Is the Reduced Worsening of Clinical Symptoms a More Realistic Expectation of Treatment Outcome in Patients with Alzheimer's Disease?

a report by

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Alzheimer's disease (AD) is a progressive, age-related neurodegenerative disorder resulting in major disability and dependence that is devastating for the patient, care-givers and family. It is characterised by memory problems, executive dysfunction, dysphasia, apraxia, agnosia and visuo-spatial difficulties. This can lead to the emergence of behavioural disturbances such as agitation, aggression, delusions, wandering and apathy, culminating in the individual's loss of independent living, as well as feelings of denial, confusion and fear. On average, the disease lasts for eight to 14 years, often with the last two to five years being spent in need of 24-hour home care or, ultimately, formal nursing-home care.[1] It is thought to affect at least 15 million people worldwide.[2] The rapidly ageing populations, both in the developed and developing worlds, mean that this number will increase, making it one of the most important public health issues of our generation.

Treatment Response in Alzheimer's Disease

Ever since the licensing of cholinesterase inhibitors (ChEIs) and memantine for the treatment of AD, there has been considerable debate about their clinical relevance, despite the statistically significant clinical effectiveness benefits demonstrated in the pivotal licensing trials.[3–5]

Cognitive impairment is a key feature of AD and this is thought to be related to brain pathology. Improvement on a cognitive scale has become a frequently accepted tool for deciding clinically relevant treatment benefits. This narrow view of treatment response as improvement may have been chosen more for its sensitivity for detecting treatment effects than for its clinical relevance. Bullock suggested that even labelling acetylcholinesterase inhibitors as cognitive enhancers at all was overly simplistic.[6] It could be argued that by focusing purely on improvement, this narrow view does not capture the totality of this rapidly and predictably deteriorating condition. The nature of the disease or syndrome of AD makes it seem unlikely that one specific treatment will provide a cure for a condition that is more akin to a metabolic syndrome if one considers the risk factors that predict its development. While age is the predominant risk factor, others include hypertension, raised cholesterol, diabetes, obesity and cerebrovascular disease, and allied to that there is at least one common susceptibility gene. This suggests that a complex treatment will be necessary. Although our traditional goals in medicine are preventing the onset of, or curing, a disease, preventing worsening of the clinical condition is a clinically relevant, realistic treatment option and a very desirable outcome.[7] When treatment options are discussed with patients and carers, prevention of worsening is often what they expect from treatment, reporting that they would be content to manage if things got no worse. Stabilisation is of the greatest importance in the moderate to severe stages of the disease where the rate of deterioration is highest. It is the increase in patient dependency in these stages of AD that causes the largest burden to families and society.

Improvement or Stabilisation?

The clinical relevance of deterioration in function and behaviour is clear. The fact that all the current therapies are assessed on their ability to improve, rather than stabilise, what is loosely termed 'cognition' is an erroneous and unhelpful paradigm. What the pivotal benefit of treatment should be has to be reconsidered in the light of what we now know from our experience in the last 10 years with the ChEIs and, more recently, with memantine.

Assessment Tools

The Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog) – is the tool that was used in the first successful licence application for a ChEI and has consequently been used in all pivotal trials since.[9–11] The ADAS-cog assesses disparate functions of the brain (memory, language, praxis and orientation), which are coalesced into a composite score. The score is weighted by memory impairment, but has validity as a measure of change.

The currently available treatments have been judged by their ability, over a six-month trial, to improve on global function and ADLs, but primarily to improve the baseline ADAS-cog score by four points. According to Stern et al.,[12] these four points are approximately the expected mode amount of cognitive decline in a six-month period. This requirement clearly recognises that untreated patients will actually decline by that amount on this cognitive scale in six months, so no decline on the ADAS-cog would surely be enough to demonstrate a significant treatment effect in this relentlessly worsening condition. There are other

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problems using the ADAS-cog. Due to the 'omnibus' sum of scores, patients with very different individual symptom severities may achieve the same global score. The scale also has some very important omissions, such as sickness behaviour (e.g. apathy and depression) and executive function (which allows the patient to translate thoughts into actions), meaning that the composite score may not be a true reflection of the individual's functioning. The ADAS-cog relies heavily on language in its assessment, for example purely measuring verbal memory but not visuo-spatial memory. It only measures short-delay free recall, not working memory or real (20–30min) delayed free recall. The ADAS-cog is also not very sensitive to change, whether improvement or reduction in functioning.

