Anticholinergic and sedative medicines

Prescribing considerations for people with dementia

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Background

Older people with dementia may be particularly susceptible to cognitive impairment associated with anticholinergic and sedative medicines. This impairment may be misattributed to the disease process itself.

Objective

This review examines clinical considerations associated with using anticholinergic and sedative medicines in people with dementia or incipient cognitive impairment. It highlights issues associated with concomitant use of cholinesterase inhibitors and anticholinergic medicines, and pharmacotherapy of conditions that commonly occur in people with dementia.

Discussion

Use of medicines with anticholinergic or sedative properties may result in adverse events by increasing the overall anticholinergic or sedative load. Patients may benefit from clinicians reviewing the anticholinergic load of the current medicine regimen before the initiation of cholinesterase inhibitors or memantine. Reducing the number and dose of anticholinergic and sedative medicines may improve cognitive function and reduce the likelihood of adverse events.

Keywords

hypnotics and sedatives; anticholinergic effects; cholinergic antagonists; dementia; cognition disorders

The number of people with dementia in Australia is predicted to quadruple from an estimated 245 000 in 2009 to approximately 1.13 million by 2050.[1] Causes of dementia include Alzheimer disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia and Parkinson disease. Medicines with anticholinergic and sedative properties are widely prescribed for older people in Australia.[2,3] People with dementia may be particularly susceptible to cognitive impairment caused by anticholinergic and sedative medicines.[4]

Medicines with anticholinergic properties

The likelihood that medicines may produce unwanted central anticholinergic effects depends in part on age related and patient specific variability in pharmacokinetic parameters, blood-brain barrier permeability, degree of cholinergic neuronal degeneration and a patient's baseline cognitive status.[4,5] Medicines specifically prescribed for their anticholinergic properties (eg. oxybutynin, benzhexol and benztropine) are well recognised by clinicians. However, clinicians may be less aware that some medicines prescribed for other purposes also have anticholinergic properties (Table 1).[2,6–8] These include the inhaled anticholinergics, ipratropium and tiotropium bromide when prescribed in their usual therapeutic doses. Even medicines with minor anticholinergic properties may contribute to unwanted central and peripheral adverse events if used in combination with other agents with anticholinergic effects. Clinically significant adverse events (Table 2) range from mild cognitive impairment to delirium. The cumulative effect of taking one or more medicines with anticholinergic properties has been termed 'anticholinergic load'.[9]

Use of medicines with anticholinergic properties in older people is associated with impaired physical and cognitive function. In a cross sectional study of 364 people aged more than 80 years living in Italy, the use of medicines with serum anticholinergic activity was associated with poorer physical performance battery scores, reduced hand grip strength and compromised activities of daily living.[10] In 932 community dwelling people aged more than 65

Table 1. Medicines with clinically significant anticholinergic effects that are commonly used in older people with dementia[6–8]				
	Antipsychotics	**Antidepressants**	**Medicines for urinary incontinence**	**Antihistamines**
Strong anticholinergic effects – avoid using in people with dementia	Chlorpromazine Olanzapine Pericyazine	Tricyclic antidepressants (eg. amitriptyline, doxepin, imipramine)	Darifenacin** Oxybutynin Propantheline Solifenacin** Tolterodine**	Brompheniramine*** Chlorpheniramine*** Cyproheptadine Diphenhydramine*** Promethazine***
Moderate anticholinergic effects – use with caution in people with dementia	Haloperidol Prochlorperazine Quetiapine Risperidone Ziprasidone	Desvenlafaxine Duloxetine* Fluoxetine Mirtazapine Paroxetine Reboxetine* Venlafaxine		

* New medicine: reported adverse effects profile is consistent with moderate anticholinergic effects

** Not included on the schedule of PBS/RPBS benefits

*** Found in cold and flu treatments, may be purchased over-the-counter

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Table 2. Examples of anticholinergic side effects
Confusion/hallucinations/delirium Dry mouth Pupil dilatation/blurred vision Urinary retention Constipation Tachycardia/arrhythmias
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years in the Women's Health and Aging Study conducted in the United States, use of medicines with anticholinergic properties was associated with difficulties in balance and mobility.[11] There is mixed evidence in relation to an association between anticholinergic medicines and increased mortality.[12–14]

Medicines with sedative properties

Medicines with sedative properties include benzodiazepines and other hypnosedatives, antipsychotics, anticonvulsants, antidepressants, opioid analgesics and tramadol, and histamine H1 receptor antagonists commonly used for allergic conditions. Many anticholinergic medicines also have sedative properties. Medicines with sedative properties have been linked to depressive symptoms, worsening cognition, respiratory depression, impaired muscle strength and falls and fractures.[15–19] The cumulative effect of taking one or more medicines with sedative properties has been termed 'sedative load'.[20] All medicines with sedative properties – not only those prescribed for intentional sedation – may contribute to an older person's sedative load.

