CAP—advancing the evaluation of preclinical Alzheimer disease treatments

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Abstract

If we are to find treatments to postpone, reduce the risk of, or completely prevent the clinical onset of Alzheimer disease (AD), we need faster methods to evaluate promising preclinical AD treatments, new ways to work together in support of common goals, and a determination to expedite the initiation and performance of preclinical AD trials. In this article, we note some of the current challenges, opportunities and emerging strategies in preclinical AD treatment. We describe the Collaboration for Alzheimer's Prevention (CAP)—a convening, harmonizing and consensus-building initiative to help stakeholders advance AD prevention research with rigour, care and maximal impact—and we demonstrate the impact of CAP on the goals and design of new preclinical AD trials.

Introduction

Alzheimer disease (AD) is the most common cause of dementia. This devastating illness takes a substantial toll on clinically affected individuals and family caregivers, and places an

overwhelming financial burden on society.[1] Investigational agents, repurposed medications, dietary supplements and lifestyle interventions may have the potential to reduce the risk of progressing to the clinical stages of AD, but they have not been adequately assessed to date. Therapeutic trials of investigational AD-modifying agents in clinically affected people have provided the necessary safety information to support their evaluation in at-risk individuals who have not yet developed cognitive impairment. To exert the maximum effect, some of these interventions may need to be started before the clinical onset of AD, when extensive neuropathology is already present. In addition, trials of investigational amyloid-modifying agents in cognitively unimpaired individuals who are at risk of AD might provide a better test of the amyloid hypothesis than trials in clinically affected people.[2–4] If a treatment could delay clinical onset by even a few years, enormous public health benefits would ensue.[5]

We use the term 'preclinical AD treatment' to refer to interventions that are initiated in cognitively unimpaired at-risk people, and are intended to postpone, reduce the risk of, or completely prevent the clinical onset of AD.[6] This term encompasses 'secondary prevention' therapies, which are initiated in cognitively unimpaired individuals who, on the basis of biomarker features and/or genetic background, are thought to be in the preclinical stages of AD, and 'primary prevention' therapies, which are introduced prior to the preclinical stages of AD and require much larger sample sizes and longer treatment durations to adequately test their effectiveness. The phrase preclinical AD treatment is intended to reflect the recent reconceptualization of AD as a progressive sequence of pathophysiological changes that includes preclinical, mild cognitive impairment (MCI) and dementia stages, as defined in the National Institute on Aging–Alzheimer's Association (NIA–AA) revised guidelines for diagnosis.[7–9] It also intends to address the view expressed publicly by FDA officials that a treatment would not be approved for the 'prevention of AD' unless it was shown to prevent the clinical onset of AD for the rest of a person's life, whereas demonstrating its efficacy in the treatment of preclinical AD—for example, to slow preclinical cognitive decline or reduce time to clinical onset—might be an acceptable alternative.[10–12]

The effort to conduct preclinical trials has faced a number of barriers. For instance, if progression to dementia is used as the primary end point, thousands of healthy research participants and very lengthy trial durations are required to evaluate putative preclinical AD treatments, unless the trial is enriched for participants in or nearing the preclinical stages of AD. A small number of large, expensive and lengthy prevention trials have evaluated approved hormonal therapies or dietary supplements in cognitively unimpaired older adults, but have failed to meet their primary end point of delaying progression to the clinical diagnosis of probable AD or all-cause dementia.[13–17] Other trials, targeting a variety of lifestyle factors, have reported beneficial effects on specific aspects of cognition and functional abilities,[18–20] and a multidomain intervention focused on diet, exercise, cognitive training and vascular risk monitoring resulted in improved cognitive performance.[21] While brain imaging and cerebrospinal fluid (CSF) biomarker analyses have been shown to detect and track preclinical AD in observational studies, for a biomarker to be accepted by regulatory agencies as a surrogate end point, it may be necessary to demonstrate that the effects of AD treatment on that biomarker are reasonably likely to predict a clinical benefit.[22] Furthermore, we need sensitive cognitive and other clinical outcomes that are acceptable to regulatory agencies.

