Cholinesterase inhibitors in Alzheimer’s disease — an update

Alzheimer’s disease affects an ever growing number of people, with almost half a million patients in the UK alone. Unfortunately approaches to treating Alzheimer’s disease are limited and cholinesterase inhibitors are the most commonly used agents. Guidance from the National Institute for Health and Clinical Excellence (NICE) for these treatments is controversial because of the restrictions it places on their use. This article explores the use of cholinesterase inhibitors in the UK by focusing on the NICE guidance and reviews the mechanisms of action, clinical usage and efficacy of these agents.

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Alzheimer’s disease affects approximately 465,000 people in the UK, with increasing prevalence as people live longer. The impact of the condition is also felt on a global scale affecting 26.6 million people worldwide and with predictions of a quadrupling in number by 2050.

Increasing recognition and awareness of dementia has been seen in recent years. In the last 10 years, the Department of Health has launched the National Framework for Older People (2001) and the more recent Living well with dementia: a national dementia strategy (2009). However the controversial decision by the National Institute for Health and Clinical Excellence (NICE) to recommend limiting the use of cholinesterase inhibitors in Alzheimer’s disease attracted much public and media attention and led to a legal challenge in the High Court.

It is generally recognised that cholinesterase inhibitors, such as donepezil, have a therapeutic effect by improving cognitive symptoms and outcomes in activities of daily living (ADLs) in Alzheimer’s disease. However, even the strongest proponents of their use recognise that the demonstrated benefits have only been modest. For a condition where other pharmacological alternatives are sadly lacking and response to treatment cannot be predicted, clinicians often find themselves using these agents in the hope they produce a benefit.

Memory loss is universal and is the presenting symptom in the vast majority of cases of Alzheimer’s disease. It should be noted that the symptoms may be split into three separate general groups. The first and most recognised group is comprised of cognitive symptoms, which include memory problems and executive dysfunction. The second group consists of the functional impairment as manifested by an inability to perform the activities of daily living (e.g., bathing and dressing). The third and final group consists of behavioural and psychological symptoms, which include agitation, depression and hallucinations (Table 1).

Pathology and mechanism of action

Alzheimer’s disease is a progressive neurodegenerative condition in which neuronal death accompanies both amyloid plaque deposition and neurofibrillary tangle formation. Coupled to these pathological changes are declines in neurotransmitter transmission. A key neurotransmitter is acetylcholine, whose decline in the neuronal synapse has been implicated in the
memory loss and cognitive decline witnessed in Alzheimer’s disease.

The German psychiatrist Alois Alzheimer first described Alzheimer’s disease in 1907, but it was not until 1997 that the first pharmacological treatment for the condition, donepezil, was licensed for use in the UK. Donepezil is a cholinesterase inhibitor and aims to increase acetylcholine synaptic availability by inhibiting acetylcholine breakdown, thus improving cognitive function (Figure 1). Two other cholinesterase inhibitors, rivastigmine and galantamine, are also now available.

While all cholinesterase inhibitors increase cholinergic transmission by decreasing acetylcholine breakdown at the synapse, they have some pharmacological differences. Donepezil and galantamine are both reversible inhibitors, while rivastigmine is classed as a “pseudo irreversible” inhibitor due to its prolonged reversible action. Galantamine and rivastigmine act competitively on acetylcholinesterase and their oral absorption is delayed by food intake. Donepezil, however, is a non-competitive inhibitor of acetylcholinesterase and its absorption is independent of food. Rivastigmine is extrahepatically metabolised while extensive hepatic metabolism, via cytochromes 2D6 and 3A4 is demonstrated with donepezil and galantamine. Despite this hepatic metabolism, there have been no in vivo clinical trials that have investigated the effect of cholinesterase inhibitors on the clearance of drugs metabolised by CYP3A4 or by CYP2D6.

There are two cholinesterase enzymes present in the human body, acetylcholinesterase and butyrylcholinesterase. Donepezil and galantamine both selectively inhibit acetylcholinesterase. Rivastigmine inhibits both enzymes, but this has not been demonstrated to be of clinical relevance. Galantamine in addition to its acetylcholinesterase inhibition also demonstrates allosteric modulation at nicotinic cholinergic receptor sites, which is hypothesised to also increase cholinergic transmission. This additional property has not been shown to be clinically significant in Alzheimer’s disease.

Another agent is memantine, which is not an cholinesterase inhibitor and works via blockade of N-methyl-D-aspartic acid (NMDA) receptors. Although it has a licence for treatment of moderate-to-severe Alzheimer’s disease, NICE does not support its clinical use.

Clinical use

Donepezil, rivastigmine and galantamine are all licenced for the treatment of mild-to-moderate severe Alzheimer’s disease. Additionally, rivastigmine has a licence for the treatment of mild-to-moderate dementia as a result of Parkinson’s disease.

In 2006, NICE proposed draft guidelines that reversed its previous recommendations for the drugs by stating that they were not cost-effective treatments. After much debate and a further review of trial data, the final guidance recommended that the drugs could be used to treat patients with moderately severe Alzheimer’s disease as defined by a mini mental state examination (MMSE) score of between 10 and 20. Therefore, the agents are not recommended for those with mild Alzheimer’s disease. People with mild Alzheimer’s disease who were already receiving donepezil, galantamine, or rivastigmine at the time the guidance was published were allowed to continue until they, their carers and/or specialist considered it appropriate to stop.

