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Trial Designs and Outcomes to Monitor Novel Therapeutics in Alzheimer's Disease

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Introduction

The various etiological hypotheses for Alzheimer's disease (AD) need to be tested in patients using designs and outcomes that are appropriate. This chapter reviews the principles of symptomatic treatment versus disease modification, the natural history of AD, and designs to slow down its progression. It should be noted that the diagnosis of AD implies first a diagnosis of dementia, followed by an assessment of its etiology. The accuracy of the clinical diagnosis of AD is in the order of 85% once dementia is clinically detected, but less than 50% in the prodementia stage of amnesic mild cognitive impairment (aMCI) using clinicopathological correlations (Petersen et al., 2006).

Symptomatic Treatment Versus Disease Stabilization

The main thrust of therapeutic research in AD has so far been directed at improvement of symptoms, using cholinesterase inhibitors (ChEI) and the NMDA receptor antagonist memantine. The initial expectations were primarily a cognitive enhancement effect, but these drugs improve cognition only transiently, stabilize activities of daily living (ADL), and delay emergence or improve existing behavioral and psychological symptoms of dementia (BPSD), such as apathy, agitation, and hallucinations. Although the improvement above baseline is small, these results are clinically meaningful in a neurodegenerative condition that leads to death within 3–8 years after the onset of symptoms (Winblad et al., 2001).

The current interest is in disease modification. A delay of progression from no or minimal symptoms to diagnosable dementia would have an obvious value from a public health point of view, and delaying progression from mild AD to more advanced stages would also be considered important, even if there were no symptomatic improvement. Delaying progression in severe stage would obviously not be considered appropriate, although much more can be done to improve symptoms and quality of life at that

stage. The study design currently favored by pharmaceutical sponsors and regulators to prove disease modification is a fixed time comparison of decline of clinical outcomes and rate of brain atrophy. Another study design is survival to a clinically important disease milestone, which may offer more clinical applicability and allow for pharmacoeconomic estimates. A combined approach (fixed time measures and survival-to-clinical events) may be possible (Andrieu, Rascol, Lang, Grandjean, & Vellas, 2006).

It should be noted that a sustained symptomatic therapeutic effect (akin to levodopa in Parkinson's disease) would stabilize progression of disease without modification of the underlying pathophysiology. There are thus different perspectives on symptomatic versus disease stabilization for regulators approving a label versus users (patients, caregivers, clinicians, and third-party payers).

Natural History of Alzheimer's Disease

The natural history of AD can be broadly considered as a presymptomatic stage during which a number of pathological events take place over many years, an early symptomatic or prodromal stage (aMCI) with cognitive and at times neuropsychiatric manifestations, and symptomatic mild, moderate, and severe stages. Hoping for reversibility of pathological changes, the early stages of AD can be targeted for disease modification, requiring different trial designs and outcomes (Table 1).

Disease milestones have been defined in AD (Table 2). Some of these can be a target for treatment, with considerable face validity and potential impact

TABLE 1. Examples of trial design and outcomes for disease modification at early stages of AD.

Stage	Population	Trial design	Primary outcome
Presymptomatic	Healthy elderly	Survival over 5–7 years	Incident dementia
Prodromal	Amnesic MCI	Survival over 2–3 years	Progression to dementia
Mild dementia	AD in the community	Parallel groups over 18 months	Cognition and global impression of change

TABLE 2. Clinical milestones in AD.

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

on care (Galasko, Edland, et al., 1995). For example, if the studies in aMCI using ChEI had demonstrated a sustained delay in progression to dementia, such patients would have been actively treated with these drugs worldwide. Delaying loss of autonomy for self-care and even death in moderate-to-severe stages of AD using α -tocopherol in only one study performed by the Alzheimer disease cooperative study group (Sano et al., 1997) has influenced clinical practice to use vitamin E in all stages of AD, at least in the USA, until a meta-analysis showed higher mortality associated with vitamin E at doses of 400 IU per day or higher (Miller & Pastor-Barriuso, 2005). Delaying the loss of autonomy for ADL or the emergence of some of the BPSD could reduce the burden of the caregiver and delay the need for 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 course of disease. In most patients, early changes in mood and anxiety precede the formal diagnosis of AD, with spontaneous improvement as insight is lost about the disease. Cognitive and functional (ADL) decline are relatively linear over time, whereas BPSD and caregiver burden peak midway into the disease course and improve through the severe stage (Gauthier, Thal, & Rossor, 2001). 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 decline is faster in the moderate stage, which may be related to the sensitivity of measurement scales or to the natural progression of AD.

TABLE 3. Symptoms through the stages of AD and relevant outcomes.

