Reducing adverse drug events (ADEs) for your veteran patients

Effective use of medicines can extend the longevity and improve the quality of life for many of your veteran patients. Managing medicines however can present particular challenges for both doctors and veterans.

The risk/benefit of treatment must be individualized on the basis of co-morbidities, life-expectancy and polypharmacy. ADEs are more common in the elderly and some high risk medicines should be avoided.

This Therapeutic brief discusses selected ‘high-risk’ medicines which are likely to cause ADEs in elderly veterans. It asks you to consider either an alternative medicine with a more favourable risk/benefit profile OR, when not appropriate for your patient, a management strategy to help avoid ADEs including non-pharmacological therapy.

Two widely used criteria for identifying ‘high-risk’ medicines in the elderly are the Beers (USA) and McLeod (Canadian) criteria. These medicines have been found to be associated with an increased risk of hospitalisations and death. The criteria for including a medicine on these lists is that the medicine places the elderly at a markedly increased risk of an ADE and there are alternatives with more favourable risk/benefit profiles.

We have selected medicines that are frequently used for elderly veterans, for which alternative medical approaches are available (Table 1).

Over 35000 Australian veterans are currently using at least one of the selected ‘high-risk’ medicines. Approximately one third of unplanned hospital admissions involving the elderly are medication-related. It is estimated that 50% of these cases are potentially preventable.

We acknowledge that there are many other medicines with a high risk of ADEs which could be discussed but these were not included because there is clearer evidence to support their use in the elderly and fewer alternative management options.


Key messages

- Know the ‘high-risk’ medicines which are more likely to cause ADEs in your elderly patients.
- Recognise the clinical signs and symptoms of these ADEs.
- Consider the individual veteran’s risk/benefit profile and individualise therapy on the basis of co-morbidities, life expectancy, polypharmacy and the goals of therapy.
- Avoid these ‘high-risk’ medicines if possible. If it is impractical to avoid them, manage the risk of an ADE by:
  - Checking regularly with your patient for clinical signs and symptoms that may indicate an ADE.
  - Instructing your patient or their carer on symptoms associated with an ADE and advising them when to seek help.
  - Reviewing the need for each medicine regularly and using for the shortest time possible.

Table 1: Selected ‘high-risk’ medicines*

- Long-acting benzodiazepines (Diazepam, nitrazepam and flunitrazepam)
- Methyldopa
- NSAIDs
- Highly anticholinergic tricyclic antidepressants (TCAs) (Amitriptyline, doxepin and imipramine)
- Oxybutynin
- Dextropropoxyphene (alone or in combination)
- Amiodarone

* Adapted from Beers and McLeod.

# All NSAIDs contribute to renal, cardiac and GI adverse effects. Indomethacin, piroxicam and higher strength slow release formulations of naproxen and ketoprofen have been identified for further review (Figure 1).


Veterans’ Medicines Advice and Therapeutics Education Services

Therapeutic Brief 8 – Reducing adverse drug events for your veteran patients
Why are elderly veterans more likely to experience ADEs?

Veterans are more vulnerable to an ADE compared to the general Australian population as they are older and take more medicines.\(^5\)

Some events and medical conditions occur more commonly in the elderly. These include cognitive impairment, delirium, incontinence, constipation, falls, hip fractures, insomnia, parkinsonism, heart failure and gout.\(^2\)

Medicines may exacerbate or contribute to these events and result in further functional decline and reduction in autonomy for the older person.\(^2\)

There are three main mechanisms by which medicines may cause problems in the elderly:

1. **Age-related changes to metabolism and excretion**

Medicines can accumulate due to age-related reduced organ function. Impairment of kidney or liver function can result in reduced elimination and therefore greater amounts of a given drug in the body. This may result in increased magnitude of the response, risk of ADEs and risk of drug-drug interactions. These age-related changes in renal function can be exacerbated by medicines such as NSAIDs, which in turn could lead to a further decrease in the clearance of renally excreted medicines.

2. **Altered sensitivity to medicines**

Sensitivity to medicines can be either enhanced or decreased with age (e.g. increased CNS effects with long-acting benzodiazepines and indomethacin or amiodarone-induced cardiac arrhythmias).