In this article, we note emerging strategies for the accelerated evaluation of preclinical AD treatments, and some of the work that has set the stage for implementing these strategies. We describe a convening and consensus-building mechanism called the Collaboration for Alzheimer's Prevention (CAP), which is designed to help stakeholders advance AD prevention research in a coordinated, transparent and effective way, and we demonstrate the impact of CAP on the goals and design of six preclinical AD trials.

Emerging strategies

Observational studies have provided a conceptual framework for characterizing preclinical AD, and they continue to define biomarker and cognitive trajectories during this stage.[23–25] These studies have contributed to the development of standardized data acquisition methods and optimized data analysis tools, and have begun to provide sample size estimates for the evaluation of preclinical AD treatments in cognitively unimpaired individuals.

New strategies have been proposed in order to minimize the number of research participants, decrease the duration of trials, and maximize fiscal efficiency in the evaluation of promising preclinical AD treatments in therapeutic trials. First, trials can recruit research participants who, on the basis of genetic background and age[23,26–30] and/or preclinical AD biomarker features,[31] are at increased imminent risk of progression to the clinical stages of AD. Second, sensitive indicators of cognitive decline associated with preclinical AD are being developed and validated for potential qualification.[32–34] Third, studies could be designed to clarify the likelihood that the effects of a preclinical AD treatment on AD biomarkers will predict a clinical benefit (that is, are theragnostic). Fourth, registries to support enrolment in preclinical studies are being established.[35] Fifth, run-in and adaptive trial designs, which capitalize on longitudinally assessed potential trial participants or make treatment arm adjustments during the course of the trial, can be employed. Sixth, agreements to make de-identified preclinical AD trial data and biological samples publicly available on completion of the trial could help inform the design of future trials. Last, new methods of collaboration and communication to support each other's goals are being implemented.

The CAP initiative

AD prevention research requires stakeholders to work together in new ways, capitalize on complementary resources, exchange ideas and information, and develop a consensus on the scientific methods and regulatory guidelines that are needed to conduct preclinical AD trials. CAP was established by a variety of stakeholders to learn from and support each other's efforts, navigate uncharted territory, share problems and potential solutions, facilitate consensus building, harmonize trial outcomes for comparability, and advance the evaluation of putative preclinical AD treatments. The founding members of CAP include representatives from the Alzheimer's Disease Cooperative Study (ADCS), the Alzheimer's Prevention Initiative (API), the Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU), the Alzheimer's Association, the FDA and National Institute on Aging (NIA) at the NIH, and the Fidelity Biosciences Research Initiative.

CAP has reached out to other investigators to help harmonize procedures and measurements, develop cognitive and clinical end points, and facilitate comparisons. CAP processes allow these investigators to exchange information about their progress and plans, vet issues that they have addressed in their trials, and benefit from the feedback of the FDA, NIA and other stakeholder groups. CAP also helps investigators to guard against inadvertently impeding each other's efforts; for example, the API and DIAN-TU groups created a joint plan for site selection and coordination of enrolment for US-based trials in preclinical autosomal dominant AD (ADAD).

Themes being addressed by CAP include scientific, medical and operational issues, such as the necessary level of safety data needed before using a drug in preclinical trials, trial design, recruitment and retention, disclosure of genetic or biomarker risk to study participants, primary and secondary end points, assessment of functional decline, and data-sharing and sample-sharing mechanisms (Box 1). Where possible, CAP works to standardize procedures and harmonize data collection to facilitate future comparisons. The group seeks ways to share data and samples with the research community, and assists other investigators and organizations in the planning of their own prevention trials. Although CAP is primarily focused on drug trials, nonpharmacological preclinical AD trials would also benefit from CAP resources and discussions, particularly regarding recruitment, primary outcome, sample and data collection standardization, and data-sharing mechanisms. In addition, CAP continues to host symposia to share our thinking with the broader scientific community, and will hold open meetings engaging industry, academic, regulatory and other stakeholder groups.

