Pharmacotherapy for dementia: a review of cholinesterase inhibitors and memantine

CW Wong MBBS, MRCP(UK), FHKAM (Medicine), FHKCP

ABSTRACT

Both cholinergic deficit and glutamatergic dysfunction contribute to the pathophysiology of Alzheimer’s disease (AD) and are the rationale for the use of cholinesterase inhibitor (ChEI) and memantine for AD. Donepezil, rivastigmine, and galantamine are the 3 common ChEIs available in the market. Although they have slightly different modes of action, their primary action is to prevent the breakdown of acetylcholine and their clinical efficacies are similar. ChEIs are widely used for mild-to-moderate AD and other types of dementia; however, their clinical efficacy is modest and only a subset of AD patients shows significant clinical benefits. Memantine is an N-methyl-D-aspartate (NMDA) receptor blocker approved for moderate-to-severe AD. Although its clinical efficacy is also modest, it has additional behavioural benefits. The combination of ChEI and memantine is possibly not superior to ChEI monotherapy. The evidence supporting ChEI and memantine use in other types of dementia is limited.

INTRODUCTION

Advances in the understanding of dementia pathophysiology enable the development of pharmacotherapy specific for dementia. To date, cholinesterase inhibitor (ChEI) and memantine are the only medications approved for treating dementia. They are primarily developed for Alzheimer’s disease (AD), but in clinical practice they are frequently prescribed for off-label use in other types of dementia such as vascular dementia (VD) and dementia with Lewy bodies (DLB). Although they seem to bring hope to demented patients and their families, they cannot cure the dementia or stop the disease process; they can only help to alleviate symptoms and possibly delay disease progression. It is important to note that their clinical efficacy is not high and not all patients can benefit from their use. In this review, the rationale behind the use of ChEI and memantine for AD, their efficacy and adverse effects, their combined use, and their use in other types of dementia are discussed.

CHOLINESTERASE INHIBITORS

Cholinergic hypothesis

The cholinergic hypothesis postulates that cholinergic dysfunction in the central nervous system contributes to cognitive decline associated with advanced age and AD.1,2 Medial septal nucleus, nucleus of the diagonal band of Broca and nucleus of basalis of Meynert in the basal forebrain are the major sources of cholinergic innervation of the cerebral cortex and hippocampus. These cholinergic neurons use acetylcholine as the neurotransmitter, which is synthesised by choline acetyltransferase and is degraded by acetylcholinesterase (AChE). Cholinergic function in the brain is involved in a variety of cognitive functions, in particular those of memory formation and learning ability.3 It is
corroborated by demonstrating that scopolamine, a centrally acting anticholinergic agent, impaired memory performance in young healthy people to a level compatible to normal aged people, whereas physostigmine, a reversible AChE inhibitor and pharmacological antagonist of scopolamine, can reverse the memory impairment. These initial pharmacological studies, demonstrating the change of cognitive performance by drugs that interfere with the central cholinergic system, constitute the basis for the cholinergic hypothesis. Subsequent behavioural studies using animal models to demonstrate the pharmacological blockade of the central cholinergic system or lesion-induced damage to the basal forebrain cholinergic system resulting in the impairment of learning and memory give further support for the likely association of the central cholinergic system with cognitive deficits, which are consistent with ageing and early AD.2,6,7

In post-mortem studies of neurochemical and histopathological changes in the brain tissue from patients with AD, the markers of pre-synaptic cholinergic system function (choline acetyltransferase and AChE activities) were significantly reduced, which were strongly correlated with the degree of cognitive impairment, numbers of senile plaques and neurofibrillary tangles in the corresponding cortex, and the distribution of histopathological abnormalities of AD.8-10 Furthermore, there is a significant loss of basal forebrain cholinergic neuron in AD patients.11,12 An in vivo positron emission tomography study that has revealed nicotinic acetylcholine receptor (nACR) deficits as an early phenomenon of AD also supports the cholinergic hypothesis.13

Taken together, cholinergic dysfunction has an adverse effect on cognitive performance and cholinergic dysfunction is found in AD patients. There seems to be a link between cholinergic dysfunction and the pathogenesis of AD. However, there are challenges to the cholinergic hypothesis; whether it is a primary event in the pathogenesis of AD, or a secondary event that leads to clinical manifestations of AD remains to be determined. Overall, pathogenesis of AD is a complicated process and involves numerous potentially pathogenic or causative factors such as β-amyloid, nerve growth factor, and other neurotransmitter system anomalies (γ-aminobutyric acid and serotonergic), thus AD cannot be simply explained by one hypothesis. Nonetheless, the cholinergic hypothesis contributes to the development of cholinergic replacement therapy to palliate the cognitive decline associated with AD.

