Medications for treating people with dementia: summary of evidence on cost-effectiveness

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Medications play an important role in the treatment of dementia, seeking to address problems with cognition, behaviour and depression. In this summary note, we consider economic evidence concerning anti-dementia medications (including combination therapy), antipsychotics and antidepressants.

Key points:

- Cholinesterase inhibitors, which are the most widely used anti-dementia medications, are effective in treating Alzheimer's disease, not only in the mild-to-moderate stage but also when symptoms become more severe. There is also a strong economic case for their use: they are more cost-effective than placebo ('best supportive care'), and probably also cost-saving.
- The evidence in support of combination therapy (a cholinesterase inhibitor plus memantine) is less clear on clinical grounds, and there does not appear to be a strong economic case.
- There is no clinical or economic case for using antidepressant medication to treat people with Alzheimer's disease who have comorbid depression.
- There are potentially serious risks associated with using antipsychotic medications to treat the psychological and behavioural symptoms of dementia, and there is no economic case for their use.

ANTI-DEMENTIA MEDICATIONS

What are they?

Anti-dementia medications are widely considered to be effective in the treatment of Alzheimer's disease, at least in the mild-to-moderate stages. Acetylcholinsterase inhibitor (AChEI) medications (often called cholinesterase inhibitors) – donepezil (formerly marketed as Aricept in the UK), rivastigmine (formerly Exelon) and galantamine (Reminyl) - are recommended by current NICE guidance (2011; currently being revised) for people with mild-to-moderate Alzheimer's disease (AD) [1]. There is also now some evidence that cholinesterase inhibitors (particularly donepezil) can be effective for people with severe AD. Memantine (formerly marketed as Ebixa) has a different mechanism of action (a NMDA receptor antagonist) and is recommended by NICE for people with severe AD, and for people with moderate disease who cannot tolerate cholinesterase inhibitors. Combinations of these medications are increasingly being used.

For people with dementia with Lewy bodies or Parkinson's disease dementia, NICE recommends that cholinesterase inhibitors might be prescribed if there are distressful non-cognitive symptoms (such as hallucinations) or behaviours that challenge. Most evidence on anti-dementia medications relates to patients with AD or mixed dementias.

International evidence suggests that the effectiveness and cost-effectiveness of these medications depend on the severity of AD. Most evidence relates to these medications taken as monotherapy, but there is growing evidence on these medications taken in combination. Here we first look at monotherapy and then at combination therapy, summarising the evidence on effectiveness and cost-effectiveness.

Monotherapy

Effectiveness

The technology appraisal commissioned by what is now the National Institute for Health and Care Excellence (NICE) is the best source of evidence on effectiveness. The appraisal is currently being revisited. The 2012 appraisal concluded that, for people with *mild-to-moderate* AD, donepezil (10mg daily), galantamine and rivastigmine had positive impacts on cognition, although the magnitude of effect has been debated [2]. The appraisal was less supportive of memantine at that level of severity.

The effects of these medications on *global and functional outcomes* were mixed with galantamine, while better functional and global outcomes were reported with rivastigmine. Functional outcomes include an individual's ability in the activities of daily living such as bathing, feeding and other personal care tasks. In terms of *behavioural outcomes*, no significant effects were found with galantamine and rivastigmine. Memantine showed a significantly positive effect in improving global outcomes. When donepezil was compared with rivastigmine, there were significant differences in functional and global outcomes in favour of rivastigmine. Relative to donepezil or galantamine, a significantly better impact on behavioural outcomes (such as anxiety, agitation and aggression) was found with rivastigmine.

A more recent systematic review and meta-analysis on memantine monotherapy compared to placebo for treating people with Alzheimer's disease concluded that there were significant improvements in cognitive function, behavioural disturbances, activities of daily living and global function [5].

There is less evidence for patients with *more severe* AD. Cholinesterase inhibitors can achieve modest improvements in cognition, functioning and clinical global impression for people with *moderate-to-severe* AD [6, 7] and people with *severe* AD [8, 9]. Memantine is effective in moderate and severe AD [10]. The DOMINO trial, funded by the Medical Research Council and Alzheimer's Society and conducted in the UK, was a double-blind, randomised controlled trial. It examined a number of medication options for patients with moderate-to-severe AD, including continued use of donepezil as monotherapy for patients who had been treated with donepezil through the mild-to-moderate stages of their disease. Continued treatment with donepezil was associated with cognitive and functional benefits over 12 months compared to tapering and discontinuing this medication [11].

