

SUBMISSION ON BEHALF OF THE BRITISH GERIATRICS SOCIETY TO THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL: DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE

BACKGROUND

Alzheimer's disease (AD) is the most common cause of dementia and is a progressive neurodegenerative illness for which at present there is no cure. The management involves both nonpharmacological and pharmacological approaches. This submission will concentrate mostly on the acetylcholinesterase inhibitors (AChEI), donepezil, rivastigmine and galantamine as well as the NMDA receptor antagonist memantine and their use in AD. It is important however to mention in context other treatments that are used for patients with dementia.

DEMENTIA AND ALZHEIMER'S DISEASE

Dementia is a devastating neurodegenerative illness which causes a progressive and relentless cognitive and functional decline. It is accompanied by various degrees of behavioural symptomatology and leads inevitably to death. Dementia has an enormous impact on carers, extended families and society. According to an estimate from the World Health Organisation (WHO), dementia is responsible for more years lived with disability in people older than 60 years (11.2 per cent) than stroke (9.5 per cent), cardiovascular disease (5.0 per cent) or cancer (2.4 per cent)¹. The latest UK report on prevalence and costs indicates that there are 821,884 people with dementia costing £23 billion per year, Most of the cost – £12.4 billion per year – is met by unpaid carers. Social care costs are £9 billion, health care £1.2 billion and productivity losses £29 million. In terms of societal cost, dementia also posed by far the greatest economic burden at £23 billion compared to cancer at £12 billion, coronary heart disease at £8 billion and stroke at £5 billion².

AD is responsible for approximately two thirds of cases of dementia, followed by Vascular dementia (VaD) and Dementia with Lewy bodies (DLB)^{3,4}. Increasingly, however, prospective clinicopathological studies show an overlap between subtypes of dementia and cerebrovascular disease is the most common concomitant pathology⁵. This is particularly the case the older the population sample.

MANAGEMENT OF AD

There have been considerable advances in the understanding of the underlying pathways involved in AD. The precise cause of AD however remains unknown. There is no definitive diagnostic test so the clinical management involves establishing a diagnosis of "probable Alzheimer's Disease", and then intervention appropriate to the stage of the. **The National Dementia Strategy refers to the following: all people with dementia should have access to a pathway of care that delivers a rapid and competent specialist assessment, an accurate diagnosis, sensitively**

communicated to the person with dementia and their carers; and treatment, care and support provided as needed following diagnosis⁶. This appraisal is focused on pharmacological interventions which provide symptomatic relief. In most situations, management is likely to involve the treatment of neuropsychiatric or behavioural symptoms which can present at any stage of disease but are usually more common as AD progresses. These symptoms include apathy, mood problems, agitation, aggression and delusions and hallucinations. These features are common⁷⁻¹⁰, often difficult to treat¹¹ and are a much stronger predictor of both carer stress¹² and entry into institutional care than cognitive impairment¹³⁻¹⁵ and so are important targets for therapeutic intervention.

ACETYLCHOLINESTERASE INHIBITORS (AChEI)

The major neurochemical abnormality in AD is a deficit in the cholinergic system. AChEI were designed to inhibit the enzymes that degrade acetylcholine and so increase cholinergic activity. AChEI (Donepezil, rivastigmine, galantamine) have been shown in double blind placebo controlled trials to produce modest but significant changes in cognition, function and neuropsychiatric symptoms which are accompanied by significant improvements in global rating scales in patients with mild to moderate Alzheimer's disease¹⁶. Despite variations in the modes of action the efficacy of the drugs is similar¹⁶. A more recent systemic review and meta-analysis of the placebo-controlled studies came to similar conclusions but suggested there may be some subtle differences - adjusted indirect comparison of placebo-controlled data did not find statistically significant differences among drugs with regard to cognition, but found the relative risk of global response to be better with donepezil and rivastigmine compared with galantamine (relative risk = 1.63 and 1.42, respectively). Indirect comparisons also favored donepezil over galantamine with regard to behavior. Across trials, the incidence of adverse events was generally lowest for donepezil and highest for rivastigmine¹⁷.