**Mode of action of cholinesterase inhibitors**

The 3 common ChEIs available in the market are donepezil, rivastigmine, and galantamine. All these ChEIs enhance cholinergic transmission by inhibiting AChE activity to increase the availability of acetylcholine to interact with postsynaptic acetylcholine receptors. Although they have slightly different modes of action, their clinical efficacy is related primarily to the degree of inhibition of AChE. Donepezil is a specific and reversible inhibitor of AChE. In contrast, rivastigmine is a pseudo-irreversible inhibitor of both AChE and butyrylcholinesterase (BuChE). AChE and BuChE are 2 types of cholinesterase in the body. AChE selectively hydrolyses acetylcholine and is found mainly in the brain, whereas BuChE is a non-specific cholinesterase that hydrolyses many different choline esters including acetylcholine and is found mainly at the periphery. The level of AChE is significantly decreased but that of BuChE increased in AD patients.14 Thus, it was proposed that rivastigmine with dual inhibition of AChE and BuChE could further increase the availability of acetylcholine for neurotransmission. However, clinical trials failed to show the expected additional therapeutic advantage.15-19 Instead, there is a concern about the further increased risk of adverse events, particularly gastrointestinal, as a result of the peripheral BuChE inhibition. Galantamine is a selective and reversible inhibitor of AChE, and has additional modulating action on nACR to increase the release of acetylcholine and thereby facilitate neurotransmission.20 The latter action is thought to have therapeutic implications, as early and consistent loss of nACR and its activities significantly contribute to the reduction in central cholinergic neurotransmission in AD patients.13 However, similar to rivastigmine, galantamine did not show a significant difference in clinical efficacy among the other ChEIs.15-17,19

**Efficacy of cholinesterase inhibitors**

Table 1 summarises the efficacy of ChEIs for the treatment of dementia from meta-analyses of randomised controlled trials. All the meta-analyses exclusively addressed AD except for one17 that included a few studies on other dementia types such
as VD and Parkinson’s disease dementia (PDD). Most studies included patients with mild-to-moderate dementia, and more studies evaluated the efficacy of donepezil than rivastigmine or galantamine. Most studies were of 24 to 26 weeks duration and a few were up to one year or longer. The efficacy comprises 4 domains: cognition, global function, behaviour, and quality of life. In the studies, the scales commonly used to measure the cognitive function were the Alzheimer’s Disease Assessment Scale cognitive subscale (ADAS-cog) [70-point scale], the Mini-Mental State Examination (MMSE) [30-point scale], and the Severe Impairment Battery (SIB) [100-point scale]. For the global function, the scales used were the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus) [7-point scale], the Clinical Global Impression of Change (CGIC) [7-point scale], and the Alzheimer’s Disease Cooperative Study-Activities of Daily Living 19- or 23-item (ADCS-ADL19/23) [54-point for 19-item scale and 78-point for 23-item scale]. The behavioural outcome was assessed using the Neuropsychiatric Inventory (NPI) [120-point for 10-item scale and 144-point for 12-item scale].

Overall, the improvement in scores is more persistent in cognition and global function in the ChEI-treated group. Some studies demonstrated a dose effect, with a higher dose resulting in a greater effect. Nonetheless, the change is generally modest; the mean difference of change from baseline between the treatment and placebo groups was <4 points in the ADAS-cog scale and the difference in the CIBIC-plus scale between the treatment and placebo groups was ≤0.5 point, which may not be translated into a clinically significant benefit. Few studies reported on the proportion of patients who achieved a clinically important improvement in cognition (ADAS-cog ≥4-point change from baseline) and global function (CIBIC-plus or CGIC ≤3-point). This ranged from 15.4% to 60% in the treatment group as compared with 7.8% to 36% in the placebo group on cognition, and 0.4% to 46% in the treatment group as compared with 0% to 25% in the placebo group on global function. 10% and 9% more patients in the treatment group than the placebo group, respectively, achieved a significant cognitive and global improvement. This suggested that the clinical response was quite variable; not all patients could benefit but only a subset of patients achieved clinically significant improvement despite the fact that the average effect of ChEI was modest and clinically insignificant. Individual characteristics determining good response deserves further study.

