POLYPHARMACY

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Soon you will receive a ***multimeds self-administered patient questionnaire*** to identify people at higher risk of drug related problems, a medicines grid to provide a visual representation of medication use and a SIMPLE schema for medicines review.

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POLYPHARMACY

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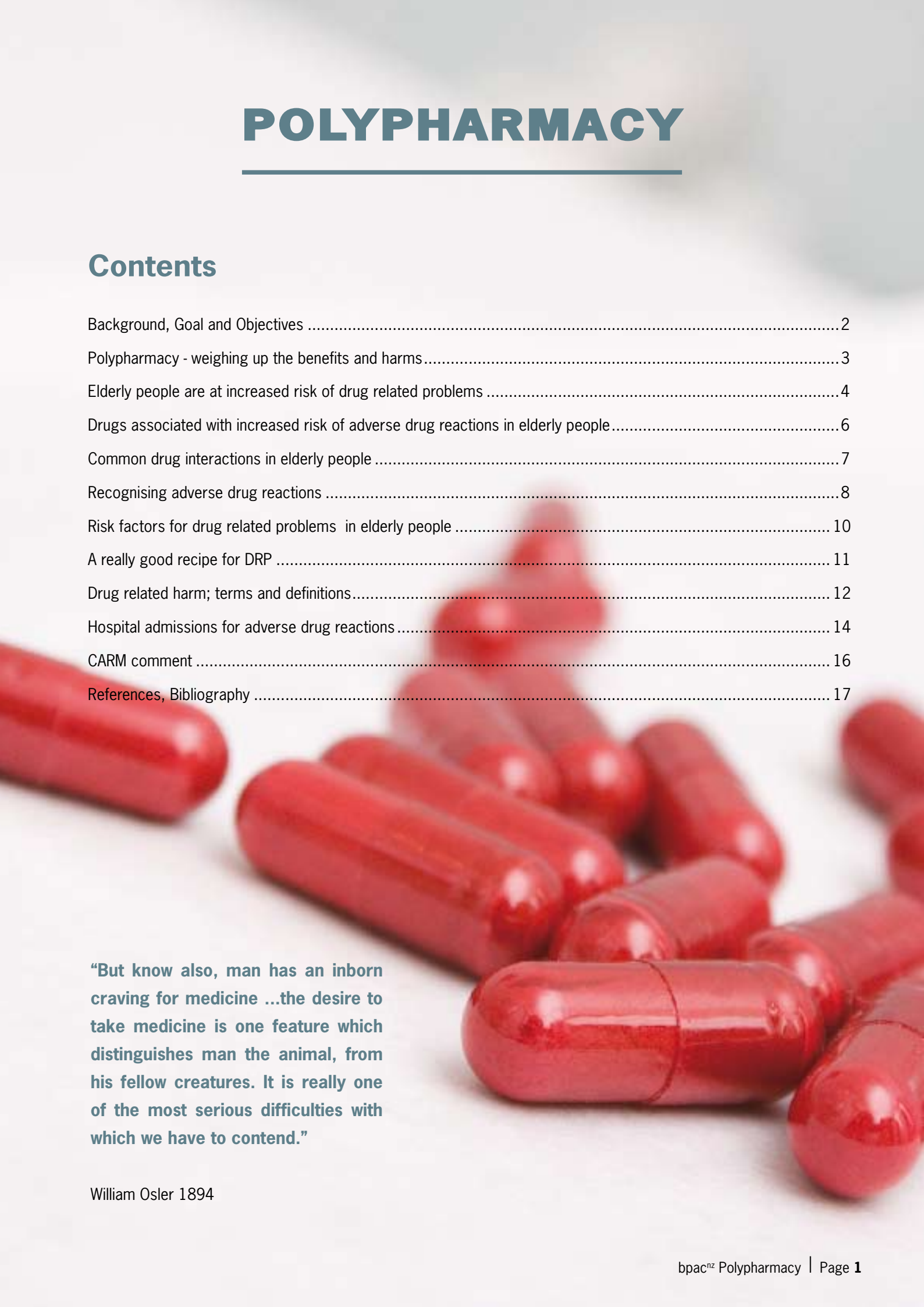


"But know also, man has an inborn craving for medicine ...the desire to take medicine is one feature which distinguishes man the animal, from his fellow creatures. It is really one of the most serious difficulties with which we have to contend."

