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Age-related disorders

Short communication

Assessment of outcome in clinical trials in mild Alzheimer's disease: urgent time for a rethink?

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Abstract

Introduction

A major barrier for clinical trials in Alzheimer's disease is the lack of sensitive clinical endpoints for the early stages. Until recently, regulatory agencies have required demonstration of improvement in two disease domains, cognition plus functional or global status, as the evidence of symptomatic improvement during clinical trials for Alzheimer's disease. However, the model of Alzheimer's disease progression indicates impairment in cognition occurs earlier than changes in function and new draft guidance from the Food and Drug Administration considers change in cognition as an endpoint. The aim of this paper is to assess the outcomes of clinical trials in mild Alzheimer's disease.

Short communication

The Alzheimer's disease assessment scale – cognitive subscale is the most widely used assessment of cognition in clinical trials; however, analysis of its psychometric properties, show it lacks the sensitivity to detect change in cognition in mild Alzheimer's disease. There is a need to develop a new outcome measure capable of capturing the subtle changes associated with mild AD in a reliable and valid way.

Conclusion

Given the heterogeneity of AD phenotypes, development of a reliable, valid and clinically meaningful outcome measure is complex and challenging and will require discussion and co-operation between researchers, clinicians, industry and patients and their advocates to achieve success.

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Introduction

The pathological processes associated with brain degeneration in Alzheimer's disease (AD), such as amyloid deposition and the creation of neurofibrillary tangles, are known to occur before changes are observed in cognition and function in daily life[1,2]. Major efforts are underway to find disease modifying treatments able to arrest these processes, and particularly, target the amyloid and tau pathways. Lack of success of new treatments in clinical trials has thus far been attributed to the need to intervene earlier in the disease process, and the absence of sensitive clinical endpoints in the early stages of AD.

Until recently, regulatory agencies, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA), have been reluctant to accept cognitive status alone as the primary endpoint for clinical trials in AD, preferring a combination of cognition and function[3]. However, impairment of cognition occurs earlier than changes in function in daily life, and mild cognitive impairment is widely understood to have no notable effects on daily living[4]. The model of disease progression in AD implies that by the time changes in function begin to become evident, the primary pathological processes are almost complete, and brain damage has become irreversible[1].

The focus has thus moved to cognitive outcomes in mild AD, and in recognition of the fact that functional improvements cannot be expected to be observed alongside improvement in cognition in mild AD, sympathy has recently been expressed by the FDA for using change in cognition as an endpoint, either as part of a composite or alone[5]. However, this raises a number of issues about the assessment of outcome in mild AD, and there is a need for debate about these issues, and progress towards a consensus view.

Short communication

The Alzheimer's disease assessment scale – cognitive (ADAS-Cog) is the most widely used assessment of cognition for clinical trials. The ADAS-Cog is simple to administer and is relatively brief, and this makes it attractive as an instrument for clinical trials. It has thus become established as a gold standard for the assessment of cognition in AD and has been used as a primary endpoint in over 170 clinical trials.

Over recent years, questions have been raised regarding the suitability of the ADAS-Cog to assess those with mild AD[6-8]. These questions cover three main issues; the appropriateness of the cognitive domains tested, the psychometric properties and the variability in administration and scoring of the ADAS-Cog.

The ADAS-Cog focuses on memory and language, but does not include tests of executive function, working memory and attention. This focus is reasonable in later stages of the disease, when there is a global deterioration of cognition. However, in the early stages of the disease, there is now good evidence for different phenotypes of impairment, including distinct amnestic and dysexecutive

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patterns[9]. There is thus a need for assessment strategies that recognise the potential for individual differences in patterns of cognitive breakdown early in AD.

Early work on the psychometric properties of the ADAS-Cog was based on a small numbers of cases[10], but later studies with larger samples indicated that the scale generally had satisfactory properties[11,12]. Cano et al.[13] evaluated the psychometric properties of both the individual components of the ADAS-Cog and the total score. Convergent validity with respect to Mini Mental Status Exam scores was satisfactory (0.63) and ADAS-Cog scores were not affected by age or gender. Test-retest and internal consistency reliability were also found to be high (0.93 and 0.84, respectively). ADAS-Cog total scores did not exhibit floor or ceiling effects; however, when assessed at the individual component level, 7 of the 11 components demonstrated floor or ceiling effects and skewed scores. Furthermore, component level ceiling effects were found to increase as the severity of AD decreased. Therefore, the ADAS-Cog may underestimate differences in cognitive ability in those with mild to moderate AD, and this may limit the sensitivity of the ADAS-Cog to the effects of interventions in mild AD.