Evidence for benefits on the behavioural and quality of life outcomes was limited, as both outcomes were evaluated less frequently and showed inconsistent results.

Most studies were of <1-year duration; long-term outcomes, such as maintenance of activities of daily living and delaying the need for institutionalisation, are difficult to evaluate. One large trial, the AD2000 study, measured the rate of institutionalisation and progression of disability in mild-to-moderate AD patients did not, however, show a significant benefit of donepezil over placebo at 3 years. Besides, most studies tended to include relatively healthy patients without significant medical illness. Thus, whether the results or conclusions could be applied to demented patients with comorbidities, which constitute a significant proportion of patients in clinical practice, are in doubt.

There are a few head-to-head comparative studies of different ChEIs, but these did not demonstrate superiority of one ChEI to another. Indirect comparison by subanalysis of data for different ChEIs also indicated similar efficacy. However, in a meta-analysis using the adjusted indirect comparison reported that the relative risk of being a global responder favoured donepezil and rivastigmine than galantamine, and the behavioural response to donepezil was better than that to galantamine.

The US Food and Drug Administration has approved ChEIs for the mild-to-moderate stage of AD and has expanded the indication for donepezil and rivastigmine transdermal patches to include severe AD. In the UK and other European countries, ChEI are licensed for the treatment of mild-to-moderate AD only.

**Adverse effects of cholinesterase inhibitors**

Adverse effects are related to the increased cholinergic activity. The most common ones are gastrointestinal symptoms (nausea and vomiting, diarrhoea, abdominal pain), anorexia, and muscle cramp. Other adverse effects include weight loss and urinary incontinence. Furthermore, cholinergic stimulation on the vagus nerve can provoke.
bradycardia, heart block or syncope, which may lead to permanent pacemaker insertion or precipitate fall-related injuries. Thus, ChEI should not be used in patients with sick sinus syndrome and cardiac conduction defects. Besides, patients with severe asthma and chronic obstructive airways disease, and active peptic ulcer disease should also avoid ChEIs, as increased airway reactivity and gastric acid secretion following cholinergic stimulation can worsen the conditions.

Overall, the rate of withdrawal due to adverse effects was higher in the ChEI-treated group than in the placebo group. Although there was no significant difference among the 3 ChEIs in terms of serious adverse effects, both rivastigmine and galantamine tended to have more adverse effects, especially at high doses, which may be reflected in their higher withdrawal rate due to adverse events than that for donepezil.

The incidence and severity of the adverse reactions are dose-related. These can be reduced by starting at low dose and titrating gradually over several weeks or months to their maintenance dose. Patch formulary (transdermal patch) may be worth trying if the patient cannot tolerate the adverse gastrointestinal effects, as it has been shown to cause less nausea and vomiting than the oral form.

**MEMANTINE**

**Glutamatergic system**

Glutamate is the most prominent neurotransmitter in the body and can be found throughout the brain. It is the main excitatory neurotransmitter in the central nervous system. It acts on the glutamate receptors, N-methyl-D-aspartate (NMDA) receptor, to permit calcium ions flow into the post-synaptic neuron for excitatory transmission, which is important for cell signalling and synaptic plasticity in the process of memory formation and learning. Other glutamate receptors include the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, the kainite and metabatropic receptors. Nonetheless, it appears that the NMDA receptor specifically plays a role in the pathogenesis of AD. Glutamate is also used in the brain to synthesize γ-aminobutyric acid (GABA) which is the main inhibitory neurotransmitter in the central nervous system and is important in regulating neuronal excitability.

After release and acting on the glutamate receptors, the excess glutamate in the synapse is cleared by glutamate transporters, predominantly present on glia. There are 5 different forms of glutamate transporters: glial glutamate and aspartate transporter (GLAST), glial glutamate transporter (GLT-1), excitatory amino acid carrier (EAAC1), and excitatory amino acid transporters (EAAT4 and EAAT5); in which GLT-1 level are highest in the forebrain. Once transported to glia, glutamate is converted to glutamine by glutamine synthetase. It is then transported back to the pre-synaptic neuron where glutamine is converted back to glutamate by mitochondrial glutaminase for use as a neurotransmitter again. Thus, through the glutamate transporter and glutamine synthetase, the extraneuronal glutamate level can be regulated to prevent the overstimulation of the glutamate receptor and the resultant excitotoxicity.

