

# Efficacy of pharmacological treatment of dementia

## Eficácia do tratamento farmacológico da demência

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**Abstract** Over the last 25 years an increasing number of studies have been performed to evaluate therapeutic agents for people with dementia. Although numerous agents have been trialed at this stage there little evidence that therapeutic agents can prevent dementia or ameliorate the progression of dementia of any type. There is some evidence that specific medical management in high risk individuals can prevent strokes, and thus probably prevent vascular dementia, although this is extrapolating from the available evidence. There is considerable evidence that cholinesterase inhibitor are effective for cognitive symptoms in people with mild to moderate AD, and there is some evidence that they are also effective for other behavioural and functional symptoms. The currently available cholinesterase inhibitors seem to have approximately the same sized effect and thus the choice of agent may be largely determined by the incidence of side-effects. These agents have modest effects and a cautious therapeutic trial is indicated for those subjects with mild to moderate AD.

**Keywords** Cholinesterase inhibitors. Alzheimer disease. Dementia, vascular. Therapeutics. Review literature.

**Resumo** Durante os últimos 25 anos, um número crescente de ensaios clínicos vem sendo conduzido com objetivo de avaliar a eficácia terapêutica de drogas para o tratamento de indivíduos com demência. Embora várias medicações tenham sido testadas, até o momento há pouca evidência de que essas drogas possam prevenir a síndrome demencial ou interferir em sua progressão, qualquer que seja a etiologia. Há alguma evidência de que intervenções específicas podem reduzir o risco de acidente vascular cerebral em indivíduos com alto risco e, assim, prevenir o desenvolvimento de demência vascular – embora isto seja uma extrapolação feita a partir dos dados disponíveis. Há evidência relativamente robusta de que os inibidores da colinesterase são eficazes para o tratamento dos sintomas cognitivos de pessoas com doença de Alzheimer (DA) de gravidade leve à moderada, e há alguma evidência de que esses medicamentos também podem melhorar outros sintomas comportamentais e funcionais frequentemente associados à DA. Os inibidores da colinesterase atualmente disponíveis no mercado parecem ter efeito terapêutico semelhante, e, portanto, a escolha da droga é frequentemente determinada pela incidência de efeitos colaterais. Esses medicamentos têm efeito clínico modesto e podem ser indicados com cautela para o tratamento de pacientes com DA de gravidade leve à moderada.

**Descritores** Inibidores da colinesterase. Doença de Alzheimer. Demência vascular. Terapêutica. Literatura de revisão.

### Introduction

Over the last five years effective medications for the symptomatic treatment of people with Alzheimer's Disease (AD) have become widely available. In general these medications have only modest benefits, but their use has necessitated comprehensive assessments of older people presenting with cognitive symptoms. The assessment of people with dementia often results in the provision of information to caregivers and care planning. The latter may produce substantial benefits,<sup>1</sup>

perhaps even greater than the benefits gained from the pharmaceutical interventions themselves.<sup>2</sup>

The pharmacological management of people with dementia can be divided into symptomatic and treatments designed to prevent dementia. The treatment of established dementia can be further divided into symptomatic and interventions that aim to alter the progression of the disease process. At this stage there are no treatments that have been shown to alter disease progression for the commonest forms of neurodegene-

rative dementia – that is, AD and dementia with Lewy bodies. In addition, there is no direct evidence that treatment alters the progression of vascular dementia after the clinical diagnosis has been made. There is some evidence that interventions can prevent strokes in high-risk patients and this evidence will be briefly reviewed. Thus, this review will focus on the symptomatic treatment of the cognitive symptoms of people with dementia.