The evidence is for up to one year in the double blind trials. Although difficult to interpret in the context of the placebo controlled limb, one study suggested benefit for donepezil in cognition and function for up to 2 years¹⁸. In a 2 year double blind placebo controlled comparison study, donepezil and rivastigmine were equipotent but more adverse events were seen with rivastigmine¹⁹. The data beyond 1 year for AChEI is mostly open label and should be interpreted with caution. However the projected decline²⁰ is accurate out to 3 years and the data shows that all AChEI appear to reduce the projected rate of cognitive decline at 3 years^{21,22}. Over 48 months use of galantamine, about one-third of patients showed little decline, while one-third showed important decline²³. There is some evidence that Nursing Home placement may be reduced^{24,25}.

The English National Dementia Strategy is predicated on early diagnosis of AD (UK Dementia Strategy 2009). European and US consensus statements refer to use of AChEI as soon as diagnosis is made^{26,27}. NICE treatment guidance restricts use of AChEI to moderate AD as defined by cognition only, using MMSE < 20²⁸. This is problematic in practice, attaching inappropriate significance to particular MMSE scores, rather than taking a holistic view of the patients functioning in everyday life. The available evidence suggests that effects of AChEI are the same in all stages of AD^{16,29} and that a delayed start to treatment is detrimental for patients³⁰. An

observational study from Spain suggested greater benefits in terms of cognition and functionality of starting donepezil in mild than moderate AD patients³¹.

The data suggests that patients, caregivers and physicians will still observe some decline on AChEI after a period of stabilization, but this may be slower and later than expected if the patients were left untreated. This applies across all domains of AD - not simply cognition - and function can be relatively preserved, even if cognitive scores are falling³².

On average, patients may return to their pre-treatment status between 9 and 12 months after treatment initiation. However, a return to pre-treatment level does not mean that the treatment effect has disappeared. At this point, the patient may still function better than he or she would have done without treatment. The length of treatment should depend on several individual patient factors. The earlier the diagnosis is made and the slower the rate of disease progression, the longer the treatment period will tend to be. Treatment duration must therefore be evaluated on an individual basis, and the patient's status compared with what would have been expected without treatment.

LIMITATIONS

There is a clear dose response relationship for AChEI and each drug should be increased to the maximum tolerated dose using a minimum of 4 weekly titration steps. While not a major problem there are potential difficulties with patients not reaching maximum dose and thus not achieving optimum benefit. Only donepezil is effective at the initial dose of 5mg but dose should still be increased to 10mg. AChEI appear to be well tolerated and safe. Contraindications are the presence of significant electrocardiographic abnormalities, peptic ulcer disease and significant chronic obstructive pulmonary disease. Adverse events are more common at time of initiation of treatment and dose increase and are mostly gastrointestinal – nausea, vomiting or diarrhoea which often respond to symptomatic treatment. Symptomatic bradycardia and syncope can occur but is rare³³. In one study the five most common side effects were, in order of frequency of presentation: nausea, agitation, vomiting, headache and fainting. In the long term, the most frequent side effects from AChEI, generally speaking, are muscle cramps, tremors, nightmares, nausea, vomiting, fatigue, vertigo and loss of weight³⁴.

There are difficulties with the decision on when to withdraw therapy. The effectiveness of AChEI will eventually wear off and this needs to be discussed with patients and carers at the outset when treatment is started and at intervals as they remain on therapy. Setting a fixed measurement, e.g. MMSE score, as a 'when to stop treatment limit' is not evidence based or clinically rational. The evidence relating to withdrawal is mainly with donepezil. Studies show that cognitive decline and emergence of adverse behaviours can occur after withdrawal when the drug was still having an effect^{35,36}. If a clinical evaluation is conducted with a view to stopping or switching treatment, it is crucial that all domains are evaluated and that the patient is evaluated at more than one point in time before the decision is made. If a trial of withdrawal is indicated then patients, carers and primary care physician must be advised of the possibility of acute cognitive and behavioural deterioration and the need to reintroduce medication as quickly as possible if deterioration is observed. The

ongoing DOMINO-AD trial should provide evidence to inform decisions about stopping donepezil treatment³⁷.

