Pharmacotherapy of Alzheimer's disease

David Wilkinson

Abstract

Pharmacotherapy of Alzheimer's disease (AD) has progressed in the past ten years from the use of psychotropic medications for sedation to the use of rational treatments aimed at neurotransmitter replacement. The acetylcholinesterase inhibitors (AChEIs) donepezil, rivastigmine and galantamine have shown consistent efficacy across the spectrum of very mild/mild/moderate and severe AD. They also improve non-cognitive aspects of AD (e.g. neuropsychiatric symptoms, caregiver burden, activities of daily living). Donepezil has been shown to be effective against placebo for 1 year, and results of trials of ChEIs in other types of dementia (e.g. vascular dementia, dementia with Lewy bodies, Parkinson's disease) have also been positive. Memantine, an N-methyl-D-aspartic acid receptor antagonist, influencing glutamate transmission, has been approved for moderate to severe AD. It has a better tolerability profile than the AChEIs and seems to have particular advantages on the non-cognitive symptoms related to agitation and language. All the compounds improve attention and alertness and have global benefits for patient and carer, which are not always reflected in improvements in cognitive scores. Future treatments are being sought that may influence the underlying amyloid pathology and have a more disease-modifying effect.

Keywords Alzheimer's disease; cholinesterase inhibitors; donepezil; rivastigmine; galantamine; memantine

Alois Alzheimer's first described the condition that bears his name more than 100 years ago, and until the past 10 years the condition has been largely managed, rather than treated, with many community supports for the informal carers, often culminating in a move into residential or nursing home care. Pharmacotherapy was limited to the use of tranquillizers and antidepressants, used outside their licensed indications to control behavioural disturbances. However, drugs are now licensed to treat Alzheimer's disease (AD) (e.g. donepezil, rivastigmine, galantamine and memantine). These agents have provided clinicians with not only rational treatment options, but also have provided an incentive for more accurate diagnoses. The positive effects of these drugs on cognition have been confirmed in numerous placebo-controlled trials and their clinical utility further demonstrated in clinical practice. More recent work on the effects of acetylcholinesterase inhibitors (AChEIs) on behavioural symptoms, activities of daily living and caregivers' burdens have also been encouraging. Several clinical trials also indicate their efficacy in other dementias (e.g. vascular dementia, dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD)).

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Measuring outcomes

The outcome of treatment has focused on the measurement of subtle changes in cognition largely because they are easily measurable rather than because they encompass the essence of the disease, which is predominantly behavioural. This has posed a considerable problem for a disorder that by definition is relentlessly deteriorating, particularly when the test that is most used, the Mini-Mental State Examination (MMSE), has poor test–retest reliability and may not decline year to year.[1] Translating the clear advantages found in group mean responses from placebo-controlled trials into an individual patient's response is misguided, because we do not have the placebo patient to compare with, only the patient's own baseline. For example, the advantage over placebo clearly apparent in the trials can occur even though the patient may have declined below their own baseline (Figures 1 and 2). Unfortunately, clinical guidelines often demand improvement, so evidence of individual decline is often seen as reason to stop therapy. This seems to be a problem peculiar to dementia, because discontinuing therapy in a patient with another chronic condition (such as Parkinson's disease (PD), hypertension, angina or diabetes), who has become worse whilst on treatment, would not be acceptable. Indeed, many patients and carers do not ask for improvement but say they would be happy if the condition did not worsen or if the inevitable decline were lessened. The use of cognitive scales alone as an arbiter of treatment success has proved counterproductive in clinical practice and there is a need to look more holistically at the patient response; relying less on change in a crude cognitive score and more on assessing measures such as behavioural or non-cognitive symptoms, quality of life and carer burden to assess the clinical improvement overall.

Treatment strategies

The finding of impaired synthesis and secretion of acetylcholine (ACh) in cholinergic neurons in brains of AD patients combined with the finding of low levels of choline acetyltransferase in the AD brain led workers to believe that increasing acetylcholine levels in the brain offered a strategy for treatment of AD similar to L-dopa for PD. Despite this initial finding, it is now clear that cholinergic deficits are not specific to AD. Indeed, the