### Cholinesterase inhibitors

Some 25 years after the cholinergic hypothesis was first postulated,<sup>3</sup> the use of cholinesterase inhibitors has become an established part of the symptomatic treatment of cognitive symptoms of people with dementia. Initial studies demonstrated that the cholinergic system played an important role on memory functioning<sup>4</sup> and that cholinergic neurones were preferentially affected by AD pathology.<sup>5</sup> Furthermore, studies of the enzyme involved in the formation of acetylcholine observed that choline acetyltransferase is depleted in the brains of people with AD who have come to post mortem.<sup>6</sup>

The first drug of this class to be successfully tried in human beings was tacrine. Although an early report was extremely promising,<sup>7</sup> subsequent trials were not so and considerable concern was raised regarding its hepatotoxicity.<sup>8</sup> A systematic review,<sup>9</sup> summarising 12 trials which included 1984 subjects, found a modest but beneficial effect of tacrine on cognitive symptoms of AD mainly using two methodologies. Firstly, benefits were found using standardised global cognitive scales such as the Mini-Mental Status Examination (MMSE) and the Alzheimer's Disease Assessment Scale - Cognitive Sub-Score (ADAS-Cog). A standard way to report the benefits of these drugs is to subtract the changes over the treatment period observed in the placebo group from the changes observed over the same time period in the active group. Using this method, this meta-analysis demonstrated a benefit of 0.6 [95% confidence interval] [0.23, 1.0] points on the MMSE over a 12-week treatment period and 2.1 [1.4, 2.8] points on the ADAS-Cog. The second methodology utilises the less objective impression of the clinician as to whether the patient has improved or deteriorated by overall impression, the Clinical Global Impression (CGI). Again the changes over time periods are compared between the active and placebo groups, but as this measure is a categorical one, the usual practice is to calculate the odds ratio of observing either improvement or deterioration in the active group compared to the placebo group. Using this technique the review showed that patients treated with tacrine had 1.6 [1.2, 2.1] greater chance of improving than patients treated with placebo over varying periods of treatment.

Unfortunately, tacrine exhibited toxicity in two major ways. Firstly, hepatotoxicity, which was not necessarily dose related and was mostly detected biochemically, resulted in withdrawal of medication in many subjects. Secondly, in common with all the cholinesterase inhibitors, dose-related toxicity was responsible for several cholinergic side-effects, such as nausea, vomiting, diarrhoea and abdominal pain. The

combined effect of these side-effects resulted in a 3.6 [2.8, 4.7] fold increased risk of withdrawal in the tacrine group compared to the placebo group.

Concerns about side-effects and particularly hepatotoxicity inhibited widespread use of tacrine, but because of its demonstrable efficacy, other centrally acting cholinesterase inhibitors were trialed. These newer cholinesterase inhibitors have not been troubled by frequent severe hepatic side-effects, and as a group are reasonably well tolerated. The first of the new generation of cholinesterase inhibitors which gained widespread marketing approval was donepezil. This medication has been extensively trialed and was the first of the medications where the majority of the trials used the standardised methodology proposed by the Food and Drug Administration of the United States of America.<sup>10</sup> A meta-analysis of donepezil summarising eight trials, involving 2664 participants has been reported.<sup>11</sup> The trials involved subjects with mild to moderate AD. For cognition, using the ADAS-Cog, there was a statistically significant improvement for both 5 and 10 mg/day of donepezil at 24 weeks compared to placebo, 1.9 points [1.1, 2.6] and 2.9 points [2.2, 3.7] respectively. At 52 weeks (based on a single study) 10mg/day of treatment with donepezil was associated with a 1.7 points [0.8, 2.6] improvement on MMSE. For the CGI, there were benefits associated with 5 mg /day and 10mg/day of donepezil compared with placebo at 24 weeks. The odds ratio (OR) of showing no improvement on active treatment compared to placebo was 0.5 [0.4, 0.7] for the 5mg/day dose and 0.5, [0.3, 0.7] for the 10mg/day dose. There were significantly more withdrawals before the end of treatment from the 10mg/day (but not the 5mg/day) donepezil group compared with placebo. After 24 weeks of treatment the incidence of nausea, vomiting, diarrhoea and anorexia in the 10mg/day group was increased compared with placebo, but the incidence was less than 10% of subjects. The odds of withdrawal was 1.4 [1.03, 1.80]. The Progressive Deterioration Scale (PDS), measuring change in activities of daily living, showed a benefit of 3.8 [1.7, 5.9] points with 10mg/day donepezil compared with placebo at 52 weeks (based on one study only).