NEED FOR REGULAR FOLLOW UP AND REVIEW

Because AChEI are only symptomatic treatments, one cannot expect an initial cognitive improvement observed in the first few months of therapy to be sustained indefinitely. However, one should expect that the patient who is treated early and persistently with medication for AD will show less evidence of behavioural, functional, and cognitive deterioration over a period of time than one would expect in the absence of pharmacotherapy. Thus, treatment success includes not only short-term improvement of symptoms but also less decline over the long term. Determination of treatment success therefore also requires awareness of the typical progression of untreated AD³⁸. It is therefore important that patients are regularly reviewed by specialist services to advise on management particularly as AD is a progressive disorder. In addition NICE guidelines recommend regular follow up.

IMPORTANCE OF CONTINUING TREATMENT TO MAXIMISE BENEFITS

Treatment persistence is a crucial factor to delay patient functional and cognitive impairment. In the initial few weeks of treatment if significant adverse events occur then patients will need to stop that particular medication. However adverse events are not seen to the same extent with different AChEI so a trial of an alternative AChEI may be appropriate. In one naturalistic study, 14.5% of the patients showed intolerance to AChEI during the first 15 days. Of those patients who initially tolerated the treatment, 18.5% gave it up after a mean duration of 13.36 months and a mean dose of 7.5 mg/day of donepezil or 14.3 mg/day of galantamine. The mean duration of the treatment in patients who did not abandon the treatment was 25.4 months and the mean dose was 8.1 mg/day of donepezil or 20.0 mg/day of galantamine³⁹. Another study showed significant differences in the global treatment persistence among AChEI, with higher persistence in patients treated with donepezil compared to those who received rivastigmine, galantamine or memantine⁴⁰. The key for those staying on treatment seems to be an element of stabilisation⁴¹. In a study designed to address the possible benefits of continuation of treatment with donepezil, patients who had declined or were unchanged after 12-24 weeks were randomized to placebo or donepezil. Among patients for whom clinical benefit was uncertain, improvements in cognition and behaviour were observed for those who continued donepezil treatment compared with the group switched to placebo. Initial decline or stabilisation does not necessarily indicate a lack of efficacy, and the decision to discontinue treatment should be based on an evaluation of all domains (cognition, behaviour and ADL) and performed at several timepoints⁴².

SWITCHING OF MEDICATION

One difficulty in clinical practice concerns those patients who deteriorate rapidly despite treatment. The options from a clinical standpoint are to continue with existing treatment or to switch to an alternative AChEI, to add memantine to the existing AChEI or to switch to memantine (see memantine section for more details). There are

few well designed switching studies to guide decision making. All are open label and most refer to switching from donepezil. There are fewer studies on switching from galantamine, while rivastigmine is the most common agent patients are switched to. The data suggest that about 50% of patients will respond when switched to another AChEI^{43,44,45}. Because of this evidence and as seen in clinical practice if this strategy is deployed, we would recommend that the guidance include a statement that non-response or intolerance to one cholinesterase inhibitor does not mean that others should not be tried.

POLYPHARMACY

Major considerations in older people include comorbidity and polypharmacy. It is important to consider kidney and liver function. There are few important drug interactions with AChEI. There is an increasing recognition that medications with anticholinergic properties can affect the efficacy of AChEI. Concomitant use of anticholinergic medication is seen in about 35% patients^{46,47}. Patients with AD deserve to receive the optimum benefit from cholinesterase inhibitor treatment, which can only be achieved through diligent and appropriate use of concurrent pharmacotherapy.