3. **Indirect contribution to ADEs**

Medicines which through adverse effects can indirectly contribute events such as falls, functional urinary incontinence and cognitive impairment (e.g. medicines with anticholinergic properties, long-acting benzodiazepines and dextropropoxyphene).

Some medicines (e.g. long-acting benzodiazepines and dextropropoxyphene) may involve all 3 effects, as illustrated in the Figure 1.

**Practice point:** When making a diagnosis in the elderly, always consider ADEs first.

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**Spotlight on long-acting benzodiazepines**

Analysis of RPBS benzodiazepine dispensings shows that 3 in 100 veterans are dispensed at least one long-acting benzodiazepine each month.\(^5\)

This represents a significant level of long-acting benzodiazepine use in the veteran population. Despite an increasing average age of veterans, the trend has not changed over the past five years (2000-2005). While these medicines may have been appropriate for your patients in the past, it is timely to consider a review as your patient ages.

Long acting benzodiazepines such as diazepam, flunitrazepam and nitrazepam make older people especially vulnerable to sedation, ataxia, falls, confusion, incontinence, respiratory depression and short-term memory impairment.

For people with chronic medical problems or those who are dependent on a long acting benzodiazepine for sleep problems, cessation may be difficult. However, stopping a benzodiazepine can often be achieved gradually provided the patient, family and/or nursing staff shares in the approach.\(^9\)

**Management**

**Withdrawal from night-time dose of benzodiazepine.**\(^10\)

Give patients/carers specific information about the health benefits they may expect from stopping (reduced risk of falls, nocturnal incontinence and improved cognitive functioning).

Reassure them that the medicine is probably no longer helping them to sleep and that any sleep disorder they may now have is associated with withdrawal, not a recurrence of the original problem.

Withdraw gradually: tablets can be halved, quartered, taken on alternate nights or taken intermittently to minimise withdrawal effects.

The duration of withdrawal is highly variable and can last for 6–8 weeks.

Review/advise patient and carer on good sleep hygiene principles (e.g. avoiding heavy meals and caffeine containing beverages close to bed-time).\(^11\)

**Practice point:** When stopping, starting or changing medicines ensure your patient/carer has the most recent list of ALL their medicines and monitor for compliance and ADEs.
### Figure 1: Body systems affected by selected ‘high-risk’ medicines.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Body system affected</th>
<th>Adverse Drug Event</th>
<th>Management of ADEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long acting Benzodiazepines</td>
<td>Brain/sight, Bladder*</td>
<td>Can cause over sedation, ataxia, confusion, respiratory depression, short-term memory impairment and increased falls risk.(^{12}) Increase the risk of functional incontinence.(^{10})</td>
<td>Trial withdrawal. Remember withdrawal needs to be gradual and over at least 14 days. During and after successful withdrawal non-drug strategies should be utilised. If a benzodiazepine is necessary, use a short-acting option and for a time-limited period. However, this does not guarantee avoidance of benzodiazepine-related ADEs.(^{13})</td>
</tr>
<tr>
<td>Anticholinergics (amitriptylline, doxepin, imipramine and oxybutynin)</td>
<td>Brain/sight, Heart/CVS, Bladder*, Bowel</td>
<td>Increase the risk of confusion, delirium, impaired cognitive function, sedation, falls, behavioural problems, blurred vision and incontinence.(^{12}) Increase the risk of postural hypotension and arrhythmias.(^{12}) Tricyclic antidepressants increase the risk of urinary incontinence in the elderly (all types) and urinary retention. Oxybutynin increases the risk of urge, stress and overflow incontinence.(^{10}) Increase the risk of constipation which is an important cause of urinary incontinence in the elderly,(^{10}) which in turn can increase the risks of an urinary tract infection and subsequent confusion.(^{10})</td>
<td>Trial alternative antidepressant when used for depression (e.g. SSRI). When a TCA is prescribed for neuropathic pain, consider gabapentin. For urinary incontinence, consider time-limited trial of oxybutynin and non-pharmacologic therapy. Avoid anticholinergic medicines in combination with anticholinesterase inhibitors (e.g. donepezil, rivastigmine) which are being used to increase acetylcholine in the brain.</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Brain/sight, Heart/CVS, GI tract, Renal</td>
<td>All NSAIDs can affect mental alertness, especially upon initiation and when the dose is increased.(^{14}) Of all NSAIDs indomethacin produces the most CNS adverse effects. Can increase the risk of hypertension, heart failure and bleeding.(^{12}) May exacerbate or cause new gastrointestinal ulcers.(^{12}) Can increase the risk of renal impairment, fluid retention and electrolyte changes.(^{12})</td>
<td>Consider ceasing high dose product. Use NSAIDs at lowest effective dose and those with lowest potential for GI risk (e.g. low dose ibuprofen &lt;1200mg/day).(^{15}) Monitor renal function, particularly when there is a change in clinical condition or intercurrent illness which results in dehydration.</td>
</tr>
<tr>
<td>Other medicines</td>
<td>Brain/sight, Heart/CVS, Renal, Bladder*</td>
<td>Methyldopa increases the risk of depression.(^{12}) Dextropropoxyphene can cause sedation, confusion and delirium which may lead to an increase in falls risk. Amiodarone can induce thyroid dysfunction.(^{12}) Amiodarone increases the risk of cardiac arrhythmias.(^{12}) Amiodarone can induce hepatitis and changes in metabolism of other medicines.(^{12}) Dextropropoxyphene increases the risk of functional incontinence through over-sedation.</td>
<td>Amiodarone - review ongoing need with specialist. Consider alternatives for dextropropoxyphene and methyldopa.</td>
</tr>
</tbody>
</table>

