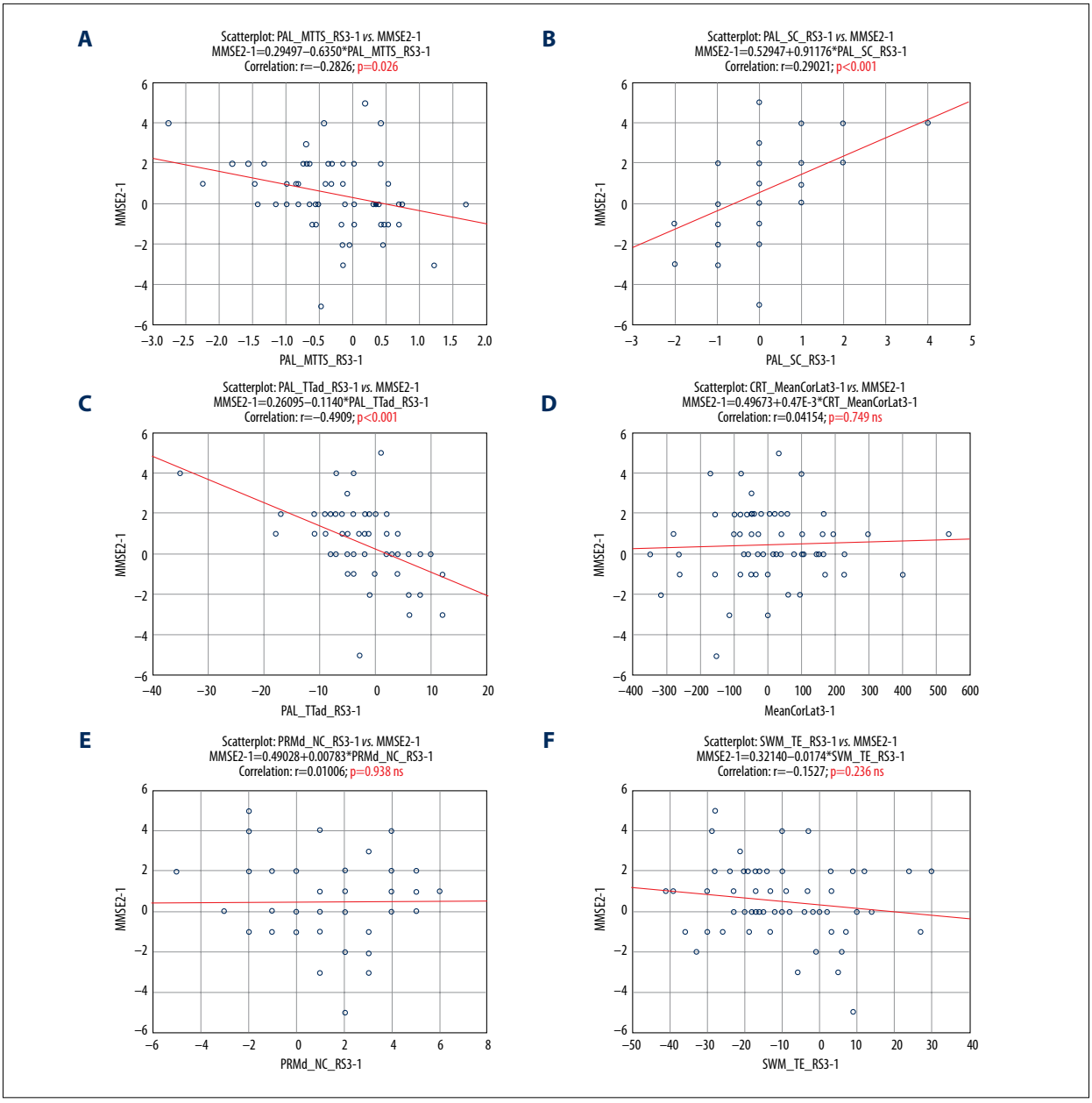

Figure 2. Correlations between the cognitive change in CANTAB Test Measures and MMSE over the 4-month treatment period. (**A**) Scatterplot: Correlation between the change of CANTAB PAL test "Mean Trials to Success" measure results from Test 1 at Baseline to Test 3 after 4 months of treatment with the MMSE test score change (MMSE2-1) from Baseline to Final assessment after 4 months. (**B**) Scatterplot: Correlation between the change of CANTAB PAL test "Stages completed" measure results from Test 1 at Baseline to Test 3 after 4 months of treatment with the MMSE test score change (MMSE2-1) from Baseline to Final assessment after 4 months. (**C**) Scatterplot: Correlation between the change of CANTAB PAL test "Total trials (adjusted)" measure results from Test 1 at Baseline to Test 3 after 4 months of treatment with the MMSE test score change (MMSE2-1) from Baseline to Final assessment after 4 months. (**D**) Scatterplot: Correlation between the change of CANTAB CRT test "Mean correct latency (ms)" measure results from Test 1 at Baseline to Test 3 after 4 months of treatment with the MMSE test score change (MMSE2-1) from Baseline to Final assessment after 4 months. (**E**) Scatterplot: Correlation between the change of CANTAB PRM delayed test "Number correct" measure results from Test 1 at Baseline to Test 3 after 4 months of treatment with the MMSE test score change (MMSE2-1) from Baseline to Final assessment after 4 months. (**F**) Scatterplot: Correlation between the change of CANTAB SWM test "Total errors" measure results from Test 1 at Baseline to Test 3 after 4 months of treatment with the MMSE test score change (MMSE2-1) from Baseline to Final assessment after 4 months.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

An even more interesting finding of this study is that while no CANTAB test except for PAL was able to detect significant cognitive change due to the first single dose of donepezil, at least 1 measure of 3 other CANTAB tests was a significant predictor of long-term donepezil treatment in AD. "CRT Mean correct latency", "PRM delayed; Number correct", and "SWM Total errors" were significant predictors of cognitive improvement after 4-month treatment. The nature of the predictive indicators of CRT, PRM delayed (PRMd), and the SWM was different. Although for PRMd, both the baseline results at Test 1 and the cognitive change between Test 1 and Test 2 were significant predictors of treatment efficacy, and no other significant predictors were left in GRM by Backward removal procedure, a very different predictive structure was found in CRT and SWM. For CRT, only the baseline result at Test 1 was a significant predictor of a cognitive nature, with Education and donepezil usage before Test 1 (treated AD group) being other significant predictors of long-term efficacy of treatment. The change of "CRT Mean correct latency" between Test 