

Drug-related morbidity and mortality – the elderly at risk

Medicines to be wary of in the elderly

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The catch cry of the millenium:
"Elderly mortality and morbidity"

In 1990 Hepler and Strand¹ identified a 'new disease' as Drug-Related Morbidity and Mortality, which incorporated treatment failure through a number of mechanisms as well as the production of new medical problems through the use of medicines.

Johnson and Bootman² later used a pharmacoeconomic model to identify that, in the USA, the expenditure on treating drug-related morbidity and mortality is the same as the expenditure on the medicines themselves, and this was the second most costly disease after cardiovascular disease. They predicted that 25–50% of the drug-related morbidity and mortality might be prevented through improved medicines management.

Studies have repeatedly demonstrated a high prevalence of significant adverse drug reactions in the elderly and in many cases this has contributed to hospitalisation.

In a study conducted in the 1970s 1 988 consecutive admissions of elderly patients to hospital was studied. The authors found that 15.3% of patients on drugs had significant adverse drug reactions and in 10.5% of cases these adverse reactions contributed to their hospitalisation.³

More recent studies suggest between 5 and 10% of hospital admis-

sions for the elderly are medicines related – including adverse effects, medicine interactions, over- or under-compliance, or unnecessary medicines.^{4,5,6,7,8,9}

The widely varying results of these studies reflect factors such as differences in population studies and variations in the definition of drug-related adverse events.

When interpreting these results it is important to remember that adverse reactions which cause hospital admissions are the 'tip of the iceberg'.

Overall outpatient population studies have found an adverse reaction of 5–10% in the general elderly population, and slightly under 1% of all patients are sent to hospital because of these.^{10,11,12}

**Covering 'old' ground:
What makes the elderly more at risk of drug-related morbidity and mortality?**

The elderly, because of pharmacokinetic and pharmacodynamic factors, are more at risk of drug-related morbidity and mortality, as noted in Table 1.

It is well documented that older patients are more likely to have a misadventure because of changes in drug absorption, distribution, metabolism and excretion associated with ageing and greater use of medication.^{3,5,7,9}

**Medicines that are problematic in the elderly
(or the 'hit parade of the elderly')**

In studies of medicines-related hospital admissions and adverse effects of medicines in the elderly there are some medicines that consistently rank highly (Table 2).^{5,7,9,10,11,13,14}

This may relate to the frequency of use of the medicines in the community, and use of the medicines is unavoidable in many situations, but an awareness of the medicines is important. If there is no alternative to be used, then the principles of prescribing in the elderly should be applied (see Table 2), and the patient should be actively monitored objectively for the potential adverse effects.

1. Psychoactive medicines

The changes in sensitivity of the elderly population to these centrally acting drugs makes this class one of the few for which age is regarded as more than a secondary risk factor.⁷

Psychoactive agents are commonly used in nursing homes. In a cohort study of 18 nursing homes over 12 months, more than 36% of residents used antidepressants, 24% used hypnotics/sedatives and 17% used antipsychotic medication;²⁶ in another study 50% of all prescriptions for people aged 60–69 were for

psychoactive agents, increasing to 56% in those older than 70 years.¹⁵

Not surprisingly these agents were also among the most frequently implicated agents associated with adverse drug reactions.^{4,5,8,13}

1.1 Antidepressants

Inappropriate prescription of antidepressants as nocturnal sedatives is a common occurrence.^{4,5,14,18,19}

It is well known that tricyclic antidepressants may precipitate confusion, postural hypotension, urinary retention and constipation. They can also affect cardiac conduction, are potentially fatal in overdose and are particularly associated with falls even in relatively low doses.^{4,5,14,18,19}

Amitriptylene has the greatest propensity for anticholinergic side effects and should be avoided.^{18,19}

The Selective Serotonin Reuptake Inhibitors (SSRIs) are less likely to cause sedation and are less cardiotoxic but can cause headache, agitation and insomnia and fluoxetine has a high association with the risk of syncope.¹⁶

It must also be borne in mind that SSRIs are inhibitors of the hepatic cytochrome P450 system and have a high association with drug-drug interactions by reducing the metabolism of tricyclic antidepressants, antipsychotic drugs, some B-blocking agents and anti-arrhythmic drugs.¹⁷

1.2 Hypnotics/sedatives

Hypnotics, particularly benzodiazepines, can cause drug dependency, excessive sedation, confusion and ataxia. The longer acting hypnotics especially have been associated with a significantly increased risk of fractured neck of femur in the elderly.⁸

Benzodiazepine use is common in elderly women who are often prescribed these agents at high doses and frequently more than one at a time.^{15,18} That the elderly have increased sensitivity to benzo-

diazepines was exemplified in an early study in which the effects of a single 10 mg dose of nitrazepam

were compared with that of placebo in healthy young and elderly people.