Cost-effectiveness

All three cholinesterase inhibitors and memantine are now off patent in the UK, and so their prices are considerably lower today than at the time when some of the economic evaluation studies were conducted, and when NICE commissioned the appraisal published in 2012 [2]. This means that previous cost-effectiveness conclusions, including between medications, may need to be revised.

That NICE appraisal [2] and a related paper [12] had updated previous NICE guidance on cholinesterase inhibitors and memantine. It reached slightly different cost-effectiveness conclusions from the previous NICE appraisal in 2004: the changes were due to lower medication prices and the emergence of better effects over time. From the modelling analyses, the 2012 appraisal concluded that all cholinesterase inhibitors were more cost-

effective than 'best supportive care' for people with *mild-to-moderate* AD. There was a 99% probability that the cholinesterase inhibitors were more cost-effective than best supportive care by reference to standard NICE thresholds, assuming no effects on longevity and that the medication costs were offset by delaying institutional admissions. In fact, it was very likely that cholinesterase inhibitors were actually cost-*saving*. Donepezil was found to be the most favourable option for people with mild-to-moderate AD: it was less expensive and more effective, both when compared to other medications and in comparison to best supportive care.

Later analyses by the same research team focused on changes in the cost-effectiveness of donepezil in response to a range of assumptions about the costs and effects of this medication compared to best supportive care [13]. These results showed that cost-effectiveness conclusions were highly sensitive to assumptions about costs.

For people with mild-to-moderate AD, cholinesterase inhibitors enhance the effects of maintenance cognitive stimulation therapy and improve its cost-effectiveness [14].

For people with *moderate-to-severe* AD, conclusions from the NICE appraisal were different. There had been few trials with relevant effectiveness or cost-effectiveness data by the time of that appraisal. The economic modelling found a probability of only 38% that memantine would be cost-effective at the NICE willingness-to-pay threshold of £30,000 per QALY [2]. Subsequently, the DOMINO randomised controlled trial – mentioned earlier - offered new economic evidence for treatment of patients with more severe AD who had already been treated with donepezil at earlier disease stages. It was able to examine cost-effectiveness with medications now at their much lower current generic prices [15]. It found that the probability that donepezil was more cost-effective than placebo for people with moderate-to-severe AD was high, implying that there was both a clinical and an economic case to continue treatment with this medication even when AD become moderate or severe, rather than discontinue it (the current NICE recommendation). The cost-effectiveness of donepezil continuation compared to discontinuation was demonstrated when looking at each of a number of outcomes - cognition, functioning (activities of daily living) and health-related quality of life (QALYs) – and whether costs measured only health and social care service use or additionally the costs of unpaid care.

The primary analyses in the DOMINO study were based on outcome and cost data collected over a 1-year period, but it was also possible to look at the risk of nursing home placement over a 4-year period [16]. Donepezil discontinuation increased the risk of such placement in the first year, but not over the full 4-year period.

Combination therapy

Effectiveness

Increasingly, combinations of a cholinesterase inhibitor with memantine are being used, certainly in the mild-to-moderate stage of Alzheimer's disease, but also being tried for people with more severe symptoms.

The 2004 appraisal commissioned by NICE included analyses that suggested significant positive effects of combination therapy (memantine and donepezil) in improving cognition, functional, global, and behavioural outcomes for people with *mild-to-moderate* AD. The 2012 appraisal found only one new study (of galantamine combined with memantine [17]) which showed no significant benefits of combination therapy due to the possible drug interactions which might cancel out individual treatment effects. The appraisal pooled data from trials combining memantine with cholinesterase inhibitor and found no additional benefit over cholinesterase inhibitor alone.

For people with moderate-to-severe AD, the DOMINO study found no significant differences in cognition, functioning (activities of daily living), behavioural outcomes or carer health status between treatment with donepezil alone and treatment with donepezil and memantine combined [11]. There were also no differences in QALYs [14].

A later systematic review and meta-analysis, including studies published up to 2014, was more supportive of combination therapy [18]. It concluded that, compared to monotherapy, combination therapy with cholinesterase inhibitors and memantine improved cognition, behaviour, activities of daily living and overall clinical impression.