The FDA and the European Medicines Association (EMA) have been highly supportive, available and flexible in considering various approaches to the evaluation of investigational preclinical AD treatments. In addition, the FDA issued draft guidance on the kinds of clinical end points that might qualify for use in early clinical and preclinical AD trials,[36] and it noted the importance of continued dialogue, collection of additional findings, and expert consensus in the field. Similarly, the EMA is in the process of updating their AD guidance, taking into consideration the most up to date scientific advances in understanding and treating the disease.[37]

New prevention trials

Six preclinical AD trials have been announced that have capitalized on the work of CAP and related resources (Tables 1 and 2). Four of the trials have already commenced, and the others will start soon. Most of the trials rely on a combination of public and private investments; pharmaceutical companies' investigational agents and regulatory know-how; philanthropic support; and academic investigators' observational study data, which are needed to inform preclinical AD trial design and sample size estimates (see Supplementary Box 1 online for a summary of the funding sources of the trials). Most of the trials also leverage the experience of investigators with regard to optimal acquisition and analysis of biomarker end points, and strategies to help clarify the predictive, prognostic and theragnostic value of biomarker end points.

ADCS A4 trial

The A4 (Anti-Amyloid Treatment in Asymptomatic Alzheimer's) trial[38,39] is based on the hypothesis that individuals with preclinical AD represent an ideal population in which to test amyloid-based therapeutics for the sporadic form of the disease. For this study—a collaboration between Eli Lilly and the NIA-funded ADCS—clinically normal individuals aged 65–85 years will be screened by amyloid PET for the presence of elevated fibrillar amyloid levels in the brain. With appropriate psychological assessment, education and counselling, these individuals will be informed of the results of the amyloid imaging. Those who have elevated amyloid levels will be invited to participate in the 3-year placebo-controlled trial of solanezumab,[40] administered by intravenous infusion every 4 weeks. The primary outcome measure is a composite of cognitive assessments that is sensitive to amyloid-mediated cognitive decline in normal older individuals.[32] Secondary outcome measures include an iPad-based computerized cognitive composite known as C3; participant-reported outcome instruments; assessment of activities of daily living; functional and volumetric MRI; amyloid imaging; and, in a subset of participants, CSF analysis and tau PET imaging.

Enrolment of 500 individuals each in the active and placebo groups will provide 80% power to demonstrate a 35% slowing of cognitive decline with the 3-year course of treatment. An additional cohort of 500 individuals without elevated brain amyloid will be followed up in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN) study, funded by the Alzheimer's Association, to allow further characterization of the impact of brain amyloid and other factors on cognition in clinically normal individuals. On the basis of recent draft guidelines from the FDA, as well as a regulatory review of the A4 programme, if the study demonstrates benefit on the primary cognitive outcome, solanezumab might qualify for accelerated approval for the treatment of preclinical AD. The A4 platform may be appropriate for the study of other potential anti-amyloid-β (Aβ) treatments, alone or in combination with potential anti-tau treatments.

API trials

API is a collaborative research programme that currently includes two potentially license-enabling preclinical AD treatment and biomarker development trials. The participants are cognitively unimpaired individuals who, on the basis of genetic background and age, are at particularly high risk of progression to clinical onset of ADAD (the API ADAD Trial[41]) or late-onset AD (the API Apolipoprotein E4 [APOE4] Trial). The programme also includes registries to support enrolment in preclinical AD trials (the Colombian API Registry and the web-based Alzheimer's Prevention Registry[42,43]), and biomarker and observational cohort studies,[44,45] the findings from which are intended to help accelerate the evaluation of preclinical AD treatments.[6,27] The API APOE4 Trial also includes a sub-study to evaluate the impact of *APOE* genetic risk disclosure in the era of AD prevention trials. Both of the API trials are funded by the NIH, philanthropy, and their respective industry partners Genentech (API ADAD Trial) and Novartis Pharma AG (API APOE4 Trial). The API ADAD Trial began enrolment the second-half of 2013; API APOE4 Trial initiation will depend on regulatory authority input and drug availability, but will occur no earlier than the end of 2015.

