Reducing the load: Medicines best avoided in patients with dementia

Dementias are progressive disorders characterised by impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia, executive function). The result is a clinically significant loss of cognitive function. Prevalence increases exponentially with age from 1% at age 65 to nearly 40% at age 90.¹

Causes of dementia include; Alzheimer’s disease (60%), dementia with Lewy bodies (5%), frontotemporal dementia, vascular (multi-infarct) dementia (15%) and Parkinson’s disease.

Dementia frequently has more than one cause and medical illnesses which can exacerbate poor cognition are also common in patients with dementia.

There are currently over 245,000 Australians with dementia. This is estimated to increase to 592,000 by 2030 and 1,130,000 by 2050.²

Patients with dementia are more sensitive to the cognitive impairment induced by commonly used medicines, especially those with anticholinergic properties. This impairment may be misattributed to advancement of the disease process. Co-prescribing medicines with weak anticholinergic properties may still produce an adverse effect on cognition because of the cumulative ‘anticholinergic load’.

Medicines which can cause sedation impact on cognition and increase the risk of falls. Some medicines have both anticholinergic and sedating properties making appropriate selection for veterans with dementia even more challenging. This therapeutic brief will outline how these commonly used medicines can adversely affect veterans with dementia and, where possible, suggests alternative medicines or strategies.

Medicines used to treat dementia

Acetylcholine is the main neurotransmitter involved in creating new memories and levels fall markedly as dementia progresses. The cholinesterase inhibitors (sometimes called anticholinesterases) - donepezil, rivastigmine and galantamine - increase cholinergic transmission by inhibiting the enzyme acetylcholinesterase. A transient improvement in cognition may occur in some patients however, the underlying disease process will continue. Cholinesterase inhibitors are PBS subsidised for the treatment of mild to moderately severe Alzheimer’s disease.³ They are associated with prominent gastrointestinal adverse effects and can also cause drowsiness and urinary incontinence.⁴ Failure to recognise these symptoms as side effects can potentially lead to further prescribing (‘prescribing cascade’). Medicines with anticholinergic effects are prescribed for up to 1 in 3 patients receiving cholinesterase inhibitors. Concurrent use of these medicines may exacerbate dementia symptoms or reduce the effectiveness of cholinesterase inhibitors.⁵,⁶

Memantine is a glutamatergic antagonist which may benefit cognition resulting in the need for fewer hours of direct patient care.¹ It is PBS subsidised for the treatment of moderately severe to severe Alzheimer’s disease.⁷ Adverse effects can include confusion and drowsiness.⁸

Key points

- People with dementia are more sensitive to anticholinergic effects of medicines.
- Many commonly used medicines have anticholinergic effects which can be cumulative.
- Reduce the load by reducing the number and dose of medicines with anticholinergic and sedative effects given to those with dementia.
- Avoid co-prescribing medicines with anticholinergic effects in combination with a cholinesterase inhibitor.
Medicines with anticholinergic effects

Patients with dementia are extremely sensitive to the cognitive impairment induced by medicines with anticholinergic properties and their use should be avoided where possible. Clinically significant mental status changes range from mild cognitive impairment to delirium; medicines with anticholinergic effects are the most common cause of drug-induced delirium.9

Many medicines from a number of therapeutic classes have anticholinergic effects. Some such as atropine, oxybutynin, benzhexol and benztrapine, are used specifically for their anticholinergic properties. Others have anticholinergic properties unrelated to their primary use, including antihistamines and antipsychotics (see table 2). It is advisable to avoid strongly anticholinergic medicines in those with cognitive impairment and to be aware of the ‘anticholinergic load’ which results from medicines with less anticholinergic potential being co-prescribed.