The exact pathology underlying the disruption of glutamatergic neurotransmission in AD is not clear, although over-activation of the NMDA receptor with subsequent excitotoxicity of the neuron is the end result. The glutamatergic neurotransmission has been found to be severely disrupted in the neocortical regions and hippocampus. Both the glutamate transporter and glutamine synthetase activities are reduced, which result in excessive glutamate in the synapse. It then causes excessive and prolonged activation of glutamate receptors; thereby impairing the detection of an incoming physiological signal for normal neurotransmission. Furthermore, glutamate receptor overstimulation enables an excessive influx of calcium ions into the neuron and triggers a series of events in the apoptotic pathway and eventually results in neuronal death. Besides, β-amyloid, a hallmark of AD, can alter glutamate receptor activity and its sensitivity to glutamate, and disturb the normal glutamatergic neurotransmission and cause excitotoxic damage to the neuron.

**Mode of action of memantine**

Memantine, a derivative of amantadine, is a non-competitive, low-to-moderate affinity NMDA receptor antagonist. It works primarily by regulating the activity of glutamate to prevent overstimulation of a receptor from excessive glutamate, but does not affect the normal glutamatergic neurotransmission. Therefore, the physiological function of glutamate can be maintained.
In addition, memantine can also act on the serotonergic (5-HT, receptor), cholinergic (nAChR), and dopaminergic (D₂, receptor) systems. Nonetheless, clinical relevance of these activities for the treatment of AD requires further studies. Memantine has also been shown to have a neuroprotective action. It can protect neuronal degeneration induced by β-amyloid, block the increased phosphorylation of tau, alleviate oxidative stress, and has an anti-inflammatory effect against neuroinflammation.

**Efficacy of memantine**

Table 2 summarises the efficacy of memantine for the treatment of dementia from meta-analyses of randomised controlled trials. The number of studies on memantine is fewer than that on ChEI, and the duration of most studies is up to 26 to 28 weeks. Meta-analyses of memantine trials for all stages of dementia showed significant benefits of memantine on cognitive (ADAS-cog / SIB), global (CIBIC-plus), functional (ADCS-ADL), and behavioural (NPI) domains. However, evaluation according to the severity of dementia showed memantine benefited patients with moderate-to-severe AD on all 4 domains, whereas a clear beneficial effect was lacking in mild-to-moderate AD. Similar to ChEIs, the efficacy is modest among patients with moderate-to-severe AD on cognition, global impression, and activities of daily living. Contrary to ChEI, memantine demonstrated a consistent benefit on behavioural outcome, with delusion, agitation, aggression, and irritability being the most responsive symptoms. Based on these findings, memantine has been approved for moderate-to-severe AD in the US and European countries.

**Adverse effects of memantine**

Memantine seems to be better tolerated than ChEIs. It is well tolerated with an adverse effect profile similar to that of a placebo; the dropout rate and the proportion of patients with adverse effect are comparable to those of the placebo. Headache, confusion, dizziness, and constipation are the most frequently reported adverse effects. Other adverse effects include high blood pressure, somnolence, and vomiting. Conditions that raise urine pH (such as sodium bicarbonate and carbonic anhydrase inhibitor intake, and severe urinary tract infection) may reduce memantine clearance and lead to accumulation of memantine in the body, thus increase the risk of adverse effects.

**COMBINATION THERAPY**

The cholinergic and glutamatergic systems are mutually influenced such that the synaptic connection between the 2 systems facilitate the process of learning and memory. ChEIs and memantine target on these 2 systems and are the current available symptomatic drug treatment specific for dementia. To facilitate their use, combination therapy using both ChEIs and memantine is postulated, and their complementary activity is suggested to produce greater effects than either drug alone.