The API trials have benefited from CAP resources in a variety of ways. Both trials employ a novel, empirically derived measure of cognitive performance, and embed a variety of AD biomarkers in order to assess whether a treatment's effects on biomarker are reasonably likely to predict a clinical benefit. The procedures used to acquire brain images and fluid samples were guided by CAP-driven harmonization efforts, so as to allow comparison across programmes. In line with the aims of CAP, both API trials secured precedent-setting agreements with their respective industry partners to ensure that the trial data and biological samples are made available to the research community following the completion of each trial. CAP discussions bolstered the identification, selection and refinement of the composite cognitive test scores that serve as the primary end points in the API trials.[33,34]

DIAN-TU trials

The Dominantly Inherited Alzheimer Network (DIAN) was funded by the NIA in 2008, in part to enable future clinical trials.[46] This international, multicentre, observational study is now well established,[30,47] and has enrolled more than 400 longitudinally evaluated participants from families with a known causative mutation for ADAD in the *PSEN1*, *PSEN2* or *APP* gene.[23] The DIAN-TU was established with funding from the Alzheimer's Association, the DIAN Pharma Consortium[48] and the NIA to design and implement global trials in ADAD.

The DIAN-TU biomarker trial[49] is a multidrug, multitarget adaptive platform[29] to measure the effects of drugs via a comprehensive set of CAP-harmonized AD biomarkers (amyloid deposition, CSF Aβ and tau, MRI brain atrophy, functional connectivity MRI, diffusion tensor imaging, ^{18}F-FDG-PET, and tau PET). This 2-year study is a randomized, blinded, pooled-placebo-controlled multiarm trial of gantenerumab (an antibody targeting aggregated Aβ), solanezumab (an antibody targeting soluble Aβ), and future drugs as they become available, in asymptomatic to mildly symptomatic ADAD mutation carriers. Enrolment commenced in December 2012, and the trial has sites in Australia, Canada, France, Italy, Spain, the UK and the USA, with additional geographical regions being added.

The DIAN-TU Adaptive Prevention Trial (APT) will leverage the existing infrastructure of the DIAN-TU biomarker trial to perform a registration-enabling trial of prevention of cognitive decline. The goal will be to determine whether drugs with proven safety and biomarker efficacy can slow or prevent cognitive and clinical impairment due to AD. DIAN-TU APT will be a 4-year randomized, double-blind, placebo-controlled trial of as yet unspecified drug(s) in asymptomatic ADAD mutation carriers ($n = 133$ per arm). The study will utilize cognitive and clinical measures informed by and complementing CAP outcomes, which will be correlated with CAP-harmonized candidate surrogate AD biomarkers.

TOMMORROW study

Supported by Takeda and Zinfandel Pharmaceuticals, the TOMMORROW study[50,51] is a global, phase III, multicentre, double-blind, randomized, placebo-controlled clinical trial with two goals: first, to qualify a biomarker risk assignment algorithm (BRAA) for assigning 5-year risk of developing MCI due to AD, and second, to evaluate the efficacy of low-dose

pioglitazone to delay the onset of MCI due to AD in cognitively normal, high-risk individuals, as identified by the BRAA.[26,28,52]

The study will use *TOMM40* poly-T genotype, *APOE* genotype and age to distinguish individuals who may be at high or low risk of developing MCI due to AD in the next 5 years. The high-risk individuals will be randomly assigned to low-dose pioglitazone—a glucose-lowering PPAR-γ agonist approved for the treatment of type 2 diabetes—or placebo. A small group of low-risk individuals will receive placebo only. Dose selection was aided by the results of a memory task-dependent functional MRI study.

Tommorrow will enrol approximately 5,800 cognitively normal participants between the ages of 65 and 83 years, and will apply operationalized clinical criteria for MCI due to AD,[7] the primary end point event in the trial. The study treatment period will be determined by event (conversion) occurrence, and is anticipated to be approximately 5 years. Along with the Clinical Dementia Rating scale, the key assessments include 12 neuropsychological measures representing five key cognitive domains affected in early symptomatic AD. An independent expert committee will adjudicate the diagnosis of MCI due to AD. A key secondary outcome is cognitive decline, which is determined by change from baseline in the treatment groups on a composite score derived from the cognitive test battery. The study was designed with input from international experts in the field, and was finalized following discussions with both US and European Union regulatory authorities. Enrolment was initiated in August 2013.