<table>
<thead>
<tr>
<th>Table 1. Anticholinergic side effects</th>
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<tbody>
<tr>
<td>Anticholinergic side effects</td>
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<tr>
<td>Confusion/hallucinations/delirium</td>
</tr>
<tr>
<td>Dry mouth</td>
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<tr>
<td>Pupil dilatation/blurred vision</td>
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<tr>
<td>Urinary retention</td>
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<tr>
<td>Constipation</td>
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<td>Tachycardia/arrhythmias</td>
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Table 2. Examples of medicines with clinically significant anticholinergic effects used in the elderly8,10,11

<table>
<thead>
<tr>
<th>Antipsychotics</th>
<th>Antidepressants</th>
<th>Medicines for urinary incontinence</th>
<th>Antihistamines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong anticholinergic effects – avoid using in those with dementia</td>
<td>Chlorpromazine, Olanzapine, Pericyazine</td>
<td>Tricyclic antidepressants e.g. Amitriptyline, Doxepin, Imipramine</td>
<td>Darifenacin**, Oxybutynin, Propantheline, Solifenacin**, Tolterodine**</td>
</tr>
<tr>
<td>Moderate anticholinergic effects – use with caution in those with dementia</td>
<td>Haloperidol, Prochlorperazine, Quetiapine, Risperidone, Ziprasidone</td>
<td>Desvenlafaxine, Duloxetine*, Fluoxetine, Mirtazapine, Paroxetine, Reboxetine*, Venlafaxine</td>
<td></td>
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</tbody>
</table>

*This is a new medicine; the reported adverse effects profile is consistent with moderate anticholinergic effects.9
**Not included on the PBS/RPBS.
***Note that these medicines, found in cold and flu treatments, may be purchased over the counter by patients.

Urinary incontinence and dementia

Urinary incontinence is common and often treated with anticholinergic medicines.

Urinary incontinence in those with dementia is often multifactorial and can be exacerbated by a number of medicines. It is important to exclude medicines as a contributing factor, particularly cholinesterase inhibitors and diuretics. Medicines which can cause constipation such as verapamil, opioids and antipsychotics can worsen urinary incontinence.12

Non-pharmacological options are first line and include: limiting alcohol and caffeine intake, avoiding constipation and straining, prompted or scheduled voiding and allowing adequate time for complete bladder emptying.

Treatment with anticholinergic medicines is often not necessary however, if they are to be trialled, ensure the patient and carers are aware of potential adverse effects. Cease after 4 weeks if there is no benefit. Consider referral to a continence service.

Depression and dementia

The diagnosis of depression in cognitively impaired patients is difficult and there are relatively few studies to guide selection of antidepressant.13 After addressing relevant psychological and social issues, a therapeutic trial of antidepressant medicine may be appropriate. Combination antidepressant treatment should not be used in patients with co-morbid dementia because of likely increased anticholinergic load and other adverse effects. On the basis of half life, minimal pharmacokinetic interaction and low anticholinergic effect, citalopram or sertraline are the preferred SSRIs for use in those with dementia.
Medicines with sedative effects

Medicines with sedative effects worsen cognitive impairment and increase the risk of falls in the elderly. People with dementia are already at increased risk of falling so it is important to avoid or minimise exposure to these medicines. Medicines with sedative effects come from a number of therapeutic classes including benzodiazepines, antidepressants, antipsychotics, antihistamines, opioids and anticonvulsants. Many also have anticholinergic properties.

Alcohol can compound the sedative effects of medicines.

Insomnia, anxiety and dementia

Older people often require less sleep. Those with dementia may have a reversal of normal diurnal rhythms which can worsen cognition. Non-pharmacological treatment should always be first line. Consider underlying issues which may be contributing to disturbed sleep, for example: medicines, medical conditions, or environmental factors. Avoid hypnotics where possible; reserve for short-term (less than 2 weeks) use in the treatment of acute insomnia (temazepam 5-10mg at night if required) as an adjunct to non-pharmacological therapy. For those patients already on long term benzodiazepines, consider discontinuing by slowly reducing the dose to maximise cognitive function and reduce risk of falls. Monitor patients closely for signs of agitation and anxiety.

Low dose tricyclic antidepressants are sometimes used in the elderly to treat insomnia but should be avoided as they increase the risk of falls and because of their anticholinergic effects. Sedating antihistamines are best avoided for the same reasons.