CURRENT NICE GUIDANCE

The main conclusion of the first NICE Technology Appraisal of these drugs (No. 19, published Jan 2001)⁴⁸ which advocated that the three drugs should be made available in the NHS as one component of the management of those with mild and moderate AD was very welcome. The impression for those that used the medication regularly was that results in the clinic were at least as good as in the clinical trials. The recent NICE guidance²⁸ on the use of the medications caused a lot of controversy. For many clinicians there was a great difficulty around the area of making a diagnosis as early as possible (as promoted in the National Dementia Strategy) and then not being able to prescribe effective medication. until the patient had clinically deteriorated to the “moderate stage” on a purely cognitive screening scale (MMSE). We would suggest that this is a very simplistic view of AD and that judgement of severity and appropriateness of treatment is made on an overall assessment which takes into account functional and behavioural problems and the effect on the caregiver. The recommendation of discontinuation when a patient reaches the “automatic cutoff” on cognitive testing only of 10/30 on MMSE is also not rational. Interestingly, it does appear that medication usage has increased over the past 2-3 years.

MANAGEMENT OF NEUROPSYCHIATRIC / BEHAVIOURAL SYMPTOMS

This remains a very difficult area for clinicians. These symptoms are common and persistent in AD⁴⁹. Their presence is associated with worse prognosis. Neuropsychiatric symptoms, whatever their type, cause great distress to both patient and carer. In many situations the caregiver stress associated with neuropsychiatric symptoms is very high and is a significant precipitant of institutionalization of the patient. These symptoms are usually listed as: apathy, aberrant motor behaviour,

appetite disturbance, irritability, agitation / aggression, sleep disturbance, depression, anxiety, delusions, disinhibition, hallucinations, elation. These symptoms can occur in over 50% of patients in more advanced stages of the disease⁴⁹ but can manifest suddenly and unpredictably at any time. The difficulty lies in the pharmacological management of these symptoms. In many situations antipsychotics have been used. Only risperidone is licensed for short term use in patients with agitation where review should take place after 6 weeks on treatment. Antipsychotics are widely used for many of the other symptoms listed. The evidence for benefit is lacking and there is a major likelihood that these medications cause deterioration in cognitive function and increase mortality. For example, whilst anti-psychotics have been shown to be of some limited benefit, older patients with dementia are particularly vulnerable to extra-pyramidal and cardiac side effects of these agents, whilst risperidone and olanzapine that were widely prescribed previously for neuropsychiatric symptoms have been the subject of CSM guidance (March 2004) which recommends they should not be prescribed to people with dementia because of a three-fold increased risk of stroke and possible increased mortality. Other psychotropic medications eg anxiolytics and hypnotics are often used to treat some of these symptoms and again the evidence base for such prescribing is lacking.

These dangers were highlighted recently in the report on antipsychotic prescribing⁵⁰. Below is the direct quote from the opening letter of Professor Banerjee **“Using the best available information, I estimate that we are treating 180,000 people with dementia with antipsychotic medication across the country per year. Of these, up to 36,000 will derive some benefit from the treatment. In terms of negative effects that are directly attributable to the use of antipsychotic medication, use at this level equates to an additional 1,620 cerebrovascular adverse events, around half of which may be severe, and to an additional 1,800 deaths per year on top of those that would be expected in this frail population”**. In the DART-AD trial^{51,52} continuation compared with cessation of antipsychotic medication was associated with increased mortality. This may suggest that longer-term treatment may result in up to 167 additional deaths among 1,000 people with dementia treated with antipsychotics over a two-year period. So, these data suggest that mortality may increase with length of time taking antipsychotics.

In another study, patients who were taking antipsychotic drugs and sedatives had a significantly higher risk of deterioration than those who were taking none. Higher risk of deterioration was observed in those who were taking both antipsychotic and sedative drugs together. Patients taking drugs licensed for dementia, drugs affecting the renin-angiotensin system and statins had a significantly lower risk of deterioration than those who were not taking any of these drugs⁵³.