William Osler 1894

POLYPHARMACY

Background

Drug related problems cause significant preventable morbidity and mortality. Their economic cost is estimated to rank fourth in the developed world, behind cardiovascular disease, cancer and diabetes. Drug related problems include adverse drug events, adverse drug reactions and drug interactions. Polypharmacy has various definitions and connotations in the literature ranging from the use of 4, 5, 6 or more drugs in combination to the more simplistic addition of just one inappropriate drug to an existing drug regimen. The addition of any drug is one too many if it provides no benefit and causes potential harm. Our definition of polypharmacy for the purpose of this campaign is: "the addition of one or more drugs to an existing regimen which provides no additional therapeutic benefit and/or causes drug related harm". Elderly people on multiple medications are at particularly high risk of drug related problems.

Goal

The goal of this campaign is to decrease drug related problems in elderly people by reducing prescribing factors associated with increased risk.

Objectives

- To raise awareness of the increased risk of drug related problems associated with polypharmacy and to provide tools, including medicines review, to identify and manage high risk patients.
- Identify and raise awareness of major categories of adverse drug reactions and high risk drug combinations in New Zealand.
- Reduce the inappropriate use of high risk drugs and drug combinations especially in elderly people.
- Reduce the "prescribing cascade" phenomenon.

"Don't treat risk factors. Don't even treat disease. Treat patients, and treat them as individuals"

Professor John Campbell, 2005

Polypharmacy - weighing up the benefits and harms

The use of multiple drugs is accepted best practice for common chronic conditions such as hypertension and diabetes. Conscientious clinicians, who adhere to evidence-based guidelines, will often find themselves prescribing six or more drugs for people with several chronic conditions. However, trials investigate populations and clinicians treat individuals.

The difficulty is balancing the potential benefits of these drugs, as described in the guidelines, with the risk of harm from the high number of drugs used. Clinicians need to consider carefully numbers needed to treat, numbers needed to harm, long term prognosis and the wishes of individual patients.

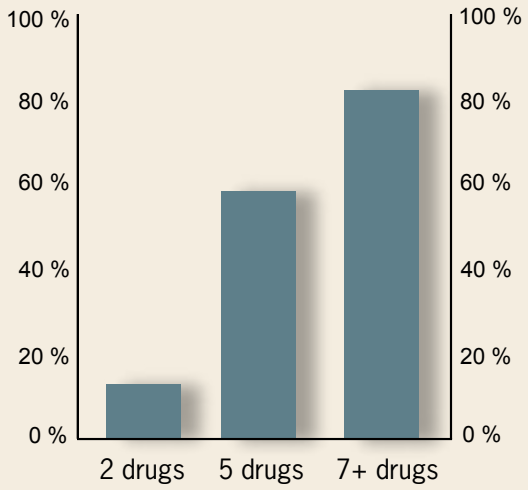
Polypharmacy	
Potential benefits	Risk of harm
Synergistic combinations allow lower doses and therefore less adverse effects than individual drugs. e.g. treatment of hypertension	Synergistic adverse effects increase risk of harm. e.g. may increase risk of falls due to postural hypotension
Supplemental drug may decrease adverse effect of initial drug. e.g. anticholinergic added for drug induced extrapyramidal effects	Increased complexity of the regimen can lead to confusion, error and poor adherence. e.g. multiple tablets, multiple doses, increased risk of side effects
Additional drug may improve outcomes. e.g. addition of spironolactone to ACE inhibitor for heart failure	Increased opportunities for drug interactions. e.g. increased risk of hyperkalaemia
Multiple drugs may be needed for multiple conditions. e.g. diabetes plus osteoarthritis	More drugs = more opportunity for adverse effects. Difficult to predict interactions within a complex regimen. e.g. ACE inhibitor plus NSAID increases the risk of renal failure

Many people on five or more drugs will be taking an unfamiliar or even unique combination (Bjerrum, 1998). The potential benefits and risks of harm of such regimens will not have been subject to research and are often difficult to predict.

