

OUTCOMES FOR CLINICAL TRIALS IN MILD-TO-MODERATE DEMENTIA TO EVALUATE DRUGS WITH PRESUMABLY SYMPTOMATIC EFFECTS

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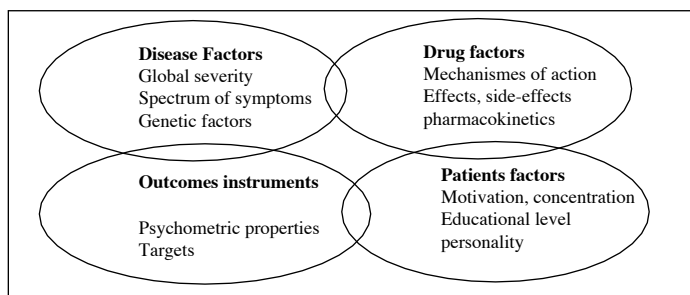
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A short and selective review on outcomes which have proven to detect relevant changes with symptomatic drugs for Alzheimer's disease (AD) is presented. The methodology, the definition of the relevant treatment population and the scope of outcome parameters have been well developed during the last 10 years. Issues related to clinical and methodological problems with these outcomes will be outlined.

Some general issues need to be clarified, which apply to all outcomes: We need to have a clear definition of the specific patient population, e.g. severe Dementia versus very severe, or (amnesic) MCI versus early Dementia, respectively. Questions of expectations towards drug effects are also important: a clinically important difference of a potential drug effect needs to be defined by experienced clinicians as a basis of relevance, which then may influence sample size calculations for a trial. Then, all assessment instruments should of course possess acceptable psychometric properties, and should be capable of detecting changes in cognition over time / with compound. For disorders such as AD and for clinical trials, practical issues e.g. the combination of tests should not exhaust the patient, are also important [1]. Several key methodological features of design need to be considered, which determine the relevance of the results obtained from clinical trial, e.g. the sample size and trial duration as well as an estimation of the minimal clinically important difference [2].

Figure 1

Schematic framework of determinants of outcome and their interaction. Several factors from different sources determine which outcomes are useful depending on the aims of clinical trials



For the EMEA-CHMP, symptomatic treatment targets in AD can be divided into 3 categories: enhanced cognition, non-deterioration in activities of daily living and/or improvement in behavioral dysfunction. From a clinical standpoint, these targets relate to important aspects of the symptomatology of AD as follows:

Impact on cognitive outcomes

Primary typical and definite symptoms in AD are those cognitive deficits, which arise from or center around episodic memory impairments.

The standard assessment tool used to evaluate cognition in AD trials, the ADAS-cog, measures not only memory but also language, orientation, and the ability to plan and execute simple tasks. Ample evidence shows that all three registered compounds, i.e. donepezil, galantamine, and rivastigmine, are able to produce improvements in cognitive function over periods of 3 to 6 months. Although most studies of ChEIs have assessed patients with mild to moderate AD, cognitive improvement has also been demonstrated with donepezil in early AD (MMSE 21-26) and moderate to severe AD (MMSE 5-17), and with rivastigmine in "advanced moderate" AD (MMSE <14) [3]. Memantine monotherapy reduced cognitive decline in mild to moderate AD (MMSE 10-22) and moderate to severe AD (MMSE 3-14).

a) Competition among assessment instruments: It has been argued that the ADAS-cog is an imperfect instrument and that it neglects important aspects of the symptomatology, especially in early AD (see paper by Harrison, this meeting).

b) Duration of study and limitations of design: The highest level of evidence on the efficacy of antidementia drugs in AD can mainly be derived from short-term studies of 6 (to 12) months duration. However, longer-duration extension studies have been published for donepezil (2.8-4.9 years), galantamine (1-3 years), rivastigmine (1-5 years), and memantine (1 year). However, these data have limited evidence due to considerable drop-outs, the lack of a placebo group and unblinded evaluation of treatment effects [4, 5]. All comparisons of the long-term treatment data with projected placebo or historical controls suggest that treated patients show better long-term cognitive performance than what would be likely without antidementia drug treatment [3].

c) How to account for drop-outs is a separate methodological issue, the most frequently used LOCF methods has been alleged as unsuitable for neurodegenerative disorders.