AChEI (and memantine, see below) have been associated with beneficial behavioral outcomes in many randomized clinical trials and open-label studies⁵⁴. A recent review concluded that most studies are not designed to test the psychotropic properties of antidementia drugs. Trials with negative behavioural outcomes are most likely to involve patients who are institutionalized and have few behavioral disturbances at baseline⁵⁴. Similar conclusions were reached in another recent review which concluded that “The evidence base regarding the efficacy of cholinesterase inhibitors in BPSD is limited, in part due to methodological considerations. In the absence of alternative safe and effective management options, the use of cholinesterase

inhibitors is an appropriate pharmacological strategy for the management of behavioural and psychological symptoms of dementia in AD⁵⁵.

If AChEI have beneficial effects on psychotic symptoms, it would follow that use of antipsychotic agents could be reduced in patients taking AChEI. This was reported for rivastigmine in one study. The overall usage of antipsychotics was considerably lower for patients taking rivastigmine (9.8%) compared with those not taking cholinesterase inhibitors (25.6%). Patients taking rivastigmine were 64% less likely (relative risk = 0.36; $p < 0.0001$) to take antipsychotics compared with patients not taking cholinesterase inhibitors, after adjusting for demographic covariates, comorbid conditions, and use of other CNS drugs and anticonvulsants. Age was the only other factor that influenced antipsychotic use; older patients were significantly more likely to start antipsychotics than younger patients. These findings may imply that rivastigmine use could delay the onset of behavioural symptoms that require treatment with antipsychotic medications⁵⁶.

The effects of AChEI may be linked to specific symptoms as donepezil was not found to affect agitation compared to placebo⁵⁷.

Cholinesterase inhibitors potentially have an important role to play in the management of behavioural disturbances in some patients, particularly in those intolerant of, or showing marked side effects to, the older antipsychotics.

It is interesting that total annual expenditure on dementia-related medications, including dispensing fees, was £228 million. Nearly half of this expenditure, £100 million, was on anti-dementia drugs (i.e. donepezil, galantamine, rivastigmine and memantine), with the remaining expenditure, £128 million, being due to prescriptions for psychotropic medications².

ACHEI IN OTHER DEMENTIA SYNDROMES

There have been a number of studies demonstrating efficacy of cholinesterase inhibitors in patients with VaD, mixed AD/VaD, DLB and Parkinson's disease dementia⁵⁸⁻⁶³. Whilst these studies do not have a direct bearing on the current appraisal, which is concerned with AD, they are important in terms of the management of mixed dementia cases which many clinicians have hitherto not considered suitable for treatment under current NICE guidance. This has meant that many patients who may benefit from these treatments have been deprived of them. To address this issue, we would fully support the position previously adopted that the population should include "people with AD or people whose dementia is considered to be predominantly AD". This is not only a sensible pragmatic approach but one for which there is an increasing evidence base regarding therapeutic efficacy.

MILD COGNITIVE IMPAIRMENT

With the advent of treatments for AD and the increasing awareness of cognitive disorders in late life, patients are now presenting for assessment at earlier stages, when they have a mild and relatively isolated deficit, either in memory or some other cognitive function, but do not fulfil criteria for AD or other dementia^{64,65}. This is

referred to as Mild Cognitive Impairment (MCI). Current management of this patient group consists of confirming the diagnosis, by excluding other medical or psychiatric conditions that may affect cognition and ensuring criteria for AD and other dementias are not met and offering support and monitoring. MCI is an important condition as a number of follow-up studies suggest that such patients represent a very high risk group for developing or “converting” to dementia, with a meta-analysis suggesting an annual conversion rate of 9.6% in memory clinics (Mitchell and Shrir feski). However, early identification and follow-up of MCI subjects is indicated, so that dementias such as AD can be diagnosed as early as possible, as requested by patients and carers and so that maximum support including medication can be offered at the earliest stage. At present there is no evidence to support the use of AChEI in MCI.

