ORIGINAL ARTICLE

Outcomes for Assessment of Symptomatic and Stabilization/Disease Modifying Drugs

Serge Gauthier

ABSTRACT: The safety and efficacy of current symptomatic drugs for AD was established using parallel groups taking different doses of active drugs vs placebo over three to twelve months, whereas drugs with potential stabilizing/disease modifying effects are being tested by adding new compounds or placebo to standard symptomatic drugs over 12 to 18 months. Delaying progression to disease milestones may offer additional validity to these studies. It is unclear if biological and neuroimaging markers will add to the clinical evidence.

RÉSUMÉ: Critères d'évaluation des médicaments agissant sur les symptômes et stabilisant/modifiant l'évolution de la maladie. La sécurité et l'efficacité des médicaments agissant sur les symptômes, qui sont utilisés actuellement pour traiter la MA, ont été évaluées par des études de groupes parallèles prenant différentes doses de médicaments actifs comparées à un placebo pendant trois à douze mois, alors que les médicaments destinés à stabiliser ou à modifier le cours de la maladie sont évalués actuellement en ajoutant de nouveaux produits ou un placebo aux médicaments standards ciblant les symptômes, pendant 12 à 18 mois. Le fait de retarder la progression vers les étapes importantes du déclin pourrait améliorer la validité de ces études. Il n'est pas certain que les marqueurs biologiques et les marqueurs de neuro-imagerie ajouteront quoique ce soit aux données cliniques.

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Any therapy, whether pharmacological or not, requires proof of safety and efficacy. This background article for the 2nd Canadian Conference on Antidementia Guidelines will outline the various trial design issues that have been encountered in the modern pharmacological treatment of Alzheimer's disease (AD). The experience gained so far has been predominantly in the symptomatic treatment of AD, using parallel groups designs over three to twelve months. A number of randomized clinical studies attempting to modify progression of AD are under way, using parallel groups designs over one year or longer.

The natural history of AD will be described first, introducing the concepts of disease stages, disease milestones, and symptomatic domains which fluctuate in intensity as the disease runs through its course. Lessons from the symptomatic studies using cholinesterase inhibitors and memantine will be summarized. Current disease modification study designs will be outlined.

Natural history of Alzheimer's disease

The natural history of AD can be broadly considered as a pre-symptomatic stage, during which a number of pathological events take place, an early symptomatic or prodromal stage with affective and/or cognitive manifestations, and symptomatic mild, moderate and severe stages. Each of these stages could be targeted for specific treatments, requiring different trial designs and outcomes (Table 1).

Disease milestones can also be defined in typical AD (Table 2). Some of these can be a targets for treatment, with considerable face validity and impact on care.[1] For example studies in Mild Cognitive Impairment (MCI) of the amnestic type could have demonstrated that the diagnosis of dementia (predominantly AD) is delayed over 2 to 3 years.[2] Delaying loss of autonomy for self-care and even death in moderate to severe stages of AD using alpha-tocopherol in only one study by the Alzheimer Disease Cooperative Study group[3] has influenced clinical practice to use vitamin E in all stages of AD, at least in the USA. Delaying loss of autonomy for instrumental or basic activities of daily living (ADL) or the need for nursing home care would translate into pharmaco-economic benefit. Delaying emergence of some of the behavioral and psychological

From the Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, Verdun, Quebec, Canada.

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Reprint requests to: Serge Gauthier, Alzheimer Disease Research Unit, McGill Centre for Studies in Aging, 6825 LaSalle Blvd., Verdun, Quebec, H4H 1R3, Canada.

Table 1: Examples of trial design and of primary outcomes for each stage of Alzheimer's disease

Stage	Target Population	Trial Design	Primary Outcome
Presymptomatic	Healthy persons at risk	Survival over 5 years	Incident dementia
Prodromal	Mild Cognitive Impairment Amnestic sub-type	Survival over 3 years	Conversion to dementia
Mild to moderate	AD in the community	Six months parallel groups	Cognition and global impression of change
Moderate to severe	AD in the community or in assisted living	Six months parallel groups	Cognition and ADL, behaviour or global impression of change
Severe behavior	AD in institution	Six months parallel groups	Cognition and behavior

symptoms of dementia (BPSD) would reduce caregiver burden and delay nursing home placement.

