The Cogstate Computerized Cognitive Test Battery as a Single Primary Endpoint in Preclinical Alzheimer's Disease

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Cogstate

Objectives

Unlike clinically defined stages of Alzheimer's disease, the preclinical stage recognizes no functional impairment and may be defined using biomarkers alone. Clinical trials do not require integrated cognition-function single primary, or separate cognition-function or cognition-global co-primary endpoints and can utilize single cognitive primaries. However, a long-duration, extending into the MCI stage and beyond, may be needed to demonstrate prevention of MCI and dementia. There is a need for meaningful outcomes that are valid and reliable across the healthy-MCI spectrum (Stages 1-3), cover cognitive domains known to worsen in preclinical disease and define MCI, and correlate with ATN biomarkers.

Methods

The Cogstate computerized test battery has been extensively validated in healthy elderly controls, MCI, and mild-moderate dementia. Further development and validation has established validity and reliability in the preclinical stage in the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing (AIBL), Mayo Clinic Study on Aging, Wisconsin Registry for Alzheimer's Prevention (WRAP) and AIBL Rates of Change (ROCS) sub-study.

Iterative Process of Development and Validation of Clinical Outcome Assessment (COA) Instruments According to FDA

1 Identify Context of Use (COU) and Concepts of Interest (COIs)

Context of Use: **Preclinical AD COAs must be suitable for Stages 1-3 at least. Trials will be long and patients entering a trial at Stage 1 or 2 may progress to Stage 3 or 4 in that time.**

FDA Draft Early AD Guidance

Stage 1: Patients with characteristic pathophysiologic changes of AD but no evidence of clinical impact.

Stage 2: Patients with characteristic pathophysiologic changes of AD and subtle detectable abnormalities on sensitive neuropsychological measures, but no functional impairment.

Stage 3: Patients with characteristic pathophysiologic changes of AD, subtle or more apparent detectable abnormalities on sensitive neuropsychological measures, and mild but detectable functional impairment.

Concepts of Interest: **COAs for cognition should cover multiple domains including memory and executive functions.**

Duke-Margolis Working Group (Richardson et al, 2018)

- Cognitive performance-based outcome (PerfO) assessments "may be designed to capture complex underlying cognitive processes that are not as obviously linked to real-world functioning (e.g. neuropsychological tests)"
- "type and/or level of evidence used to establish the content validity of a PerfO measure… indirectly linked to real-world functioning may be different from that… where the link to real-world functioning is more direct and translatable"

Examples

ADCS-PACC

Three key domains based on unpublished literature review of sensitivity to change in preclinical AD; "face validity as an indicator of AD-related clinical progression" (Donohue et al, 2014)

1. Episodic Memory
2. Executive Function
3. Orientation

EPAD / Literature Review *(Mortamais et al, 2017)*

- Episodic memory decline most salient cognitive function, correlating with high levels of amyloid deposition and hypoconnectivity across large-scale brain networks
- Prospective studies point to early decline in episodic and semantic memory processing as well as executive functions in the predementia period

2 Draft Instrument and Evaluate Content Validity

Domain	Test	Paradigm
Information processing speed	Detection (DET)	Simple Reaction Time
Visual attention	Identification (IDN)	Choice Reaction Time
Working memory	One Back (OBK)	N-back working memory
Visual learning	One Card Learning (OCL)	Pattern separation
Verbal learning	International Shopping List (ISLT)	Verbal list learning

Domain	Test	Paradigm
Verbal episodic memory	International Shopping List – Delayed Recall (ISRL)	Delayed recall
Visuospatial memory	Continuous Paired Associate Learning (CPAL)	Paired-associative learning
Executive function	Groton Maze (GMLT)	Hidden path-way maze learning
Episodic memory	Face Name Associative Memory (FNAME)	Paired-associative learning
Visual episodic memory	Behavioral Pattern Separation Object (BPSO)	Pattern separation

3 Cross-sectional Evaluation of Measurement Properties

Cross-sectional Measurement Properties

Association to biomarkers (Racine et al, 2016)

- Eight studies investigating AD relevant biomarker correlates of Cogstate measures have been published
  - ✓ A majority (7/8) found an association with amyloid
  - ✓ The eighth found an association with hippocampal volume and glucose metabolism

Correlation with traditional neuropsychological tests

- Construct validity with traditional measures of memory and executive function e.g. Auditory Verbal Learning, Stroop, Trail Making and Symbol Coding (e.g. Racine et al, 2016)

4 Longitudinal Evaluation of Measurement Properties/Interpretation Methods

Longitudinal Measurement Properties

Test-retest

- Adequate to excellent reliability evident in healthy adults, MCI and AD dementia (e.g. Lim et al, 2013)

Change over time

- Sensitivity to change in preclinical AD (e.g. Harrington et al, 2017; Baker et al, 2018)

Interpretation Methods

Clear association to function as measured by CDR-SB and clinical stages of MCI and AD dementia (e.g. Maruff et al, 2014)

Conclusions

Published data show the Cogstate tests to have a high degree of utility, strong content validity and good metric properties in the context of preclinical AD

5 Modify Instrument

Modification and Iterative Development

Several large databases exist to support further analyses of the Cogstate tests (e.g. A4, ADNI, AIBL, WHAP, DIAN)

- Statistical modeling to determine an optimal single outcome measure (e.g. weighting and combining items)
- Formal reassessment of measurement properties
- Assessment of interpretation methods
  - ✓ Anchor and distribution-based methods
    - Association to MCI diagnosis/clinical staging
    - Association to functional loss

Longitudinal Data Available to Support Further Development

Project Name	Population(s)	Cogstate Tests
A4	Preclinical AD	DET, IDN, OBK, OCL, FName, BPSO
ADNI2 Pilot Addendum	Cognitively Normal (CN), Mild Cognitive Impairment (MCI)	DET, IDN, OBK, OCL
ADNI3	CN, MCI	DET, IDN, OBK, OCL
AIBL	CN, MCI, AD	DET, IDN, OCL, CPAL
ROCS	CN, MCI, AD	DET, IDN, OCL, CPAL, ISLT, ISRL
WHAP	CN, MCI, AD	DET, IDN, OCL, CPAL
DIAN - TU	CN, MCI, AD	ISLT, GMLT, DET, IDN, OBK, OCL