MEMANTINE FOR MODERATE TO SEVERE AD

AChEI are licensed for the treatment of those with moderate AD but there is currently no licensed treatment for severe AD apart from memantine which is also licensed for moderate AD. Memantine is a non-competitive glutamate NMDA receptor antagonist and, at, lower doses it may promote synaptic plasticity⁶⁶. It has been postulated to work through its NMDA receptor action by modifying the excitotoxicity that has been hypothesised to play a role in the progressive neural loss that underlies AD. Memantine has also been shown to inhibit A- β amyloid production and decrease its toxicity⁶⁷ as well as to increase brain derived neurotrophic factor (BDNF)⁶⁸, mechanisms currently of uncertain significance with regard to clinical efficacy. Memantine has also been found to have antagonistic effects on type 3 serotonin receptors through the use of patch clamping. Memantine’s 5HT-3 antagonism may protect against the gastrointestinal side effects of ChEIs when used in combination therapy⁶⁹.

Reviews of memantine studies, including a Cochrane review, confirm benefit on cognitive and functional decline and indicate that the drug is well tolerated^{70,71}. The Summary of Product Characteristics (SPC)⁷² as provided by the EMEA summarizes adverse drug reactions (ADRs) found in clinical trials in mild to severe dementia. In 1784 patients treated with Memantine and 1595 patients treated with placebo, the overall incidence rate of adverse reactions with memantine did not differ from those with placebo; the adverse events were usually mild to moderate in severity. The most frequently occurring adverse events with a higher incidence in the memantine group than in the placebo group were dizziness (6.3% vs 5.6%, respectively), headache (5.2% vs 3.9%), constipation (4.6% vs 2.6%), somnolence (3.4% vs 2.2%) and hypertension (4.1% vs 2.8%).

The trial of Tariot et al supports beneficial effects of memantine on global outcome as well as neuropsychiatric symptoms⁷³. This study, along with other evidence^{74,75}, shows that memantine can be safely co-prescribed with a cholinesterase inhibitor.

Additional analyses supported this effect on neuropsychiatric/behavioural symptoms. Wilcock et al conducted a pooled analysis of 3 large 6-month studies of memantine using the NPI as an efficacy variable⁷⁶. They found a statistically significant improvement in behavioral outcomes, especially in measurements of agitation/aggression. Gauthier et al conducted a study with a shorter time period and a larger study group⁷⁷. This study used the NPI as well and also yielded statistically

significant improvement in patients receiving memantine over those receiving placebo. These studies suggest that memantine may be a good treatment option for patients with AD and behavioral symptoms.

The possible effects of memantine on neuropsychiatric functioning are indirectly supported by data from the French national Health Care Database. In a sample of 4600 memantine treated patients psychotropic drug use before and after onset of memantine was analyzed. Before memantine onset, an increasing trend for psychotropic drug use could be seen. After memantine initiation, psychotropic drug use stabilized (but did not decrease)⁷⁸.

Finally, a study published in 2009 compiled memantine data from all clinical trials and from pivotal studies between 1992 and 2008 for a post-hoc analysis⁷⁹. Patients in nursing homes or assisted living facilities were excluded because they have significantly different baselines. The study found that a meta-analysis of all the study groups showed statistically significant improvement in both the NPI and BGP for patients receiving memantine over placebo. However, the behaviors with statistically significant improvement were agitation/aggression, irritability/lability, and delusions. Perhaps more importantly, this study found a delay in the emergence of behavioral symptoms with memantine compared to placebo. Improvement in these measurements and prevention of emergence would ease the burden for care givers and increase the time to institutionalization.

For many patients and their families, who are often care givers as well, staying out of long-term care facilities is a primary goal. A recent study conducted at the University of Pittsburgh evaluated 943 patients with probable AD and followed them long-term (mean time was 62.3 ± 35.8 months). They compared patients receiving memantine and ChEI with those receiving just ChEI and those receiving neither. They found that patients treated with ChEI had a decreased risk to institutionalization over those with no drug and the patients who received both memantine and ChEI had the greatest decrease risk (a decrease in risk over the ChEI monotherapy of 3.4). So while memantine/ChEI combination therapy may improve AD patients' outcomes cognitively, functionally, behaviorally, and globally, it may also help patients stay at home longer and delay time to institutionalization⁸⁰.