*While recognizing that incontinence in older people is often multifactorial we have remained with the standard division into urge, stress, functional and overflow to help classify medicine effects.\(^{10}\)
Incontinence and constipation

Many medicines contribute to urinary incontinence and constipation. The incidence of urinary incontinence increases with age and other risk factors include: being female, impaired cognition (e.g. delirium and dementia), diabetes, bladder outflow obstruction, obesity, neurological disorders, UTIs, constipation and impaired mobility.

Constipation may contribute to urinary incontinence by mechanical obstruction which may increase the risk of E.coli urinary tract infections. More commonly constipation causes increased stimulation of the bladder resulting in premature detrusor contractions.

A special case - Amiodarone

Amiodarone has been included in this brief as it is an inherently toxic medicine with a narrow therapeutic index as well as having a propensity for interactions (e.g. warfarin) and ADEs. Not all patients initiated on amiodarone for acute atrial fibrillation require long-term therapy. If long-term therapy is required ensure baseline and regular monitoring adheres to recommendations (www.tga.gov.au). Amiodarone interacts with two other high-risk medicines, warfarin and digoxin, to increase their plasma concentrations. Amiodarone causes several serious ADEs such as association with QT interval problems and risk of provoking torsades de pointes, alterations in thyroid function, hepatitis and pulmonary fibrosis.

What to tell your patient

As you age you may need to use less of your medicine or you may need to change to a different medicine.

When starting a new medicine you should report any side effects to your doctor/pharmacist.

Report any side effects from ALL medicines. Especially if it alters your lifestyle (e.g. reduced ability to walk, drive, think clearly and participate in sport or leisure activities).

Medicines are generally very safe and effective, however the less medicine you take the lower the possibility of side effect.

Useful websites and information resources:

- For more information on therapy with benzodiazepines, withdrawal of therapy and other management strategies go to http://www.racgp.org.au/your-practice/guidelines/drugs-of-dependence-b/
- For more information on managing NSAID-related adverse events go to https://www.veteransmates.net.au/topic-4
- For more information on alternatives to TCAs go to https://www.veteransmates.net.au/topic-5
- For general advice contact NPS Medicines Line on 1300 633 424 or see the webpage at: http://www.nps.org.au/

References

5 Veterans’ Datamart, University of South Australia, QJMPPRC. Accessed June 2005.