Validity and reliability of a composite cognitive outcome measure for clinical trials in dementia with Lewy bodies

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Performance outcome (PerfO) assessments

PerfO Assessment

- A measurement based on standardized task(s) actively undertaken by a patient according to a set of instructions. A PerfO assessment may be administered by an appropriately trained individual or completed by the patient independently

- For example
    - Measures of gait speed (e.g., timed 25-foot walk test using a stopwatch or using sensors on ankles)
    - Measures of memory (e.g., word recall test)

- Important when assessing what a patient can do, not what they perceive they are able to do or report retrospectively they have done

Establishing Clinical Benefit

- A positive clinically meaningful effect of an intervention, i.e., a positive effect on how an individual feels, functions, or survives.
    - How long a patient lives
    - How a patient feels or functions in daily life

- When selecting your performance measure, consideration should be taken that the measure represents clinically meaningful concepts

- Utilize both qualitative and quantitative evidence to inform decision making

Best Glossary; ISPOR PerfO Good Practices Task Force; FDA Guidance

Disease Model: The Patient Experience

"I don't think myself that I am particularly memory deficient… I have to say… I have on the other hand become slow… I think a little slower… sometimes I forget… a key word which I am going to say… yes… when I talk to people and that… but it comes soon… in a minute or so I can fill in what was missing… that's what it's like still"
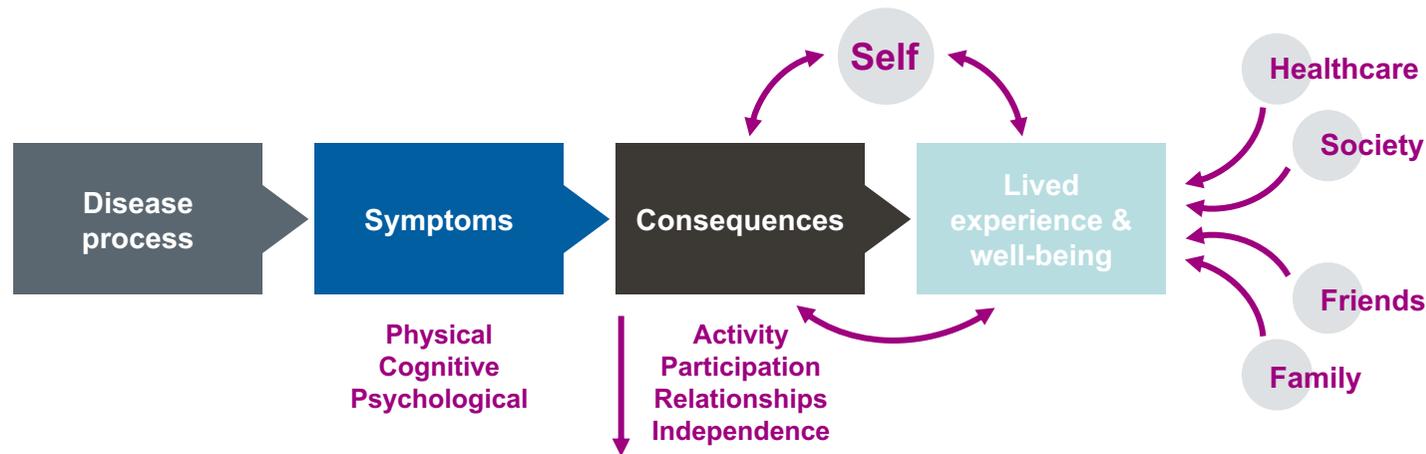

Figure 1 Experience of living with DLB. The ongoing disease-process is generating symptoms influencing function and behaviours. This leads to secondary consequences relating to sense of self and well-being, a relationship which is bidirectional. External processes can feed into this model, in turn influencing lived experience and sense of self.

Disease Model: Clinical Presentation

Table 1   Revised[1,2] criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB)

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) [123]iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

McKeith et al., Neurology 89, 2017

Cognitive Function

"persistent memory impairment may not necessarily occur in the early stages, but is usually evident with progression"

"Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent…"

"Fluctuating cognition with pronounced variations in attention and alertness"

AscenD-LB Study Design

- **Double-blind placebo-controlled parallel group study conducted at 22 centers in the US and 2 in the Netherlands**

- **Inclusion Criteria:**

  - Mild-to-moderate probable dementia with Lewy bodies (MMSE 16-28) by consensus criteria (McKeith et al, Neurology, 2017; 89:88–100)

  - Positive DaTscan™

    - *If DaTscan™ negative, could also be enrolled with history of polysomnography-confirmed REM sleep disorder (6 study participants so enrolled)*

  - Currently receiving cholinesterase inhibitor therapy (> 3 months and stable dose > 6 weeks).