Fortunately, other tools are now being used in research trials alongside the ADAS-cog, such as a battery of neuropsychological tests, which cover the key cognitive domains impaired in AD. These seem to be far more reflective of functioning.

Prevention of Worsening in Clinical Trials

Raskind et al. studied the effects of the ChEI rivastigmine on preventing decline in each of the domains measured in a pooled analysis of three studies.[13] What they showed was that only 22% of those patients in the high dose range (6–12mg) worsened by four points on the ADAS-cog[8] over six months compared with 36% on placebo. They also separately showed reduced levels of decline in the global assessment and in the Progressive Deterioration Scale, a measure of functional decline. This study concluded that the benefits of AD therapy should be seen in the context of the progressive deterioration of this condition and that benefit may be obtained not only from improvement, but also from stabilisation and reduced worsening of symptoms.

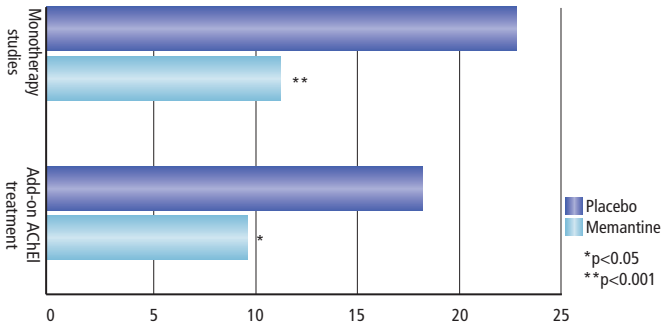
Analysing single domains could be criticised as it involves the risk of wrongly identifying isolated test performance fluctuation as treatment effect. A more clinically significant analysis was undertaken on a pooled analysis of six randomised controlled trials of memantine in mild to severe AD.[14] In this study, a more exact definition of worsening was defined. Patients had to concurrently worsen on three key domains of AD: cognition, global assessment and function. The strength of analysing the combination of assessments lies in the use of all available information in the key domains of AD to determine whether the patient is worsening or not. In this analysis, patients were deemed to have shown marked clinical worsening if they demonstrated a worsening in the functional scale and the global assessment and had deteriorated by four points or more on ADAS-cog in the mild to moderate studies, or five points or more on Severe Impairment Battery in the moderate to severe studies.

The result of this *post hoc* pooled analysis showed that about twice as many placebo-treated patients (21%) showed this marked and clinically significant deterioration compared with those on memantine (11%). This is a statistically and clinically significant reduction in morbidity. This was a robust finding that was demonstrated in all the individual studies, regardless of AD severity or whether memantine was given alone or to patients already stabilised on a ChEI (see *Figure 1*).

Regulatory Interpretation of Outcomes – National Institute of Health and Clinical Excellence

The desire to demonstrate improvements in cognition has been even more debased when considering outcomes in milder patients in whom

Figure 1: Percentage of Patients with Mini-mental State Examination (MMSE) <20 Showing Marked Clinical Worsening at Six Months in Meta-analysis of Six Memantine Studies



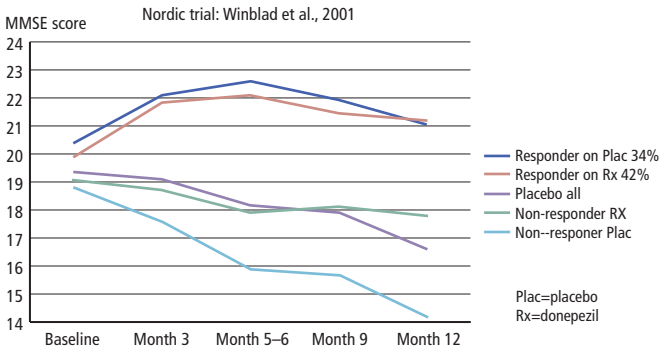
memory alone is the predominant symptom. In this case, the cognitive assessments that are heavily weighted towards memory function are dogged by the problem of ceiling effects. In addition, other measures used, for example assessing function and behaviour impairment in patients with mild cognitive impairment, are naturally unlikely to show improvement in symptoms they do not already possess. The lack of ability to demonstrate a cost-beneficial improvement in scales designed for more serious impairments has been used as the reason for not approving the use of ChEIs in mild AD in the UK by the National Institute of Health and Clinical Excellence (NICE).[15] This completely ignores the basic tenet of medicine that prevention is better than cure. The potential of ChEIs to prevent decline in early or mild AD has been wrongly influenced by the fact that they have been singularly unhelpful in a number of large studies in patients with minimal cognitive impairment (MCI).[16] This is a condition without dementia in which impaired memory is the major complaint. This cannot be seen as evidence of the lack of efficacy in mild AD, which of course is not necessarily related (although undoubtedly some patients with MCI will be at the very early stages of AD).