1 and Test 2 had no predictive value. For "SWM Total errors" only the change between Test 1 and Test 2 was a significant predictor for the long-term treatment efficacy of donepezil in AD, while baseline results of "SWM Total errors" at Test 1 had no predictive value. In addition, the "SWM Total errors" was the significant predictor with a group of other predictors: the global dementia severity at baseline (MMSE result in the Test 1), baseline depression level (GDS score at the time of Test 1), and Age (Figure 1F2).

Regarding the predictive value of CANTAB tests for MMSE results (as a global measure of dementia) after 4 months of treatment, significant correlation of change of MMSE over 4 months-long treatment period was found with the change between Test 1 and Test 3 (4 months of treatment) of "PAL Mean trials to success" (Figure 2A), "PAL Stages completed" (Figure 2B), and "PAL Total trials (adjusted)" (Figure 2C). The correlation was weak and statistically insignificant for "CRT Mean correct latency" (Figure 2D), "PRM delayed; Number correct" (Figure 2E), and "SWM Total errors" (Figure 2F). Therefore, the initial response to the first single dose of donepezil is a significant predictor of long-term response of MMSE only for PAL test measures. This kind of PAL advantage over other CANTAB tests regarding the successful prediction of global dementia severity (MMSE results) may be explained by the fact that PAL assesses episodic recall memory and new learning [45]; the decline in these cognitive processes is a major constituent of dementia syndrome in mild and mild-to-moderate AD. The explanation may be of another kind: PAL test seems to be more sensitive to cholinergic stimulation than other CANTAB battery tests [46], but cholinergic deficiency is a hallmark of AD. As PAL test results rapidly react to cholinergic changes in the brain, PAL retains its significance as a predictor from the first single dose to the more long-term treatment efficacy, even though cholinergic receptors become down-regulated over time due to repetitive cholinergic stimulation.

We wondered why in the PAL test the GRM backward removal method leaves no other significant predictors except for PAL-related indicators (contrary to other CANTAB tests). It may be hypothesized that the predictive ability of PAL-related indicators (baseline result and the change in response to a single dose of DPZ), which are so much stronger than other predictors like age, education, and gender, are not able to withstand the GRM backward removal stepping procedure according to the indicated removal criteria and are eliminated from the model as insignificant. As the final result is the best model of the simplest models, it does not show that another indicator has no influence at all, but only that this influence is relatively small in comparison with the influence of PAL-related predictors, especially the change from Test 1 to Test 2.

