**SUBMISSION ON BEHALF OF THE ROYAL COLLEGE OF PSYCHIATRISTS BY THE FACULTY OF OLD AGE PSYCHIATRY TO THE NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE**

**2010 HEALTH TECHNOLOGY APPRAISAL (REVIEW OF TA 111): DONEPEZIL, GALANTAMINE, RIVASTIGMINE AND MEMANTINE FOR THE TREATMENT OF ALZHEIMER'S DISEASE**

## Background

Dementia affects approximately 5% of the over 65's and 20% of the over 80's [1-3]. Most recent estimates are that around 820,000 people in the UK are affected [4], with 20,000 of these under the age of 65 [5]. Alzheimer's disease (AD) is the most common cause of dementia in older people, responsible for approximately two thirds of cases, followed by Vascular dementia (VaD) and Dementia with Lewy bodies (DLB)[6 7]. Increasingly, however, prospective clinicopathological studies from both hospital and community samples demonstrate increasing overlap between subtypes of dementia [7-9]. For example, the community based, MRC funded, Cognitive Function and Ageing Study (CFAS) in the UK found that mixed pathology was the most common correlate of cognitive impairment in older people [7]. AD is a devastating, terminal illness which causes a progressive and relentless decline in cognition and functional ability, together with variable changes in personality and behaviour leading, on average, to death within seven years from diagnosis. It causes immense distress to patients, their carers and families and has an enormous impact on society. Recent reports indicate dementia costs the UK £23 billion per year, with around half of this met by informal care costs [4]. Importantly, annual cost per person with dementia is around 5 times greater than other major chronic diseases (stroke, heart disease, cancer). The burden of care is set to increase substantially, with an estimated doubling of dementia cases in the UK within the next 30 years [10]. For these reasons AD is at the top of the Government priorities both for NHS service delivery and for research.

## Management of AD and alternative pharmacological approaches

Despite considerable progress in identifying clinical and genetic risk factors for AD and in characterising the molecular pathways associated with neuronal loss, including amyloid deposition leading to plaques and tau phosphorylation causing tangles, aetiology of AD still remains unknown [11, 12]. Before the advent of cholinesterase inhibitors (CholEI), clinical management focused on establishing accurate clinical diagnosis (in particular ruling out potentially treatable or reversible causes of cognitive impairment), providing patients and carers with accurate information and necessary support, optimising Health and Social Service provision and appropriately managing associated complications when they occurred, in particular treating neuropsychiatric and behavioural problems and carer stress. Non-cognitive symptoms in dementia include agitation, behavioural disturbances (e.g. wandering, aggression), depression, delusions and hallucinations. These features are common [13-16], persistent and often difficult to treat [17] and are a much stronger predictor of both carer stress [18] and entry into institutional care than cognitive impairment [19-21] and so are important targets for therapeutic intervention. This is a key issue which will be addressed later, but it is important to note the best evidence base for pharmacotherapy apart from CholEI and memantine for non-cognitive symptoms is for antipsychotics (also known as neuroleptics) [22]. Non-pharmacological approaches are advocated as a first line, but while they may be helpful for

some mild symptoms, they do not help most people with more severe symptoms. For example, only 14% of AD subjects with clinically significant agitation responded (in terms of remission of agitation to less than a clinically significant level) to a 4 week non-pharmacological intervention in the MRC funded CALM-AD study [23]. Efficacy for both older typical and newer atypical antipsychotics has clearly been established in several well conducted randomised controlled trials (RCTs) and these drugs help symptoms such as agitation and psychosis [22]. Risks of antipsychotics for people with dementia have long been known, especially the severe sensitivity reactions that can occur in those with dementia with Lewy bodies [24]. However, since 2004 emerging evidence has shown serious and adverse consequences of using these agents in older people with dementia because of an increased risk of stroke and cerebrovascular like events [25] as well as an increased mortality rate [26] which can persist many years following drug exposure [27]. The estimated absolute risk difference is 1%, meaning that for every 100 people with dementia who receive antipsychotics for 3 months, one death may occur as a result of drug treatment. These drugs are still very widely prescribed to people with dementia, up to 40% of residents in UK care homes and an estimated 180,000 people in the UK[28]. Both a recent government report ("Time for Action") [28] and the UK Dementia strategy [29] highlight the need to dramatically reduce rates of antipsychotic drug prescribing to people with dementia, with a goal to reduce rates by 2/3 in two years. Annual expenditure on dementia related medication is £228 million, around £100 million of which is on anti-dementia drugs being reviewed here, but even more (£128 million) is on antipsychotics [28]. There is now consistent evidence that the use of CholEI and memantine reduces the need for prescription of antipsychotic medication [30-32]. **Because of the important and serious adverse events (stroke, increased mortality) from antipsychotics, it is vitally important that the important clinical benefits of cholinesterase inhibitors and memantine on non-cognitive symptoms is recognised as very few alternative pharmacological approaches for these distressing symptoms exist. We would urge the Appraisal Committee to take this important public health matter very seriously in considering guidance on these drugs and ensure their use is not so restricted that clinicians are forced to consider the use of drugs like antipsychotics with much more serious adverse effects.**

Though many studies of putative agents for AD are underway, unfortunately there are no treatments, either available now or likely to be available in the next few years, which have been shown to prevent, arrest or reverse the underlying disease process – or indeed rival CholEI and memantine in terms of efficacy for AD. In particular, initial trials of amyloid vaccination ran into problems because of toxicity [33] and phase 2 and 3 studies of a variety of approaches to modify disease process by reducing amyloid have so far been negative [34, 35]. A number of other agents with potential benefit, either because of theoretical mechanism of action or because of an apparent protective effect emerging from epidemiological studies, including oestrogen replacement, steroidal and non-steroidal anti-inflammatories, COX-2 inhibitors, vitamin E and others have unfortunately proved ineffective [36-41]. Other phase 3 studies of disease modification are ongoing, but one of the current compounds considered to be the most promising to date, Dimebon, which had an initially very positive study [42] has now been tested in a large and well conducted RCT with negative (as yet unpublished) results reported [43]. This is important as during the first two appraisals of the CholEI in 2001 and 2005/06 it was the general view these drugs would be the first of several promising and effective compounds to appear. Unfortunately, this has not been the case, with no sign of other effective drugs in the pipeline. **The failure of all other therapeutic studies over the last 10 years means that our current anti-dementia drugs, i.e. cholinesterase inhibitors and memantine, are likely to be the only drugs available for AD treatment over the next 5- 10 years.**

**Cholinesterase inhibitors (CholEI)**

The introduction of the CholEI marked a major and very positive step forward in the management of people with AD. These drugs were a rational pharmacological development based on the known profound cholinergic neurochemical deficit in the disorder, a deficit which showed a high correlation with clinical severity [44]. The efficacy of donepezil, rivastigmine and galantamine has been demonstrated in several large, well designed, pivotal Phase 3 double-blind placebo-controlled RCTs [45-52] and confirmed in subsequent studies [53-56]. These have not only confirmed initial results but demonstrated efficacy over longer periods, efficacy on non-cognitive symptoms and efficacy in more severely impaired populations. Mean magnitude of effect of treatment remains as before, the equivalent to the natural deterioration which might be expected in six to nine months of the disease, though if only responders are maintained on treatment (as with current Guidance) patients can stay above baseline for 18 months or longer [57]. No clear predictors of drug response have yet emerged, in particular, age, sex, genotype do not appear to predict response [58, 59]. Improvements on medication have been shown to be accompanied by consistent physiological changes including increased glucose metabolic activity on PET, improved blood flow and cholinergic receptor changes on PET and SPECT [60-65], increased neuronal activation on fMRI [66], reduced slow wave activity on EEG [67] and stabilisation of serial changes in pathological CSF markers of amyloid and tau [68].