The concentration on improvement from baseline rather than reduction of expected decline has been integral to the NICE decision. In reviewing their guidance on the use of these drugs, they asked the pharmaceutical companies to provide trial data on placebo and treatment responders and non-responders as defined by their previous 2001 guidance.[17] A responder would be a patient who, after six months of treatment, showed an improvement or no decline in the very brief screening tool, the Mini-Mental State Examination (MMSE), and an improvement in function and global assessment.[18] What they also showed, using a published one-year trial of donepezil versus placebo, was that the magnitude of MMSE change was similar in both groups of 'responders', but that the percentages were naturally greater in the treated group (42%) than in the placebo group (34%). Those untreated patients in the placebo group who did not satisfy the responder definition did markedly worse on the MMSE than the so-called non-responders on treatment (see *Figure 2*). This clearly demonstrated a drug effect in all patients and indicated that those who are deteriorating on treatment will still be better off than those left untreated, even based on a narrow view of outcome like the MMSE.

This narrow view of efficacy in the condition, which expects improvement rather than reduced worsening, has led some agencies to see the ChEIs as not cost-effective. Wallin et al. have argued for the cost-effectiveness of ChEIs (in this case, tacrine) by looking at other outcomes.[20] They found

Figure 2: Responders and Non-responders in a One-year Placebo-controlled Trial of Donepezil versus Placebo

The Nordic trial using the responder analysis from 1st NICE guidance (TA. No. 19)



(n=142 on donepezil/n=144 on placebo)

that the mortality rate did not differ between their different outcome groups, but that treated patients improved or remained stable to the extent that it prolonged the time until the need for nursing-home placement, suggesting a reduced stay in costly nursing-home care, thus indicating that ChEIs are cost-effective. This study supports that of Knopman et al., who demonstrated that patients treated with a high dose of the ChEI tacrine were less likely to need nursing-home placement compared with those receiving lower doses.[21]

The Notion of Improvement and Quality of Life

Cognitive function, not just memory, is influenced by the attention and concentration deficits that are prone to fluctuate in dementia. When patients and care-givers seek treatment, they often state that while improvements in memory would be desirable, memory impairment *per se* is manageable, whereas the changes in behaviour and function and personality are not. Quality of life for the patient and care-giver is naturally a major concern and while cognition, or at least memory, has been an easily measurable target, it does not always reflect the entirety of the disability that dementia causes. Any treatment that can prevent that disability from worsening, with its concomitant reduction in quality of life, must be seen as clinically important. Patients with AD can achieve years of good and enjoyable quality of life if the symptoms are stabilised and, of course, the earlier this stabilisation occurs in the course of the disease the closer we can approximate the effect of a cure. To clinicians, patients and their families, preservation of critical aspects of function, or the delay in clinical decline, is as important as any early improvements in cognition. Care-givers, of course, can also be affected by the rapid decline in language, comprehension and orientation, which impacts on the patients' ability to cope with basic daily activities such as communicating and toileting, and those patients who retain insight can become extremely angry and frustrated as a result. Quality of life for the patient is markedly enhanced by the retention of their independence of thought, allowing the patient the ability to express their desires and the possibility that they understand when they need help and retain the insight to call for it. In more severe AD patients, even small changes in function such as poverty of speech, the inability to comprehend simple commands such as helping with dressing and feeding or the patient no longer wandering at night can have a profound effect on quality of life of both patient and care-giver. If the decline in these functions remains unabated, it will lead to the patient being isolated from their families and an increase in the amount of direct care needed.

The notion of improvement as the only relevant treatment benefit is unrealistic for many patients who progress to the moderate or severe stages of AD. It is the emergence or worsening of behaviours such as agitation, wandering, aggression and delusions that cause most distress to care-givers and are ultimately the deciding factor on whether patients can be maintained in their own home or have to be moved into residential or nursing-home care. In the absence of an improvement, stabilisation of the illness and the prevention of worsening in functional activities, along with the emergence or worsening of distressing behaviours, should be seen as a clinically meaningful treatment goal.