We would strongly support making memantine available within the NHS for patients with moderate to severe dementia.

COST EFFECTIVENESS

It is somewhat difficult for BGS to comment on cost effectiveness, in that we have no specific expert to help with this analysis and the time for consultation was short. BGS commented during the last review on cost effectiveness issues in a general way. Pharmacoeconomic analysis is a very complicated issue for generalists who do not have specific training in the methods used. In addition AD is a very complex disorder and application of models is therefore very difficult. It is therefore confusing even to specialists in AD that a number of cost effectiveness studies have been published with greatly varying results. It is useful to mention a few of these in this submission.

In the Health Technology Assessment publication on 2006⁸¹, the following statement summarised the analysis "For donepezil, rivastigmine and galantamine, the cost

savings associated with reducing the mean time spent in full-time care do not offset the cost of treatment sufficiently to bring estimated cost-effectiveness to levels generally considered acceptable by NHS policy makers. It is difficult to draw conclusions on the cost-effectiveness of memantine”.

A critique then appeared in Pharmacoeconomics from the individuals who developed the AHEAD model which was adapted for use by NICE⁸². The authors commented “As the developers of the AHEAD model, we examined the appropriateness of NICE's economic analyses and presentation of results. We attempted to replicate NICE's results by modifying the original AHEAD model. Sensitivity analyses were then run using the modified AHEAD model to evaluate the extent of uncertainty in predictions. The AHEAD(NICE) analyses resulted in an incremental cost-effectiveness ratio for galantamine of 82,000 pound per QALY gained (year 2003 values) from the perspective of the UK NHS and Personal Social Services. This was later revised to 46,000 pound per QALY, compared with < 9000 pound per discounted QALY gained (year 2001 values) in the original AHEAD model. Using our modified AHEAD with effectiveness estimates matching those of AHEAD(NICE), we show that NICE's choice and presentation of sensitivity analyses obscured the instability of their estimates. In the final NICE evaluation, the recommendation to delay treatment with cholinesterase inhibitors until patients have moderately severe disease was based on critical assumptions in the economic analyses that had little evidence to support them. The case of NICE's guidance on cholinesterase inhibitors highlights the importance of transparent and valid economic evaluations and the dangers of using inappropriate modelling technologies, basing analyses on a limited subset of the available data, and insufficiently reflecting the uncertainty in estimates that are intended to inform decision makers”. IMPORTANTLY THESE AUTHORS HAD NO CONFLICT OF INTEREST DECLARED IN THIS MANUSCRIPT.

In another recent publication⁸³ the following was concluded “In the baseline scenario (24 months, patients initially with mild AD) incremental cost-effectiveness for direct medical costs was 20,353 euro/QALY. When all costs were taken into account, donepezil treatment was the dominant strategy. Incremental cost-effectiveness ratios vary according to the selected perspective. For the baseline scenario, donepezil treatment is cost-effective with a probability of 95% for a threshold efficiency of 25,000 euro/QALY”. Julio López-Bastida

Cost-effectiveness analyses indicate that memantine is dominant to no pharmacotherapy in patients with moderate to severe Alzheimer's disease for treatment periods of 2–5 years in regard to the cost per quality-adjusted life-year (QALY) gained^{84,85,86,87}. Compared with monotherapy with donepezil, combination therapy with memantine plus donepezil was associated with an incremental cost-effectiveness ratio of \$US382 per QALY gained over 1 year (2005 values), but for periods greater than 1 year, combination therapy was dominant to donepezil alone⁸⁸.

There are several additional reports of cost effectiveness, with a variation in results. It is important when reading these to see whether these are independent or are supported by the manufacturers.

There have always been concerns about the applicability of QALY type analyses to older people. In relation to pharmacoeconomic modelling and AD, one review concluded⁸⁹ that “Cost-benefit analysis needs refinement with better tools than

quality-adjusted life-years, and the policy implications of restricting treatments in a progressive neurodegenerative disorder need more careful consideration”.

The BGS would welcome the use of a transparent model that has general support in evaluating these technologies in AD.

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