"First do no harm"

Hippocrates, 460-355 BC

Figure 1. Risk of harm increases with number of drugs taken



The risk of an adverse drug event has been estimated at 13% for two drugs, 58% for five drugs and 82% for seven or more (Fulton & Allen, 2005).

Elderly people are at increased risk of drug related problems

Elderly people are at particular risk of drug related problems because of complex drug regimens involving multiple drugs and the physiological changes which accompany aging. Up to 30 percent of hospital admissions in the elderly may be associated with drug related problems (Hanlon, 1997).

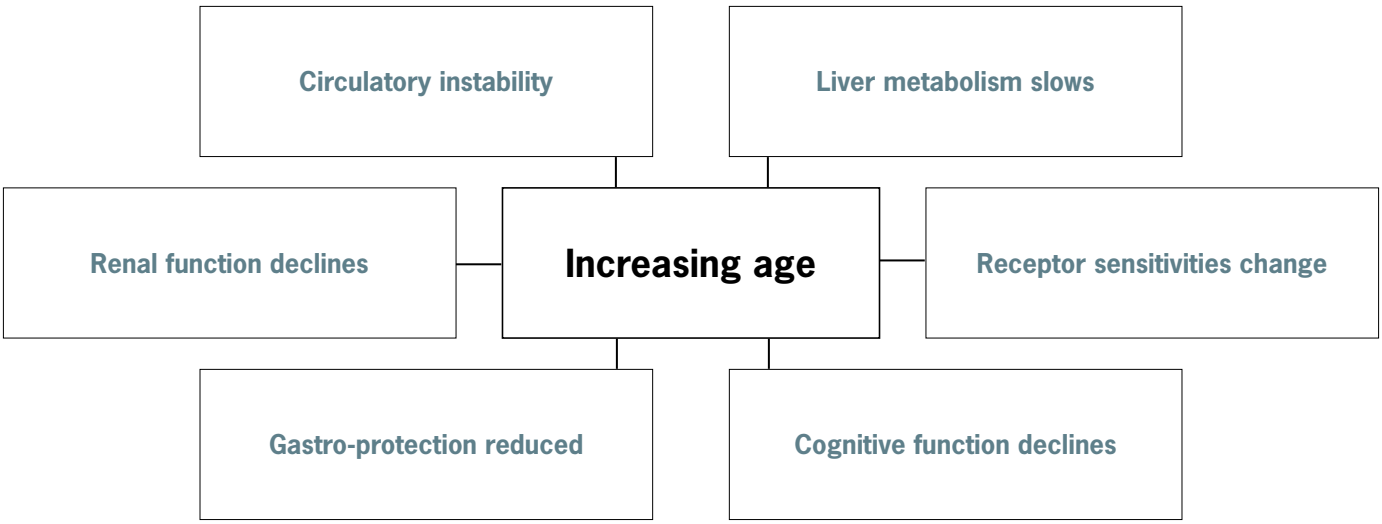
Large clinical trials often exclude elderly people and those with co-morbidities. This means that subjects of trials are often very different from the elderly patients with multiple co-morbidities seen in practice. A UK study found stroke patients in primary care were on average 12 years older than patients in the research which formed the basis of national guidelines for blood pressure lowering for patients with stroke (Mant, 2006). The guidelines, therefore, cannot be applied uncritically to the patients of these practices.

Prescribers need to consider the special needs of elderly patients when following clinical guidelines. If they do not, they are likely to expose their patients to increased risk of drug related problems.

Changes which accompany aging make people particularly susceptible to drug related problems.