Symptomatic domains in dementia include cognition, ADL and behavior. One can even add a domain of changes in mobility, since patients with AD will manifest some features of parkinsonism late in the disease. In most patients early changes in mood and anxiety precede the formal diagnosis of AD, with spontaneous improvement as insight about the disease is lost. Cognitive and functional (ADL) decline are relatively linear over time, whereas BPSD peak midway into the disease course and resolve spontaneously through the severe stage as mobility becomes impaired. These natural fluctuations in the intensity of individual symptomatic domains through the stages of AD have an impact into trial design and outcomes (Table 3). It should be noted that studies could be of shorter duration and /or of smaller numbers of subjects in moderate compared to mild stages of AD because of the faster rate of decline in the moderate stage, which

Table 2: Clinical milestones in Alzheimer's disease

- Emergence of cognitive symptoms
- Conversion from amnestic MCI to diagnosable dementia
- Loss of instrumental ADL
- Emergence of BPSD
- Nursing home placement
- Loss of self-care ADL
- Death

Table 3: Examples of impact of symptoms through stages of addon trial design

Stage	Prominent features	Types of outcomes	Examples
Mild	Depression may be present; few BPSD		
	Cognitive decline slow but predominant feature	Cognition	ADAS-cog
	Some instrumental ADL losses	Instrumental ADL	ADCS-ADL, DAD
Moderate	Cognitive decline more rapid	Cognition	ADAS-cog
	Functional decline more rapid	Instrumental & basic ADL	DAD, ADCS-ADL
	BPSE emerge	Behavior	NPI, BEHAVE-AD
Severe	Cognitive losses harder to measure (floor effect)	Cognition	SIB
	Few basic ADL remaining	Basic ADL	ADCS-ADLsevere
	BPSD abating	Behavior	NPI
	Parkinsonism emerging	Parkinsonism	UPDRS

ADAS-cog - Alzheimer Disease Assessment Scale – cognitive subscale,[4] ADCS-ADL - Alzheimer Disease Cooperative Study ADL scale,[5] BEHAVE-AD - Behavioral symptoms in Alzheimer's disease,[6] DAD - Disability Assessment in Dementia,[7] NPI - Neuropsychiatric Inventory,[8] SIB - Severe Impairment Battery,[9] UPDRS - United Parkinson Disease Rating Scale[10]

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may be related to the sensitivity of measurement scales, or to the progression of AD.

Symptomatic clinical trials using cholinesterase inhibitors and memantine

The modern treatment for AD was initiated by the report that tacrine improved some aspects of cognition and daily life. The follow-up confirmatory studies used cross-over and parallel group designs. The FDA published "guidelines"[11] which greatly influenced the choice of primary outcomes for proof of efficacy of drugs improving symptoms in AD: a cognitive performance-based scale such as the ADAS-cog and an interview-based impression of change became the primary outcomes in mild to moderate AD, defined operationally as scores between 10 to 26 on the Mini Mental State Examination (MMSE;[12]). Unfortunately, these FDA guidelines caution against the 'pseudospecificity' of measurable benefits on neuro-psychiatric manifestations in AD delayed research in this symptomatic domain. More recent discussions and publications from the FDA and other regulatory agencies have been more open to ADL and behavior as important outcomes.

The following study designs have been used in the proof of efficacy for cholinesterase inhibitors: parallel groups over 3 to 12 months, and survival to a predefined clinical endpoint over one year or longer.

The parallel groups offer the possibility of short-term (minimum of three months) studies comparing the efficacy of different doses of the drug versus placebo. The primary analysis is done on outcomes at the end of the study, using the Last Observation Carried Forward (LOCF) or Intent to Treat (ITT) to compensate for missing values in case of drop outs. Although LOCF/ITT has been favored by the FDA, regulatory agencies may now accept that the primary efficacy analysis be done on Observed Cases (OC), eg completers, for studies of 12 months or longer duration. For practical purpose both types of analysis are performed. Although 'cognitive enhancement' was the main hope for CIs as a therapeutic class, the reality that has emerged from six months studies with open-label extensions and the one-year placebo-controlled Nordic study[13] is that although there is a small but statistically significant improvement in cognition peaking at three months with the cholinesterase inhibitors, the most clinically relevant finding has been the stabilization of cognitive decline with 'return to baseline' at 9 to 12 months for the actively treated groups at the higher therapeutic doses, compared to placebo treated groups who decline steadily. It should be noted that this natural decline varies greatly between studies in AD, and is even less evident in AD with cerebrovascular disease or in vascular dementia, where control of vascular risk factors appear to modify progression, at least in studies of six months duration.[14]

Survival studies have targeted primarily loss of ADL, and have successfully demonstrated a delay in the loss of autonomy for patients on CIs compared to placebo. Parallel group studies of six months duration ranging from mild to moderately severe AD (MMSE 5 to 26) have also established that ADL are stable on treatment, but with no return of instrumental ADL (so called tutoring effect).

Aberrant behavior has been the most difficult domain to study, although it may be the most important aspect of dementia for the caregivers. The availability of general BPSD scales such as the Neuropsychiatric Inventory (NPI), as well as specific scales such as Cohen-Mansfield Agitation Inventory,[15] has not allowed yet unequivocal demonstration of benefit in severe stages of AD. New methods of analysis of behavior have been proposed,[16,17] and will likely be more successful in defining categories of BPSD symptoms most responsive to CIs (anxiety, hallucinations), memantine (agitation) and other drugs.