There are large-scale randomised controlled trials (RCTs) and the corresponding meta-analyses to compare the efficacy of memantine and ChEI combination therapy with ChEI monotherapy. In a meta-analysis that pooled 3 double-blind RCTs with a total of 971 mild-to-severe AD patients, a small but significant effect size was reported in favour of combination therapy among patients with moderate-to-severe AD on cognitive, functional, and neurobehavioural outcomes. In another meta-analysis of 1317 moderate-to-severe AD patients from 3 double-blind RCTs, in which 2 studies recruited are the same as for the former meta-analysis, a small benefit of combination therapy was reported on cognition, behaviour and mood, and global improvement but not on function. In a most recent meta-analysis of 7 studies (5 double-blind RCTs and 2 open-label RCTs) with a total of 2182 mild-to-severe AD patients, clinically significant benefit of combination therapy was reported, particularly in moderate-to-severe AD patients, in term of cognition, behavioural disturbances, activities of daily living, and overall impression. Overall, the combination therapy appears to be safe and well tolerated. Adverse effect and dropout rate were not significantly different from the ChEI monotherapy group and tended to be even lower in the combination therapy group.

Despite the apparent beneficial effects in moderate-to-severe AD from these studies, the clinical relevance of the superiority of combination therapy over ChEI monotherapy is unclear, because only minimal benefits were measured on the rating scales and the supporting evidence from such studies was incomplete. All the studies involved solely the addition of memantine to the existing ChEI monotherapy, but not the simultaneous initiation...
Table 1: Summary of meta-analyses of randomised controlled trials for the efficacy of 3 cholinesterase inhibitors (ChEIs) — donepezil (D), rivastigmine (R), and galantamine (G)

<table>
<thead>
<tr>
<th>Meta-analysis study</th>
<th>No. of studies included</th>
<th>Treatment duration (weeks)</th>
<th>Severity of dementia</th>
<th>Cognitive function</th>
<th>Global function</th>
<th>Behaviour/mood</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodda et al., 2009</td>
<td>9, 2, 3</td>
<td>12-170, 24-26, 12-26</td>
<td>Mild to severe</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Only 3 studies reported significant improvement; most studies had low score at baseline and allowed the use of psychotropic drugs</td>
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<tr>
<td>Hansen et al., 2008</td>
<td>12, 3, 7 (+4 head-to-head comparative studies of different ChEIs)</td>
<td>12-60, 13-26, 12-26</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment: 2.67* (D), 3.01* (R), 2.76* (G)</td>
<td>Outcome in favour of treatment: relative risk: 1.88 (D), 1.64 (R), 1.15 (G)</td>
<td>-</td>
<td>Outcome in favour of treatment: 4.3* (in 4 D studies) vs. 1.44* (in 3 G studies)</td>
</tr>
<tr>
<td>Raina et al., 2008</td>
<td>24, 9, 10 (+3 head-to-head comparative studies of different ChEIs)</td>
<td>12-104, 14-52, 12-26</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment but not clinically significant; highly inconsistent in R</td>
<td>Outcome in favour of treatment in D</td>
<td>Outcome not in favour of treatment in D and R; results were mixed in G</td>
<td>Outcome in favour of treatment in one G study</td>
</tr>
<tr>
<td>Birks, 2006</td>
<td>6, 4, 3 (+1 head-to-head comparative studies of different ChEIs)</td>
<td>24-52, 26, 22-26</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment: 1.4-3.9* at 6 months; R showed most variation</td>
<td>Outcome in favour of treatment: odds ratio: 1.56 (for those with improvement), 1.84 (for those with improvement or no change) at 6 months</td>
<td>-</td>
<td>Outcome in favour of treatment: 2.44* (in 2 D and 1 G studies) at 6 months</td>
</tr>
<tr>
<td>Takeda et al., 2006</td>
<td>13, 4, 6 (+3 head-to-head comparative studies of different ChEIs)</td>
<td>12-60, 13-26, 12-26</td>
<td>Mild to moderate</td>
<td>Outcome in favour of treatment: higher dose with greater effect in D and G</td>
<td>Outcome in favour of treatment in D and R</td>
<td>-</td>
<td>Of 3 studies reported on D, using non-validated rating scales for dementia, 2 showed improvement (not always significant) and one was observed to be better in placebo</td>
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<tr>
<td>Kaduszkiewicz et al., 2005</td>
<td>12, 5, 5</td>
<td>6-156, 13-26, 12-26</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment: 1.5-3.9*</td>
<td>Outcome in favour of treatment: 0.26-0.54*</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ritchie et al., 2004</td>
<td>9, 5, 6</td>
<td>12-52, 10-26, 12-26</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment: higher dose with greater effect in D and R</td>
<td>Outcome in favour of treatment in one R study</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lanctôt et al., 2003</td>
<td>8, 3, 5</td>
<td>12-54, 26, 12-26</td>
<td>Mild to severe</td>
<td>10% more cognitive responders (+4-point improvement) in treatment than placebo group</td>
<td>-</td>
<td>9% more global responders (CIBIC-plus or CGIC rated ≤3-point) in treatment than placebo group</td>
<td>-</td>
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</tbody>
</table>