Efficacy of all three agents over placebo, in terms of international agreed endpoints for antidementia trials, has been clearly established in several domains, including improved cognitive performance (on scales such as the MMSE and ADAS-Cog), global improvement (using the Clinicians Interview Based Impression of Change (CIBIC and CIBIC+)) and benefits on activities of daily living (ADL). Independent reviews, including those by the Cochrane collaboration, have also concluded that there is clear evidence of efficacy of all three agents [69-74]. Placebo-controlled studies have been conducted showing efficacy of CholEI over one and two years [55, 75 76], while open label studies show benefit can continue for up to 5 years [77-79]. Benefit is also apparent in mild, moderate and severe AD [53, 56, 80] and there is increasing evidence, though not from RCTs, that nursing home placement may be delayed in those taking CholEI in the longer term [81, 82].

Head to head studies have been reported, though these are of relatively small size and no clear evidence of superiority of one agent over another has yet emerged [83-85]. Gastrointestinal side effects appear more frequent with rivastigmine [76], which is relevant because current Guidance suggests using the drug with the lowest acquisition cost (rivastigmine), which may not be the one that is best tolerated or best for patients. There is substantial experience of the range of side effects obtained with the CholEI; in general the drugs are well tolerated and side effects relatively minor, though gastrointestinal and other problems may require patients to change drug. Cardiac effects such as bradycardia are probably the most worrying to emerge thus far and monitoring of heart rate before and during therapy should be undertaken [86]. Previous differences in administration between donepezil (once daily) and rivastigmine and galantamine (twice daily) are less relevant now since galantamine is available in a once daily extended release preparation and there is now a daily patch option for rivastigmine.

Even though AD populations included in trials of CholEI had relatively low levels of behavioural disturbance, so making it more difficult to show an effect on improving behaviour, there is increasing evidence that the drugs have a beneficial effect on behavioural and psychological symptoms of dementia (BPSD) in patients with AD, including in more severely impaired patients [49, 53, 54, 87]. This is particularly so for symptoms such as apathy and psychosis, symptoms which are common in patients with dementia, a major problem for

caregivers resulting in carer stress and institutionalisation and are often problematic symptoms to treat using other pharmacological management strategies. Cholinesterase inhibitors now have an important role to play in the management of such behavioural disturbances in some patients, particularly in light of the need to reduce antipsychotic prescribing to improve patient safety [28]. Use of CholEI has been shown to reduce the risk of being also prescribed antipsychotics by 64%[30].

There have been a number of studies demonstrating efficacy of CholEI in patients with VaD, mixed AD/VaD, DLB and Parkinson's disease dementia [88-94]. 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 and we continue to support the position previously taken by NICE (both in TA111 and the 2006 NICE/SCIE Guideline) that people with mixed dementia should be managed according to what is considered the predominant cause of their dementia.

**Do the drugs affect disease progression?**

This remains a controversial area but is of key importance in considering when the drugs are started and how long they are continued for. Accumulating, though not yet definitive, evidence suggests the agents may be acting as more than symptomatic treatments. Physiological changes showing alteration of brain function and CSF markers have been cited above. At the biochemical level cholinergic stimulation has been shown to reduce the phosphorylation of tau (a key element in tangle formation) and the formation of A-$\beta eta_{1-42}$ (a key event in the formation of insoluble amyloid fibrils leading to plaque formation)[95, 96]. In animal models nicotinic stimulation caused a dramatic reduction in laying down of A-βeta pathology [97]. A preliminary blinded study showed a significant reduction in rate of hippocampal atrophy on serial MRI in donepezil treated patients [98], whilst long term unblinded clinical data from all three agents consistently show that those who are kept on long term therapy may show a reduction in expected rate of disease progression compared to naturalistic controls [77, 81, 99, 100] and people on CholEI experience less clinical worsening than those on placebo [101]. Finally, there are several studies showing that a delay in starting the drug, by way of partaking in a randomised controlled trial and receiving placebo, produces less benefit when patients subsequently enter an open label study than if they had been on active agent from the beginning [102-105]. **These studies form a growing body of evidence that whether or not cholinesterase inhibitors have an effect on disease modification, they have the greatest clinical benefit when started early. This has clear relevance to the current NICE Guidance that, in contrast to the evidence, states that these agents should not be started until the moderate stages of dementia.**

**Health Economic Studies**

The previous NICE Appraisal took a certain view on economic modelling, using an adapted AHEAD model. The criticisms of this approach have been well argued elsewhere, including the use of carer rated quality of life data for patients which has not been validated, and the fact the model produced vastly different results on cost effectiveness depending on very minor variations in the assumptions made in the 2006 HTA report (£45,000 to over £150,000 per QALY for donepezil). However, even this presentation of results has been challenged and others have shown the model to be more unstable than results reported by NICE [106]. Importantly, several other health economic analyses have now been published, with the overwhelming majority suggesting a cost per QALY much lower than obtained using the NICE AHEAD model. The drugs reduce caregiver time, allow patients to remain independent

for longer and there is increasing evidence of a delay in institutional care [107-116]. Savings of over $11,000 per patient have been estimated over a 2 year period [114, 115]. Lopez-Bastida et al [117] calculated cost-effectiveness of around Euro 20,000-25,000 for donepezil in early AD. Measurements of quality of life and health economic studies in AD remain relatively under-developed and prone to considerable variation in terms of the model chosen and the assumptions used. It is key that any model should include long term benefits, effects on non-cognitive symptoms and benefits to carers. The Dementia strategy outlines the economic benefits of early intervention with regard to delayed institutionalisation [29], the "spend to save principle", something we consider was not given proper weight in the previous NICE economic model. While the effects of CholEI are often criticised for being modest, all aspects of dementia management produce modest yet tangible benefits but sum together to optimise patient management. Person centred care is very much a part of high quality care for people with dementia, yet the benefits it produces are also quite modest [118]. A modest improvement does not equate to an improvement that is not clinically important or valued by patients and carers.

Finally, we understand that patents for the CholEI start to expire in 2012, relatively soon after the new Appraisal Determination is due to be published. Since cost is largely driven by drug cost in the modelling, and a price drop following patent expiry can be modelled with reasonable precision, any health economic analysis should determine a) the maximum cost of medication which would equate to cost effectiveness according to NICE criteria at different stages of dementia and b) how cost-effective calculations would change following patent expiry. If the latter is not thought possible then it would be vital for NICE to revisit this important aspect in 2012 following patent expiry, rather than waiting for a routine 3 year re-appraisal.

**Current NICE guidance for CholEI**

We very much welcomed some aspects of the current Technology Appraisal of these drugs (No. 111) which advocated that the three drugs should be made available in the NHS as one component of the management of those with AD. A change from the first Technology Appraisal, following re-analysis on RCT data from the one year Nordic study [55], was that treatment was clearly shown to benefit all patients treated with CholEI, and that the initial 2001 guidance, that only those who showed a clinical response to the drugs at 3 months should be continued on treatment, was flawed. This re-analysis confirmed what one might suspect clinically – that assessing treatment response in a condition with a naturally progressive course in the absence of a clinically applicable biomarker is extremely difficult. The concept of reducing the rate of clinical worsening has been introduced, and this makes clinical and pragmatic sense when considering efficacy of CholEI [101]. We also welcomed the flexibility introduced during the review and appeals process which recognised the limitations of relying solely on the MMSE. It was disappointing that this change required legalistic appeal, as we and other groups had lobbied very hard during the appraisal and initial appeal process that reliance on the MMSE was inappropriate for such a complex condition. However, current Guidance still does not reflect the problems in those with high educational attainment, who often score above 20 despite having a moderate level of dementia. Since the normal range for a MMSE score can vary between 24 and 30, paradoxically this MMSE limitation disadvantages those who were scoring at the high end (30) before the start of their dementia as they have to drop 10 points, compared to only 4 for someone with lower educational attainment. **This important issue should be recognised and addressed in the revised Guidance, and would be easily dealt with through less reliance on a single MMSE measure, and greater emphasis on a more holistic clinical staging of the disease process.**

We remain disappointed with two other aspects of the current guidance which are not consistent with the evidence base. The first is the limitation to those with moderate to severe disease (approx MMSE 10-20) and the second is the requirement to stop medication when MMSE reaches 10. The Guidance also implies that these key management decisions with long term consequences should be taken on the basis of a single assessment of just one domain (cognition) that is affected in AD. Decisions about treating hypertension would never be made on the basis of a single assessment of blood pressure, and without taking all other factors into account.