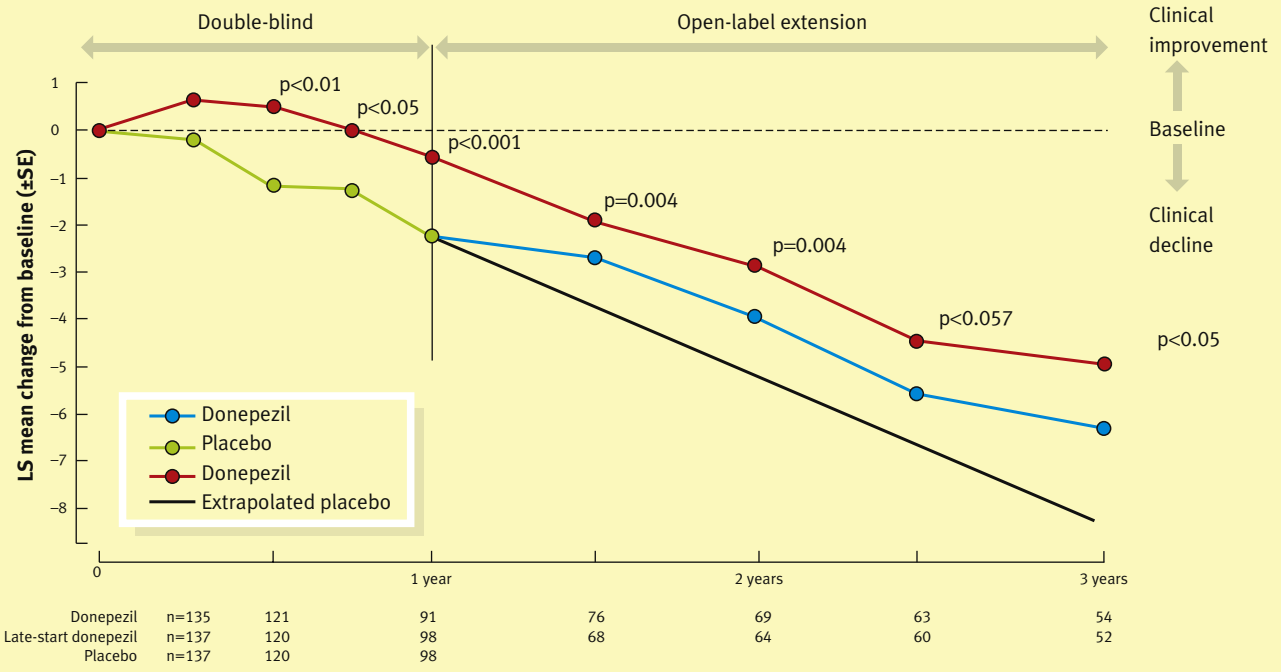
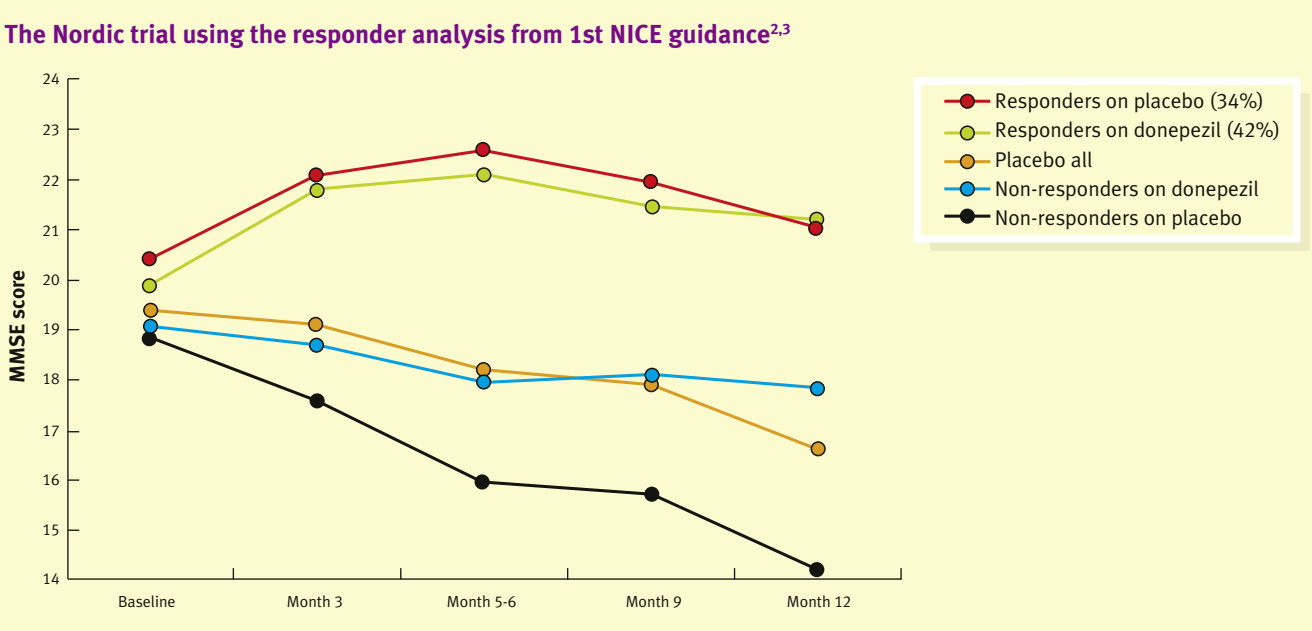


Figure 1

pathology initially ascribed to AD is not as specific as was once thought. There are few dementia cases diagnosed using clinical criteria that do not have some evidence of mixed pathology at post-mortem. It is therefore not surprising that drugs used to treat cholinergic deficits may exert effects on a range of dementia pathologies through some common pathways. AD is a complex brain disorder and is as much about the imbalance between systems as any individual deficit. In fact, there are many other



Definition response at 5–6 months and studying that cohort retro- and prospectively. Proportion of responders was lower in placebo than in drug cohort (34% and 42%, respectively). Y-axis does not represent full scale of MMSE. Despite placebo responders achieving as high a response on MMSE as donepezil responders, so-called non-responders on treatment achieved better results than non-responders on placebo.

Figure 2