Clinical Outcome Assessments for Clinical Trials in Rare Tauopathies

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Objectives

Tauopathies may be classified by neuropathological phenotype. Clinically, PSP, CBD, MSA, and DLB may be grouped as atypical parkinsonism; FTLD distinguished by behavioral, language and MND variants; and AGD, PART and ARTAG hard to distinguish from AD. Thus, overlapping measurement concepts exist for clinical outcome assessments (COAs).

Methods

A literature review was conducted in PubMed (since 2010, English language, humans) using terms for rare tauopathies and COAs. Abstracts were included if describing use of COA and excluded if case studies or not including at least one rare tauopathy. A parallel review was conducted in clinicaltrials.gov of Phase 2 and 3 trials.

Introduction/Overview

Development and selection of clinical outcome assessments (instruments for measuring how patients feel and function) for rare tauopathies is complicated by:

- Overlapping and syndromic nature of clinical presentation e.g.,
  - PSP categorized as atypical parkinsonism or FTD clinical syndrome and/or neuropathologically as a tauopathy
- Presence of cognitive impairment and dementia e.g.,
  - PSP with and without cognitive impairment/dementia

This has led to:

- Trials in mixed populations e.g.,
  - Parkinsonism: PD, PSP, MSA, Essential tremor
- Application or adaptation of COAs for multiple populations e.g.,
  - Use of Clinical Dementia Rating in PART, PSP, CBD, FTD
  - FTLD modified CDR
- Use of multiple COA types and measurement of multiple concepts within trials e.g., Global, Motor, Cognitive and Behavioral/Neuropsychiatric assessments

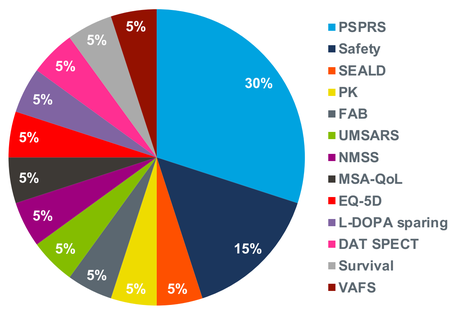
Results

166 publications mentioned COAs (PSP 58%, CBD 4%; FTD 3%; PART 1%, mixed population 33%). Across rare tauopathy studies, there were combinations of COAs assessing global, motor, cognitive and behavioral concepts. Tauopathy specific instruments were infrequent. Generic COAs were common across multiple different tauopathies. Thirty-four Phase 2 and 3 trials were identified (56% PSP, 41% FTD, 3% CBD). In PSP studies, four used PSP-RS as primary and two a co-primary (PSP-RS plus either UPDRS or SEADL).

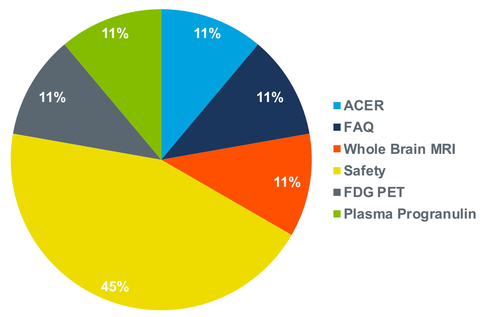
Table 1: COAs listed in published research abstracts by tauopathy

	Domain	Global					Motor	Cognitive				Behavioral/ Neuropsychiatric		
TA	**COA**	**UPDRS**	**PSP-RS**	**CDR**	**MDRS** (Mattis Dementia Rating Scale)	**NMSS**	**Hoehn & Yahr**	**MMSE**	**MoCA**	**NTB Other** (Neuropsychological Test Battery Other)	**FAB** (Frontal Assessment Battery)	**AES** (Apathy Evaluation Scale)	**NPI** (Neuropsychiatric Inventory)	**GDS** (Geriatric Depression Scale)
PSP		✓	✓		✓	✓		✓	✓	✓	✓			✓
CBS		✓	✓	✓			✓		✓	✓	✓	✓		
FTD				✓				✓		✓	✓		✓	
PART		✓		✓				✓		✓				

Phase 2/3 Industry Trials: Listed Primary/Co-primary outcomes in PSP



Phase 2/3 Industry Trials: Listed Primary/Co-primary outcomes in FTD



Conclusions

FDA draft rare disease guidance states, “Sponsors should recognize the need to develop new assessment tools, or modify existing ones, early to maximize time to develop and evaluate a new tool before relying upon it”. In selecting COAs for rare tauopathies, sponsors should consider target concepts; studies for tool evaluation; simple tools (e.g. disease specific global impression, ‘most bothersome symptom’); psychometrics; and use of performance-based assessments to complement self/observer report.

Current assessment approaches may be:

- High burden
- Lacking patient relevance

Considerations for future clinical trials should include:

- Fit-for-purpose COA reviews, with a focus on content validity and patient/trial burden
- Development of patient relevant PRO assessment tools
- Relevant concepts for ClinRO in cognitive impairment/dementia
- Development of standardized PerfO as supportive (cite rare guidance)