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Consultant Pharmacist Continuing Education Series | April 2019

DEPRESCRIBING CHOLINESTERASE INHIBITORS

Dementia affects nearly half a million Australians. Three in 10 people over the age of 85 and almost one in 10 people over 65 have dementia. It is the single greatest cause of disability in older Australians. People with dementia account for 52% of all residents in residential aged care facilities.Alzheimer's disease is the most prevalent type of dementia. It is progressive, significantly impacting on cognition, function, behaviour, lifespan and healthcare use. Current therapies for Alzheimer's disease do not modify the course of the disease and are not universally beneficial. Regular assessment and discussion with families and carers is necessary to balance the chance of benefit and risk of harm in the context of the resident's care goals.

Treatment

None of the available drugs prevents Alzheimer's disease or modifies its progression. There are currently two classes of medicines available to treat the symptoms of dementia. Cholinesterase inhibitors (also called anticholinesterases) and memantine show, at best, modest efficacy in improving cognition and/or reducing the rate of cognitive and functional decline. Regular review of anticholinesterases and memantine is necessary as these medicines have the potential for adverse effects, which may outweigh any perceived or observed benefits. Any pharmacological management for Alzheimer's disease must be done in conjunction with optimising the management of comorbidities, including behavioural symptoms, rationalising other medicines, and ensuring adequate education, carer support and provision of services.

Cholinesterase inhibitors

Cholinesterase inhibitors or anticholinesterases are indicated for the treatment of mild-to-moderately severe Alzheimer's disease. They include:

- Donepezil (Aricept, Aridon, Aridon APN)
- Galantamine (Galantyl, Gamine XR, Reminyl)
- Rivastigmine (Exelon)

Donepezil, rivastigmine and galantamine seem to have similar efficacy. Rivastigmine is also available as a patch (Exelon, Rivastigmelon).

Nausea and vomiting are less common with the patch than with oral rivastigmine. A beneficial effect, if any, is generally observed within 3–6 months of starting treatment. Some patients may benefit from anticholinesterases for 3 years or more; but others show little tangible effect. Common side effects of anticholinesterases include nausea, vomiting, diarrhoea, anorexia, abdominal pain, dyspepsia, headache, insomnia, vivid dreams, depression, fatigue, drowsiness, dizziness, tremor, weight loss, muscle cramps, urinary incontinence, increased sweating, hypertension, and fainting. Cholinesterase inhibitors are contraindicated with an active peptic ulcer, or gastrointestinal or ureteric obstruction. Cholinesterase inhibitors may aggravate peptic ulcer disease, seizures, heart block, bradyarrhythmias (including sick sinus syndrome), Parkinson's disease, asthma, and COPD. Treatment with medicines with anticholinergic activity reduces the therapeutic effect.

Memantine

Memantine (Ebixa, Memanza, Memantine) is indicated for moderate-to-severe Alzheimer's disease. Memantine may be associated with a modest reduction in clinical deterioration associated with Alzheimer's disease. Memantine may sometimes be added to cholinesterase inhibitor therapy. However, one study showed no improvement in cognitive and functional outcomes over 12 months when added to a stable dose of donepezil compared to donepezil alone. Memantine commonly causes confusion, dizziness, drowsiness, headache, insomnia, agitation, hallucinations, dyspnoea, and hypersensitivity. Rare side effects include seizures, rash, renal failure, cholestatic hepatitis, heart failure, and bradycardia.

Risk/benefit

It is estimated that about one-third of cholinesterase inhibitors and memantine use is potentially inappropriate. Benefits of cholinesterase inhibitors and memantine usually reduce over time. The likely harms outweigh the likely benefits to the individual resident. A proportion of people who have used these medications for over 12 months or outside an approved indication may be able to

continued over

stop the medication with minimal clinically relevant negative consequences. Treatment should be stopped if there are significant adverse effects, poor compliance or lack of stabilisation or improvement of symptoms.

Deprescribing

Deprescribing is the process of withdrawing (or reducing the dose of) inappropriate medications with the aim of optimising medication use and patient outcomes. Recently published Australian guidelines recommend shared decision making between residents and their caregivers. A trial discontinuation is recommended for residents whose cognition and/or function has significantly worsened over the past 6 months. It is also recommended if no benefit is seen during treatment and in severe or end-stage dementia.

A three-step process is recommended:

1. Determine treatment goals
2. Discuss benefits and harms of continuing and ceasing medication, from the start of therapy and throughout
3. Monitor after discontinuation, while informing carers that the individual will continue to decline after discontinuation

This approach may reduce adverse drug reactions and medication burden, leading to improved quality of life in people with dementia.

Tapering and monitoring

Discontinuation of cholinesterase inhibitors and/or memantine may lead to a worsening of cognitive function. However, quality of life and function may not be altered by discontinuation. Hence it is important to consider the values, preferences and experiences of the resident, their family and caregivers if deprescribing is to be considered.

Tapering of cholinesterase inhibitors and/or memantine is recommended to reduce the likelihood of severe withdrawal reactions. Abrupt cessation may be appropriate when seizures or severe bradycardia occur.

Withdrawal reactions may include:

- altered level of consciousness
- hallucinations
- delusions
- insomnia
- increased anxiety and agitation
- altered mood

Guidelines recommend halving the dose of cholinesterase inhibitors or memantine every 4 weeks to the lowest available dose, followed by discontinuation. Close monitoring during this period is necessary to detect cognitive, functional and neuropsychiatric symptoms. If severe symptoms such as agitation, aggression, hallucinations or reduced consciousness occur within a week of dose reduction or cessation, cholinesterase inhibitors can be restarted at the previous minimum effective dose. If cognition, behavioural or psychological symptoms or function worsen within 2 to 6 weeks of dose reduction or cessation this may indicate a re-emergence of Alzheimer's disease symptoms. If these signs or symptoms emerge in 6 weeks to 3 months, it may indicate progression of Alzheimer's disease or a re-emergence of symptoms. If symptoms emerge after three months of dose reduction or cessation, it is likely to be due to the natural progression of the disease.

Any decision to deprescribe cholinesterase inhibitors or memantine should consider the individual resident and families as well as their values, preferences and goals of care.

A guide to deprescribing cholinesterase inhibitors is available at *https://www.primaryhealthtas.com.au/wp-content/uploads/2018/09/A-Guide-to-Deprescribing-Cholinesterase-Inhibitors.pdf*

References
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