

Summary Statement for the ALS Cognitive-Frontotemporal Dementia (FTD) Subgroup

We have identified a group of cognitive and behavioral instruments which should be considered for ALS studies and that are appropriate for either self-administration or administration by health care providers who are not formally trained as psychologists or neuropsychologists. These instruments do not constitute definitive diagnostic assessments for behavioral and cognitive dysfunction, but rather serve as tools available for use by members of a typical ALS health care professional team (i.e., physicians, nurses, therapists, and social workers). These measures can assist in determining whether an individual demonstrates sufficient cognitive and/or behavioral dysfunction to warrant further attention and investigation. More detailed descriptions of each measure follow this summary, and we hope they will be useful to help design the best combination of tests to fit the research or clinical purpose desired.

Table 1 summarizes the recommended instruments, highlighting the importance of adequate breadth of assessment, to include four clinical categories: cognition, behavior, depression, and pseudobulbar affect (PBA). The table also includes the administration time, availability, and whether each measure is ALS-specific.

We recommend that studies of cognition and behavior in ALS should include, at a minimum, one measure of cognition and one of behavior, selected from those classified as “Core” in Table 1. One screening measure of depression should also be strongly considered when assessing cognition and behavior. Finally, many studies of cognition and behavior can be augmented by using a PBA measure. Table 1 denotes whether each measure constitutes a Core, Supplemental, or Exploratory common data element (CDE), based on the NINDS CDE classification, with some minor modifications to make the classifications more specifically applicable to the cognitive and behavioral realm:

1. Core: at least one measure should be administered in ALS studies of cognition and behavior
2. Supplemental: important for some types of studies of cognition and behavior
3. Exploratory: emerging or not yet validated but may have importance in the near future

Depending on the goals of a study, the importance of assessing all four domains may take priority over the CDE classification system when studying cognition and behavior.

The field of cognitive dysfunction in ALS is an evolving one, and some instruments described in this document are in the process of undergoing validation studies or additional development. A determination of whether to include an instrument in the Core, Supplemental, or Exploratory category was based not only on published validity studies, but on whether the instrument has been widely used by researchers in the ALS community; is in the process of being validated in the ALS population; or was considered to be particularly useful by an expert panel. Admittedly such recommendations are imperfect. We do not anticipate that these recommendations will be the final word in the field in a permanent sense, but rather we anticipate that these categories may change over time, and that instruments may be added to or removed from this list as additional data becomes available. Recently published revised diagnostic criteria for frontotemporal syndromes in ALS⁽¹⁾, may impact the development or revision of certain measures.

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Table 1 List of Recommended Measures: ALS Cognitive-FTD CDE's

Name	CDE Classification	Construct Measured	ALS Specific (Yes/No)	Availability	Administration Time
Abrahams Written Verbal Fluency*	Core	Cognition	Yes	Author	5 minutes
ALS Cognitive Behavioral Screen* (ALS-CBS)	Core	Cognition, Behavior	Yes	Author	5 minutes
Edinburgh Cognitive and Behavioural ALS Screen* (ECAS)	Core	Cognition, Behavior	Yes	Author	15–20 minutes
Frontal Behavior Inventory (FBI)	Supplemental	Behavior	No	Author	15–25 Minutes
UCSF Screen Battery	Supplemental	Cognition, Behavior, Depression and PBA	Yes	Author	45 Minutes
ALS Depression Inventory (ADI-12)	Supplemental	Depression	Yes	Public Domain	5 Minutes
Amyotrophic Lateral Sclerosis-Frontotemporal Dementia Questionnaire (ALS-FTD-Q)	Supplemental	Behavior	Yes	Copyrighted	10 minutes
Beck Depression Inventory-II (BDI-II)	Supplemental	Depression	No	Copyrighted	6 Minutes
Cambridge Behavioral Inventory-Revised (CBI-R)	Supplemental	Behavior	No	Author	15 Minutes
Center for Neurologic Study-Lability Scale (CNS-LS)	Supplemental	PBA	No	Author	5 Minutes

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Name	CDE Classification	Construct Measured	ALS Specific (Yes/No)	Availability	Administration Time
Emotional Lability Questionnaire (ELQ)	Supplemental	PBA	Yes	Author	10–15 Minutes
Frontal Behavior Inventory-ALS Version (FBI- ALS)	Supplemental	Behavior	Yes	Author	15–25 Minutes
Frontal Behavior Inventory Modified by Heidler-Gary (FBI-Mod)	Supplemental	Behavior	No	Public Domain	10 Minutes
Frontal Systems Behavior Scale (FrSBe)	Supplemental	Behavior	No	Copyrighted	10 Minutes
Hospital Anxiety and Depression Scale (HADS)	Supplemental	Depression	No	Copyrighted	5 Minutes
Motor Neuron Disease Behavioural Instrument (MiND-B)	Supplemental	Behavior	Yes	Author	5 Minutes
Neuropsychiatric Inventory (NPI)	Supplemental	Behavior	No	Author	10–30 Minutes
Neuropsychiatric Inventory-Questionnaire (NPI-Q)	Supplemental	Behavior	No	Author	10 Minutes
Penn State Screen of Frontal and Temporal Dysfunction Syndromes (PSSFTS)	Supplemental	Cognition, Behavior	Yes	Author-Copyrighted	20 Minutes

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Name	CDE Classification	Construct Measured	ALS Specific (Yes/No)	Availability	Administration Time
Geriatric Depression Scale (GDS)	Exploratory	Depression	No	Public Domain	5 Minutes
Hamilton Depression Rating Scale (HAM-D)	Exploratory	Depression	No	Author	20–30 Minutes
Neuropsychiatric Inventory-Clinician Version (NPI-C)	Exploratory	Behavior	No	Author	10–45 Minutes

*One of these three Core cognitive instruments: Abrahams Written Verbal Fluency, ALS Cognitive Behavioral Screen, or Edinburgh Cognitive and Behavioural ALS Screen should be used based on study requirements.