* Mean difference in point change from baseline to endpoint between treatment and placebo groups
† Mean difference in points between treatment and placebo groups
<table>
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<tr>
<th>Meta-analysis study</th>
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<td></td>
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<td>Alzheimer's Disease (AD) Assessment Scale cognitive subscale</td>
<td>Severe Impairment Battery</td>
<td>Neuropsychiatric Inventory</td>
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<tr>
<td>Schneider et al.,** 2011</td>
<td>3</td>
<td>24</td>
<td>Mild to moderate</td>
<td>Outcome not in favour of treatment in mild AD; only small effect in moderate AD</td>
<td>Outcome not in favour of treatment in mild AD; only small effect in moderate AD</td>
<td>Outcome not in favour of treatment</td>
</tr>
<tr>
<td>Raina et al.,** 2008</td>
<td>5</td>
<td>12-28</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment in mild-to-moderate AD and vascular dementia but not clinically significant</td>
<td>Outcome in favour of treatment in moderate-to-severe AD</td>
<td>Outcome in favour of treatment in one study with concomitant donepezil intake</td>
</tr>
<tr>
<td>Winblad et al.,* 2007</td>
<td>6</td>
<td>24-28</td>
<td>Moderate to severe</td>
<td>Outcome in favour of treatment</td>
<td>Outcome in favour of treatment</td>
<td>Outcome in favour of treatment</td>
</tr>
<tr>
<td>Doody et al.,* 2007</td>
<td>6</td>
<td>24-28</td>
<td>Mild to severe</td>
<td>Outcome in favour of treatment in moderate-to-severe AD but heterogeneous benefit</td>
<td>Outcome in favour of treatment in moderate-to-severe AD</td>
<td>Outcome in favour of treatment in moderate-to-severe AD</td>
</tr>
<tr>
<td>McShane et al.,** 2006</td>
<td>6</td>
<td>26</td>
<td>Mild to severe</td>
<td>Marginal beneficial effect in mild-to-moderate AD: 0.99*</td>
<td>Barely detectable benefit in mild-to-moderate AD: 0.13*; outcome in favour of treatment in moderate-to-severe AD: 0.28*</td>
<td>Outcome not in favour of treatment in moderate-to-severe AD: 2.76*</td>
</tr>
</tbody>
</table>

* Mean difference in point change from baseline to endpoint between treatment and placebo groups
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of memantine together with ChEI. Although it reflects the real-life situation that ChEI is used first in the course of the disease and then followed by the addition of memantine in the advanced stage, it cannot exclude the possibility that the effect is provided mainly by memantine rather than the combination effect. Furthermore, there are no studies comparing the combination therapy with memantine monotherapy, and all the studies carried out so far have been of short duration of up to 24 weeks. The exception is the DOMINO trial, which provided additional information on these issues. After one year of observation, the DOMINO trial showed both donepezil and memantine monotherapy were associated with cognitive and functional benefits in patients with moderate-to-severe AD, whereas there was no additional benefit of adding memantine in individuals who had continued on donepezil, and the efficacy of donepezil and memantine did not differ significantly in the presence or absence of the other.46 Taken together, the evidence at present showed at best slight effects or unclear clinical significance of adding memantine on top of ChEI, and the combination therapy could only be considered in moderate-to-severe AD patients at most. Nonetheless, combination therapy is widely considered as a treatment practice in many centres.

**MILD COGNITIVE IMPAIRMENT AND OTHER DEMENTIA VARIETIES**

**Mild cognitive impairment**
Both ChEI and memantine are not recommended for patients with mild cognitive impairment (MCI). The evidence so far does not support their use as they did not significantly improve cognition or functional status or delay the progression to dementia.47,48 Instead, they were associated with adverse effects, particularly gastrointestinal problems. The prognosis of MCI is highly heterogeneous; some patients remain the same, some improve, and some become demented. Anti-dementia treatment for selected MCI patients with a high chance of progression to dementia may yield tangible benefits. Further studies are needed to better characterise these people with MCI who are likely to progress to dementia.