Another interesting problem is why there is a lack of correlation between CRT and MMSE. It might be related to the fact that the CRT is a measure of time and time is not evaluated in MMSE at all. If so, then CRT is an additional measure of efficacy not present in MMSE or ADAS-Cog. CRT, as SWM did not show significant changes due to a first single dose of DPZ, which might be related to the fact that they are not very rapidly reactive to the cholinergic status of the brain. It may be supposed that the improvement in cholinergic neurotransmission is able to improve the functioning in other neurotransmitter systems or mechanisms; therefore, CRT and SWM results showed significant improvement after 4 months of treatment, while still not correlating with MMSE. In addition, it should be noted that SWM measures reflect different cognitive domains underrepresented in the MMSE and ADAS-Cog. Working memory and strategy use, which are reflected by SWM, are frontal functions, while MMSE and ADAS have no constituents representing working memory or frontal function. In the case of SWM, the lack of correlation with MMSE may be merely a consequence of the different cognitive domains assessed by SWM and MMSE.

The change in PRMd is not significant after a single dose, but showed significant improvement after 4 months [46]. Again, this suggests that global improvement due to cholinergic treatment over longer periods of time is not associated with improvement in the cholinergic system alone, but may be related to a much wider systemic up-regulation of many brain systems, providing their own share in the overall improvement.

Our results suggest that for more comprehensive assessment of the global severity of dementia and for more accurate measurement of change in clinical trials, it would be desirable to use a computerized, reasonably short, but still comprehensive selection of psychometric tests as a mean for assessment of

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

end-points. This may allow achieving more exact and reliable evaluation of the efficacy of an investigational drug.

This study has some limitations and may have some valuable and significant extensions. Only typical amnestic AD patients were included in the study. Significant vascular comorbidities and depression were eliminated by Inclusion/Exclusion criteria. Recent evidence demonstrates that the severity of vascular factors correlates directly with the intensity of cognitive disturbances in AD [47]. Recent research in AD showed significant heterogeneity of AD itself [48,49]. This heterogeneity of AD is not reflected by the results of our study due to restrictive Inclusions/exclusion criteria. But in all pivotal large clinical trials for AD medications, Inclusion/Exclusion criteria are similarly strict. Homogeneity of typical AD and exclusion of comorbidities is beneficial for the confirmation of the efficacy of the investigational medication, but do not represent the situation in real clinical practice, in which many AD patients have significant vascular comorbidities, depression, and atypical variants of AD. Vascular dysfunction and insulin resistance associated with Type 2 diabetes may play a significant role in the pathogenic processes of Alzheimer disease [50]. We did not investigate the neuroimaging indicators of progression in this study. Neuroimaging indicators may be able to significantly strengthen the predictive value of the cognitive and demographic predictors, as has been shown in the case of quantitative MRI with the measurement of diffusion and perfusion alterations [51]. In this study we did not use electrophysiological indicators of AD progression, such as P300 and N200 Event-related Evoked Potentials (ERPs), which are the indicators of neurobiological nature and may provide additional and independent information regarding AD progression in comparison with the cognitive markers, which are behavioral indicators by their very nature [52].

Conclusions

The cognitive changes produced by the first single DPZ dose in CANTAB PAL, PRM, and SWM test measures are able to predict the long-term efficacy of DPZ in AD. Baseline CANTAB PAL, PRM, and CRT test results were predictive. The relationship between CANTAB cognitive predictors and other clinical and demographic predictors is markedly different among various CANTAB tests and relate to the cognitive domains reflected in the test.

Conflict of interest

The authors declare they have no conflicts of interest.