The next cholinesterase inhibitor which has received widespread interest in AD has been rivastigmine. Rivastigmine is a 'pseudo-irreversible' inhibitor of acetyl- and butyrylcholinesterases, but there is little evidence that this theoretical biochemical advantage produces demonstrable benefits in humans with AD. A systematic review<sup>12</sup> has been completed on rivastigmine with the assistance of *Novartis*, which has allowed the inclusion of several unpublished studies. Once again the studies have included subjects with mild to moderate AD. Seven trials, involving 3370 participants, were included in the meta-analysis. High-dose rivastigmine (6 to 12 mg daily) was associated with a 2.1 [1.5, 2.7] improvement on the ADAS-cog score compared with placebo, and a 2.2 [1.1, 3.2] point improvement on the PDS after 26 weeks of treatment. For low dose treatment (1-4 mg daily), there was a significant but small benefit on the ADAS-Cog of 0.8 [0.2, 1.5]. For CGI there were benefits

associated with 1-4 mg daily rivastigmine compared with placebo at 26 weeks, the odds of showing no improvement on active treatment compared to placebo, OR 0.7, [0.6 to 0.9] and for the 6-12 mg daily OR 0.7 [0.6 to 0.9]. There were statistically significantly higher numbers of events of nausea, vomiting, diarrhoea, anorexia, headache, syncope, abdominal pain and dizziness among patients taking high-dose rivastigmine than among those taking placebo. The risk of withdrawal from the studies were greater on 6-12 mg rivastigmine daily (24%) compared to the placebo groups (9%) OR 3.0 [2.3 to 3.8]. There was some evidence that adverse events might be less common with more frequent, smaller doses of rivastigmine which may result in a better benefit to side-effect profile. The meta-analysis revealed benefit on cognitive function as measured by ADAS-cog test scores for the thrice-daily dosage of rivastigmine compared with twice-daily dosage at 26 weeks of 1.3 [0, 2.6] points. The meta-analyses of withdrawals by 26 weeks due to adverse events showed that there were significant differences in favour of the thrice-daily compared with the twice-daily dosage OR 0.6 [0.3, 1.0]

Another cholinesterase inhibitor which has considerable evidence accumulated is galantamine. Galantamine is an alkaloid originally extracted from the Caucasian snowdrop and daffodil bulbs, but now is synthesised, and is a reversible, competitive inhibitor of acetylcholinesterase with very little butyrylcholinesterase inhibitory activity.<sup>13</sup> A recent meta-analysis<sup>14</sup> summarised 7 trials, with 6 being Phase II or III industry-sponsored multicentre trials. Trials of 5 months or more were aggregated in the analyses as '6 months'. Overall, galantamine showed benefits at daily doses of 16-32 mg/day. For cognitive function a dose of 16-32 mg/day was associated with an improvement of 3.1 to 3.3 points on the ADAS-Cog as measured on an intention-to-treat basis. At 24 mg/day, the difference between active and placebo groups was 3.3 [2.7, 3.9] points. For global ratings (CGI), trials of 6 months duration were associated with benefits at doses of 16-36mg/day. At 24-32 mg/day the odds of improvement were 2.0 [1.6, 2.5] compared to placebo on an intention-to-treat basis. The Disability Assessment of Dementia gave statistically significant results in favour of treatment based on one study only. At 24 mg/day a benefit of 2.8 [0.1, 5.7] points was found in comparison to the placebo group. Galantamine's adverse effects appear similar to those of other cholinesterase inhibitors, in that it tends to produce gastrointestinal effects acutely and with dosage increases. Overall, people treated with galantamine at doses of 24-32 mg/d were more likely to discontinue participation in trials than were people treated with lower doses or placebo. At 24mg/day the odds of discontinuation were 1.7 [1.3, 2.2] and at 32 mg/day were 3.2 [2.5, 4.2]. At 32 mg/day 38% withdrew early compared to 16% on placebo.