**Starting medication – the exclusion of mild AD**

One of the major clinical difficulties with the current NICE guidance is the requirement not to start medication unless MMSE score is 20 or below. This was linked to the use of the previous economic model, whose shortcomings have been discussed. In terms of efficacy from RCTs, studies which have included those with mild AD (scores above 20) are positive [119], indeed some show greater functional benefits are apparent in those with milder disease [120]. The obvious ceiling effects of scales like the MMSE and ADAS-Cog, meaning that they are insensitive to change at high scores, was not recognised in the last Appraisal as a very likely explanation for apparently less cognitive benefit in those with higher MMSE scores. The issue of high premorbid educational attainment has been discussed above. Insufficient weight has been placed on non-cognitive symptoms and preserving function which is key at the earlier stages of dementia. There is also now a very unhelpful dissociation between NICE Guidance and national policy as well as patient and carer wishes. The National Dementia Strategy [29] emphasises above all the importance of an early diagnosis of dementia. The rapid development of Memory Clinics and similar Memory Assessment services has rightly encouraged patients to come forward at an earlier stage in their dementia. Patients and families naturally wish for and expect treatment at an early stage, and very understandably at the stage at which their cognitive and functional status can be maintained at the highest level for the longest period. The Dementia Strategy specifically requires that "…..and treatment, care and support provided as needed following diagnosis".

CholEI are clearly effective at these earlier stages, and have been licensed for mild to moderate AD, yet mild AD subjects are currently denied these treatments which are available in most other civilised societies for this devastating illness which has no other treatment option. The UK is well down the international league table in terms of prescription of anti-dementia drugs, coming around 11$^{th}$ out of 14 major countries, showing that many more AD subjects are benefiting from treatment in other countries than in the UK. Evidence was discussed above which consistently shows that in the longer term, the earlier the treatment starts, the better the outcome [104, 105]. **We remain unconvinced by the economic approach used to deny mild AD subjects effective treatments and urge the Appraisal Committee to reconsider this issue in the light of new developments in terms of wider healthcare policy and the National Dementia strategy. The Dementia strategy outlines the economic benefits of early intervention with regard to delayed institutionalisation, something not given proper weight in the previous NICE economic model.**

**Stopping medication at stage of severe dementia (MMSE 10)**

Efficacy for CholEI has been clearly demonstrated in more severely impaired patients. For example, Feldman et al [53] investigated donepezil in patients with moderate to severe AD as assessed by a score of 5-17 on the MMSE. The drug was well tolerated and donepezil treated subjects showed global benefit on the CIBIC+, the primary outcome measure, and all secondary measures including the MMSE and Severe Impairment Battery (SIB). Similar findings were reported in a study of a Nursing Home population by Tariot et al [56]. These and

other re-analyses of data from earlier studies splitting patients according to MMSE score [87, 121-123] show absolutely no evidence that global or neuropsychiatric benefits are any less in more severely impaired patients than in those with mild to moderate disease [124]. Since studies have now demonstrated efficacy of cholinesterase inhibitors in patients with MMSE scores as low as 5[125], we feel the current guidance regarding stopping when an MMSE score of 10 has been reached is neither evidence based nor compatible with a clinician's responsibility to do no harm to patients, since a clear decline on stopping treatment has been apparent in RCTs with a washout period [46].

It is also quite possible to have a very low score on the MMSE because of severe language problems (aphasia) whilst lower scores are also associated with hearing and visual impairments, low educational level, learning disability, having English as a second language and advancing age. Whilst, of necessity, initial pharmaceutical trials imposed certain cut-offs for pragmatic reasons to describe samples, as now there are many studies which have shown efficacy of CholEI in those with more severe AD, including those with MMSE scores below 10, we do not see any evidence based justification to stopping medication at MMSE of 10. Indeed, as discussed above, the evidence is that the greatest benefit is seen in those who take the drugs for the longest time. Clinicians therefore not only find this part of the guidance difficult in clinical practice, but it flies in the face of more recent evidence that the drugs remain beneficial even in those with lower MMSE scores. Moreover, the presence and severity of non-cognitive symptoms increases as dementia severity increases and is often clinically the key reason for wanting to continue prescribing for this group. A withdrawal syndrome of mood changes, agitation and poor sleep has been described [126], whereas longer follow up suggests increased aggression, repetitive questioning, somatic complaints and decreased participation in social/leisure activities as all being more common in people who discontinue cholinesterase inhibitors by comparison to those who remain on treatment [127]. A discontinuation syndrome of aggression and insomnia has also been suggested for memantine [128]. Emergence of these symptoms in people who had been taken off medication would very likely lead to increased prescription of antipsychotic drugs and this is an important reason why caution is needed when making a decision to stop medication.

Currently, an MRC funded RCT is ongoing, the DOMINO trial [129], which takes those on stable donepezil with MMSE around 10 and randomises subjects to ceasing medication, continuing donepezil, switching to memantine or combination (donepezil plus memantine) therapy. This study will produce important evidence (results available in 2011) to inform the debate about stopping, but until these results are available it is inappropriate to rely on a non-evidence based and arbitrary cognitive cut-off to determine whether medication should be withdrawn. **Reliance on stopping medication based on a strict and very arbitrary cognitive threshold is inappropriate when it is well established these drugs can have important benefits on both cognitive and non-cognitive symptoms in those with more severe AD.**

Changes should be made to the Guidance on when to stop medication and one way of reconciling these issues, while still being consistent with the licensed indication of mild to moderate AD, is to alter the definition of severity of AD from a strict (and arbitrary) cut-off on the MMSE to a more holistic and clinically meaningful staging system which better reflects the complexities of the disease. Specialists in the field of dementia make judgments regarding severity of dementia on the basis of much more than cognitive information. There are validated staging systems which combine information from multiple domains in making assessments about severity (for example the Clinical Dementia Rating scale of Hughes and colleagues [130] which has clear definitions for staging dementia as none, questionable, mild,

moderate and severe can be quickly and easily applied in the clinic using information available from the standard clinical assessment). Clinicians are well used to making sensible and pragmatic decisions about continuing medication in patients and in clinical practice it usually becomes clear that, either when a point of severe dementia is reached, or earlier in the illness when there is a rapid and relentless decline, then a trial of withdrawal of medication is a sensible and appropriate course of action. **We would strongly recommend a move to a more holistic staging system, such as that of the clinical dementia rating of Hughes et al [130], with recommendations about stopping being based on this combined with clinical judgement of the drugs no longer providing benefit.**

**Switching drugs**

There have been studies on switching agents, though none has been carried out in a truly double-blind fashion [131-134]. However, the evidence available suggests that switching between cholinesterase inhibitors (either because of lack of efficacy or intolerable side effects) is safe, that any side effects which may have occurred on one of the three agents do not necessarily recur on starting another and that benefit can be seen in around 50% of cases. As such, we would advocate the guidance to include a statement that non-response or intolerance to one cholinesterase inhibitor does not mean that others should not be tried.

