

The treatment of dementia: appendix



What is the evidence for the efficacy of drug treatments?

Issues in interpreting the results of RCTs

Quality of reporting and methodology of the studies of drug treatment in dementia varies, and many issues need to be considered when interpreting their results. These include the characteristics of the participants in the studies, the outcome measures used, the length of study duration, the effects of attrition, and the relationship between statistical significance and clinical significance.

The differences in the scores between treatments identified in clinical trials, though statistically significant, may not represent a clinically meaningful change when the range of possible scores is considered (e.g. 0 to 70 for ADAS-cog). Data on the proportion of patients who respond to active and placebo treatments with a pre-specified clinically significant change in scores (e.g. 4 or more on the ADAS-cog) are rarely provided, but would be helpful in identifying the number of patients that gain a worthwhile benefit from treatment.

Clinical trials of drugs in dementia, with a few exceptions, have been industry-sponsored and placebo-controlled. There is little evidence from head-to-head studies with which to evaluate the benefit/harms of one drug compared with another.

The European Medicines Agency draft guideline on the development of medicinal products for the treatment of dementia suggests that, in order to show symptomatic improvement, robust and clinically meaningful changes in favour of the drug over placebo are required in both cognitive and functional (activities of daily living) endpoints. Overall clinical response (global assessment) is considered a secondary endpoint.²²

Alzheimer's disease

A systematic review and meta-analysis of 16 placebo-controlled trials (≥ 12 weeks) in people with Alzheimer's disease ($n=7,954$) identified that treatment with AChIs resulted in a 9%, (95%CI 6% to 12%) improvement in the

Rating scales used in dementia

An overview of some of the rating scales used in dementia can be found at www.alzheimer-insights.com/insights/vol2no3/vol2no3.htm. **Table 1** contains a list of the abbreviations for the rating scales referred to in this appendix.

Table 1: Rating scales used for the assessment of dementia

ADAS-cog	Alzheimer's Disease Assessment Scale – cognitive subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study – Activities of Daily Living inventory
ADFACS	Alzheimer's Disease Functional Assessment and Change Scale
CGIC	Clinical Global Impression of Change
CGC-plus	Clinical Global Change Scale – plus input from families/carers
CIBIC-plus	Clinician Interview-Based Impression of Change plus caregiver input
MMSE	Mini Mental State Examination
NPI	Neuropsychiatric Inventory
PDS	Progressive Deterioration Scale
QoL-AD	Quality of Life – Alzheimer's Disease
SIB	Severe Impairment Battery

proportion of global responders, but at the expense of an 8% (95%CI 5% to 11%) increase in adverse events, most of which led to study withdrawal.¹³ The number of patients who needed to be treated (NNT) with an AChI compared with placebo in order to demonstrate a minimal improvement or better 12 (95%CI 6 to 16) was similar to the number of patients who needed to be treated to produce one additional adverse event (NNH) 12 (95% 10 to 18).¹³

A subsequent systematic review of 22 studies questioned the scientific basis for recommending AChIs, because of the small

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clinical benefits shown and the methodological weaknesses of the studies. Nineteen out of 22 RCTs showed statistically significant differences between treatment groups and placebo, in favour of the AChIs. However, the mean gains of 1.5 to 3.9 points in cognitive function, as measured with the 70-point ADAS-cog, fell below the 4 points that a panel of experts from the US Food and Drug Administration proposed as the minimum for a clinically important effect.²³

A systematic review of 27 RCTs (carried out for NICE TAG 111) concluded that the AChIs were beneficial when assessed using cognitive decline measures with **mild-to-moderately severe** Alzheimer's disease.¹⁰ However, drugs showed inconsistent benefits with regard to measures of global outcomes, function, or behaviour and mood. A selection of the findings from the meta-analyses of efficacy for each of the AChIs from the NICE guidance are summarised in **Panel 2**.¹¹

Results from two trials of memantine monotherapy in people with **moderately severe-to-severe dementia** (mostly Alzheimer's disease) were inconsistent. For example, whereas one study identified a statistically significant improvement for deterioration compared with placebo as assessed by the SIB (−4.0 vs. −10.1, $P < 0.001$), another found no significant

difference (−2.0 vs. −2.5, $P = 0.616$). One trial compared the effects of adding memantine to existing donepezil treatment with donepezil alone and identified less deterioration in cognitive function (e.g. SIB: 0.9 vs. −2.5, $P < 0.001$), activities of daily living (ADCS-ADL19: −2.0 vs. −3.4, $P = 0.03$) and global outcomes (CIBIC-plus: 4.4 vs. 4.7, $P = 0.03$) in those receiving the combined treatment.¹⁰

Two six-month RCTs, both including about 250 patients with **severe Alzheimer's disease**, have identified statistically significantly less deterioration with donepezil in cognitive decline compared with placebo.^{24,25} However, the difference (about 5–6 points on the 100-point SIB scale) is of uncertain clinical significance. Although one study suggested a statistically significant smaller decline in activities of daily living scores relative to placebo (ADCS-ADL-severe: 1.7 points, $P = 0.03$),²⁴ the other identified no difference.²⁵

Vascular dementia

AChIs and memantine are not currently licensed for the treatment of vascular dementia. Donepezil (5 and 10mg) and galantamine (24mg daily) have been shown to have a small treatment effect over a 24-week period on cognition (about 2 points on the ADAS-cog) which has not been shown to have any significant benefit to the person with

Panel 2: Selected efficacy outcome measures from the meta-analyses of RCTs of AChIs vs. placebo in Alzheimer's disease¹¹