Psychomotor testing showed that motor function was

depressed in both groups but the effects on cognitive function were greater in the older subjects despite similar plasma concentrations and half lives of the drug.¹⁹

It is important to remember that there is no truly safe benzodiazepine for the elderly!

If a hypnotic has to be used it is important to choose a short course of a hypnotic with a short half life and a path of excretion which is less affected by the ageing process (i.e. conjugation instead of oxidation) e.g. temazepam.

Both diazepam and nitrazepam should be avoided as they have long half lives and are metabolised by oxi-

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Table 1. Factors that result in the elderly being more at risk of drug related morbidity and mortality

Pharmacokinetic factors (Factors which affect the concentration and distribution of medicines)	<ul style="list-style-type: none"> Reduced organ function, particularly for renally excreted medicines and medicines with first-pass hepatic clearance Reduced lean muscle and increased fat, resulting in a different distribution of medicines and accumulation
Pharmacodynamic factors (The effect of medicines at the site of action)	<ul style="list-style-type: none"> Increased sensitivity to medicines, particularly anticholinergic medicines and medicines affecting cognitive function Impaired homeostatic mechanisms
Physical functional status	<ul style="list-style-type: none"> Visual problems resulting in difficulty reading instructions or labels to identify the tablets Hearing problems may mean the patient misunderstands verbal instructions or explanations Arthritis making opening containers difficult Reduced muscle tone and balance
Cognitive function	<ul style="list-style-type: none"> Difficulty remembering new instructions Compliance issues because of memory or misunderstanding about medicine
Financial factors	<ul style="list-style-type: none"> The cost of medicines may result in non-collection or poor compliance
Multiple medical conditions	<ul style="list-style-type: none"> These usually require multiple medicines, resulting in interactions, particularly when enzyme inducers or inhibitors are required Disease-medicine interactions

Table 2. Summary of problematic medicines in the elderly

Offending Agent	Effect
Psychoactive medicines — antidepressants, hypnotics/sedatives, antipsychotics	Anticholinergic effects such as impaired functional ability, agitation, confusion, blurred vision, urinary retention, constipation, postural hypotension
NSAIDs	Risk of gastric ulceration, exacerbation of hypertension and renal impairment
Anticoagulants	Haemorrhagic risk and many drug-drug interactions with warfarin
Antihypertensives — particularly diuretics	High dose diuretics lead to hypotension, dehydration and electrolyte disturbances. Observe ceiling dose effect for thiazides and monitor electrolyte levels for all diuretics.
Digoxin	Decreased clearance with this narrow therapeutic agent in elderly can mean risk of exceeding therapeutic concentrations leading to confusion, weakness, nausea, vomiting and cardiac arrhythmias. Monitor renal function and potassium levels.
Antibiotics	Usually type B reactions relating to idiosyncratic variations and hence can be unpredictable. Most commonly seen with Trimethoprim/Sulphamethoxazole combinations. Also often associated with treatment of urinary tract infections.

dation pathways which decline with age.^{15,17,18}

If an elderly patient has a long term dependency on benzodiazepines and there is evidence of increased confusion, falls, sedation or gait problems, very gradual weaning should be attempted and non pharmacological therapy for insomnia should be tried²⁰ including:

- treatment of pain;
- avoidance of stimulants;
- development of 'routine' prior to sleeping;
- adequate daytime activity.

1.3 Antipsychotics

Estimates of antipsychotic effectiveness vary between 16 and 40%, and while they rarely stop the patient with dementia from wandering, they do increase the risk of falls and fractures.^{17,18,19}

Low potency derivatives e.g. chlorpromazine are often used for their sedative effects, but they also have anticholinergic adverse effects which is especially harmful in the elderly. These include postural hypotension, constipation, urinary retention, cardiac arrhythmias and delirium. In pa-

tients with dementia, these agents can increase memory impairment and further decrease the functional capacity of the patient.^{17,18,19}

The high potency antipsychotics have few anticholinergic adverse effects and are less sedating but have a high frequency of extrapyramidal side effects. Elderly women are at highest risk of developing tardive dyskinesia^{8,15} and should be monitored carefully.

2. Non Steroidal Anti-inflammatory Drugs (NSAIDs)

NSAID represent a disproportionately high amount of adverse drug reactions.^{5,9,15,21,22}

A NSAID user has a threefold greater risk of developing a gastric ulcer than a non-user.

Major risk factors for developing NSAID-induced ulceration include:

- age over 60
- past history of peptic ulcer disease
- concurrent corticosteroid use.

Gastrointestinal symptoms correlate poorly with the presence of ulceration and hence may occur undetected.