**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 the stage of "mild cognitive impairment" (MCI) 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 [135, 136]. 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 AD, with rates of 10 to 15% per year [135]. Some have even gone so far as to label it early AD, though not all subjects decline and some may show improvement [137]. 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. Several studies of cholinesterase inhibitors in those with MCI have been undertaken. Although some benefits have been seen in post-hoc analysis in certain subgroups, for example those with depression [138] or those with a particular Apo E genotype, the overall results of these studies has been negative [139, 140]. At the current time, we do not consider there is any evidence to support extension of the Guidance to those who do not have established AD as the main cause for their dementia.

**Memantine for moderate to severe Alzheimer's disease**

Whilst cholinesterase inhibitors are also licensed for the treatment of those with moderate AD, there is currently no licensed treatment for severe AD apart from memantine. The mode of action of memantine in producing clinical benefit is unclear. It is a non-competitive glutamate NMDA receptor antagonist and, at lower doses, it may promote synaptic plasticity [141]. 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. As such, it is proposed as having a disease modifying effect, and in animals is neuroprotective after traumatic brain injury [142]. However, it has also been shown to inhibit A-βeta amyloid production and decrease its toxicity [143], as well as to increase brain derived neurotrophic factor (BDNF)[144], mechanisms currently of uncertain significance with regard to clinical efficacy.

Several RCTs of memantine have been carried out in patients with dementia [145-152]. Earlier studies were mainly undertaken in populations with AD and VaD combined, and showed evidence of benefit. Two well conducted studies in mild to moderate VaD reported that patients receiving 20 mg per day of memantine had less cognitive deterioration than placebo treated subjects at 28 weeks, although no discernable effect on the CIBIC+ was seen [148, 150]. Large and well conducted studies in AD have been published. Reisberg et al [149] included 252 patients with AD who were over 50 and had MMSE scores of 3 to 14. Patients were randomised to memantine 20 mg per day or placebo (126 in each group, mean MMSE score was 8). Evaluation was at 28 weeks with discontinuation slightly greater (33% -v- 23%) in those treated with placebo compared to memantine. Memantine treated patients had a better outcome on global assessment (p=0.03 for observed cases on CIBIC+), ADL and cognition (SIB). Results indicated a relative stabilisation, or slowing of decline, on memantine compared to placebo rather than clear evidence of improvement. Importantly, MMSE score did not show significant differences between groups, suggesting that this would not be an appropriate measure in the more severely impaired patient. A more global rating might be more appropriate. Tariot et al [151] reported a randomised control trial of 404 patients with moderate to severe AD (MMSE scores of 5 to 14), all stabilised on donepezil, who were randomised to memantine (up to 20 mg per day) or placebo for 24 weeks. The significant benefits of the addition of memantine were seen on cognition (SIB), ADL and neuropsychiatric symptoms (NPI). Discontinuations were low, only 7% in the memantine group and 12% in placebo treated patients. An earlier Cochrane review had concluded there was a beneficial effect of memantine on cognitive and functional decline [145]. Since then, the trial of Tariot et al supports beneficial effects of memantine on global outcome as well as neuropsychiatric symptoms. Further analysis of trial data show a benefit on non-cognitive symptoms, most especially psychosis and agitation/aggression [153], which is especially important since the CALM-AD study showed that CholEI were not helpful for the key clinical symptom of agitation in AD [23]. Given that the alternative pharmacological approach for agitation would be the use of antipsychotic medication, use of memantine would decrease the need for this [31], in line with new DoH policy and improving patient safety [28]. Memantine can be safely co-prescribed with a cholinesterase inhibitor [154, 155], though until further studies emerge it remains unclear whether co-prescription is more beneficial than mono-therapy as both positive and negative reports exist. [151, 156]

While the mechanism of action of memantine is postulated to slow disease progression, trial evidence to date does not definitively show this and results would also be compatible with a small symptomatic benefit on the background of a deteriorating illness. Some studies have suggested a slowing of rates of brain metabolic change and hippocampal atrophy [157]. Resource utilisation studies have generally shown benefits of memantine over placebo, suggesting both delay to institutionalisation and reduced caregiver input [158] and health economic benefits [159]. A recent study showed that memantine co-prescription with CholEI significantly reduced risk of institutionalisation [160] and combination therapy was shown to be beneficial in terms of reducing functional and global decline [161]. **We would strongly support making memantine available within the NHS for patients with moderate to severe dementia, most especially for the treatment of troublesome behavioural problems which may otherwise require antipsychotic therapy.**

**APPENDIX**

**Recommended changes to current NICE Guidance on donepezil, rivastigmine and galantamine**

*The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of moderate severity only (that is, subject to section 1.2 below, those with a Mini Mental State Examination [MMSE] score of between 10 and 20 points), and under the following conditions:*

**Suggest change to**

The three acetylcholinesterase inhibitors donepezil, galantamine and rivastigmine are recommended as options in the management of patients with Alzheimer's disease of mild to moderate severity under the following conditions:

*Only specialists in the care of patients with dementia (that is, psychiatrists including those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. Carers' views on the patient's condition at baseline should be sought.*

**Suggest change to**

Only specialists in the care of patients with dementia (that is, psychiatrists including old age psychiatrists those specialising in learning disability, neurologists, and physicians specialising in the care of the elderly) should initiate treatment. Carers' views on the patient's condition at baseline should be sought. Assessment of patient's dementia severity should include more than a simple cognitive score in the clinic, and take into account wider aspects of their cognitive ability (from history), their daily functioning and any behavioural changes.

*Patients who continue on the drug should be reviewed every 6 months by MMSE score and global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's MMSE score remains at or above 10 points (subject to section 1.2 below) and their global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. Any review involving MMSE assessment should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.*

**Suggest change to**

Patients who continue on the drug should be reviewed every 6 months for cognitive, global, functional and behavioural assessment. Carers' views on the patient's condition at follow-up should be sought. The drug should only be continued while the patient's global, functional and behavioural condition remains at a level where the drug is considered to be having a worthwhile effect. Any review involving a decision to cease medication should be undertaken by an appropriate specialist team, unless there are locally agreed protocols for shared care.

*When using the MMSE to diagnose moderate Alzheimer's disease, clinicians should be mindful of the need to secure equality of access to treatment for patients from different ethnic groups (in particular those from different cultural backgrounds) and patients with disabilities.*

**Suggest change to**

When using the MMSE to assess mild to moderate Alzheimer's disease, clinicians should be mindful of the need to secure equality of access to treatment for patients from different ethnic groups (in particular those from different cultural backgrounds) and patients with disabilities and in those with previous high or low levels of education.

*In determining whether a patient has Alzheimer's disease of moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:*

*where the MMSE is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties* ***or***
*where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case.*

*In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of moderate severity by making use of another appropriate method of assessment. For the avoidance of any doubt, the acetylcholinesterase inhibitors are recommended as options in the management of people assessed on this basis as having Alzheimer's disease of moderate severity.*

**Suggest change to**
In determining whether a patient has Alzheimer's disease of mild to moderate severity for the purposes of section 1.1 above, healthcare professionals should not rely, or rely solely, upon the patient's MMSE score in circumstances where it would be inappropriate to do so. These are:

where the MMSE is not, or is not by itself, a clinically appropriate tool for assessing the severity of that patient's dementia because of the patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties **or**
where it is not possible to apply the MMSE in a language in which the patient is sufficiently fluent for it to be an appropriate tool for assessing the severity of dementia, or there are similarly exceptional reasons why use of the MMSE, or use of the MMSE by itself, would be an inappropriate tool for assessing the severity of dementia in that individual patient's case (for example, high or low educational level).

In such cases healthcare professionals should determine whether the patient has Alzheimer's disease of mild or moderate severity by making use of another appropriate method of assessment. For the avoidance of any doubt, the acetylcholinesterase inhibitors are recommended as options in the management of people assessed on this basis as having Alzheimer's disease of mild or moderate severity.

