Although pharmacological treatments for Alzheimer’s disease are available, NICE says that they are only cost-effective for certain patients. Are you and your colleagues aware of which patients these are?

Medicines for Alzheimer’s disease

By Wasim Baqir, PhD, MRPharmS, and Alan Worsley, PhD, MRPharmS

Dementia is a multifactorial condition that can manifest as any of several subtypes—eg, Alzheimer’s disease (AD), vascular dementia, dementia with Lewy bodies and frontotemporal dementia. The National Institute for Health and Clinical Excellence estimates that dementia affects around 1% of those aged 60 to 65 years in the UK; this figure rises to 15% in those over the age of 65 years. Prevalence estimates can vary tenfold (2.9% to 29%) depending on the method of investigation.

AD accounts for about 60% of all dementias. Patients usually present with loss of memory, while behavioural problems are often observed as the disease progresses. The progressive decline in cognition eventually leads to a reduced ability to carry out daily living. This includes being unable to perform basic tasks such as dressing, washing and using the toilet. Without proper care, these patients are at increased risk of infection, malnutrition and falls.

NICE and the Social Care Institute for Excellence have released a guideline on supporting patients and carers with all dementias. This article will only focus on the pharmacological management of AD—the form of dementia for which the evidence base is largest.

Treatments

Currently there are three treatments recommended by NICE for the treatment of AD. These are all acetylcholinesterase (ACh) inhibitors.

ACh inhibitors

Donepezil is a reversible inhibitor of ACh, licensed to treat mild-to-moderate AD. The initial dose is 5mg daily (normally taken in the evening) for at least one month, titrating up to a maximum dose of 10mg daily. There is no need for dose reduction in patients with renal impairment. Donepezil is the most commonly used ACh inhibitor in the UK.

Galantamine, a reversible inhibitor of ACh with nicotinic receptor agonist properties, is also licensed for mild to moderately severe AD. The starting dose is 4mg twice daily for at least four weeks before titrating up to 12mg twice daily. Galantamine should be used with caution for patients with severe renal and hepatic disease.

Rivastigmine is a reversible, non-competitive inhibitor of ACh. It also inhibits butyrylcholinesterase, which potentially increases the risk of nausea and vomiting above that of other ACh inhibitors. Rivastigmine is licensed to treat mild to moderately severe AD and mild to moderately severe dementia in patients with idiopathic Parkinson’s disease. The starting dose is 1.5mg twice daily. It can be increased in steps of 1.5mg twice daily to a usual range of 3–6mg twice daily.

NICE recommends using one of these ACh inhibitors as treatment for AD that is of moderate severity only. (This guidance has been adopted in Scotland as in England and Wales.) Moderate disease severity is defined as a score of 10–20 using a mini mental state examination (MMSE). That said, NICE also states “Healthcare professionals should not rely, or rely solely, upon the patient’s MMSE score in circumstances where it would be inappropriate to do so.” It describes one such circumstance to be “where the MMSE is not a clinically appropriate tool for assessing disease severity because of the patient’s learning or other disabilities or linguistic or other communication difficulties”. In such situations, NICE advises that clinicians should use “other methods of assessment” to determine disease severity.

Side effects

The main adverse effects experienced by patients taking ACh inhibitors are nausea, vomiting, abdominal pain and dyspepsia. These are usually dose-related but can cause poor adherence to other medicines.

All ACh inhibitors can cause psychiatric side effects such as hallucinations, agitation and aggressive behaviour. According to the summary of product characteristics for donepezil, anecdotal evidence suggests that these effects resolve on dose reduction or discontinuation of treatment.

Medicines that enhance the effects of acetylcholine can cause an overstimulation of the vagus nerve, which can cause the heart rate to slow. If patients experience syncope or seizures while on treatment, the possibility of heart block or long sinusual pauses should be considered.

Other potential side effects include weight loss (leading to anorexia); sleep disorders and increased sweating. For all ACh inhibitors, adverse events should be reported to the Medicines and Healthcare products Regulatory Agency’s yellow card scheme.

Evidence

A systematic review of donepezil, rivastigmine and galantamine (consisting of 10 randomised clinical trials) showed a modest improvement in cognitive function (average reduction of 2.7 points on the 70–point ADAS-Cog scale [Alzheimer’s disease assessment scale-cognitive subscale]; 95% confidence interval 2.3–3.1; P<0.001) in patients with mild, moderate or severe AD.

Discussion points

- What flexibility is offered by the National Institute for Health and Clinical Excellence regarding which patients can be treated with acetylcholinesterase inhibitors?
- How could medicines use reviews be used to target patients with Alzheimer’s disease and should the review process be modified in any way?
Memantine

Memantine is an uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. It modulates the effects of elevated levels of glutamate that can lead to neuronal dysfunction. NICE does not recommend its use unless as part of a clinical trial.

Shared care

Treatment with ACh inhibitors should be initiated by a specialist in elderly care or psychiatry. Before starting treatment, baseline urea and electrolytes, liver function tests, blood pressure, pulse and weight should be measured. During treatment, heart rate should be checked monthly while the dose is titrated up. Blood pressure, pulse and weight should be monitored every six months. The prescribing clinician should also undertake behavioural and functional assessments, taking into account patients’ and carers’ views.

Repeat prescribing can be undertaken in primary care through the use of shared care agreements. If, after at least six months of treatment, a patient’s condition has improved and is stable, he or she can be managed in primary care.

The role of the primary care team (including GPs, nurses and community pharmacists) is to continue supplying treatment and monitor for deterioration in cognitive function. The team should be vigilant for signs of:

- Intolerance — eg, diarrhoea, weight loss, rash
- Adverse effects — eg, nausea and vomiting
- Non-adherence — ie, lack of response
- Toxicity — eg, severe nausea and vomiting, excessive salivation and sweating, bradycardia and, in severe cases, respiratory depression and convulsions

Where necessary, the patient should be referred back to the specialist.

Pharmacists should be aware of local shared care arrangements and play their part in monitoring patients who are prescribed these medicines by GPs. Community pharmacists could use directed medication reviews to support the monitoring of patients with AD.

Counselling points

Patients and carers should be made aware of the nature of the disease, the potential side effects of treatment and what to do if problems occur. The aim is to prevent non-adherence and unplanned cessation of treatment. ACh inhibitors will add to the AD-related impairment of driving and operating machinery; these tasks should be assessed initially by the specialist, with further monitoring potentially being done by community pharmacists, to ensure patients are safe. Monitoring requirements should also be discussed and the importance of attending follow-up appointments emphasised.

Many AD patients will be taking several other medicines. Impaired cognitive function might reduce their ability to adhere to these treatments. Such patients should be assessed to determine whether they require more intensive support. Interventions such as medicines compliance aids or reminder charts, and further training (eg, to help identify the signs of toxicity or deterioration) for carers should be considered.

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