Cognitive Assessments in Drug Development in Dementia and MCI: Clinical Trial Landscape Review and Recommendations for Future Neurodegenerative studies

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Background

Dementia is a progressive neurological condition that impairs brain function and daily activities, causing significant cognitive decline across multiple domains. This includes memory, language, and executive control. In contrast, Mild Cognitive Impairment (MCI) presents observable cognitive changes that do not meet dementia criteria and do not interfere with daily functioning to a greater extent.

Neurodegenerative diseases present unique cognitive assessment challenges:

- Subtle cognitive changes in early stages are difficult to detect
- Lack of standardized guidance for assessing mild cognitive decline
- Uncertainty about appropriateness of existing assessment tools
- Variability in tool selection across clinical trials

Study Objective: To identify and categorize cognitive assessments used in neurodegenerative disease trials to improve detection of mild cognitive changes

Methods

A systematic search was conducted for trials that include cognitive assessment on ClinicalTrials.gov in January 2024
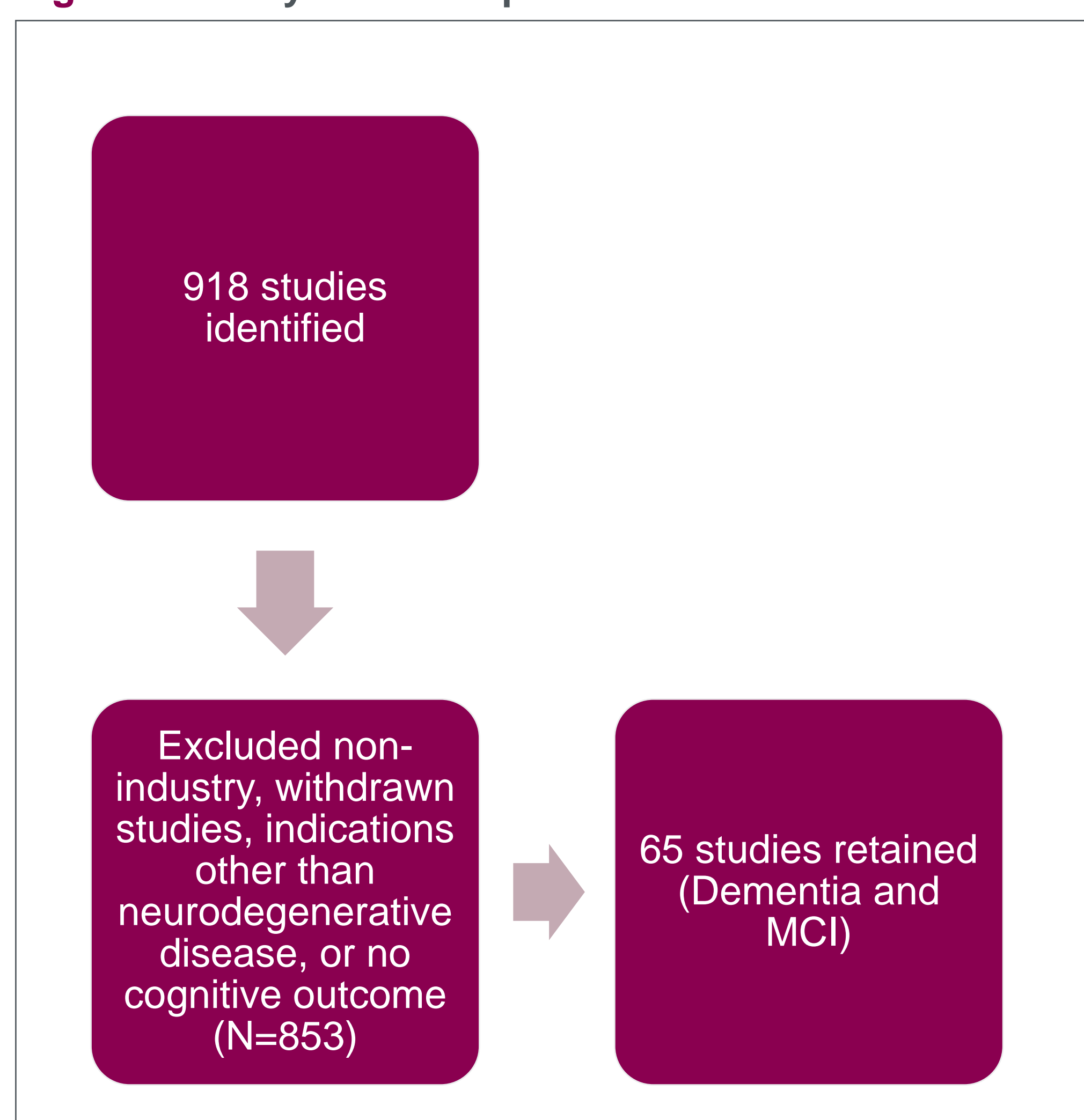
Inclusion criteria: Interventional studies; Phase II and III trials; Industry-sponsored. Exclusion criteria: Studies that did not include description of the cognitive assessment, withdrawn studies, duplicate studies, studies related to medical devices and food supplements.

Results for the following conditions were reviewed: Alzheimer's Disease, Mild Cognitive Impairment, Fronto-temporal dementia, Vascular dementia, and Lewy Body dementia.

Results

Sixty-five studies were identified (Figure 1). The majority were Phase 2 trials (N = 47), followed by Phase 3 (N = 12), Phase I/II and II/III (N = 3, each). Most studies evaluating cognitive function in individuals with dementia and MCI used cognitive batteries, with the most common being MMSE and ADAS-Cog (Figure 2 and 3), although a broader range of cognitive batteries was identified in MCI studies. Ad hoc cognitive tests to evaluate memory, attention, and processing speed developed to assess the impact of cognitive functions as well as rating scales (CDR-SOB) were more frequently conducted on studies focusing on individuals with MCI.