Memantine as a new therapeutic class has been found to be effective in a range of studies using parallel groups, in moderate to severe AD.[18] Scales appropriate for this stage of disease, such as the SIB, the ADCS-ADL, and the NPI have been used and accepted by the FDA and other regulatory agencies. Of great importance, the novel design of adding memantine or placebo to a stable dose of a CI has been used successfully, paving the way to a number of studies where novel drugs or placebo are added to 'standard treatment'.

Disease modification strategies

Although no trial design has yet lead to a successful treatment for disease modification, many attempts have been made using parallel groups over one year. Recent refinements of this design include adding the novel drug or a placebo to standard treatment over one year or longer, selection of outcomes which demonstrate relatively linear changes over time such as the Clinical Dementia Rating sum of boxes[19] and volumetric brain measurements using magnetic resonance imaging at beginning and end of year. The reasoning behind this 'add-on design' is summarized in Table 4.

Although this design appears promising, there are uncertainties and limitations. For instance the difference in rate of brain atrophy may be absent or opposite to expectations, with accelerated atrophy in the actively treated group. Although proposed by Leber in the past, a randomized washout from an active treatment will not be acceptable to all Institutional Review Boards, and a previous attempt in using this design with patients treated with propentofylline has failed to convince regulatory agencies.

Table 4: Add-on design for disease modification

- One year is the minimum period for meaningful clinical observations in mild to moderate AD considering natural decline (may need to be longer in mild AD)
- Ethically long duration studies without 'standard treatment' are not possible
- There are scales with relatively linear changes over one year, such as the CDR sum of boxes, the ADAS-cog, the DAD and the ADCS-ADL, allowing analysis for slopes of decline
- A demonstrable reduction in rate of brain atrophy associated with differences in clinical decline would offer great face validity.

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One of the most difficult issues in disease modification strategies is the decision of the stage of disease where the proposed drug is most likely to work. On this 'proof-of-concept' phase II/III efficacy and safety study hinges the entire future of the drug. For example numerous attempts at treating patients with AD in mild to moderate stages using non-steroidal anti-inflammatory drugs (NSAID) have failed, despite the weight of evidence from epidemiological research and the biological plausibility of an inflammatory response to beta-amyloid deposition: the doses may have been to low or the NSAIDS do not work prospectively. On the other hand it is possible that treatment of AD in the prodromal stages would be the most appropriate time in terms of reversibility of pathological lesions, but such studies would require three years, a very long time for a 'proof-of-concept', with drugs that must known to be safe. Enriched patients groups could be considered, such amnestic MCI with risk factors for rapid conversion to AD such as apoE4 genotype.[2]

Future strategies to delay emergence of AD

Hypothesis on the pathophysiology of AD have emerged from epidemiological research in human populations, post-mortem and biomarkers studies in patients, and animal models, and there will be a need to establish if new therapies can delay the onset of symptoms in asymptomatic persons at varying degree of risk of AD. The prototype of trial design to establish the safety and efficacy of such therapies is the ongoing five-year survival study comparing *Ginkgo biloba* to placebo in elderly subjects, with incident dementia as primary endpoint. Variations of this design may be possible, by enriching the study population with different levels of risk, such as a positive family history of AD and/or selected gene markers, although it should be remembered that any enrichment of a study population will limit the applicability of findings to the population as a whole.

Mimimum requirements for proof of symptomatic vs disease modification

At this stage of the development of anti-dementia drug treatments, there are two approved classes of drugs for AD. The evidence for efficacy was obtained from at least two pivotal studies for each drug (donepezil, rivastigmine, galantamine, memantine) with dual primary outcomes of cognition and global impression of change. It is possible that other classes of drugs will prove to have symptomatic benefit in AD and other dementias using function (ADL) or behavior rather than a global impression of change. It seems likely that cognition, if measured by a sensitive scale for the stage of disease under study (Table 3), will be required as a primary outcome, but the definition of cognition and its measurement are likely to change in order to take into account executive dysfunction which predominates over memory impairment in vascular and Parkinson-associated dementia. Proof of a disease modification effect would require biological plausibility and stabilization of progression on global impression of change, cognition or function (ADL), supported by stabilization of biological or imaging markers of disease progression. There may be no symptomatic benefit from a disease modification drug, but a symptomatic drug may have some disease modification properties.

Declaration

In the past two years Serge Gauthier has been an advisor/consultant or speaker for Glaxo-Smith-Kline, Jannsen Ortho, Lundbeck, Myriad, Neurochem, Novartis, Pfizer, Sanofi, Servier, participated in clinical trials sponsored by Janssen-Ortho, Lundbeck, Neurochem, Pfizer.

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