A case of moderate Alzheimer’s dementia would cost £23,000–35,000 per quality adjusted life year (QALY), but milder cases cost £56,000–72,000 per QALY (above NICE’s £30,000 per QALY cost-effectiveness threshold). With its economic model, NICE was criticised for not considering important

Table 1: Symptoms of Alzheimer’s disease

<table>
<thead>
<tr>
<th>Symptom group</th>
<th>Typical symptoms</th>
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<tbody>
<tr>
<td>Cognitive</td>
<td>Memory loss; language difficulties; executive dysfunction</td>
</tr>
<tr>
<td>Functional impairment</td>
<td>Inability to dress self; difficulty feeding or preparing meals; unable to tend to personal hygiene</td>
</tr>
<tr>
<td>Behavioural and psychological symptoms of dementia</td>
<td>Depression; hallucinations; delusions</td>
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</tbody>
</table>
factors such as reduced carer time, and reduced prescription of other drugs (eg, antipsychotics). Furthermore, NICE may review its guidance when the current range of cholinesterase inhibitors become generic and, therefore, cheaper.

The MMSE prescribed by NICE to distinguish the different severities of Alzheimer’s disease has been described by some as arbitrary and inconsistent. It may also be inaccurate in those with a learning disability, poor English fluency or from a different cultural group. Following a High Court judgement, the guidance was amended in 2009 so that special precautions would be made regarding applying the MMSE criteria in those with communication difficulties, different cultural backgrounds and learning disabilities.

NICE also recommends that only physicians with a specialist interest in dementia (eg, geriatricians) should initiate treatment. Furthermore, patients receiving these drugs should be reviewed every six months by MMSE score and global, functional, and behavioural assessment. The treating physician should also take account of the carer’s view of the patient’s condition during follow up. The medication should only be continued if the MMSE remains at or above 10 and the drug is thought likely to continue to have a worthwhile effect on the patient’s global, functional and behavioural condition.

**Drug efficacy**

A Cochrane review has shown that as a class of medication, the cholinesterase inhibitors are efficacious in treating Alzheimer’s disease of mild-to-moderate severity. The amount of methodologically robust data for this viewpoint is limited, as suggested by Rodda et al. However despite this limitation, in the absence of other alternative treatments, a trial of treatment with cholinesterase inhibitors is still appropriate in the treatment of Alzheimer’s disease. There have also been suggestions that pharmaceutical
Alzheimer’s disease

Key points
- Alzheimer’s disease is of growing economic, political, and medical importance as the population ages.
- The decline in cholinergic transmission seen in Alzheimer’s disease is thought to be responsible for the cognitive dysfunction including memory loss.
- Cholinesterase inhibitors are the only pharmacological agents currently recommended by NICE for the treatment of Alzheimer’s disease.
- NICE only recommends their use in moderate severity Alzheimer’s disease.
- There is limited research on the comparative effectiveness of the different cholinesterase inhibitors and more research needs to be undertaken.
- While cholinesterase inhibitors are of benefit in the cognitive and activities of daily living in Alzheimer’s disease, their benefits are modest.

industry sponsored research of cholinesterase inhibitors has perhaps subtly overplayed the impact of these agents.19

The Cochrane review was produced before two randomised control trials of cholinesterase inhibitors in severe Alzheimer’s disease were published. Findings from these trials suggested that in Alzheimer’s disease, improvements may be seen in global, functional and cognitive assessments.20,21 A review by Hsiung et al concluded that while evidence of benefit is present in the pharmacological treatment of moderate-to-severe Alzheimer’s disease, cost benefit data and optimum duration of treatment is unfortunately lacking.22

Cognitive symptoms have been modestly improved by cholinesterase inhibitors in several meta-analyses as assessed by using cognitive scales such as ADAS-Cog Scale (Alzheimer’s Disease Assessment Scale-Cognitive).6,23 Functional activity of patients treated with cholinesterase inhibitors also seems to be enhanced. Hansen et al conducted a systemic review and meta-analysis and found a small improvement in functional status.24 In regards to the effect of cholinesterase inhibitors for the management of behavioural and psychological symptoms in dementia (BPSD), evidence of efficacy is limited due to lack of methodologically robust research.25

There have been limited trials comparing different cholinesterase inhibitors and more research is needed with larger scale trials before definitive conclusions can be reached about their relative efficacy and effectiveness. Often clinicians choose an agent based on familiarity, available form and local agreements.26 Areas for further study include assessing the impact of treatment on carers, head-to-head comparison studies of the different agents, and assessment of benefit in the behavioural and psychological symptoms of dementia.

Side effects and tolerability
With any medication given to the older people, it is important to consider the side effect profile and tolerability given the polypharmacy and greater medical comorbidity in this patient group. While central inhibition may give rise to the benefits in Alzheimer’s disease, peripheral acetylcholinesterase inhibition accounts for many of the side effects seen with this class of drugs. In light of the dose-related cholinergic effects, these agents should be started at a low dose and the dose increased according to response and tolerability.27 Common side effects of increased peripheral cholinergic excess include anorexia, nausea, vomiting, diarrhoea, dyspepsia, fatigue, and weight loss. These side effects occur more frequently around increases in medication dosages and are typically of low intensity and duration. Of note, a small number of people may suffer from muscular pain and cramping with both donepezil and galantamine.11

Conclusion
NICE guidance recommends restricting the use of cholinesterase inhibitors to moderate severity Alzheimer’s disease. These drugs appear to improve, or reduce the rate of deterioration of cognitive function in addition to improving functional ability; however, these demonstrated effects appear modest. Research is limited in comparing the licenced cholinesterase inhibitors. In the absence of other recommended pharmacological interventions, clinicians often find themselves using these agents in suitable patients in the hope of a therapeutic improvement.

Conflict of interest: none declared

References


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