Stage	Prominent symptoms	Types of outcomes	Examples of scales
aMCI	Cognitive decline	Cognition	ADAS-cog
Mild	Cognitive decline	Cognition	ADAS-cog, ADCS-ADL, DAD
Moderate	Instrumental ADL	Instrumental ADL	ADAS-cog
	Cognitive and ADL decline more rapid	Cognition	
Severe		ADL	ADCS-ADL, DAD
	BPSD emerge	Behavior	NPI
	Cognitive decline	Cognition	SIB
	Self-care ADL	Basic ADL	ADCS-ADL sev
	BPSD abating	Behavior	NPI
	Parkinsonism emerging	Parkinsonism	UPDRS

ADAS-cog Alzheimer disease assessment scale-cognitive subscale (Rosen, Mohs, & Davis, 1984), ADCS-ADL Alzheimer disease cooperative study-ADL scale (Galasko, Bennett et al., 1997), DAD Disability assessment in dementia (Gélinas, Gauthier, McIntyre, & Gauthier, 1999), NPI neuropsychiatric inventory (Cummings et al., 1994), SIB severe impairment battery (Panisset, Roudier, Saxton, & Boller, 1994)

UPDRS, United Parkinson Disease Rating Scale (Fahn, Elton, & Members of the UPDRS development committee, 1987)

Symptomatic Clinical Trials Using ChEI 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 crossover and parallel group designs. The FDA published guidelines (Leber, 1990) that influenced greatly the choice of outcomes for proof of efficacy of drugs, which improve the symptoms of AD: a cognitive performance-based scale such as the ADAS-cog (Alzheimer Disease Assessment Scale-cognitive subscale) and an interview-based impression of change became the primary outcomes for the symptomatic treatment of mild-to-moderate AD, defined operationally as scores between 10 and 26 on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). Unfortunately, these FDA guidelines caution against the pseudospecificity of measurable benefits on BPSD delayed research in this important symptomatic domain. In the past few years, 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 ChEI: parallel groups over 3–12 months, and survival to a predefined clinical endpoint over 1 year or longer.

The parallel groups offer the possibility of short-term (minimum of 3 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 dropouts. Although LOCF/ITT has been favored by regulatory bodies, there is increasing support for primary analysis to be done using observed cases (OC), e.g., completers in studies of 12 months or longer duration (Sampaio, 2006). For practical purpose, both types of analyses are performed.

Survival studies with ChEI have targeted primarily loss of ADL, and have successfully demonstrated a delay in the loss of autonomy for patients on active drug compared to placebo. Parallel group studies of 6 months duration ranging from mild-to-severe AD (MMSE 26/30 to 1/30) have also established that ADL are stable on treatment with ChEI, but with no improvement of instrumental ADL (so called tutoring effect).

The most difficult domain to study, although very significant clinically, has been behavior. The availability of BPSD scales such as the NPI (neuropsychiatric inventory) has not yet allowed unequivocal demonstration of benefit in severe stages of AD in nursing home settings. New methods of analysis of behavior have been proposed (Gauthier et al., 2002; Gauthier, Wirth, & Möbius, 2005), and will likely be more successful in defining categories of BPSD symptoms most responsive to ChEI (anxiety, hallucinations), memantine (agitation), and other treatments.

Memantine a new therapeutic class has been found to be effective in a range of studies using parallel groups in moderate-to-severe AD (Doody, Winblad, & Jelic, 2004). Scales, such as the SIB (severe impairment battery),

the ADCS-ADL (Alzheimer disease cooperative study-ADL scale) modified for severe stage, and the NPI, appropriate for this stage of disease have been used and accepted by the FDA and other regulatory agencies. Of great importance is the novel design of adding memantine or placebo to a stable dose of a ChEI, which has been used successfully (Tariot et al., 2004), paving the way to a number of studies where novel drugs or placebo are added to standard treatment.

Disease-Modification Studies

In the early days of designing protocols to demonstrate slowing of AD progression, the randomized start design was considered promising (Bodick et al., 1997) but failed in the propentofylline drug development program (Whitehouse et al., 1998). Current studies use parallel groups over 18 months in mild AD, requiring the addition of the novel drug or a placebo to standard symptomatic treatments. The outcomes selected have demonstrated relatively linear changes over time such as the clinical dementia rating-sum of boxes (CDR-SB; Hughes, Berg, Danziger, Coben, & Martin 1982), the ADAS-cog, the ADCS-ADL, and the DAD. Cognitive measures usually consist of one scale, such as the ADAS-cog, but could be a *z*-score transformation of a number of well-validated tests (Visser, 2006). The latter may be required in very early AD, where there is limited impairment in recent memory and executive tasks (Nadkarni & Black, 2006). The clinical measures are supplemented by volumetric brain measurements using magnetic resonance imaging at the beginning and end of treatment (Scheltens & Barkhof, 2006). Other biomarkers can be monitored as supportive evidence for a biological effect on disease progression (Lovestone, 2006).

