Alzheimer's & Dementia: Translational Research & Clinical Interventions 4 (2018) 11-18

Featured Article

Unmasking the benefits of donepezil via psychometrically precise identification of mild cognitive impairment: A secondary analysis of the ADCS vitamin E and donepezil in MCI study

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Abstract

Introduction: Criteria for mild cognitive impairment (MCI) used in many clinical trials are susceptible to "false-positive (FP)" errors that can be avoided by an actuarial psychometric approach.
Methods: Cluster analysis was applied to baseline neuropsychological test data from 756 MCI participants in the Alzheimer's Disease Cooperative Study donepezil trial. Treatment groups were compared after FP MCI cases were removed.
Results: Cluster analyses revealed three groups: "single-domain amnestic MCI" (31%), "multi-domain amnestic MCI" (39%), and "FP MCI" (30%). After removing FP MCI cases, the donepezil treatment group had a lower rate of progression to Alzheimer's disease and better performance on cognitive tests than the placebo/vitamin E group.
Discussion: Removal of FP MCI diagnoses unmasked beneficial effects of donepezil, despite a 30% reduction in sample size. MCI subject selection based on actuarial methods with comprehensive neuropsychological test data can result in more efficient clinical trials and improved ability to detect treatment effects.

Keywords: Mild cognitive impairment; MCI; Alzheimer's disease; Dementia; Donepezil; Treatment; Neuropsychology; Misdiagnosis; False positive; Cluster analysis

1. Introduction

Mild cognitive impairment (MCI) is a transitional step between normal cognition and dementia in those with Alzheimer's pathology and is therefore a stage of Alzheimer's disease (AD) where interventions may prove useful for preventing or delaying progression to dementia [1,2]. The conventional criteria for MCI, when implemented for multicenter studies such as clinical trials targeting MCI [3] and large-scale observational studies such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) [4], have included: subjective cognitive complaints, an impaired score on a single objective memory test, clinical judgment of cognitive decline but not dementia, and intact functional abilities [5,6]. Recent research suggests, however, that this diagnostic approach to MCI may be overinclusive. When we examined performance across a battery of cognitive tests by those with conventionally diagnosed MCI using an actuarial psychometric approach with normative data and cluster analysis techniques, we found that a large subgroup (e.g., >30% of the MCI cohort in ADNI) performed within normal limits, suggesting they may represent "false-positive (FP)" diagnostic errors [7,8]. This impression was

The authors have declared that no conflict of interest exists.

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https://doi.org/10.1016/j.trci.2017.11.001

strengthened when we found that the FP MCI subgroup in the ADNI cohort had normal CSF amyloid β and tau biomarkers [8], normal positron emission tomography amyloid burden [9], normal cortical thickness measures [10], a low rate of progression to AD [8], and a high rate of reversion to "cognitively normal" within a few years [8].

The susceptibility of the conventional diagnostic approach to false positive MCI classification has major implications for clinical trials that target this population. The inadvertent inclusion of substantial numbers of cognitively normal, "disease-free" individuals in MCI cohorts involved in such trials could greatly weaken or mask meaningful results. We examined this possibility in the present study by reexamining the results of the Alzheimer's Disease Cooperative Study (ADCS) vitamin E and donepezil trial in MCI [3], after using our actuarial psychometric approach to identify and remove subjects who were classified as FP MCI. The ADCS donepezil trial, conducted between March 1999 and January 2004, was a 36-month, multicenter, randomized, double-blind, placebo-controlled study of the effects of donepezil, vitamin E, or placebo on cognitive and functional decline in participants with amnestic MCI [3]. The original results showed no difference between groups in the rate of progression to AD after 36 months, although progression to AD was lower in the donepezil group relative to the placebo and vitamin E groups during the first 12 months of treatment, and that effect persisted for 24 months in the apolipoprotein E (*APOE*) ε4 carrier group [3]. We hypothesized that potential beneficial effects of donepezil were attenuated by the inclusion of subjects with a FP MCI diagnosis in the trial and that identification and removal of these subjects would strengthen the observed effect of donepezil on cognitive performance and progression to AD.

2. Methods

2.1. Participants and procedure

Details of subject selection, randomization, clinical evaluation, neuropsychological assessment, and other trial procedures have been published [3]. The ADCS donepezil trial randomized 769 participants who met the following diagnostic criteria for MCI: (1) a memory complaint corroborated by an informant, (2) abnormal memory function defined as scoring below the education-adjusted normative cutoff value on one paragraph from the Wechsler Memory Scale–Revised Logical Memory II subtest, (3) a Mini–Mental State Examination (MMSE) score of 24–30, (4) a global Clinical Dementia Rating score of 0.5, and (5) general cognition and functional ability sufficiently preserved so that a diagnosis of AD or dementia could not be made [3]. All subjects were clinically evaluated and underwent neuropsychological testing at baseline and every 6 months thereafter. The primary outcome was development of probable or possible AD according to NINCDS-ADRDA criteria, and neuropsychological performance was also assessed. Neuropsychological data from the baseline assessment were incomplete for 13 participants. Therefore, our current analyses were based on 756 participants. The original study was approved by the relevant institutional review boards, and written informed consent was obtained from all participants. Data used for the current report were reanalyzed with permission.

2.2. Statistical analyses

Following our previous methods [8], six baseline neuropsychological test scores were converted into age-adjusted z-scores based on regression coefficients derived from a group of healthy control participants ($n = 112$) and entered into a hierarchical cluster analysis using Ward's method. The six test scores included two measures of attention/executive function (Symbol-Digit Modalities and Backward Digit Span), two language measures (Boston Naming Test and Category Fluency), and two measures of memory (Alzheimer's Disease Assessment Scale–Cognitive subscale [ADAS-Cog] Immediate and Delayed Word Recall). Resulting cluster-derived groups were compared using analyses of variance (ANOVAs) and chi-square tests with Bonferroni corrected post hoc comparisons (three cluster-derived group comparisons; $P = .05/3 = .02$).

Replicating the analysis conducted in the original study [3], a Cox proportional hazards model controlling for baseline variables (age, MMSE score, and *APOE* genotype) was used to examine time to the development of AD. Hazard ratios compared risk of progression to AD in the donepezil versus placebo/vitamin E group (the placebo and vitamin E groups were collapsed because there were no significant differences between them on any measure examined). A chi-square test was used to compare overall rates of progression to AD over the course of the 3 years.

ANOVAs were used to compare the donepezil group to the placebo/vitamin E group on neuropsychological measures used in the original study [3] at the 12-, 24-, and 36-month time points. No correction for multiple comparisons was applied, consistent with the original analysis [3]. ANOVAs were also used to examine interactions between group and *APOE* ε4 status on cognitive measures. All analyses were performed twice: (1) with all MCI participants (i.e., "original MCI sample"; n = 756) and (2) with the MCI sample that remained after FP MCI participants were excluded (i.e., "new MCI sample"; n = 530).

3. Results

3.1. Characteristics of cluster-derived MCI groups

Cluster analysis identified three subgroups (Fig. 1). A "single-domain amnestic MCI" group (aMCI-sd; $n = 235$; 31%) performed in the impaired range (>1.5 standard deviations [SDs] below mean) only on memory measures. A "multidomain amnestic MCI" group (aMCI-md; $n = 295$; 39%) performed in the impaired range (>1.5 SDs below mean) on memory measures and had several mildly impaired scores (>1 SDs below mean) on measures of executive function