Impact on behavioral symptoms

Independently or as a consequence of even subtle cognitive failing, a variety of non-cognitive symptoms appear with a fairly typical order of appearance over time [3]. There is some evidence including one prospective, randomized, placebo-controlled trial that donepezil significantly improves behavioral symptoms of AD for at least 3 months. However, if only

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randomized controlled clinical trials which had used the NPI as outcome measure were subjected to a meta analysis, no significant effects could be demonstrated by donepezil, however, there were indications that galantamine confers a significant positive effect on behavioral disturbances. No such randomized controlled data were available for rivastigmine. These treatments are therefore successful in providing short-term improvement and possibly slowed appearance and progression of behavioral symptoms. In clinical terms, AD patients treated with ChEIs may show reduced severity of existing behavioral disturbances, with a relatively low rate of appearance of new behavioral symptoms [3].

The problems related to behavioural symptoms have been discussed by the paper by Robert et al.; this meeting)

As a clinical consequence of the dementia symptoms, global ratings of the severity of dementia/disease, are generally and rightly taken as useful outcomes of symptomatic drug effects.

With respect to concept, the different instruments take the spectrum of symptomatology and the course of disease differentially into account. This lack of clear concept in addition to a lack of structured assessment produces a low reliability and a low rate of change for this outcome parameter. Theoretically, this outcome parameter is also regarded as unrelated from the patients' needs, however, the clinical relevance appears clearcut.

Impact on Function: activities of daily living (ADL)

Loss of function steadily progresses throughout the course of AD. Ratings of instrumental and basic activities of daily living are similarly useful.

It is far less common to improve ADL scores due to regained functions once they are lost. Thus, preventing further functional deterioration or delaying further loss of ADL functions should be a primary goal of AD therapy. ADL may be evaluated via several different rating scales, which are used as outcome measures in clinical trials. An analysis of secondary outcome measures in placebo-controlled clinical trials has shown reduced rates of ADL decline or stabilization of ADLs at baseline levels with donepezil, galantamine, and rivastigmine. These effects were demonstrated in trials of up to 12 months for donepezil and rivastigmine, and up to 6 months in galantamine. Five published trials have investigated loss of function as a primary outcome. In all these trials, which used donepezil, galantamine and memantine in various comparisons, over 6 or 12 months study duration and in mild-to-moderate or moderate-to-severe dementia, respectively, there were indications for a reduced rate of deterioration in ADL function with active drug.

Generally, all IADL/ADL scales require careful explanation of the scaling to the caregivers. Furthermore, subjective factors (on the side of the caregiver) and objective factors (item definitions) have some definite effect on these scales.

Impact on clinical endpoints

Maintaining ADLs can allow patients to feel more autonomous and delay the transitions to greater dependence. In principle, more robust clinical measures, i.e. loss of self-

autonomy or placement in a nursing home, could be taken as relevant clinical endpoints to demonstrate symptomatic drug effects. However, several clinical and methodological limitations limit the validity of the results from such measures. In dementia, the definition of such functional endpoints remains complex and depends on many environmental factors unrelated to the patient's clinical state. Also, problems related to differential drop-out of patients appear important [6].

Impact on caregiver issues and quality of life

The increasing loss of instrumental and basic ADLs by itself or by the resulting depression and agitation in patients, creates a substantial burden when caring for these patients, either in the family or in a nursing home. Thus, the assessment of caregiver burden (e.g. BI) has some clinical attraction as an outcome parameter, despite the fact that it is only indirectly related to the patients' state. Subjective factors (on the side of the caregiver) and objective factors (health care system specificities) have some definite effect on scales like BI, NPI, hospital admission rate, nursing home admission rate. A large variability due to uncontrolled patient factors, and due to the course of disease have also to be taken into consideration.

Furthermore, quality of life in dementia is an emerging issue for all anti-dementia trials. No generally accepted instrument is yet available. However, it may provide an important aspect of the individual patient benefit, which a patient gets from a drug and may form the basis for re-imburement of a drug in question.

Conclusion

Finally, even if new disease-modifying drugs will become available in the (near) future, they may all be weighted against the benefits delivered by symptomatic drugs. Furthermore, a combination of potentially disease-modifying drugs with symptomatic drugs appears very likely [7]. Questions of reimbursement will be connected to differential benefit assessments between these classes of drugs. Thus careful assessment of outcomes of symptomatic drugs remains an issue of importance.

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