Concomitant use of cholinesterase inhibitors and anticholinergic medicines

Cholinesterase inhibitors (donepezil, rivastigmine and galantamine) may modestly improve cognition via inhibiting the enzyme acetyl cholinesterase. Restricted supply of these medicines is subsidised through the Pharmaceutical Benefits Scheme (PBS) using the authority system for the management of mild to moderate Alzheimer disease. Concomitant use of anticholinergic medicines may decrease the effectiveness of cholinesterase inhibitors.[21] Despite this, an Australian study revealed that of 5797 people who commenced treatment with a PBS subsidised cholinesterase inhibitor between April and June 2006, 32% also received a prescription for an anticholinergic medicine in the 14 weeks before and following the first date of supply.[3] Dispensing of anticholinergic medicines also increased following initiation of cholinesterase inhibitors. Some of these anticholinergic medicines may have been prescribed to treat the adverse effects of the cholinesterase inhibitor (eg. medicines for urinary incontinence). Patients may benefit from clinicians reviewing the anticholinergic load of their current medicine regimen before initiating cholinesterase inhibitors or memantine, with the aim of minimising or ceasing medicines with anticholinergic properties.

Reducing anticholinergic and sedative load in patients with dementia

Pharmacotherapy of specific conditions

Urinary incontinence

Incontinence is often multifactorial in older patients with dementia. Medicines may contribute to urinary incontinence via agonism of alpha-1-adrenoceptors or nicotinic acid receptors leading to stress incontinence, or antagonism of beta-3-adrenoceptors or agonism of muscarinic receptors leading to urge incontinence.[22] Antagonism of muscarinic receptors may lead to overflow incontinence, while use of medicines with

sedative properties (eg. benzodiazepines, opioids and tricyclic antidepressants) may contribute to functional incontinence. Anticholinergic medicines can cause constipation, which can result in urinary retention and urge and overflow incontinence.

Cholinesterase inhibitors prescribed for patients with Alzheimer disease have also been associated with urinary incontinence.[23] In a retrospective population based cohort study of 44 884 older people with dementia, use of cholinesterase inhibitors was associated with an increased likelihood of receiving an anticholinergic medicine to manage urinary incontinence.[24] Drug induced urinary incontinence in people with dementia may be misattributed to progression of the underlying disease processes.[25] This may result in a 'prescribing cascade' if an anticholinergic medicine is then prescribed to treat the incontinence.[24]

Nonpharmacological approaches are recommended as first line treatment. Prompted or timed voiding may reduce urinary incontinence among residents of aged care facilities with dementia. For people with functional incontinence related to impaired mobility, an occupational therapist or physiotherapist may advise measures to improve toilet access (eg. removal of clutter, good lighting, nonslip flooring, ensuring the toilet is clearly marked, hand rails, raised toilet seat height and appropriate clothing). With these interventions, treatment with anticholinergic medicines may not be necessary. However, if anticholinergic medicines are to be trialled, patients and carers may require education about potential adverse events of anticholinergic medicines. Consider ceasing anticholinergics administered for urinary symptoms if there is no benefit after 4 weeks of treatment.[8]

Depression

Depressive symptoms have been reported in up to 40% of people with Alzheimer disease, which is reflected in the high prevalence of antidepressant use in this population.[26] However, there is a lack of evidence to guide antidepressant prescribing.[27] Two recent studies have suggested a less favourable risk-to-benefit ratio than previously thought. An observational study reported an increased risk of falls and fractures, stroke/transient ischaemic attack and all cause mortality among users of selective serotonin reuptake inhibitors (SSRIs) compared to tricyclic antidepressants (TCAs).[28] The Health Technology Assessment Study of the Use of Antidepressants for Depression in Dementia (HTA-SADD), which included 326 patients, reported that sertraline and mirtazapine were not more effective than placebo and were associated with an increased risk of adverse events.[29] This finding contradicted an earlier meta-analysis that included 165 patients which supported the efficacy of antidepressants for treating depression in Alzheimer disease.[30] A Cochrane review has also reported that sertraline and citalopram were associated with a reduction in agitation in people with dementia when compared to placebo in two studies.[31] Selective serotonin reuptake inhibitors tend to be less sedating than TCAs, mianserin or mirtazapine. Some TCAs (eg. amitryptiline, doxepin) are both highly sedative and anticholinergic. Combination antidepressant treatment is not appropriate due to the increased risk of adverse events, including those related to anticholinergic and sedative load.[32]