Future objectives

The AD field will look for lessons learned from these and other trials, and will continue to move preclinical AD research forward in the most effective way. Investigators will seek to clarify the theragnostic value of different biomarker end points, and optimize other methods to evaluate preclinical AD treatments. Current and future trials will contribute important information to the field as trial data are shared with the scientific community. Other initiatives around the world, such as the European Prevention of Alzheimer's Dementia (EPAD) and the Canadian Pipeline for Alzheimer's Disease Therapeutics (cPAD), are in various stages of planning. CAP must engage and harmonize with these and other emerging efforts and, in so doing, continue to help accelerate the evaluation of putative preclinical AD treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Box 1

Illustrative examples of CAP progress

Development of trial outcomes

- Cognitive and clinical end points: study population, disease stage, composites or single measure

- Biomarkers: imaging versus biofluid, effective target engagement, criteria for surrogate biomarkers

Standardization of sample and data collection

- Clinical and cognitive data: computerized assessments, types and versions of tests, timing and frequency of collection

- Imaging: scanner type, resolution, scan duration, tracer, timing and frequency of collection

- Biofluids: sample types (cerebrospinal fluid, plasma), collection tubes, sample volume, assay type, timing and frequency of collection, collection methods (for example, lumbar puncture position, needle size)

Participant recruitment and retention

- Registry development: identification and recruitment of participants

- Risk disclosure: disclosure of genetic or biomarker risk to study participants

Data and sample sharing mechanisms

Abbreviation: CAP, Collaboration for Alzheimer's Prevention.

Table 1

New trials in patients with preclinical AD

Trial	Participants	Trial duration	Compound and administration	Targeted Aβ species	Primary outcomes	Biomarker measures	Interim analysis
ADCS A4	1,000 amyloid-positive adults aged 65–85 years (500 per treatment arm)	168 weeks	Solanezumab IV every 4 weeks	Monomer	ADCS Preclinical Alzheimer Cognitive Composite	Florbetapir PET, MRI, CSF analyses, tau PET	Blinded sample size re-estimation
API ADAD	200 ADAD mutation carriers (100 per treatment arm) and 100 kindred non-carriers (placebo arm) aged 30–60 years without MCI or dementia	260 weeks	Crenezumab SQ every 2 weeks	Monomeric, oligomeric and fibrillar	API ADAD composite cognitive test score	Florbetapir PET, ^{18}F-FDG-PET, MRI, CSF analyses	After last participant enrolled completes 104 weeks of treatment
API APOE4 *	Approximately 1,340 APOE*ε4 homozygotes aged 60–75 years without MCI or dementia	260 weeks	CAD106 IM quarterly, CNP50 (oral pill) daily	Multiple species	API composite cognitive test score, time to diagnosis of MCI or dementia due to AD	Florbetapir PET, ^{18}F-FDG-PET, MRI, CSF analyses, tau PET	TBD
DIAN-TU Biomarker	138 ADAD mutation carriers (52 per active treatment arm, 34 pooled placebo) and 77 kindred non-carriers (placebo arm) –15 years to +10 years from parental age of symptom onset	Up to 104 weeks	Solanezumab IV every 4 weeks, gantenerumab SQ every 4 weeks	Monomer (solanezumab), aggregated (gantenerumab)	CSF Aβ (solanezumab), PiB-PET (gantenerumab)	CSF and plasma analyses, florbetapir PET, PiB-PET, ^{18}F-FDG-PET, MRI, tau PET	Biomarker interim analyses based on adaptive design
DIAN-TU Adaptive Prevention Trial	266 ADAD mutation carriers (133 per treatment arm) and 133 kindred non-carriers (placebo arm) –15 years to +10 years from parental age of symptom onset	208 weeks	TBD from DIAN-TU Biomarker	TBD from DIAN-TU Biomarker	Cognitive measure or composite TBD	CSF and plasma analyses, florbetapir PET, PiB-PET, ^{18}F-FDG-PET, MRI, tau PET	TBD
TOMMORROW	4,622 APOE/TOMM40 high-risk (2311 per treatment arm) and 600 low-risk (placebo arm) individuals aged 65–83 years without MCI or dementia	260 weeks ‡	Pioglitazone daily	Not applicable	Time to diagnosis of MCI due to AD	MRI volumetrics in subset	Futility analysis once 50% (205/410) of the anticipated events have occurred

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*
Subject to regulatory authority approval.