References:

1. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ: Epidemiology of dementias and Alzheimer's disease. Arch Med Res, 2012; 43: 600–8
2. Alzheimer's Association: 2015 Alzheimer's disease facts and figures. Alzheimers Dement, 2015; 11(3): 332–84
3. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM: Forecasting the global burden of Alzheimer's disease. Alzheimers Dement, 2007; 3: 186–91
4. Whitehouse PJ, Price DL, Struble RG et al: Alzheimer's disease and senile dementia: loss of neurons in the basal forebrain. Science, 1982; 215: 1237–39
5. Whitehouse PJ, Price DL, Clark AW et al: Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol, 1981; 10: 122–26
6. Hasselmo ME: The role of acetylcholine in learning and memory. Curr Opin Neurobiol, 2006; 16: 710–15
7. Rogers SL, Doody RS, Mohs RC, Friedhoff LT: Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med, 1998; 158: 1021–31
8. Rogers SL, Farlow MR, Doody RS et al: A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology, 1999; 50: 136–45
9. Rogers SL, Friedhoff LT: The efficacy and safety of donepezil in patients with Alzheimer's disease: Results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. Dementia, 1996; 7(6): 293–303
10. Farlow MR, Salloway S, Tariot PN et al: Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. Clin Ther, 2010; 32(7): 1234–51
11. Lee JH, Jeong SK, Kim BC et al: Donepezil across the spectrum of Alzheimer's disease: dose optimization and clinical relevance. Acta Neurol Scand, 2015; 131(5): 259–67
12. Miranda LF, Gomes KB, Silveira JN et al: Predictive factors of clinical response to cholinesterase inhibitors in mild and moderate Alzheimer's disease and mixed dementia: a one-year naturalistic study. J Alzheimers Dis, 2015; 45(2): 609–20
13. Cacabelos R: Pharmacogenomics in Alzheimer's disease. Methods Mol Biol, 2008; 448: 213–357
14. Bizzarro A, Marra C, Acciarri A et al: Apolipoprotein E epsilon4 allele differentiates the clinical response to donepezil in Alzheimer's disease. Dement Geriatr Cogn Disord, 2005; 20(4): 254–61
15. Noetzli M, Eap CB: Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. Clin Pharmacokinet, 2013; 52(4): 225–41
16. Seripa D, Bizzarro A, Pilotto A et al: Role of cytochrome P4502D6 functional polymorphisms in the efficacy of donepezil in patients with Alzheimer's disease. Pharmacogenet Genomics, 2011; 21(4): 225–30
17. Wang Z, Jiang Y, Wang X et al: Butyrylcholinesterase K variant and Alzheimer's disease risk: A meta-analysis. Med Sci Monit, 2015; 21: 1408–13
18. Lee KU, Lee JH, Lee DY et al: The effect of choline acetyltransferase genotype on donepezil treatment response in patients with Alzheimer's disease. Clin Psychopharmacol Neurosci, 2015; 13(2): 168–73
19. Paroni G, Seripa D, Fontana A et al: FOXO1 locus and acetylcholinesterase inhibitors in elderly patients with Alzheimer's disease. Clin Interv Aging, 2014; 9: 1783–91
20. Weng PH, Chen JH, Chen TF et al: CHRNA7 polymorphisms and response to cholinesterase inhibitors in Alzheimer's disease. PLoS One, 2013; 8(12): e84059
21. Csernansky JG, Wang L, Miller JP et al: Neuroanatomical predictors of response to donepezil therapy in patients with dementia. Arch Neurol, 2005; 62(11): 1718–22
22. Tanaka Y, Hanyu H, Sakurai H et al: Atrophy of the substantia innominata on magnetic resonance imaging predicts response to donepezil treatment in Alzheimer's disease patients. Dement Geriatr Cogn Disord, 2003; 16(3): 119–25