Overview of Test Types

Combined Cognitive and Behavioral Screening Exams

The Abrahams Written Verbal Fluency test, ALS Cognitive Behavioral Screen (ALS-CBS), Edinburgh Cognitive and Behavioural ALS Screen (ECAS) involve combinations of tests to create 5-, 10-, and 20-minute screening measures, respectively. Combination tests are perhaps the most useful to provide a more global assessment when time is limited. The Abrahams Written Verbal Fluency test is a simple phonemic fluency test which requires less than 5 minutes to complete. ALS-CBS includes 8 cognitive tasks and a 15-item caregiver-rated behavioral questionnaire. It takes about 5 minutes to perform, is free, and is well validated. The ALS-CBS is selected when brevity is needed without sacrificing accuracy. The ECAS is a brief (15–20 minute) assessment of specific cognitive and behavioral changes. Although the ECAS takes longer to administer than the ALS-CBS and scoring requires some calculations beyond simple addition to derive scores, the ECAS provides greater breadth of cognitive data and helps exclude subjects with alternative neurodegenerative conditions by assessing non-ALS domains like memory and visuospatial functions.

Cognitive measure

The only exclusively cognitive test discussed is the Abrahams Written Verbal Fluency test. This is a well-validated test which compensates for deficits in speaking and/or writing speed. It is very sensitive to cognitive impairment, specifically executive dysfunction, which is common in ALS. This core measure may be preferred in studies where subjects are monolingual English speakers, because non-native speakers will score lower despite strong fluency or for studies where language or retrieval is of particular interest.

Behavioral measures

Two newly added behavioral tests are included in the revised 2017 ALS Cognitive CDE. The Motor Neuron Disease Behavioural (MiND-B) is a 9-item assessment that evaluates neuropsychiatric symptoms and rates the severity of behavioural changes on a Likert scale (0–4) in patients with ALS. The Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire (ALS-FTD-Q) is a screening tool used to detect the behavioural variant of frontotemporal dementia (bvFTD) and mild behavioral disturbances in ALS⁽²⁾. The 25-item questionnaire is an observer report scale aimed at the proxy (partner, family member, or friend) of a

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patient with ALS and includes 3 cognitive items: memory, concentration, and orientation in time.

Additional behavioral tests include, the Frontal Behavioral Inventory (FBI), the Neuropsychiatric Inventory (NPI), the Frontal Systems Behavior Scale (FrSBe), and the Cambridge Behavioral Inventory - Revised. There are several versions of the FBI and NPI; the advantages and disadvantages of each version are reviewed and discussed in detail in the following pages. With further validation, the FBI-ALS is adjusted to avoid the confounders associated with symptoms of ALS versus FTD.

The NPI-C is a promising new measure allowing greater flexibility to the clinician to record and review clinical observation to document behavior change, which is particularly useful when caregiver-reporting lacks validity. The FrSBe is well validated measure that has been used in ALS studies. It takes 10 minutes to administer and additional time for scoring. The FrSBe is copyrighted, requiring purchase from the publisher. The Cambridge Behavioral Inventory - Revised is a well-validated and time-efficient care-giver completed measure. The CBI-R collapses the MND and FTD symptoms into one score. This feature makes it useful to capture both syndromes, but more difficult to disentangle them. The MiND-B is quite quick and easy and may be an effective means of rapidly assessing behavior.

Depression and Pseudobulbar Affect

It is important to assess depression in ALS to ensure that it is not the cause of cognitive or behavioral dysfunction, or a confounding variable. Depression in the clinically significant range of Major Depressive Disorder is not pervasive in ALS populations, but nonetheless needs to be excluded. We reviewed the Beck Depression Inventory-II (BDI-II), the Geriatric Depression Scale (GDS), the Hamilton Depression Scale (HAM-D), the Hospital Anxiety and Depression Scale (HADS), and the ALS Depression Inventory (ADI-12). Each of these tests has pros and cons of length, time, and sensitivity. Depending on the situation, all could potentially be used in ALS studies, although the GDS has been validated on an older population and hence may not be suitable for younger ALS patients.

It is important to assess Pseudobulbar Affect (PBA) in ALS due to the availability of treatments (Elavil and Nuedexta) and its potentially confounding affect on cognition and behavior. Two measures are discussed: the Center for Neurologic Study (CNS-LS) and the Emotional Lability Questionnaire (ELQ). Both scales are well validated, however, the ELQ was developed for ALS, allows ratings by care-givers, has a short version if no symptoms are present and a longer version if symptoms are present, which perhaps makes the ELQ more sensitive and easier to use in clinic.

More Extensive Assessments

There are many other instruments available for extensive assessment of cognitive and behavioral function. These are generally chosen and administered by individuals with specialized neuropsychological training beyond that found in most ALS multidisciplinary clinics, and are therefore not within the domain of testing recommended by this subgroup. A particular shortcoming of these recommendations is that many lack language-specific instruments, yet the newly added ECAS contains language assessment. A summary article⁽³⁾ is recommended as a source for a description of many of these measures, plus additional measures. The article addresses comprehensive neuropsychological assessment in ALS patients across domains including but not limited to language, executive functioning, memory, visuospatial functioning, and intelligence.

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