Although this design appears promising, there are uncertainties and limitations. For instance, the difference in the rate of brain atrophy may be absent or opposite to expectations, with accelerated atrophy in the actively treated group, as was seen in one of the immunotherapy studies. The planned analysis for differences in mean changes at 18 months relative to baseline, or differences in slopes of decline using nonlinear models may satisfy regulatory requirements, but may not convince third-party payers and users. Demonstration of a delay in reaching clinical milestones (such as loss of instrumental ADL present at baseline, delaying emergence of BPSD not present at baseline, delaying transition from CDR global stage 1 [mild] to 2 [moderate]) would greatly improve the translation of randomized clinical trials to clinical practice, particularly if frail (real world) populations were enrolled in phase III (Ferruci, Guralnick, & Studenski, 2004).

One of the 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 a given drug. For example, numerous attempts at treating patients

with AD in mild-to-moderate stages using nonsteroidal anti-inflammatory drugs (NSAID) have failed, despite the weight of evidence from epidemiological research and the biological plausibility of an inflammatory component to AD pathology (McGeer, Schulzer, & McGeer, 1996). It may be that treatment with NSAID in the presymptomatic or in the prodromal stages of AD would be a more appropriate time from a pathophysiology point of view, or that doses tested so far were too low. On the other hand, studies in these stages of AD require 3–5 years, a very long time for a proof of concept. Alternatively, patients groups at very high risk of progression could be considered, such as presenilin mutation carriers, or aMCI carrying the apoE4 genotype with hippocampal atrophy (Pennanen et al., 2006).

The prototype of trial designs to establish the safety and efficacy of preventive therapies in asymptomatic populations is the ongoing 7-year survival study comparing *Ginkgo biloba* to placebo in elderly subjects, with incident dementia as primary endpoint (Touchon, Portet, & Gauthier, 2006). 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 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. Nevertheless, there is building evidence that pharmacogenomics will play a major role in matching disease-modifying drugs to individual patients, so much so that ethical considerations to pharmacogenomics profiling are under study (Issa, 2003).

Conclusions

We are fortunate that many etiological hypotheses for AD have been formulated and are amenable to study in human populations. A concerted effort among basic scientists, clinical trialists, and regulators is necessary to select the best study design for the appropriate stage of disease in order to prove efficacy. There is also a need to take into account the applicability of findings for the population as a whole in terms of safety and cost benefit.

References

- Andrieu, S., Rascol, O., Lang, T., Grandjean, H., & Vellas, B. (2006). Disease modifying trials in Alzheimer's disease: Methodological and statistical issues. *The Journal of Nutrition Health and Aging*, 10, 116–117.
- Bodick, N., Forette, F., Hadler, D., Harvey, R. J., Leber, P., McKeith, I. G., et al. (1997). Protocols to demonstrate slowing of Alzheimer disease progression. Position paper from the International Working Group on Harmonization of Dementia Drug Guidelines. *Alzheimer Disease and Associated Disorders 11*(Suppl. 3), 50–53.
- Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thomson, S., Carusi, D. A., & Gombin, J. (1994). The Neuropsychiatric Inventory: Comprehensive assessment of psychopathology in dementia. *Neurology*, 44, 2308–2314.