NSAIDs can also exacerbate hypertension, cardiac failure and renal failure and should be ceased if possible in patients with these problems.^{8,17,21,22}

NSAIDs account for 25% of all adverse drug reactions reported to the Committee on Safety of Medicines so it is not surprising that in many studies, NSAID were responsible for the highest number of hospital admissions due to medical misadventures^{5,9,15,21} and in one study two-thirds of these admissions were considered to be definitely preventable.⁵

No single NSAID was implicated in the admissions, although in one study diclofenac was involved in 23% of admissions²¹ – probably reflecting the popularity of this drug.

While the COX-2 inhibitors have a place in reducing gastric erosion and/or ulcers associated with standard NSAID therapy it is important to remember that renal toxicity has been reported²³ and that warfarin concentrations may be altered.²⁴

If analgesia is necessary the use of simple analgesics such as paracetamol is preferred or perhaps a trial of no alternative agent.

In one study NSAID therapy was successfully stopped in 86% of patients and in 40% of these patients no alternative therapy was necessary.²²

Combination analgesics containing codeine and dextropropoxyphene should also be avoided as, apart from producing nausea, vomiting and constipation, dextropropoxyphene has a prolonged half life (35 hours) which means its use can often result in accumulation. Hence, it is necessary to take particular care prescribing when the patient is very elderly, when there is an associated acute disease or dehydration, and when there is pre-existing renal, hepatic, cardiac or peptic disease.²¹

3. Cardiovascular drugs

3.1 Antihypertensives; diuretics

The SHEP (Systolic Hypertension in the Elderly Programme) study demonstrated that treatment of elevated systolic blood pressure with a diuretic combined, if necessary, with a B-blocking agent reduces the rates of myocardial infarction and stroke.

At the same time, however, it should be remembered that all antihypertensives may produce postural hypotension and falls and therefore drug therapy should be initiated at lower doses.^{5,6,9,10}

Diuretics are the antihypertensive most commonly associated with ad-

verse effects in the elderly.^{5,6,9,10,15} A common reason for inappropriate prescribing of diuretics in the elderly is treatment of dependent ankle oedema caused by immobility rather than cardiac failure.^{17,25}

Diuretics are associated with hypokalaemia, impaired glucose tolerance, hyperuricaemia and postural hypotension and they may also precipitate urinary incontinence.

Hyponatraemia is a risk when a thiazide diuretic is combined with a potassium sparing diuretic and can increase the risk of hyperkalaemia.^{5,8,18}

It should be remembered that thiazide diuretics have a flat dose response curve, their maximum therapeutic effects can be obtained with smaller doses.

Non-compliance with diuretics leading to exacerbation of heart failure was also noted as a common reason for admission.^{6,10,18}

3.2 Digoxin

The relationship between digoxin toxicity and plasma concentrations is well recognised.

Eighty-seven per cent of toxic patients have serum concentrations of >2.0 mcg/L; concentrations of <2.0 mcg/L are associated with no toxicity in 90% of patients. (However, there is considerable overlap from 1.6 to 3.0 mcg/L.)

Key points

- There is a high prevalence of significant adverse drug reactions in the elderly including hospitalisation, adverse effects, medicine interactions, over- or under-compliance, or unnecessary prescribing.
- Older patients are more likely to have drug misadventure because of changes in absorption, distribution, metabolism and excretion and greater use of medication.
- Psychoactive agents, NSAIDs, digoxin, anticoagulants, diuretics and antibiotics are among the most frequently implicated agents for adverse drug reactions.
- Start low, go slow is a well known precaution.
- Therapy should be terminated if an adverse drug reaction develops or if treatment does not have a beneficial effect.

This narrow therapeutic index ensures that digoxin enjoys a regular appearance in drug-related elderly admissions.^{5,6,11,13}

The age-related decline in lean body mass together with the reduc-

Table 3. Principles for prescribing in the elderly

Use the minimal dose required	As people age down titration of dose may be appropriate. Renal function declines with age and doses of renally excreted medicines should be adjusted accordingly.
Beware of 'trigger' medicines which often interact	Digoxin, warfarin, amiodarone, SSRIs, medicines with anticholinergic effects.
Use simple regimens and once daily dosing whenever possible	Improve compliance; avoid alternate day regimens for ease of compliance.
Before adding a medicine, ensure it is not for treating an unwanted effect of another medicine	e.g. cough suppressants in a patient using ACE inhibitors
If a medicine does not appear to be effective, substitute rather than add another medicine	e.g. analgesics, gastrointestinal agents, psychoactive agents
Review the necessity of the medicine frequently	e.g. h2 antagonists, hypnotosedatives, antidepressants, antipsychotics, NSAIDs

tion in renal excretion in the elderly means that smaller doses of digoxin are generally required.

Digoxin toxicity can be insidious in onset with non-specific symptoms such as anorexia, nausea and confusion which can then develop into cardiac arrhythmias.