Physiological changes associated with aging affect a person's handling and response to drugs. Changes in the excretion and metabolism of drugs lead to increased drug concentrations, changes in receptor sensitivity cause exaggeration or blunting of drug effects, and decline in cognitive function makes adherence to a complex drug regimen difficult.

Age related changes which increase the risk of drug related problems



Some examples of age related changes to drug effects include:

- increased postural sway with benzodiazepines
- increased sensitivity to CNS drugs, e.g. benzodiazepines, opioids, antipsychotics and antiparkinson drugs
- postural instability pre-disposing to drug induced hypotension and drug related falls
- increased analgesic effect of morphine
- reduced peak diuretic response to frusemide
- increased anticoagulant effect of warfarin, and
- impaired thermoregulatory mechanisms predisposing to drug induced hypothermia

Mangoni and Jackson, 2003

Drugs associated with increased risk of adverse drug reactions in elderly people

Because of age related changes in drug handling described on page 5 certain drugs are associated with increased risk of adverse drug reactions when given to elderly people.

If the potential benefits of these drugs for an individual patient appear to outweigh the risks of harm they should be used with caution; otherwise they should be avoided.

Some drugs associated with adverse drug reactions in the elderly

Drug or drug class	Comments
All drugs	Start low, go slow. Many drugs, e.g. oxybutynin, antipsychotics, TCAs, antihypertensives need much lower doses in elderly people.
benzodiazepines	Those with a long half-life, such as diazepam, nitrazepam cause excessive and prolonged sedation. Temazepam is a better choice if necessary but all are best avoided.
cimetidine	More drug interactions and a greater potential for confusion than ranitidine.
dextropropoxyphene	Can cause confusion and excessive sedation in the elderly.
digoxin	Use low doses initially. Extra vigilance required for those who need to be on higher doses.
indomethacin	This NSAID has a high incidence of CNS effects and gastrotoxicity.
nefopam (Acupan)	CNS effects and marked anticholinergic actions; avoid.
NSAIDs	Use lowest dose necessary for the shortest period. Avoid long-term use of full dose, longer half-life drugs such as naproxen and piroxicam.
tricyclic antidepressants (TCAs)	Doxepin and amitriptyline are very sedating and have strong anticholinergic actions. Not preferred as first choice for depression in the elderly.
thioridazine (Aldazine)	Greater potential for CNS and extrapyramidal effects.

Common drug interactions in elderly people

It is impossible to remember all possible drug interactions; see how long the list is in appendix one of the BNF! A number of drug combinations are frequently used but have the potential to cause significant harm if not managed appropriately. Not every elderly adult who takes these medications together will experience an adverse reaction.

Common Drug Interactions

Drug combination	Risk of harm	Prevention
warfarin / NSAIDs	increased risk of bleeding	review need for NSAID consider paracetamol as an alternative
warfarin / amiodarone		monitor INR and adjust warfarin dose accordingly
warfarin / sulfa drugs		use alternative antibiotic
warfarin / macrolides		
warfarin / norfloxacin		
warfarin / phenytoin	increased or possible decreased effects of warfarin phenytoin concentration possibly increased	monitor phenytoin level and INR
ACE inhibitors / K^+ supplements	elevated potassium levels	monitor potassium levels discontinue K^+ supplement if not needed
ACE inhibitors / spironolactone	elevated potassium levels renal failure	monitor potassium levels and renal function
ACE inhibitors / NSAIDs	renal failure	re-evaluate need for NSAID monitor renal function avoid hypovolaemia
digoxin / amiodarone	digoxin toxicity	decrease dose of digoxin by 50% when adding amiodarone and check digoxin levels weekly until stable
digoxin / verapamil	digoxin toxicity bradycardia, heart block	check ECG re-evaluate need for these drugs
theophylline / norfloxacin and ciprofloxacin	theophylline toxicity	re-evaluate need for these drugs monitor theophylline levels
anticholinergic combinations e.g. TCA, sedating antihistamine, antipsychotic, oxybutynin, orphenadrine, benztropine, etc	sedation, confusion, blurred vision, falls	reduce numbers, strength or doses of these drugs
drugs acting on the CNS combinations of antiepileptics, antipsychotics, analgesics, antidepressants, etc	sedation, confusion, falls	reduce numbers, strength or doses of these drugs