The same approach should apply in determining for the purposes of section 1.1 above, and in the context of a decision whether to continue the use of the drug, whether the severity of the patient's dementia has increased to a level which in the general population of Alzheimer's disease patients would be marked by an MMSE score below 10 points.

*Memantine is not recommended as a treatment option for patients with moderately severe to severe Alzheimer's disease except as part of well-designed clinical studies.*

**Suggest change to**
Memantine is recommended as a treatment option for patients with moderate to severe Alzheimer's disease where there are prominent behavioural symptoms which cannot be managed by non-pharmacological means and when alternative therapeutic options would involve high risk from the use of antipsychotic medication.

**References**


**1.** Hofman A, Rocca WA, Brayne C, et al. The prevalence of dementia in Europe: a collaborative study of 1980-1990 findings. Eurodem Prevalence Research Group. *International Journal of Epidemiology.* 1991;20(3):736-748.

**2.** Anonymous. Cognitive function and dementia in six areas of England and Wales: the distribution of MMSE and prevalence of GMS organicity level in the MRC CFA Study. The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *Psychological Medicine.* 1998;28(2):319-335.

**3.** Rocca WA, Hofman A, Brayne C, et al. Frequency and distribution of Alzheimer's disease in Europe: a collaborative study of 1980-1990 prevalence findings. The EURODEM-Prevalence Research Group. *Annals of Neurology.* 1991;30(3):381-390.

**4.** Luengo-Fernandez R, Leal J, Gray A. A report produced by the Health Economics Research Centre, University of Oxford for the Alzheimer's Research Trust. DEMENTIA 2010. The prevalence, economic cost and research funding of dementia compared with other major diseases. 2010.

**5.** Harvey RJ, Skelton-Robinson M, Rossor MN. The prevalence and causes of dementia in people under the age of 65 years. *Journal of Neurology, Neurosurgery & Psychiatry.* 2003;74(9):1206-1209.

**6.** Stevens T, Livingston G, Kitchen G, Manela M, Walker Z, Katona C. Islington study of dementia subtypes in the community. *British Journal of Psychiatry.* 2002;180:270-276.

**7.** MRC/CFAS. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. *Lancet.* 2001;357:169-175.

**8.** Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study [see comments]. *Jama.* 1997;277(10):813-817.

**9.** Esiri MM, Nagy Z, Smith MZ, Barnetson L, Smith AD. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease [letter]. *Lancet.* 1999;354(9182):919-920.

**10.** Melzer D, Ely M, Brayne C. Cognitive impairment in elderly people: population based estimate of the future in England, Scotland, and Wales. *British Medical Journal.* 1997;315(7106):462.

**11.** Ritchie K, Lovestone S. The dementias. *Lancet.* 2002;360(9347):1759-1766.

**12.** de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. *Lancet Neurology.* 2004;3(3):184-190.

**13.** Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. IV: Disorders of behaviour. *British Journal of Psychiatry.* 1990;157:86-94.

**14.** Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. III: Disorders of mood. *British Journal of Psychiatry.* 1990;157:81-86.

**15.** Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. II: Disorders of perception. *British Journal of Psychiatry.* 1990;157:76-81, 92-74.

**16.** Burns A, Jacoby R, Levy R. Psychiatric phenomena in Alzheimer's disease. I: Disorders of thought content [see comments]. *British Journal of Psychiatry.* 1990;157:72-76, 92-74.

**17.** Ballard C, O'Brien J. Treating behavioural and psychological signs in Alzheimer's disease [editorial]. *British Medical Journal.* 1999;319(7203):138-139.

**18.** Donaldson C, Tarrier N, Burns A. The impact of the symptoms of dementia on caregivers. *British Journal of Psychiatry.* 1997;170:62-68.

**19.** Bianchetti A, Scuratti A, Zanetti O, et al. Predictors of mortality and institutionalization in Alzheimer disease patients 1 year after discharge from an Alzheimer dementia unit. *Dementia.* 1995;6(2):108-112.

**20.** Knopman DS, Kitto J, Deinard S, Heiring J. Longitudinal study of death and institutionalization in patients with primary degenerative dementia. *Journal of the American Geriatrics Society.* 1988;36(2):108-112.
**21.** Banerjee S, Murray J, Foley B, Atkins L, Schneider J, Mann A. Predictors of institutionalisation in people with dementia. *Journal of Neurology, Neurosurgery & Psychiatry.* 2003;74(9):1315-1316.
**22.** De Deyn PP, Katz IR, Brodaty H, Lyons B, Greenspan A, Burns A. Management of agitation, aggression, and psychosis associated with dementia: a pooled analysis including three randomized, placebo-controlled double-blind trials in nursing home residents treated with risperidone. *Clinical Neurology & Neurosurgery.* Oct 2005;107(6):497-508.
**23.** Howard RJ, Juszczak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease.[see comment]. *New England Journal of Medicine.* Oct 4 2007;357(14):1382-1392.
**24.** McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of Lewy body type [see comments]. *British Medical Journal.* 1992;305(6855):673-678.
**25.** Gill SS, Rochon PA, Herrmann N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. *Bmj.* 2005;330(7489):26.
**26.** Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials.[see comment]. *JAMA.* Oct 19 2005;294(15):1934-1943.
**27.** Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurology.* Feb 2009;8(2):151-157.
**28.** Banerjee S. The use of antipsychotic medication for people with dementia: Time for action. *A report for the Minister of State for Care Services* November 2009.
**29.** DoH. *Living well with dementia: A National Dementia Strategy. Department of Health. 3 February 2009.*; 2009.
**30.** Suh DC, Arcona S, Thomas SK, et al. Risk of antipsychotic drug use in patients with Alzheimer's disease treated with rivastigmine. *Drugs & Aging.* 2004;21(6):395-403.
**31.** Vidal JS, Lacombe JM, Dartigues JF, et al. Evaluation of the impact of memantine treatment initiation on psychotropics use: a study from the French national health care database. *Neuroepidemiology.* 2008;31(3):193-200.
**32.** Narayanan S, Beusterien KM, Thomas SK, et al. Antipsychotic drug use among nursing home residents taking rivastigmine. *Journal of the American Medical Directors Association.* Jan 2006;7(1):12-16.
**33.** Dodel RC, Hampel H, Du Y. Immunotherapy for Alzheimer's disease. *Lancet. Neurology.* 2003;2(4):215-220.
**34.** Salloway S, Sperling R, Gilman S, et al. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology.* Dec 15 2009;73(24):2061-2070.
**35.** Wilcock GK, Black SE, Hendrix SB, et al. Efficacy and safety of tarenflurbil in mild to moderate Alzheimer's disease: a randomised phase II trial.[Erratum appears in Lancet Neurol. 2008 Jul;7(7):575]. *Lancet Neurology.* Jun 2008;7(6):483-493.
**36.** Aisen PS. The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. *Lancet. Neurology.* 2002;1(5):279-284.
**37.** Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild to moderate Alzheimer disease: a randomized controlled trial. Alzheimer's