Digoxin causes nausea, vomiting and cardiac arrhythmias as well as non-specific side effects such as confusion and weakness.^{18,19}

4. Anticoagulants

The anticoagulant warfarin is conspicuous in the top 5 of the 'hit parade' in many studies.^{5,8,9,15,26}

In one study looking at adverse drug events in a nursing home almost 80% of all potential adverse drug events were associated with the use of warfarin, primarily the development of excessively high INR values (the mean INR in these patients was 6.1).²⁶

It is well known that anticoagulation with warfarin significantly reduces the incidence of stroke in patients with atrial fibrillation^{27,28,29} and the benefit is greatest in the elderly.

Careful selection is required, however, since the elderly are more sensitive to the anticoagulant effects of warfarin and lower doses are generally needed to achieve anticoagulant effect (as much as 25% less) in this age group than in younger patients.^{25,27,28}

Coupled with reduction in requirement is the fact that the elderly are more at risk of taking drugs which can enhance warfarin activity e.g. co-trimoxazole, omeprazole, cimetidine etc. or other drugs which can increase risk of bleeding e.g. NSAIDs.^{27,28,29}

Hence the potential benefits and risks need to be estimated for each individual e.g. a patient with a history of falls or cognitive impairment would not be a better candidate for warfarin therapy and better suited to aspirin.

5. Antibiotics

In a cohort study consisting of 2 185 people 65 years and older it was found

that antibiotics caused the most adverse effects (15%) and in several other studies was among the top 5.^{5,26,30}

The effects experienced were mainly gastrointestinal complaints and rash and were described as non-preventable due to being 'type b' or idiosyncratic/allergic type reactions.²⁶

Specific problems noted are as follows:

Increased risk of Stevens-Johnson syndrome and blood dyscrasias have been associated with the use of Trimethoprim-sulphamethoxazole combinations.

Flucloxacillin may cause cholestasis, especially if treatment extends beyond 14 days and the elderly are more prone to develop peripheral neuropathy and pneumonia associated with nitrofurantoin.²⁵

Aminoglycosides may accumulate in elderly patients with reduced renal function hence these agents should be given less frequently and regular monitoring of aminoglycoside levels is required.¹⁷

It is interesting to note that the prescribing of antibiotics for urinary tract infections was responsible for many adverse drug effects relating to antibiotic use.¹⁷

Principles for prescribing in the elderly (or the 'many years checklist')

All of the drugs associated with a high number of adverse drug reactions with the exception of antibiotics are type A reactions (pharmacological) and evaluation of the studies shows that many of these reactions, including the fatal ones, could have been avoided.^{6,10,13}

It is no surprise that adverse drug reactions have been shown to increase with the number of drug prescriptions in exponential progression and that the elderly who experience adverse effects are more frequently on moderate polypharmacy i.e. 4–5 drugs.^{7,13}

'Start low, go slow' is a well-known precaution that is yet to pass its use-by date.

Some studies show an increasing incidence of ADRs in patients over 50 but a decreased incidence in patients over 80 despite a high drug consumption reflecting that it may not be easy to detect when an ADR has occurred in an elderly patient, i.e. the incidence of headache (the most frequently occurring subjective symptom) decreased sharply in patients over 70, whereas the incidence of rash (an objectively determined ADR was not affected by age).⁷

By applying some simple prescribing principles it may be possible to reduce the risk of exposing your elderly patients to an adverse drug reaction (Table 3).

Intelligent non-compliance or deviant behaviour?

It is also important to remember that adherence to long-term medication is often poor and this may relate to mild ADRs which may not have been reported. Up to 75% of elderly patients may not adhere to prescribed medication, with clinically significant results, such as disease breakthrough in 25%.²⁵

Patients may also hoard unused drugs for future use, leading to more confusion for both patient and doctor.

Reasons for non-compliance include poor instruction, excessively complex drug regimens, differing perceptions of what is important by doctor and patient, adverse drug reactions and inconvenience.^{15,17,19,25}

Improving adherence to prescribed medication²⁵

- Consider the possibility of poor compliance;
- clear dialogue between patient and doctor;
- regular face-to-face review of medication by doctor and patient;
- simple drug regimens;
- written instructions.

Summary

It is well documented that older patients are more likely to have a misadventure because of changes in drug absorption, distribution, metabolism and excretion associated with ageing and greater use of medication.

In studies of medicines-related hospital admissions and adverse effects of medicines in the elderly there

are some medicines that consistently rank highly including psychoactive agents, NSAIDs, diuretics, digoxin, anticoagulants and antibiotics.

This may relate to the frequency of use of the medicines in the community, and use of the medicines may be unavoidable in many situations.

For elderly patients with reduced renal or hepatic clearance, disease or

altered homeostasis it is important that drug therapy be started with the lowest dose likely to be effective. Therapy should be terminated if an adverse drug reaction develops or if treatment does not have a beneficial effect.

Start low, go slow is a well-known precaution that is yet to pass its use-by date.

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