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

23. Shimada A, Hashimoto H, Kawabe J et al: Evaluation of therapeutic response to donepezil by positron emission tomography. Osaka City Med J, 2011; 57(1): 11–19
24. Miranda LF, Gomes KB, Silveira JN et al: Predictive factors of clinical response to cholinesterase inhibitors in mild and moderate Alzheimer's disease and mixed dementia: a one-year naturalistic study. J Alzheimers Dis, 2015; 45(2): 609–20
25. Sabbagh M, Cummings J, Christensen D et al: Evaluating the cognitive effects of donepezil 23 mg/d in moderate and severe Alzheimer's disease: analysis of effects of baseline features on treatment response. BMC Geriatr, 2013; 13: 56
26. Wattmo C, Wallin AK, Minthon L: Functional response to cholinesterase inhibitor therapy in a naturalistic Alzheimer's disease cohort. BMC Neurol, 2012; 12: 134
27. Raschetti R, Maggini M, Sorrentino GC et al: A cohort study of effectiveness of acetylcholinesterase inhibitors in Alzheimer's disease. Eur J Clin Pharmacol, 2005; 61(5–6): 361–68
28. Saumier D, Murtha S, Bergman H et al: Cognitive predictors of donepezil therapy response in Alzheimer disease. Dement Geriatr Cogn Disord, 2007; 24(1): 28–35
29. Goveas JS, Xie C, Ward BD et al: Recovery of hippocampal network connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. J Magn Reson Imaging, 2011; 34(4): 764–73
30. Robbins TW, James M, Owen AM et al: Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia, 1994; 5: 266–81
31. Collie A, Darekar A, Weissgerber G et al: Cognitive testing in early-phase clinical trials: development of a rapid computerized test battery and application in a simulated Phase I study. Contemp Clin Trials, 2007; 28: 391–400
32. Egerházi A, Berecz R, Bartók E, Degrell I: Automated Neuropsychological Test Battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. Prog Neuropsychopharmacol Biol Psychiatry, 2007; 31(3): 746–51
33. Pietrzak RH, Maruff P, Snyder PJ: Methodological improvements in quantifying cognitive change in clinical trials: an example with single-dose administration of donepezil. J Nutr Health Aging, 2009; 13(3): 268–73
34. Yurko-Mauro K, McCarthy D, Rom D et al: Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement, 2010; 6(6): 456–64
35. Fowler KS, Saling MM, Conway EL et al: Computerized neuropsychological test in the early detection of dementia: prospective findings. J Int Neuropsychol Soc, 1997; 3: 139–46
36. Fowler KS, Saling MM, Conway EL et al: Paired associate performance in the early detection of DAT. J Int Neuropsychol Soc, 2002; 8: 58–71
37. Gould RL, Brown RG, Owen AM et al: Functional neuroanatomy of successful Paired Associate Learning in Alzheimer's disease. Am J Psychiatry, 2005; 162: 2049–60
38. Jakala P, Sirvio J, Riekkinen M, Koivisto E, Kejonen K, Vanhanen M, et al. Guanfacine and clonidine, alpha 2-agonists, improve paired associates learning, but not delayed matching to sample, in humans. Neuropsychopharmacology, 1999; 20: 119–30
39. Stefano GB, Kream RM: Personalized- and one-medicine: Bioinformatics foundation in health and its economic feasibility. Med Sci Monit, 2015; 21: 201–4
40. Jann MW, Shirley KL, Small GW: Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. Clin Pharmacokinet, 2002; 41(10): 719–39
41. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975; 12: 189–98
42. Yesavage JA, Brink TL, Rose TL et al: Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res, 1982; 17: 37–49
43. Hachinski VC, Iliff LD, Zilhka E et al: Cerebral blood flow in dementia. Arch Neurol, 1975; 32: 632–37
44. McKhann G, Drachman D, Folstein M et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology, 1984; 34: 939–44
45. CANTABeclipse Test Administration Guide. Manual version 3.0.0. Cambridge Cognition Limited, 2006
46. Kuzmickienė J, Kaubrys G: Selective ability of some CANTAB battery test measures to detect cognitive response to a single dose of donepezil in Alzheimer disease. Med Sci Monit, 2015; 21: 2572–82
47. Pąchalska M, Bidzan L, Bidzan M, Góral-Półrola J: Vascular factors and cognitive dysfunction in Alzheimer disease. Med Sci Monit, 2015; 21: 3483–89
48. Stopford CL, Snowden JS, Thompson JC, Neary D: Variability in cognitive presentation of Alzheimer's disease. Cortex, 2008; 44: 185–95
49. Lam B, Masellis M, Freedman M et al: Clinical, imaging, and pathological heterogeneity of the Alzheimer's disease syndrome. Alzheimers Res Ther, 2013; 5(1): 1
50. Wang F, Guo X, Shen X et al: Vascular dysfunction associated with type 2 diabetes and Alzheimer's disease: A potential etiological linkage. Med Sci Monit Basic Res, 2014; 20: 118–29
51. Zimny A, Bladowska J, Neska M et al: Quantitative MR evaluation of atrophy, as well as perfusion and diffusion alterations within hippocampi in patients with Alzheimer's disease and mild cognitive impairment. Med Sci Monit, 2013; 19: 86–94
52. Vaitkevičius A, Kaubrys G, Audronytė E: Distinctive Effect of donepezil treatment on P300 and N200 subcomponents of auditory event-related evoked potentials in Alzheimer disease patients. Med Sci Monit, 2015; 21: 1920–27

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]