Disease Cooperative Study. *Journal of the American Medical Association.* 2000;283(8):1007-1015.
**38.** Reines SA, Block GA, Morris JC, et al. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. *Neurology.* 2004;62(1):66-71.
**39.** Aisen PS, Davis KL, Berg JD, et al. A randomized controlled trial of prednisone in Alzheimer's disease. Alzheimer's Disease Cooperative Study. *Neurology.* 2000;54(3):588-593.
**40.** Aisen PS, Schafer KA, Grundman M, et al. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial.[see comment]. *Jama.* 2003;289(21):2819-2826.
**41.** Isaac MG, Quinn R, Tabet N, Isaac MGEKN, Quinn R, Tabet N. Vitamin E for Alzheimer's disease and mild cognitive impairment. *Cochrane Database of Systematic Reviews.* 2008(3):CD002854.
**42.** Doody RS, Gavrilova SI, Sano M, et al. Effect of dimebon on cognition, activities of daily living, behaviour, and global function in patients with mild-to-moderate Alzheimer's disease: a randomised, double-blind, placebo-controlled study. *Lancet.* Jul 19 2008;372(9634):207-215.
**43.** Pfizer, Inc. Pfizer And Medivation Announce Results From Two Phase 3 Studies In Dimebon (latrepirdine*) Alzheimer's Disease Clinical Development Program [Press Release, 3 March 2010]. New York and San Francisco: Pfizer Inc; 2010.
**44.** Perry EK, Tomlinson BE, Blessed G, Bergmann K, Gibson PH, Perry RH. Correlation of cholinergic abnormalities with senile plaques and mental test scores in senile dementia. *British Medical Journal.* 1978;2(6150):1457-1459.
**45.** Burns A, Rossor M, Hecker J, et al. The effects of donepezil in Alzheimer's disease - results from a multinational trial. *Dementia & Geriatric Cognitive Disorders.* 1999;10(3):237-244.
**46.** Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. *Neurology.* 1998;50(1):136-145.
**47.** Rogers SL, Friedhoff LT. The efficacy and safety of donepezil in patients with Alzheimer's disease: results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial. The Donepezil Study Group. *Dementia.* 1996;7(6):293-303.
**48.** Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. *British Medical Journal.* 2000;321(7274):1445-1449.
**49.** Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C. A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. *Neurology.* 2000;54(12):2269-2276.
**50.** Raskind MA, Peskind ER, Wessel T, Yuan W. Galantamine in AD: A 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. *Neurology.* 2000;54(12):2261-2268.
**51.** Rosler M, Anand R, Cicin-Sain A, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *British Medical Journal.* 1999;318(7184):633-638.
**52.** 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.
**53.** Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. *Neurology.* 2001;57(4):613-620.

**54.** Gauthier S, Feldman H, Hecker J, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *International Psychogeriatrics.* 2002;14(4):389-404.
**55.** Winblad B, Engedal K, Soininen H, et al. A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD.[see comment]. *Neurology.* 2001;57(3):489-495.
**56.** Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting.[see comment]. *Journal of the American Geriatrics Society.* 2001;49(12):1590-1599.
**57.** Matthews HP, Korbey J, Wilkinson DG, Rowden J. Donepezil in Alzheimer's disease: eighteen month results from Southampton Memory Clinic. *International Journal of Geriatric Psychiatry.* 2000;15(8):713-720.
**58.** Pakrasi S, Mukaetova-Ladinska EB, McKeith IG, O'Brien JT. Clinical predictors of response to Acetyl Cholinesterase Inhibitors: experience from routine clinical use in Newcastle. *International Journal of Geriatric Psychiatry.* 2003;18(10):879-886.
**59.** Rigaud AS, Traykov L, Latour F, Couderc R, Moulin F, Forette F. Presence or absence of at least one epsilon 4 allele and gender are not predictive for the response to donepezil treatment in Alzheimer's disease. *Pharmacogenetics.* 2002;12(5):415-420.
**60.** Kemp PM, Holmes C, Hoffmann S, et al. A randomised placebo controlled study to assess the effects of cholinergic treatment on muscarinic receptors in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2003;74(11):1567-1570.
**61.** Nobili F, Koulibaly M, Vitali P, et al. Brain perfusion follow-up in Alzheimer's patients during treatment with acetylcholinesterase inhibitors. *Journal of Nuclear Medicine.* 2002;43(8):983-990.
**62.** Nobili F, Vitali P, Canfora M, et al. Effects of long-term Donepezil therapy on rCBF of Alzheimer's patients. *Clinical Neurophysiology.* 2002;113(8):1241-1248.
**63.** Vennerica A, Shanks MF, Staff RT, et al. Cerebral blood flow and cognitive responses to rivastigmine treatment in Alzheimer's disease. *Neuroreport.* 2002;13(1):83-87.
**64.** Nordberg A. PET studies and cholinergic therapy in Alzheimer's disease. *Revue Neurologique.* 1999;155(Suppl 4):S53-63.
**65.** Nakano S, Asada T, Matsuda H, Uno M, Takasaki M. Donepezil hydrochloride preserves regional cerebral blood flow in patients with Alzheimer's disease. *Journal of Nuclear Medicine.* 2001;42(10):1441-1445.
**66.** Rombouts SA, Barkhof F, Van Meel CS, Scheltens P. Alterations in brain activation during cholinergic enhancement with rivastigmine in Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002;73(6):665-671.
**67.** Rodriguez G, Vitali P, De Leo C, De Carli F, Girtler N, Nobili F. Quantitative EEG changes in Alzheimer patients during long-term donepezil therapy. *Neuropsychobiology.* 2002;46(1):49-56.
**68.** Stefanova E, Blennow K, Almkvist O, Hellstrom-Lindahl E, Nordberg A. Cerebral glucose metabolism, cerebrospinal fluid-beta-amyloid1-42 (CSF-Abeta42), tau and apolipoprotein E genotype in long-term rivastigmine and tacrine treated Alzheimer disease (AD) patients. *Neuroscience Letters.* 2003;338(2):159-163.
**69.** Lanctot KL, Herrmann N, Yau KK, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *Canadian Medical Association Journal.* 2003;169(6):557-564.
**70.** Olin J, Schneider L. Galantamine for Alzheimer's disease.[update in Cochrane Database Syst Rev. 2002;(3):CD001747; PMID: 12137632][update of Cochrane Database Syst Rev. 2001;(1):CD001747; PMID: 11279727]. *Cochrane Database of Systematic Reviews.* 2001(4):CD001747.

**71.** Birks JS, Harvey R. Donepezil for dementia due to Alzheimer's disease.[update of Cochrane Database Syst Rev. 2000;(4):CD001190; PMID: 11034704]. *Cochrane Database of Systematic Reviews.* 2003(3):CD001190.
**72.** Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews [computer file].* 2000(4):CD001191.
**73.** Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. *Clinical Interventions In Aging.* 2008;3(2):211-225.
**74.** Birks J, Grimley Evans J, Iakovidou V, et al. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews.* 2009(2):CD001191.
**75.** Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology.* 2001;57(3):481-488.
**76.** Bullock R, Touchon J, Bergman H, et al. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Current Medical Research & Opinion.* Aug 2005;21(8):1317-1327.
**77.** Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. *Archives of Neurology.* 2004;61(2):252-256.
**78.** Rogers SL, Doody RS, Pratt RD, Ieni JR. Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study. *European Neuropsychopharmacology.* 2000;10(3):195-203.
**79.** Bullock R, Dengiz A. Cognitive performance in patients with Alzheimer's disease receiving cholinesterase inhibitors for up to 5 years. *International Journal of Clinical Practice.* Jul 2005;59(7):817-822.
**80.** Burns A, Bernabei R, Bullock R, et al. Safety and efficacy of galantamine (Reminyl) in severe Alzheimer's disease (the SERAD study): a randomised, placebo-controlled, double-blind trial.[see comment]. *Lancet Neurology.* Jan 2009;8(1):39-47.
**81.** Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. *Journal of Neurology, Neurosurgery & Psychiatry.* Mar 2002;72(3):310-314.
**82.** Feldman HH, Pirttila T, Dartigues JF, et al. Treatment with galantamine and time to nursing home placement in Alzheimer's disease patients with and without cerebrovascular disease. *International Journal of Geriatric Psychiatry.* May 2009;24(5):479-488.
**83.** Wilkinson DG, Passmore AP, Bullock R, et al. A multinational, randomised, 12-week, comparative study of donepezil and rivastigmine in patients with mild to moderate Alzheimer's disease. *International Journal of Clinical Practice.* 2002;56(6):441-446.
**84.** Jones RW, Soininen H, Hager K, et al. A multinational, randomised, 12-week study comparing the effects of donepezil and galantamine in patients with mild to moderate Alzheimer's disease. *International Journal of Geriatric Psychiatry.* 2004;19(1):58-67.
**85.** Wilcock G, Howe I, Coles H, et al. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. *Drugs & Aging.* 2003;20(10):777-789.
**86.** Hernandez RK, Farwell W, Cantor MD, et al. Cholinesterase inhibitors and incidence of bradycardia in patients with dementia in the veterans affairs new England healthcare system. *Journal of the American Geriatrics Society.* Nov 2009;57(11):1997-2003.
**87.** Burns A, Spiegel R, Quarg P. Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. *International Journal of Geriatric Psychiatry.* 2004;19(3):243-249.