- **Randomized 1:1 to 40 mg neflamapimod or matching-placebo capsules**

  - Dosing regimen based on weight: subjects weighing <80 kg received capsules twice-daily (BID) and those weighing ≥80 kg received capsules three-times-a-day (TID)
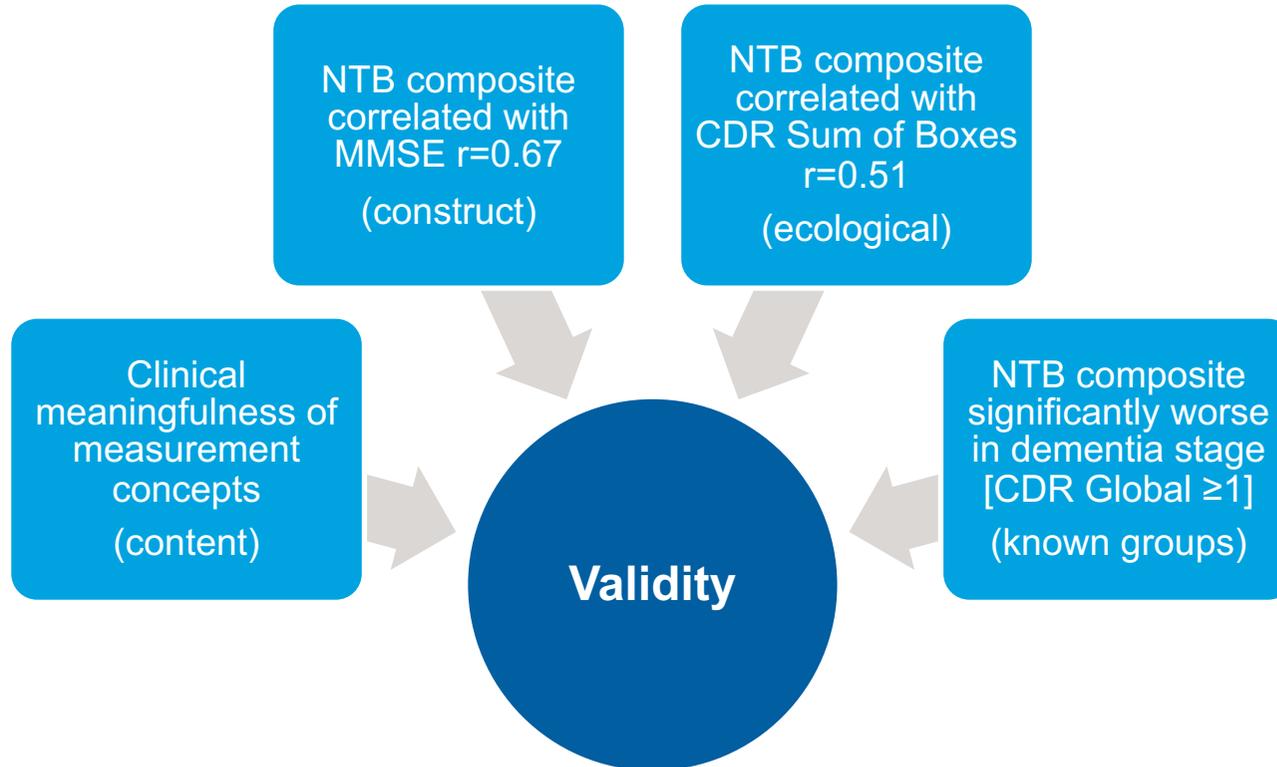
Neuropsychological Test Battery (NTB)

Task/Item	Primary Cognitive Concepts	Paradigm
Detection*	Psychomotor function	Simple Reaction Time
Identification*	Visual attention	Choice Reaction Time
One Card Learning*	Visual learning	Pattern Separation
One Back*	Working memory	N-back working memory
Letter Fluency*	Executive function	Verbal (phonemic) fluency
Category Fluency*	Executive function	Verbal (phonemic) fluency
International Shopping List	Verbal learning	Verbal list learning (immediate recall)
	Verbal memory	Verbal list learning (delayed recall)

*Composite z-score, in which individual tests are equally weighted

Demonstrated good reliability across screening and baseline assessments: **ICC=0.86**

Validity as a unitary construct with multiple sources of supporting evidence

NTB composite correlated with MMSE r=0.67

(construct)

NTB composite correlated with CDR Sum of Boxes r=0.51

(ecological)

Clinical meaningfulness of measurement concepts

(content)

NTB composite significantly worse in dementia stage [CDR Global ≥1]

(known groups)

Validity

Conclusions

- **Initial data suggest a composite comprised of assessments of reaction time, attention, visual learning, working memory, and verbal fluency may be a valid and reliable assessment of cognition in DLB clinical trials**

- **Attendees are recommended to also attend or access the following:**
    - ADVANCES IN PD AND LBD DRUG DEVELOPMENT 2, Sun, 20.03.2022, 11:35 AM - 01:35 PM, Room 114; EFFECTS ON COGNITION AND FUNCTION ASSESSED BY CDR-SB OF THE ORAL P38A KINASE INHIBITOR NEFLAMAPIMOD IN PATIENTS WITH MILD-TO-MODERATE DEMENTIA WITH LEWY BODIES (DLB)
    - Poster P637; DISEASE SPECIFIC GLOBAL CLINICAL RATING SCALES FOR LEWY-BODY DEMENTIA: LITERATURE REVIEW AND CONCEPT IDENTIFICATION BODIES