**Vascular dementia**
Treatment for VD is primarily to control the risk factors for cerebrovascular disease such as hypertension, diabetes mellitus, and hypercholesterolaemia, together with the use of anti-platelet agent for stroke prophylaxis.

Evidence supported the cholinergic system disruption in VD leads to the suggestion of prescribing ChEI for VD patients.49 However, clinical trials showed that both ChEI and memantine produced only small cognitive benefits in term of 1 to 2 points difference in the ADAS-cog but no corresponding effect on global, functional, and behavioural outcomes.50 As the clinical significance of ChEI and memantine on VD patients is uncertain, they are generally not approved for treating VD. VD patients vary widely in the type, location, and extent of the cerebrovascular disease. The clinical heterogeneity with variable clinical course may affect the individual response to the drugs. Further studies are needed to address which subgroup of VD patients would benefit from anti-dementia treatment. For VD patients with coexisting AD, ChEI and memantine are likely to be beneficial.

**Dementia with Lewy bodies and Parkinson’s disease dementia**
Cholinergic deficit with loss of cholinergic neurons in the basal forebrain and depletion of acetylcholine has been found in DLB and PDD patients, in whom the cholinergic deficit may be more severe than in AD patients.51 This raises the possibility that ChEIs are effective for treating DLB/PDD. The available evidence, mostly from open labelled studies and only a few from placebo-controlled studies, showed that ChEIs improved cognition and decreased visual hallucination in both DLB and PDD patients, and decreased apathy, fluctuation in attention and delusion in DLB patients.52 Most studies reported that ChEIs had no effect on the pre-existing parkinsonism. The Cochrane review of ChEI for DLB and PDD only supported the use of ChEI in patients with PDD, as it showed a positive effect on global and cognitive function, behavioural disturbance, and activities of daily living.53 For DLB, the effect of ChEI was not clear, as there was only one RCT on DLB in the review. Nevertheless, ChEI is regarded as a mainstay of treatment for DLB and PDD in many centres, despite the fact that only rivastigmine has been approved by the US Food and Drug Administration for use in mild-to-moderate PDD patients. Donepezil was also approved for use in DLB patients in Japan in 2014.
There is increasing evidence to support the use of memantine in both DLB and PDD patients. In a multi-centre double-blind RCT of memantine for the treatment of mild-to-moderate DLB and PDD patients without prior intake of ChEI, memantine provided mild improvement in global clinical status (mean difference of 0.7 point in CGIC) at 24 weeks, with PDD patients showing a more pronounced response. In a subsequent larger multi-centre double-blind RCT, similar improvement in global clinical status and additional behavioural improvement was also showed at 24 weeks, but the improvement was restricted to patients with mild-to-moderate DLB. In the most recent double-blind RCT using a Cognitive Drug Research computerised assessment system to test the attention and memory, memantine provided clinical relevant improvement in attention and episodic memory in both mild-to-moderate DLB and PDD patients. It is of particularly meaningful to the caregivers, as an improvement in attention would lighten the burden on caregiver.

Frontotemporal dementia

There are currently no approved treatment for frontotemporal dementia (FTD). Current treatment focuses on managing the symptoms, primarily problematic behaviour, using selective serotonin reuptake inhibitor and atypical anti-psychotics. The available evidence from small, open labelled studies or case reports did not show that ChEI had any benefit to patients with FTD. Their lack of effectiveness in FTD may be explained by the relative preservation of cholinergic neurons in the brain. Instead, ChEIs may cause more agitation when prescribed. Furthermore, cholinergic adverse effects of increased oral secretion are potentially harmful to a subset of FTD patients. Therefore, prescription of ChEI should be individualised, based on the clinical response and adverse effects. Memantine benefits moderate-to-severe AD patients. Its consistent behavioural benefit is of clinical relevance, as behaviour and psychological symptoms of dementia tends to increase in the later stages. Combination therapy does not show a distinctive benefit compared with ChEI monotherapy, and their use is therefore not supported on cost-effectiveness grounds. Clinical guidance for the use of ChEIs and memantine in other types of dementia needs further studies. Overall, the ChEIs and memantine have limited role in the management of dementia. Consultation should be given to patients and caregivers before the start of treatment to avoid false expectations. Pharmacotherapy should not be regarded as the only treatment for dementia. Non-pharmacological treatments together with education and support to patients and caregivers are important.

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