A systematic review of extra-motor outcome measures in clinical trials for amyotrophic lateral sclerosis.

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Summary

- Extra-motor symptoms (secondary to motor degeneration or indicative of wider pathophysiology) are increasingly recognised in Amyotrophic Lateral Sclerosis ALS [1]
- Despite recent guidelines these symptoms remain under evaluated in clinical trials [2]
- Where evaluated instruments used have not been specifically designed to evaluate symptoms in people with ALS

Background

- Extra-motor symptoms which are prevalent in, and impactful in ALS include neuropsychiatric, cognitive and behavioural change, pain, fatigue, sleep disturbances and saliva [1]
- These are associated with poorer prognosis[3], lower quality of life[4] and greater caregiver distress
- If these symptoms are not assessed in clinical trials, therapeutic benefit, or side-effects, of candidate drugs may be missed

Methods

- Search of trial registry databases and PubMed
- Phase II or III Clinical Trials of an Investigative Medicinal Product (CTIMPs) between 01/01/1994 and 16/09/2020
- No language restrictions were applied
- Extract data on use of outcome measures which evaluated extra-motor symptoms and the assessment tools used

Results

- **237** trials of investigative medicinal products were reviewed
- 31 trials (13%) did not include any assessment of extra-motor symptoms
- 49 assessment tools, or combinations of tools, were utilised in these trials

Figure 1: Extra-Motor Symptom Outcome Measures in 237 Trials in ALS

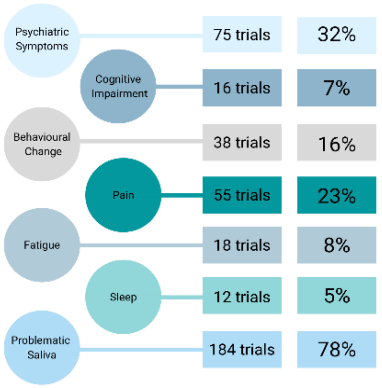

Table 1: Commonly Used Assessment Tools to Evaluate Extra-Motor Symptoms and Suitability in ALS

Assessment Tool Name	Intended Area of Focus	Extra-Motor Symptom Assessed	ALS-Specific?	Symptom-Specific?	Number of Trials Using as an Outcome Measure
C-SSRS (Columbia Suicide Severity Rating Scale)	Suicidality	Neuropsychiatric		Yes	4
HADS (Hospital Anxiety and Depression Scale)	Anxiety & Depression	Neuropsychiatric		Yes	2
ALSQOL-R (Amyotrophic Lateral Sclerosis Specific Quality of Life – Revised and Short Form)	Quality of Life	Pain, Fatigue, Neuropsychiatric, Sleep and Cognition	Yes		33
ALS-FRS (Amyotrophic Lateral Sclerosis Functional Rating Scale)	Physical function	Saliva	Yes		182
ESS (Epworth Sleepiness Scale)	Sleep	Sleep		Yes	2
ECAS (Edinburgh Cognitive Assessment Screen)	Cognition & Behavioural	Cognition & Behavioural	Yes	Yes	14

Conclusion

- ALS trials have neglected to evaluate some extra-motor symptoms
- Where evaluated, the assessment tools used may not be suitable for people with ALS with impaired motor or speech function

Recommendations

- Using measures where scoring is not impacted by physical disability or speech impairment can be helpful to improve assessment
- Further validation of established measure in people with ALS, or development of disease-specific impairment thresholds is needed
- Future clinicals trials should incorporate ALS specific extra-motor outcome measures in their design

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