Figure 1. Study selection process Flow chart

918 studies identified

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Excluded non-industry, withdrawn studies, indications other than neurodegenerative disease, or no cognitive outcome (N=853)

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65 studies retained (Dementia and MCI)

The search retrieved the following assessments:
- cognitive batteries
- individual cognitive tasks
- questionnaires/rating scales to evaluate the impact of cognitive decline on daily activities

Figure 2. Cognitive assessment tools used in Dementia studies (N=41)

Assessment Tools by Cognitive Domain	Batteries	Verbal Learning / Fluency	Memory	Attention	Executive Functioning	Processing speed	Questionnaires
Mini-Mental State Examination (MMSE)	27	0	0	0	0	0	0
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)	32	0	0	0	0	0	0
Montreal Cognitive Assessment (MoCA)	1	0	0	0	0	0	0
Cambridge Neuropsychological Test Automated Battery (CANTAB)	1	0	0	0	0	0	0
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	1	0	0	0	0	0	0
Hopkins Verbal Learning Test	0	1	0	0	0	0	0
Category Fluency Test	0	1	0	0	0	0	0
Cube Drawing Test	0	1	0	0	0	0	0
Word Recognition Test	0	0	1	0	0	0	0
Wechsler Logical Memory Scale	0	0	1	0	0	0	0
Free and Cued Selective Reminding Test (FCSRT)	0	0	1	0	0	0	0
Digit Vigilance Test	0	0	0	1	0	0	0
Detection and Identification Tasks	0	0	0	1	0	0	0
Trail Making Test	0	0	0	0	1	0	0
Verbal Fluency Tasks	0	0	0	0	1	0	0
Clock Drawing Test	0	0	0	0	1	0	0
CLOX Executive Clock Drawing Task	0	0	0	0	1	0	0
Digit Symbol Substitution Test	0	0	0	0	0	1	0
Disease Cooperative Study-Clinician Global Impression of Change (ADCS-CGIC)	0	0	0	0	0	0	1
Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB)	0	0	0	0	0	0	1

Figure 3. Cognitive assessment tools used in MCI studies (N=24)

Assessment Tools by Cognitive Domain – MCI	Batteries	Verbal Learning Fluency	Memory	Attention	Executive Functions	Processing Speed	Questionnaires
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)	8	0	0	0	0	0	0
Mini-Mental State Examination (MMSE)	9	0	0	0	0	0	0
Cambridge Neuropsychological Test Automated Battery (CANTAB)	1	0	0	0	0	0	0
Neuropsychological Test Battery (NTB)	5	0	0	0	0	0	0
Montreal Cognitive Assessment (MoCA)	1	0	0	0	0	0	0
Preclinical Alzheimer's Cognitive Composite (PACC-ADCS)	2	0	0	0	0	0	0
Parkinson's Disease-Cognitive Rating Scale (PD-CRS)	1	0	0	0	0	0	0
CogState Brief Battery (CBB)	1	0	0	0	0	0	0
International Shopping List	0	1	0	0	0	0	0
Continuous Paired Associate Learning	0	1	0	0	0	0	0
Boston Naming Test	0	1	0	0	0	0	0
Category Fluency Test	0	1	0	0	0	0	0
Phonemic Fluency	0	1	0	0	0	0	0
Rey Auditory Verbal Learning Test (RAVLT)	0	1	0	0	0	0	0
Controlled Word Association Test (COWAT)	0	1	0	0	0	0	0
Category Fluency Test (CFT)	0	1	0	0	0	0	0
Wechsler Logical Memory Scale	0	0	3	0	0	0	0
Wechsler Memory Scale (WMS)	0	0	3	0	0	0	0
Free and Cued Selective Reminding Test (FCSRT)	0	0	3	0	0	0	0
Delayed Story Recall Test (DSR)	0	0	1	0	0	0	0
Rey-Osterrieth Complex Figure Test	0	0	1	0	0	0	0
Digit Span	0	0	2	0	0	0	0
15-Item Word List Delayed Recall	0	0	1	0	0	0	0
Identification Test	0	0	0	1	0	0	0
Trail Making Test A (TMT-A)	0	0	0	2	0	0	0
Visual Cognitive Assessment Test (VCAT)	0	0	0	2	0	0	0
One Back Test	0	0	0	0	1	0	0
Groton Maze Learning Test	0	0	0	0	1	0	0
Trail Making Test B (TMT-B)	0	0	0	0	1	0	0
Judgment of Line Orientation	0	0	0	0	1	0	0
Digit Symbol Substitution (DSS)	0	0	0	0	0	3	0
Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB)	0	0	0	0	0	0	10
Global Deterioration Scale (GDS)	0	0	0	0	0	0	1

Conclusions

- The prevalence of broad cognitive batteries across both conditions suggests a tendency to use general measures rather than more nuanced domain-specific assessments
- MMSE[1] and ADAS-Cog[2] are frequently used across both MCI and dementia despite the known differences in cognitive profiles
- In MCI, individual cognitive tasks are implemented more frequently; a broader spread among lesser-known tools (PACC-ADCS[3] or NTB[4]) emerged suggesting an exploratory approach to capture subtle cognitive changes

Recommendations

- Diversify assessment tools in MCI to capture subtle cognitive changes by using more sensitive tools such as MoCA[5]
- Expand the use of domain-specific measures in MCI, such as executive functions and processing speed
- Use validated tools for longitudinal tracking (e.g. PACC-ADCS, cognitive-functional composite (CFC[6])
- Update guidelines, such as the recently published FDA draft guidance for Alzheimer's disease[7], to provide further guidance on tool selection based on disease severity

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