**88.** Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. *American Journal of Alzheimer's Disease & Other Dementias.* 2003;18(5):265-272.
**89.** McKeith I, Del Ser T, Spano P, et al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet.* 2000;356(9247):2031-2036.
**90.** Erkinjuntti T, Kurz A, Small GW, et al. An open-label extension trial of galantamine in patients with probable vascular dementia and mixed dementia. *Clinical Therapeutics.* 2003;25(6):1765-1782.
**91.** Aarsland D, Laake K, Larsen JP, Janvin C. Donepezil for cognitive impairment in Parkinson's disease: a randomised controlled study. *Journal of Neurology, Neurosurgery & Psychiatry.* 2002;72(6):708-712.
**92.** Black S, Roman GC, Geldmacher DS, et al. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke.* 2003;34(10):2323-2330.
**93.** Wilkinson D, Doody R, Helme R, et al. Donepezil in vascular dementia: A randomized, placebo-controlled study. *Neurology.* 2003;61(4):479-486.
**94.** Emre M, Aarsland D, Albanese A, et al. Rivastigmine for dementia associated with Parkinson's disease.[see comment]. *New England Journal of Medicine.* Dec 9 2004;351(24):2509-2518.
**95.** Giacobini E. Long-term stabilizing effect of cholinesterase inhibitors in the therapy of Alzheimer' disease. *Journal of Neural Transmission. Supplementum.* 2002(62):181-187.
**96.** Fisher A, Pittel Z, Haring R, et al. M1 muscarinic agonists can modulate some of the hallmarks in Alzheimer's disease: implications in future therapy. *Journal of Molecular Neuroscience.* 2003;20(3):349-356.
**97.** Nordberg A, Hellstrom-Lindahl E, Lee M, et al. Chronic nicotine treatment reduces beta-amyloidosis in the brain of a mouse model of Alzheimer's disease (APPsw). *Journal of Neurochemistry.* 2002;81(3):655-658.
**98.** Krishnan KR, Charles HC, Doraiswamy PM, et al. Randomized, placebo-controlled trial of the effects of donepezil on neuronal markers and hippocampal volumes in Alzheimer's disease. *American Journal of Psychiatry.* 2003;160(11):2003-2011.
**99.** Almkvist O, Darreh-Shori T, Stefanova E, Spiegel R, Nordberg A. Preserved cognitive function after 12 months of treatment with rivastigmine in mild Alzheimer's disease in comparison with untreated AD and MCI patients. *European Journal of Neurology.* 2004;11(4):253-261.
**100.** Doody RS, Dunn JK, Clark CM, et al. Chronic donepezil treatment is associated with slowed cognitive decline in Alzheimer's disease. *Dementia & Geriatric Cognitive Disorders.* 2001;12(4):295-300.
**101.** Wilkinson D, Schindler R, Schwam E, et al. Effectiveness of donepezil in reducing clinical worsening in patients with mild-to-moderate alzheimer's disease. *Dementia & Geriatric Cognitive Disorders.* 2009;28(3):244-251.
**102.** Doraiswamy PM, Krishnan KR, Anand R, et al. Long-term effects of rivastigmine in moderately severe Alzheimer's disease: does early initiation of therapy offer sustained benefits? *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2002;26(4):705-712.
**103.** Coyle J, Kershaw P. Galantamine, a cholinesterase inhibitor that allosterically modulates nicotinic receptors: effects on the course of Alzheimer's disease. *Biological Psychiatry.* 2001;49(3):289-299.

**104.** Farlow M, Potkin S, Koumaras B, Veach J, Mirski D. Analysis of outcome in retrieved dropout patients in a rivastigmine vs placebo, 26-week, Alzheimer disease trial. *Archives of Neurology.* 2003;60(6):843-848.
**105.** Winblad B, Wimo A, Engedal K, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. *Dementia & Geriatric Cognitive Disorders.* 2006;21(5-6):353-363.
**106.** Getsios D, Migliaccio-Walle K, Caro JJ. NICE cost-effectiveness appraisal of cholinesterase inhibitors: was the right question posed? Were the best tools used? *Pharmacoeconomics.* 2007;25(12):997-1006.
**107.** Hauber AB, Gnanasakthy A, Snyder EH, Bala MV, Richter A, Mauskopf JA. Potential savings in the cost of caring for Alzheimer's disease. Treatment with rivastigmine. *Pharmacoeconomics.* 2000;17(4):351-360.
**108.** Lamb HM, Goa KL. Rivastigmine. A pharmacoeconomic review of its use in Alzheimer's disease. *Pharmacoeconomics.* 2001;19(3):303-318.
**109.** O'Brien BJ, Goeree R, Hux M, et al. Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. *Journal of the American Geriatrics Society.* 1999;47(5):570-578.
**110.** Neumann PJ, Hermann RC, Kuntz KM, et al. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Neurology.* 1999;52(6):1138-1145.
**111.** Wimo A, Winblad B, Engedal K, et al. An economic evaluation of donepezil in mild to moderate Alzheimer's disease: results of a 1-year, double-blind, randomized trial. *Dementia & Geriatric Cognitive Disorders.* 2003;15(1):44-54.
**112.** Lyseng-Williamson KA, Plosker GL. Galantamine: a pharmacoeconomic review of its use in Alzheimer's disease. *Pharmacoeconomics.* 2002;20(13):919-942.
**113.** Getsios D, Caro JJ, Caro G, Ishak K, Group AS. Assessment of health economics in Alzheimer's disease (AHEAD): galantamine treatment in Canada. *Neurology.* 2001;57(6):972-978.
**114.** Migliaccio-Walle K, Getsios D, Caro JJ, et al. Economic evaluation of galantamine in the treatment of mild to moderate Alzheimer's disease in the United States. *Clinical Therapeutics.* 2003;25(6):1806-1825.
**115.** Marin D, Amaya K, Casciano R, et al. Impact of rivastigmine on costs and on time spent in caregiving for families of patients with Alzheimer's disease. *International Psychogeriatrics.* 2003;15(4):385-398.
**116.** Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *Journal of the American Geriatrics Society.* 2003;51(7):937-944.
**117.** Lopez-Bastida J, Hart W, Garcia-Perez L, Linertova R. Cost-effectiveness of donepezil in the treatment of mild or moderate Alzheimer's disease. *Journal of Alzheimer's Disease.* Feb 2009;16(2):399-407.
**118.** Chenoweth L, King MT, Jeon Y-H, et al. Caring for Aged Dementia Care Resident Study (CADRES) of person-centred care, dementia-care mapping, and usual care in dementia: a cluster-randomised trial.[Erratum appears in Lancet Neurol. 2009 May;8(5):419]. *Lancet Neurology.* Apr 2009;8(4):317-325.
**119.** Dooley M, Lamb H. Donepezil, a review of its use in Alzheimer's disease. *Drugs and Aging.* 2000;16(3):199-226.
**120.** Molinuevo JL, Berthier ML, Rami L. Donepezil provides greater benefits in mild compared to moderate Alzheimer's disease: Implications for early diagnosis and treatment. *Arch Gerontol Geriatr.* 2009(2009 Nov 28): [Epub ahead of print].
**121.** Gauthier S, Feldman H, Hecker J, et al. Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. *Current Medical Research & Opinion.* 2002;18(6):347-354.