Donepezil

There was a statistically significant improvement in cognition on the ADAS-cog scale for donepezil compared with placebo (meta-analysis, three trials, weighted mean difference [WMD] 5mg/day: −2.5, 95%CI −3.3 to −1.8; WMD 10mg/day: −3.0, 95%CI −3.9 to −2.1) and in global outcomes as assessed by the CGIC or CIBIC-plus. However, for functional outcomes, such as rates of institutionalisation or progression of disability, statistically significant benefits were not found in all trials. Quality of life estimates showed variable results between studies. Subgroup analyses conducted by the Medical Research Council Biostatistics Unit (MRCBU) by severity of cognitive impairment using data on trials of at least 24 weeks duration reported a change in ADAS-cog of −2.0 (99%CI −3.4 to −0.7) for mild (MMSE 21 or more); −3.9 (99%CI −7.1 to 0.8) for moderate (MMSE 15 to 20); and −3.6 (99%CI −8.0 to 0.7) for people with moderately severe (MMSE 10 to 14) Alzheimer's disease.

Galantamine

There was a statistically significant improvement in ADAS-cog for galantamine (meta-analysis, four trials, 24mg/day, WMD −3.3 (95%CI −3.9 to −2.7) versus placebo. However, no statistically significant differences were seen in global outcomes (CIBIC-plus). Results of five studies showed that there was less deterioration in activities of daily living compared with placebo. Subgroup analyses conducted by the MRCBU by severity of cognitive impairment using data on trials of at least 24 weeks duration reported a change in ADAS-cog of −2.4 (99%CI −3.3 to −1.5) for mild; −4.1 (99%CI −5.0 to −3.2) for moderate including moderately severe (MMSE 10 to 20); and −6.1 (99%CI −7.9 to −4.3) for people with moderately severe (MMSE 10 to 14) Alzheimer's disease.

Rivastigmine

There was a statistically significant improvement for rivastigmine (6–12mg/day) in ADAS-cog (meta-analysis, two trials, WMD −3.1, 95%CI −3.8 to −2.4) compared with placebo. However, there was considerable heterogeneity between studies. Statistically significant differences were seen in global outcomes (CIBIC-plus) for high-dose rivastigmine only. Three out of four studies showed statistically significant improvements in functional outcomes (PDS). Subgroup analyses conducted by the MRCBU by severity of cognitive impairment using data on trials of at least 24 weeks duration reported a change in ADAS-cog of −1.2 (99%CI −2.1 to −0.3) for mild; −3.7 (99%CI −5.1 to −2.3) for moderate including moderately severe (MMSE 10 to 20); and −5.0 (99%CI −7.4 to −2.6) for people with moderately severe (MMSE 10 to 14) Alzheimer's disease.

dementia in terms of global functioning and activities of daily living.³

A recent systematic review and meta-analysis of efficacy and adverse effects in vascular dementia identified three donepezil, two galantamine, one rivastigmine and two memantine RCTs versus placebo (6 months treatment, n=5,183). Small, statistically significant improvements in cognition, of uncertain clinical benefit, were identified in people with mild-to-moderate vascular dementia. Changes in ADAS-cog relative to placebo ranged from -1.10 (95%CI -2.15 to -0.05) for rivastigmine 12mg/daily to -2.17 (95%CI -2.98 to -1.35) for donepezil 10mg/daily. Statistically significant improvements were only seen with donepezil 5mg with regard to CGIC scores (OR 1.51, 95% 1.11 to 2.07). No behavioural or functional benefits were observed, except with donepezil 10mg on the ADFACS (-0.95, 95%CI -1.74 to -0.16). Compared with placebo, more dropouts and adverse events (anorexia, nausea, vomiting, diarrhoea, and insomnia) occurred with the AChIs, but not with memantine.²⁶

Dementia with Lewy bodies (DLB)

There is weak evidence for a benefit for rivastigmine from one RCT in people with DLB.^{27,28} Over a 20-week period, patients with probable DLB (n=120) obtained no statistically significant improvement in cognitive symptoms (MMSE), global functioning (CGC-plus), or behavioural symptoms (NPI-4 or NPI-10) (intention to treat analyses). However, some patients were reported as showing substantial improvements in behavioural symptoms, and secondary analysis of those patients completing the study (n=92) identified significant improvements on the neuropsychiatric inventory

(NPI-4 score difference 3.4, 95%CI 0.06 to 6.6, P=0.01). Significantly more patients experienced nausea, vomiting, anorexia, and somnolence with rivastigmine compared with placebo.²⁸

A Clinical Evidence review (search date February 2006) found no randomised controlled trials of donepezil, galantamine or memantine in patients with DLB.²⁹

Mild cognitive impairment (MCI)

There is little evidence to support the use of AChIs or memantine in MCI. Two studies (n=782) were identified in a Cochrane review of donepezil in 2006. Although one study demonstrated a modest benefit in cognitive function when assessed by ADAS-cog (mean difference 1.90, 95%CI 0.51 to 3.29, P=0.007) over 24 weeks, no benefit was shown for four other measures of cognition. In the other study, fewer people were diagnosed with dementia after one year on donepezil (6.3% vs. 14.7%, P=0.003) compared with placebo, although this benefit was not maintained at three years (24.9% vs. 28.2%, P=0.4).³⁰

Two studies of galantamine in MCI (n=2,057) suggest a marginal benefit over placebo. However, its use is not recommended because of an unexplained increase in mortality seen in the studies. Neither study found significant treatment effect in terms of ADAS-cog at 12 months or 24 months. However, combining data from both trials, 12–24mg/day galantamine resulted in a lower rate of conversion to dementia compared with placebo (OR 0.74, 95%CI 0.58 to 0.94) at 24 months as assessed by a change of the clinical dementia rating score from 0.5 to ≥ 1.0 .³¹

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