Insomnia

Sleep complaints are common among people with Alzheimer disease and other dementias.[33] Underlying issues that may contribute to disturbed sleep include medicines, medical conditions and environmental factors. Older people often require less sleep than younger people and it is useful to explain this to patients. Nonpharmacological treatments for insomnia are considered first line.[34] Sedative-hypnotic medicines should be prescribed for the shortest possible duration as an adjunct to nonpharmacological treatments. It is useful to agree a definite duration of treatment with the patient at the time of prescribing.[8] People already taking long term benzodiazepines may benefit from dosage reduction and slow discontinuation to maximise cognitive function and reduce the risk of falls. Despite their relatively widespread use, TCAs and sedating antihistamines are best avoided in the management of insomnia due to their anticholinergic properties.

Pain management

Opioid analgesics and tramadol may have sedative effects. The ways in which people with dementia experience and express pain is a field of ongoing research.[35] People with dementia may express pain in the form of facial expressions, body movements and behavioural disturbances such as aggression or agitation. These symptoms may be misinterpreted as behavioural symptoms of dementia. Pain may be under-recognised and undertreated, especially in advanced stages of dementia.[36] Research has reported lower overall use of analgesics among people with dementia.[37,38] However, while people with dementia may receive less analgesics overall, they may be more likely to be prescribed strong opioids (eg. transdermal fentanyl) instead of paracetamol and other analgesics with lower likelihoods of adverse events.[38] Transdermal fentanyl patches should not be prescribed to people with chronic nonmalignant pain who are opioid naive.[8] Antiepileptics used in the treatment of neuropathic pain (eg. gabapentin, pregabalin, carbamazepine, valproate) may impair cognition and cause sedation. People with dementia may also be particularly susceptible to memory impairment and cognitive decline associated with some antiepileptics.[39]

Behavioural and psychological symptoms

Behavioural and psychological symptoms of dementia are common and include agitation, aggression, hallucinations and wandering. Nonpharmacological strategies are considered first line treatment. Treatment with antipsychotics should be reserved for people with aggression and psychosis who have not responded to nonpharmacological strategies. Use of both first (eg. haloperidol) and second generation (eg. olanzapine, quetiapine, risperidone) antipsychotics is associated with an increased risk of death in people with Alzheimer disease.[40,41] In common with some other medicines commonly prescribed for older people (eg. SSRIs, TCAs, opioids) antipsychotics can also cause hyponatraemia that may result in confusion and lethargy. While second generation antipsychotics have a lower risk of tardive dyskinesia, they can cause sedation and postural hypotension. Patients with Lewy body dementia are especially susceptible to the extrapyramidal side effects of antipsychotics.[42] The dementia antipsychotic withdrawal trial (DART-AD) in the United Kingdom demonstrated that for most patients with Alzheimer disease,

withdrawal of antipsychotics had no detrimental effect on functional and cognitive status. People who continued using antipsychotics had reduced survival compared to those who received placebo (ie. those who discontinued antipsychotics treatment).[43] In Australia, risperidone is the only antipsychotic PBS listed for the management of behavioural disturbances characterised by psychotic symptoms and aggression in patients with dementia where nonpharmacological methods have been unsuccessful. Problems such as screaming/vocalising, 'sundowning' and wandering do not reliably respond to antipsychotics.

Key points

- Older people with dementia may be particularly susceptible to impaired physical and cognitive function associated with anticholinergic and sedative medicines.
- Drug induced physical and cognitive impairment in older people with dementia may be misattributed to progression of underlying disease processes.
- Medicines with weak anticholinergic or sedative properties (including nonprescription medicines) may cause adverse events by contributing to an older person's anticholinergic or sedative load. This load may be decreased by reducing the number and dose of medicines with anticholinergic and sedative properties.
- Patients may benefit from clinicians reviewing the anticholinergic load of their current medicine regimen before initiating cholinesterase inhibitors or memantine, with the aim of minimising or ceasing if possible medicines with anticholinergic properties.
- Urinary incontinence may be drug induced. Anticholinergic medicines are often not needed to treat urinary incontinence. Consider ceasing anticholinergic medicines if there is no benefit after 4 weeks.
- Depressive symptoms are common in Alzheimer disease. There is mixed evidence for the safety and efficacy of antidepressants in patients with dementia. Selective serotonin reuptake inhibitors are less sedating than TCAs, mianserin or mirtazapine. Tricyclic antidepressants may be both sedative and anticholinergic.

- For most patients with Alzheimer disease, withdrawal of antipsychotics has no detrimental effect on functional and cognitive status.

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