**122.** Blesa R, Davidson M, Kurz A, Reichman W, van Baelen B, Schwalen S. Galantamine provides sustained benefits in patients with 'advanced moderate' Alzheimer's disease for at least 12 months. *Dementia & Geriatric Cognitive Disorders.* 2003;15(2):79-87.
**123.** Wilkinson DG, Hock C, Farlow M, van Baelen B, Schwalen S. Galantamine provides broad benefits in patients with 'advanced moderate' Alzheimer's disease (MMSE < or = 12) for up to six months. *International Journal of Clinical Practice.* 2002;56(7):509-514.
**124.** Rodda J, Morgan S, Walker Z, Rodda J, Morgan S, Walker Z. Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. *International Psychogeriatrics.* Oct 2009;21(5):813-824.
**125.** Winblad B, Black SE, Homma A, et al. Donepezil treatment in severe Alzheimer's disease: a pooled analysis of three clinical trials. *Current Medical Research & Opinion.* Nov 2009;25(11):2577-2587.
**126.** Singh S, Dudley C. Discontinuation syndrome following donepezil cessation. *International Journal of Geriatric Psychiatry.* Apr 2003;18(4):282-284.
**127.** Daiello LA, Ott BR, Lapane KL, Reinert SE, Machan JT, Dore DD. Effect of discontinuing cholinesterase inhibitor therapy on behavioral and mood symptoms in nursing home patients with dementia. *American Journal of Geriatric Pharmacotherapy.* Apr 2009;7(2):74-83.
**128.** Kwak YT, Han I-W, Suk S-H, Koo M-S. Two cases of discontinuation syndrome following cessation of memantine. *Geriatrics & gerontology international.* Jun 2009;9(2):203-205.
**129.** Jones R, Sheehan B, Phillips P, et al. DOMINO-AD protocol: donepezil and memantine in moderate to severe Alzheimer's disease - a multicentre RCT. *Trials [Electronic Resource]*. 2009;10:57.
**130.** Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *British Journal of Psychiatry.* 1982;140:566-572.
**131.** Emre M. Switching cholinesterase inhibitors in patients with Alzheimer's disease. *International Journal of Clinical Practice. Supplement.* 2002(127):64-72.
**132.** Auriacombe S, Pere JJ, Loria-Kanza Y, Vellas B. Efficacy and safety of rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. *Current Medical Research & Opinion.* 2002;18(3):129-138.
**133.** Mintzer JE, Kershaw P. The efficacy of galantamine in the treatment of Alzheimer's disease: comparison of patients previously treated with acetylcholinesterase inhibitors to patients with no prior exposure. *International Journal of Geriatric Psychiatry.* 2003;18(4):292-297.
**134.** Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. *Current Medical Research & Opinion.* 2003;19(8):707-714.
**135.** Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology.* 1999;56(3):303-308.
**136.** Burns A, Zaudig M. Mild cognitive impairment in older people. *Lancet.* 2002;360(9349):1963-1965.
**137.** Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment, a population based validation study. *Neurology.* 2001;56:37-42.
**138.** Lu PH, Edland SD, Teng E, et al. Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology.* Jun 16 2009;72(24):2115-2121.

**139.** Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment.[see comment]. *New England Journal of Medicine.* Jun 9 2005;352(23):2379-2388.
**140.** Raschetti R, Albanese E, Vanacore N, Maggini M. Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. *PLoS Medicine / Public Library of Science.* Nov 27 2007;4(11):e338.
**141.** Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. *CNS Drug Reviews.* 2003;9(3):275-308.
**142.** Rao VL, Dogan A, Todd KG, Bowen KK, Dempsey RJ. Neuroprotection by memantine, a non-competitive NMDA receptor antagonist after traumatic brain injury in rats. *Brain Research.* 2001;911(1):96-100.
**143.** Miguel-Hidalgo JJ, Alvarez XA, Cacabelos R, Quack G. Neuroprotection by memantine against neurodegeneration induced by beta-amyloid(1-40). *Brain Research.* 2002;958(1):210-221.
**144.** Marvanova M, Lakso M, Pirhonen J, Nawa H, Wong G, Castren E. The neuroprotective agent memantine induces brain-derived neurotrophic factor and trkB receptor expression in rat brain. *Molecular & Cellular Neurosciences.* 2001;18(3):247-258.
**145.** Areosa SA, Sherriff F. Memantine for dementia.[update of Cochrane Database Syst Rev. 2003;(1):CD003154; PMID: 12535459]. *Cochrane Database of Systematic Reviews.* 2003(3):CD003154.
**146.** Fleischhacker WW, Buchgeher A, Schubert H. Memantine in the treatment of senile dementia of the Alzheimer type. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 1986;10(1):87-93.
**147.** Gortelmeyer R, Erbler H. Memantine in the treatment of mild to moderate dementia syndrome. A double-blind placebo-controlled study. *Arzneimittel-Forschung.* 1992;42(7):904-913.
**148.** Orgogozo JM, Rigaud AS, Stoffler A, Mobius HJ, Forette F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). *Stroke.* 2002;33(7):1834-1839.
**149.** Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease.[see comment]. *New England Journal of Medicine.* 2003;348(14):1333-1341.
**150.** Wilcock G, Mobius HJ, Stoffler A, group MMM. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *International Clinical Psychopharmacology.* 2002;17(6):297-305.
**151.** Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *Journal of the American Medical Association.* 2004;291(3):317-324.
**152.** Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). *International Journal of Geriatric Psychiatry.* 1999;14(2):135-146.
**153.** Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. *International Journal of Geriatric Psychiatry.* May 2008;23(5):537-545.
**154.** Wenk GL, Quack G, Moebius HJ, Danysz W. No interaction of memantine with acetylcholinesterase inhibitors approved for clinical use. *Life Sciences.* 2000;66(12):1079-1083.
**155.** Hartmann S, Mobius HJ. Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy. *International Clinical Psychopharmacology.* 2003;18(2):81-85.

**156.** Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT, Memantine MEMMDSG. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Current Alzheimer Research.* Feb 2008;5(1):83-89.

**157.** Schmidt R, Ropele S, Pendl B, et al. Longitudinal multimodal imaging in mild to moderate Alzheimer disease: a pilot study with memantine. *Journal of Neurology, Neurosurgery & Psychiatry.* Dec 2008;79(12):1312-1317.

**158.** Wimo A, Winblad B, Stoffler A, Wirth Y, Mobius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics.* 2003;21(5):327-340.

**159.** Gagnon M, Rive B, Hux M, et al. Cost-effectiveness of memantine compared with standard care in moderate-to-severe Alzheimer disease in Canada. *Canadian Journal of Psychiatry - Revue Canadienne de Psychiatrie.* Aug 2007;52(8):519-526.

**160.** Lopez OL, Becker JT, Wahed AS, et al. Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease.[Erratum appears in J Neurol Neurosurg Psychiatry. 2009 Sep 1;80(9):1056]. *Journal of Neurology, Neurosurgery & Psychiatry.* Jun 2009;80(6):600-607.

**161.** Atri A, Shaughnessy LW, Locascio JJ, et al. Long-term course and effectiveness of combination therapy in Alzheimer disease. *Alzheimer Disease & Associated Disorders.* Jul-Sep 2008;22(3):209-221.