Some conclusions can be drawn from the available evidence on cholinesterase inhibitors. Tacrine should probably no longer be used, as donepezil, rivastigmine and galantamine use is not complicated by high rates of hepatotoxicity, as is the case with tacrine. It is important to emphasise that none of the randomised

trials compared two or more of these medications and therefore the effects of the medications are not directly comparable. Different size of effects could have been influenced by different patient selection, investigator selection and trial methodology. Nevertheless, all the medications of this class seem to have very similar effect sizes. At higher doses galantamine and rivastigmine have a high incidence of side-effects, which in the case of rivastigmine, may be reduced by thrice daily dosing. There is no evidence that these drugs have anything but symptomatic effects, but these translate to small but measurable effects on function which probably last at least 12 months.

### Other treatments for AD

Many treatments have been trialed for the symptomatic control of AD. A systematic review of lecithin<sup>15</sup> failed to find any evidence of benefit for people with dementia. Other treatments including piracetam,<sup>16</sup> CCP choline<sup>17</sup> and hydergine<sup>18</sup> demonstrated some promise but the trials were mainly short-term and often used older methodology and thus the evidence base was not adequate to recommend their use. A systematic review of Vitamin E treatment<sup>19</sup> noted that one study showed some benefit, but at this stage the evidence is not strong enough to recommend its use. There is very little randomised trial evidence for other anti-oxidant medications. A systematic review of selegiline<sup>20</sup> demonstrated encouraging results from several trials but, apart from effects on memory, were not clear-cut enough for their use to be recommended in clinical practice. Similarly there is some evidence for ginkgo biloba in the treatment of people with dementia, but not enough to recommend its routine use.<sup>21</sup> The evidence for the use of anti-inflammatory agents is largely observational at this stage.<sup>22</sup> Similarly, any evidence for benefits of estrogen in the prevention of AD is observational at this stage and there is little evidence of any type that treatment with estrogen has benefits for people with AD.<sup>23</sup>

### Vascular dementia

There is no high quality evidence regarding interventions which specifically impede the progression of vascular dementia. Therefore, it is necessary to extrapolate from studies which have evaluated interventions to reduce the risk of stroke generally. This has been reviewed recently.<sup>24</sup> At this stage, the best evidence of the benefits of medical management for the prevention of further cerebrovascular damage is for the control of hypertension. In those patients with diabetes mellitus, anti-hypertensive treatment may be even more important than aggressive control of hyperglycaemia, although modest benefits may be obtained from this intervention as well. The use of antiplatelet agents, and in particular aspirin, is efficacious, and is preferred in patients who have high risk of stroke due to previous vascular damage without contraindications and who are not in atrial fibrillation. In those patients with atrial fibrillation consideration should be given to the use of anticoagulation. In selected patients with hypercholesterolaemia, the "statin" medications may have a definite

role. Specific agents such as pentoxifylline show some promise,<sup>25</sup> but again the results are preliminary. The use of cholinesterase inhibitors for symptomatic control of people with vascular dementia is currently being examined in many sites around the world, but at the time of writing there is a lack of evidence supporting their use.

## Conclusions

At this stage there is little evidence that pharmacological treatment can prevent dementia or ameliorate the progression of dementia. The only exception to this is that extrapolations from studies of high risk individuals indicate that modern medical management can decrease the risk of stroke and thus

probably vascular dementia. The only class of agents that have proven efficacy in the treatment of people with AD are the cholinesterase inhibitors. Before embarking on a therapeutic trial in these patients, it is prudent to ensure that the patients are similar to those subjects that were part of the clinical trials ie they have AD of mild to moderate severity. Titration should be gradual, particularly in those subjects who manifest any cholinergic side-effects. The choice of initial medication may depend largely on incidence of side-effects as their efficacy seems to be quite similar. There is little available evidence about response for one drug after trial with another, although this may be attempted after appropriately counselling patients about the lack of evidence for this approach.

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