Cost-effectiveness

There is very little economic evidence on the cost-effectiveness of combinations of medication for treating AD. For people with *mild-to-moderate AD* we could find no UK studies, and so conducted new economic modelling of combination therapy using evidence from trials and economic models developed for some other countries. For people with *moderate-to-severe AD* we could draw on the DOMINO study.

In our new simulation modelling, combination therapy was defined as one of the cholinesterase inhibitors plus memantine, and we compared costs and effects with cholinesterase inhibitor monotherapy, building on similar work undertaken in France and the USA [19, 20]. Costs were specifically for England, based on estimates in the 2014 revision of the *Dementia UK* report [21]. It was assumed that all people with *mild-to-moderate AD* lived in the community at the start of the model, but some would either move to institutional care or die over the 7-year period used in the model. Cost-effectiveness analyses were performed from three perspectives (health care alone, health and social care, and societal including unpaid care costs). All economic analyses showed the same results: combination therapy was more cost-effective than monotherapy.

In contrast, the DOMINO trial, which included people with *moderate-or-severe AD* who were already being treated with donepezil, concluded that adding memantine to donepezil was not more cost-effective than donepezil alone by reference to NICE thresholds for QALY gains [15]. The economic case for combination therapy also looked weak by reference to the two primary outcomes selected a priori for the trial (cognition and activities of daily living).

We therefore conclude that the economic case for combining memantine with a cholinesterase inhibitors is unclear. Although our economic modelling of treatment options for people with mild-to-moderate AD suggests that combination therapy is cost-effective, the evidence from the DOMINO trial of treatments for people with more severe AD did not find evidence of cost-effectiveness.

ANTIDEPRESSANT MEDICATIONS

The most thorough study of antidepressant medication treatment for people with probable or possible Alzheimer's disease and comorbid depression was the HTA-SADD trial. Two commonly used antidepressants (sertraline and mirtazapine) were compared to placebo in a parallel-group, double-blind design, with outcomes assessed at both 13 and 39 weeks [22]. The trial found no clinical advantage (measured by the Cornell Scale for Depression in Dementia) for either sertraline or mirtazapine compared to placebo. Indeed, there were more adverse events for patients treated with antidepressants compared to those receiving placebo.

The economic evaluation embedded within the SADD trial found no significant differences in costs for any hospital-based or community health or social care services between the groups over 39 weeks [23]. There were also no differences in QALYs over this period.

However, there appeared to be a small cost-effectiveness advantage for mirtazapine over sertraline and placebo when account was taken of the time spent by family members and others on unpaid care and support. The estimated costs of unpaid care were lower in the group treated with mirtazapine than in the other two groups. This may have been because mirtazapine might have helped patients to sleep better, thus reducing the need for carer inputs, but whether that is a justification for using this treatment is debateable.

ANTIPSYCHOTIC MEDICATIONS

Many people with dementia display psychological and behavioural symptoms such as agitation, aggression, wandering and sleep disturbance. These are distressing for the individual and stressful for their carers. In the past, antipsychotic medications were quite widely prescribed to manage these symptoms. However, an influential review of the available evidence concluded that antipsychotic medications 'appear to have only a limited positive effect in treating these symptoms but can cause significant harm to people with dementia' [24, p.5]. Among the harms are a high risk of stroke in the first few weeks after initiating antipsychotic treatment, and a doubling of the risk of mortality. The report strongly recommended that people with dementia should only receive antipsychotics when they really need them, and that use of these medications should be reduced across the NHS. Non-pharmacological management of psychological and behavioural symptoms should be more widely available.

Available *economic evidence* on the use of antipsychotics is mixed. The strongest evidence comes from the Clinical Antipsychotic Trial of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD) study conducted across 42 US sites. It looked at the clinical and economic case for three widely used antipsychotics (olanzapine, quetiapine and risperidone) compared to placebo using a double-blind randomised controlled trial design that included people with Alzheimer's disease who experience hallucinations, delusions or agitation. Costs over a 9-month period were lower for the placebo group than for any of the groups treated with antipsychotics [25]. The only outcome difference found in the trial was that placebo was better than olanzapine in relation to activities of daily living. In other words, antipsychotic treatment was not cost-effective.

A subsequently published study used modelling methods to compare olanzapine with no treatment for people with symptoms of agitation or psychosis related to AD [26]. It concluded that olanzapine was cost-effective. However, our view is that the CATIE trial provides stronger evidence, and we therefore conclude that there is no economic case for antipsychotic use.

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