Hobart et al.[14] analysed the AD neuroimaging initiative data using Rasch analysis and found satisfactory fit to the model. The 11 item version represents a continuum on which cognitive performance can be measured and summing components to give a total score is acceptable. However, a significant issue is that one of the subscales (word recognition) that had the least evidence of ceiling effects showed poorest fit to the model. This suggests that a component that is useful in the assessment of mild AD may not be part of the continuum of cognitive impairment measured by the ADAS-Cog.

In addition to issues with the psychometric properties of the ADAS-Cog, there also appears to be variability in the administration and scoring methods employed[15]. More recently, Schafer et al.[16] found 58 out of 70 experienced raters made errors when scoring the ADAS-Cog. Doraiswamy et al.[12] also report a considerable amount of measurement error which may have arisen from factors such as patient frustration, incorrect scoring or distraction during testing. Variability in administration methods and errors in scoring have the potential to undermine the results of multi-centre clinical trials and these are issues that warrant careful monitoring.

The neuropsychological test battery (NTB)[17] has recently been added as a candidate primary efficacy measure by the EMA. Research evidence suggests that the NTB is superior to the ADAS-Cog, in particular, its ability to detect reduced impairment as a result of treatment in a sample of people with mild AD. The increased sensitivity of the NTB to detect change would allow smaller sample sizes to be used in future clinical trials. However, the NTB's focus on memory and executive function, mean additional tests are required for a targeted assessment of relevant cognitive functions.

Support has been expressed for adapting existing tools such as the ADAS-Cog to measure mild AD[14]. Although this is attractive in maintaining the status quo, we believe that it may be misconceived, and that tools designed for the later stages of the disease are a poor starting point for assessment of mild AD. As mentioned above, the clinical effects of mild AD are different from the later stages of the disease. The assessment of outcomes is currently an active area of AD research and much has been done to capitalise on advances in technology to improve the accuracy and sensitivity of measures. Recent discussions have highlighted these emerging assessment methods, but as yet, no conclusions have been reached as to which test or combination of tests would be capable of capturing the subtle changes in cognition and function associated with early AD in a reliable and valid way.

Discussion

There is an urgent need to take stock, and consider issues underlying cognitive endpoints for clinical trials in mild AD and develop a new outcome measure that is modelled on and reflects the clinical experience of the patient in the early stages of AD.

Questions that need to be addressed include the 'what', and the 'how' of assessment of cognitive outcomes. A number of issues pertaining to the 'what' of assessment require debate and resolution:

- Is the idea of isolated cognitive endpoints acceptable to all stakeholders, and can this have a meaningful clinical correlation?
- Should the focus be solely on areas of cognition that change early in the disease, or should assessment seek to be more comprehensive?
- How can different phenotypes of early cognitive impairment be accommodated?
- Should the assessment seek to judge the importance of different aspects of cognition, or does cognition serve simply as a surrogate marker of disease progress?
- What is of clinical relevance to a patient with early AD?

Questions concerning the 'how' of assessment also abound, and put practical constraints on 'what' is assessed:

- Should assessment be primarily through objectively scored tests or are subjective rater judgement scales the preferred model?
- What are the practical constraints on the length of assessment, and other procedural aspects?

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- How will the influence of education level and general ability on cognition be allowed for in assessment?
- What constraints are imposed by practice effects when attempting to detect decline in cognition?

Conclusion

Given the acknowledged inadequacy of current outcome measures and the new FDA guidance, there is a need to develop a new outcome measure capable of capturing the subtle changes in cognition and function associated with mild AD, in a reliable and valid way. To develop a reliable, valid and clinically meaningful outcome measure is complex and challenging. Consultation between researchers, clinicians, industry and patients and their advocates is essential to achieving success.

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