Pain and dementia

Pain may go unreported and unrecognised in those with more advanced dementia and can present as behavioural disturbance. Validated scales are available for assessment of pain in people with dementia, such as the Abbey Scale (see further information). Depending on the cause of pain behavioural strategies may be helpful, particularly if associated with depression and anxiety. Regular paracetamol is the starting point for the management of mild pain, moving up the analgesic ladder as necessary towards strong opioids for severe pain. Opioids can have sedative and anticholinergic effects. Fentanyl patches should not be prescribed for opioid-naive people. Anticonvulsants used in the treatment of neuropathic pain - such as gabapentin, pregabalin, carbamazepine and valproate - often cause sedation and confusion. Carbamazepine also has anticholinergic properties.

Antipsychotics

The behavioural and psychological symptoms associated with dementia are the most common reasons why older people receive antipsychotic medicine. Side effects of antipsychotics include drowsiness, dystonia, parkinsonism and tardive dyskinesia. They may also cause hyponatraemia resulting in confusion and lethargy. Second generation antipsychotics have a lower risk of tardive dyskinesia but can still cause sedation and postural hypotension. As shown in Table 2, some have anticholinergic properties and can precipitate delirium.

Patients with Alzheimer’s disease treated with risperidone have been shown to be twice as likely to develop extrapyramidal symptoms as those receiving placebo. In those with dementia all antipsychotics have been associated with an increased risk of death (predominantly due to strokes) compared to placebo.

Patients with Lewy body dementia are especially susceptible to the extrapyramidal adverse effects of antipsychotics, even in low doses.

Management of behavioural disorders in dementia

Behavioural and psychological symptoms are common in dementia and can include agitation, aggression, hallucinations and wandering. Most behavioural symptoms have a precipitant and it is important to evaluate the patient to exclude delirium related to medicine or an underlying medical problem such as a UTI, chest infection, urinary retention or faecal impaction. Evidence suggests that non-pharmacological strategies may be effective in reducing agitation and anxiety in people with dementia and should be trialled first. These may include more personalised care, environmental modifications, orientation cues and increased physical activity.

Treatment with antipsychotics should be reserved for those with aggression and psychosis who have not responded adequately to non-pharmacological strategies. The risk of harm to the patient and carers with or without medicine needs to be considered.

Note that problems such as screaming, ‘sundowning’ and wandering do not respond to antipsychotics.
Start at a low dose and increase slowly, using regular not ‘as required’ dosing in order to achieve stable levels of the medicine. Haloperidol 0.25 to 0.5mg orally per day may be used, increasing at weekly intervals up to a maximum of 2mg daily. An alternative is risperidone 0.25mg orally twice daily, increasing slowly to a maximum range of 0.5 to 1mg twice daily.\textsuperscript{12} It is essential to frequently review: the response to treatment, the development of any adverse drug effects and the need for ongoing treatment. The use of more than one antipsychotic is not recommended. Dose reduction or trial withdrawal should be attempted after 3 months or earlier as behavioural problems are often transient. Aim to reduce the dose by 50% every 2 weeks and cease after 2 weeks on the minimum dose.\textsuperscript{17}

Consider the use of a medicines review* to:

1. Screen for medicines with anticholinergic or sedative effects (prescribed and over-the-counter).
2. Assess a veteran’s ability to manage medicines and his/her suitability for a DVA Dose Administration Aid Service (see further information).
3. Identify areas where the medicine regimen may be simplified.

*Either a Home Medicines Review (HMR) or a Residential Medication Management Review (RMMR)

Further information

1. Prescribing criteria for cholinesterase inhibitors and memantine
2. Psychotropic Therapeutic Guidelines 2008
   (Benzodiazepine withdrawal)
   www.tg.org.au
3. Therapeutic Brief 18, Insomnia Management: Effective approaches for a common problem
   www.veteransmates.net.au/VeteransMATES/documents/module_materials/M18_TherBrief.pdf
4. Continence Foundation of Australia
   www.continence.org.au
   Also, for more information on the Abbey Scale
6. Alzheimer’s Australia
   www.alzheimers.org.au
7. Therapeutic Brief 12, Antipsychotics in Dementia
   www.veteransmates.net.au/VeteransMATES/documents/module_materials/M12_TherBrief.pdf
8. DVA Dose Administration Aid Service

References