- Doody, R. S., Winblad, B., & Jelic, V. (2004). Memantine: A glutamate antagonist for treatment of Alzheimer's disease. In S. Gauthier, P. Scheltens, & J. L. Cummings (Eds.), *Alzheimer's disease and related disorders annual 2004* (pp. 137–144). London: Martin Dunitz.
- Fahn, S., Elton, R., & Members of the UPDRS development committee. (1987). United Parkinson's disease rating scale. In S. Fahn, C. Marsden, M. Golstein & D. B. Calne (Eds.), *Recent development in Parkinson's disease* (pp. 153–163). Florham Park, NJ: Macmillan Healthcare.
- Ferruci, L., Guralnick, J. M., & Studenski, S. (2004). Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: A consensus report. *Journal of the American Geriatrics Society*, 52, 625–634.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.
- Galasko, D., Edland, S. D., Morris, J. C., Clark, C., Mohs, R., & Koss, E. (1995). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part IX. Clinical milestones in patients with Alzheimer's disease followed over 3 years. *Neurology*, 45, 1451–1455.
- Galasko, D., Bennett, D., Sano, M., Ernesto, C., Thomas, R., Grundman, M., et al. & the Alzheimer's Disease Cooperative Study. (1997). An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzheimer Disease and Associated Disorders 11*(Suppl. 2), S33–S39.
- Gauthier, S., Thal, L. J., & Rossor, M. N. (2001) The future diagnosis and management of Alzheimer's disease. In S. Gauthier, (Ed.), *Clinical diagnosis and management of Alzheimer's disease* (pp. 369–378). London: Martin Dunitz.
- Gauthier, S., Feldman, H., Hecker, J., Vellas, B., Ames, D., Subbiah, P., et al. (2002). Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *International Psychogeriatrics*, 14, 389–404.
- Gauthier, S., Wirth, Y., & Möbius, H. J. (2005). Effects of memantine on behavioral symptoms in Alzheimer's disease patients: An analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *International Journal of Geriatric Psychiatry*, 20, 459–464.
- Gélinas, I., Gauthier, L., McIntyre, M., & Gauthier, S. (1999). Development of a functional measure for persons with Alzheimer's disease: The Disability Assessment for Dementia. *The American Journal of Occupational Therapy*, 53, 471–481.
- Hughes, C. P., Berg, L., Danziger, W. L., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry*, 140, 566–572.
- Issa, A. M. (2003). Ethical perspectives on pharmacogenomic profiling in the drug development process. *Nature Reviews*, 1, 300–308.
- Leber, P. (1990). *Guidelines for Clinical Evaluation of Antidementia Drugs*. Washington, DC: US Food and Drug Administration.
- Lovestone, S. (2006). Biomarkers in Alzheimer's disease. *The Journal of Nutrition Health and Aging*, 10, 118–122.
- McGeer, P. L., Schulzer, M., & McGeer, E. G. (1996). Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiological studies. *Neurology*, 47, 425–432.

- Miller, E. R., & Pastor-Barriuso, R. (2005). Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. *Annals of Internal Medicine*, 142, 37–46.
- Nadkarni, N. K., & Black, S. E. (2006). Cognitive outcomes. In K. Rockwood, & S. Gauthier, (Eds.), *Trial designs and outcomes in dementia therapeutic research* (pp. 85–112). Boca Raton, FL: Taylor & Francis.
- Panisset, M., Roudier, M., Saxton, J., Boller, F. (1994). Severe Impairment Battery: A neuropsychological test for severely demented patients. *Archives of Neurology*, 51, 41–45.
- Pennanen, C., Testa, C., Boccardi, M., Laakso, M. P., Hallikainen, M., Helkala, E. L., et al. (2006). The effect of apolipoprotein polymorphism on brain in mild cognitive impairment: A voxel-based morphometric study. *Dementia and Geriatric Cognitive Disorders*, 22, 60–66.
- Petersen, R. C., Parisi, J. E., Dickson, D. W., Johnson, K. A., Knopman, D. S., Boeve, B. F., et al. (2006). Neuropathologic features of amnesic mild cognitive impairment. *Archives of Neurology*, 63, 665–672.
- Rosen, W. G., Mohs, R. C., & Davis, K. L. (1984). A new rating scale for Alzheimer's disease. *The American journal of psychiatry*, 141, 1356–1364.
- Sampaio, C. (2006). Alzheimer disease: Disease modifying trials. Where are we? Where do we need to go? A reflective paper. *The Journal of Nutrition Health and Aging*, 10, 113–115.
- Sano, M., Ernesto, C., Thomas, R. G., Klauber, M. R., Schafer, K., Grundman, M., et al., for the members of the Alzheimer's Disease Cooperative Study. (1997). A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *The New England Journal of Medicine*, 336, 1216–1222.
- Scheltens, P., & Barkhof, F. (2006). Structural neuroimaging outcomes in clinical dementia trials, with special reference to disease modifying designs. *The Journal of Nutrition Health and Aging*, 10, 123–128.
- Tariot, P. N., Farlow, M. R., Grossberg, G. T., Graham, S. M., McDonald, S. M., & Gergd, I. (2004). Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil. *The Journal of American Medical Association*, 291, 317–324.
- Touchon, J., Portet, F., & Gauthier, S. (2006). Prevention trials in AD: One step forward? *Neurology*, 67, (Suppl. 3), s21–s22.
- Visser, P. J. (2006). Role of cognitive testing in disease modifying AD trials. *The Journal of Nutrition Health and Aging*, 10, 131–133.
- Whitehouse, P. J., Kittner, B., Roessner, M., Rossor, M., Sano, M., Thal, L., et al. (1998). Clinical trial designs for demonstrating disease-course-altering effects in dementia. *Alzheimer Disease and Associated Disorders*, 12, 281–294.
- Winblad, B., Brodaty, H., Gauthier, S., Morris, J. C., Orgogozo, J.M., Rockwood, K., et al. (2001). Pharmacotherapy of Alzheimer's disease: Is there a need to redefine treatment success? *International Journal of Geriatric Psychiatry*, 16, 653–666.

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