There is an increasing body of evidence that the use of ChEIs or memantine offers considerable respite from the more distressing aspects of the disease in this group of patients who are most in need of treatment. For some reason, these benefits are not accepted by those who demand to see improvements from baseline in cognitive scores as the primary outcome – a hurdle uniquely created for AD and not for other similarly chronic deteriorating illnesses. We need a more realistic and holistic approach to treatment outcomes in neurodegenerative diseases, and lack of clinical worsening as a goal should be part of that. ■

1. Hughes CP, Berg L, Danziger WL, et al., A new clinical scale for the staging of dementia, *British Journal of Psychiatry*, 1982;140:566–72.
2. Mayeux R, Sano M, Treatment of Alzheimer's disease, *N Engl J Med*, 1999;341:1670–79.
3. Clegg A, Bryant J, Nicholson T, et al., Clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine for Alzheimer's disease, A systematic review, *Int J Technol Assess Health Care*, 2002;18(3):497–507.
4. Trinh N H, Hoblyn J, Mohanty S, et al., Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in alzheimer's disease: a meta-analysis, *JAMA*, 2003;289:210–16.
5. Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt H P, et al., Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials, *BMJ*, 2005;6(331)(7512):321–7.
6. Bullock R, The wrong trousers – Is marketing acetylcholinesterase inhibitors as cognitive enhancers the best strategy?, The newsletter for healthcare professionals working in AD: *Knowledge*, Autumn/Winter 1997;7.
7. Winblad B, Brodaty H, Gauthier S, et al., Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success?, *Int J Geriatr Psychiatry*, 2001;16:653–66.
8. Rosen W G, Mohs R C, Davis K L, A new rating scale for Alzheimer's Disease, *Am J Psychiatry*, 1984;141:1356–64.
9. Davis KL, Thal LJ, Camzu ER, et al., A double-blind placebo-controlled multicentre study of tacrine for Alzheimer's disease. The Tacrine Collaborative Study Group, *New Engl J Med*, 1992;327(18):1253–9.
10. Rogers SL, Farlow MD, Doody RS, et al., A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease, *Neurology*, 1998;50:136–45.
11. Corey-Bloom J, Anand R, Veach J, A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease, *International Journal of Geriatric Psychopharmacology*, 1998;1:55–65.
12. Stern RG, Mohs RC, Davidson MT, et al., A longitudinal study of Alzheimer's disease: measurement, rate, and predictors of cognitive deterioration, *Am J Psychiatry*, 1994;151:390–96.
13. Raskind M, Kumar V, Malaty L, et al., Rivastigmine for Alzheimer's Disease: Improvement versus reduced worsening, Primary Care Companion, *J Clin Psych*, 2000;2(4):134–8.
14. Wilkinson D, Anderson HF, Prevention of the worsening of clinical symptoms in moderate to severe Alzheimer's disease in patients treated with memantine, Poster presentation EFNS Glasgow 2006.
15. National Institute for Health and Clinical Excellence, Final Appraisal Determination, donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's Disease, 2006;www.nice.org.uk/TA111.
16. Petersen RC, Thomas RG, Grundman M, et al., for the Alzheimer's Disease Cooperative Study Group, Vitamin E and donepezil for the treatment of mild cognitive impairment, *N Engl J Med*, 2005;352(23):2379–88.
17. National Institute for Health and Clinical Excellence Technology Appraisal No 19, Guidance on the use of donepezil, rivastigmine and galantamine for the treatment of Alzheimer's Disease, 2001;www.nice.org.uk/guidance/TA19.
18. Folstein MF, Folstein SE, McHugh PR, 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician, *J Psychiatr Res* 1975;12:189–98.
19. Winblad B, Engedal K, Soininen HR, et al., and the Donepezil Nordic Study Group, A one-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD, *Neurology*, 2001;57:489–96.
20. Wallin AK, Gustafson L, Sjögren M, et al., Five-year outcome of cholinergic treatment of Alzheimer's disease: early response predicts prolonged time until nursing home placement, but does not alter life expectancy, *Dementia and Geriatric Cognitive Disorders*, 2004;18:197–206.
21. Knopman D, Schneider L, Davis K, et al., Long-term tacrine (Cognex) treatment: effects on nursing home placement and mortality, *Neurology*, 1996;47:166–77.