†Estimate. Exact duration depends on the number of progression events. Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; ADAD, autosomal dominant AD; ADCS, Alzheimer's Disease Cooperative Study; API, Alzheimer's Prevention Initiative; APOE, apolipoprotein E; CSF, cerebrospinal fluid; DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; IM, intramuscularly; IV, intravenously; MCI, mild cognitive impairment; PiB, Pittsburgh compound B; SQ, subcutaneously; TBD, to be determined.

Table 2

Cognitive and clinical assessments in the new preclinical AD trials

Trial	Primary end points	Computerized assessments	Extended battery
ADCS A4	ADCS Preclinical Alzheimer Cognitive Composite: 16-item Free and Cued SRT Total Recall; WMS-R Logical Memory—Delayed Recall; WAIS-R Digit Symbol; MMSE—Total	Face–Name Associative Memory Exam; Object Pattern Separation Test; CogState One Card Learning and One-Back Tests, and Detection Task	Cognitive Function Inventory; ADCS Activities of Daily Living—Prevention Instrument; C-PATH Participant Reported Outcome; MAC-Q; Brief Resource Utilization Inventory; CDR
API ADAD	API ADAD Composite Cognitive Test Score: 10-word delayed recall; Ravens Progressive Matrices (set A); 15-item MiNT; Consortium to Establish a Registry for Alzheimer's Disease Constructional Praxis; MMSE—Orientation to Time	NA	RBANS; Free and Cued SRT; Subjective Memory Questionnaire; GDS; NPI; Functional Assessment Staging Tool; CDR
API APOE4	API Composite Cognitive Test Score: RBANS List Recall; RBANS Story Memory; RBANS Line Orientation; RBANS Digit Coding; Ravens Progressive Matrices—subset; MMSE—Orientation to Time and Orientation to Place Time to diagnosis of mild cognitive impairment or dementia due to AD	NA	RBANS; Everyday Cognition Scale; GDS; NPI-Q; CDR
DIAN-TU Biomarker	NA	ISLT (12 items)—Immediate and Delayed; CogState One Card Learning and One-Back Tests; Object Pattern Separation Test; CogState GMLT; CogState Identification Task	WMS-R Logical Memory—Delayed Recall; Trailmaking Test—Part A and B; Digit Span—Forward and Backward; Ravens Progressive Matrices (set A); WAIS-R Digit Symbol; MMSE; NPI-Q; FAQ; GDS; MAC-Q; CDR
DIAN-TU Adaptive Prevention Trial	Composite or single cognitive outcome from: ISLT (12 items) Delayed; CogState One Card Learning and One-Back Tests; WMS-R Logical Memory—Delayed Recall; CDR—Sum of Boxes	ISLT (12 items)—Immediate and Delayed; CogState One Card Learning and One-Back Tests; Object Pattern Separation Test; CogState GMLT; CogState Identification Task	WMS-R Logical Memory—Delayed Recall; Trailmaking Test—Part A and B; Digit Span—Forward and Backward; Ravens Progressive Matrices (set A); WAIS-R Digit Symbol; MMSE; NPI-Q; FAQ; GDS; MAC-Q; CDR
TOMMORROW	Time to progression to adjudicated clinical diagnosis of mild cognitive impairment due to AD	NA	California Verbal Learning Test (2nd edition); BVMT-R; Trailmaking Test—Part A and B; Digit Span—Forward and Backward; MiNT; Semantic Fluency (animals); Lexical/Phonemic Fluency; Clock Drawing Test; BVMT-R Figures (copy condition); CDR; MAC-Q; NPI; GDS

Abbreviations: AD, Alzheimer disease; ADAD, autosomal dominant AD; ADCS, Alzheimer's Disease Cooperative Study; API, Alzheimer's Prevention Initiative; BVMT-R, Brief Visuospatial Memory Test—Revised; CDR, Clinical Dementia Rating; DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; GDS, Geriatric Depression Scale; GMLT, Groton Maze Learning Test; ISLT, International Shopping List Task; MAC-Q, Memory Complaint Questionnaire; MiNT, Multilingual Naming Test; MMSE, Mini-Mental State Examination; NA, not applicable; NPI, Neuropsychiatric Inventory; NPI-Q, NPI Questionnaire; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SRT, Selective Reminding Task; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.