"The ingenuity of man has ever been fond of exerting itself to varied forms and combinations of medicines." William Withering, 1785

Recognising adverse drug reactions

Adverse drug reactions are often unrecognised and therefore not managed. Even worse a new drug may be prescribed to treat a symptom which has not been recognised as being caused by an existing medication.

This leads to a prescribing cascade where the additional drug prescribed increases the risk of more adverse reactions raising the risks of further prescribing to treat these new symptoms.

People with communication difficulties such as those with Alzheimer's disease, dysphasia or intellectual disabilities are at particular risk of having unrecognised adverse drug reactions.

Common presentations of adverse drug reactions in the elderly

Symptom	Possible causative or aggravating drugs
Confusion	benzodiazepines, phenothiazines (e.g. chlorpromazine, promethazine, methotrimeprazine), anticholinergic drugs, TCAs, opioids, antiparkinson drugs, anticonvulsants, corticosteroids, NSAIDs, cimetidine, ranitidine or sudden benzodiazepine withdrawal
Unsteadiness and falls	combinations of drugs with sedating properties (e.g. TCAs, anticonvulsants, phenothiazines, sedating anti-histamine, antipsychotic, benztropine, opioids) anticholinergics
Constipation	calcium channel blockers (especially diltiazem and verapamil), phenothiazines, tricyclics, anticholinergic drugs
Depression	long term benzodiazepine use, high doses of TCAs (especially amitriptyline and doxepin)
Dyspepsia	NSAIDs
Electrolyte disturbances	loop and thiazide diuretics (hypokalaemia, hyponatraemia), potassium sparing diuretics (hyperkalaemia), antidepressants (SSRIs, venlafaxine - hyponatraemia, syndrome of inappropriate antidiuretic hormone)
Heart failure, hypertension	NSAIDs
Hypotension and falls	combinations of drugs acting on the circulation
Hypothermia	phenothiazines, risperidone, benzodiazepines, alcohol, opioids
Insomnia	theophylline and decongestants
Parkinsonian symptoms	metoclopramide, methotrimeprazine, prochlorperazine
Urinary retention	anticholinergic drugs. Many drugs, including OTC decongestants, can cause or aggravate urinary problems
Stress incontinence	alpha-blockers (e.g. doxazosin), calcium channel blockers

Examples of the prescribing cascade:

Ankle oedema due to a calcium channel blocker leads to prescribing of a diuretic.
This type of oedema does not respond to a diuretic.

Prescribed or over-the-counter NSAID drug causes an increase in blood pressure and the addition of an antihypertensive drug.
NSAIDs cause a small rise in BP and may tip the balance into the hypertensive category. Review the need for the NSAID in these patients.

A patient on amitriptyline 50 mg nocte for pain. After a dose increase from 25 – 50 mg the patient complains of incontinence and oxybutynin is prescribed. The incontinence worsens and the dose of oxybutynin is increased. The patient also complains of constipation and a stimulant laxative is prescribed.
Amitriptyline has anticholinergic actions and can cause urinary retention leading to overflow incontinence which was not recognised. Oxybutynin also has anticholinergic actions but is used for urge incontinence. The situation worsens, the person gets constipated and a laxative is prescribed.

"I do not want two diseases – one nature-made, one doctor-made"

Napoleon Bonaparte, 1820

Risk factors for drug related problems in elderly people

- Use of narrow therapeutic index drugs, such as digoxin, warfarin, lithium, anticonvulsants increases the risk of drug toxicity and drug interactions.
- Use of multiple drugs increases risks of unpredicted interactions.
- Use of drugs commonly associated with drug related problems requiring hospital admissions, such as warfarin, NSAIDs, ACE inhibitors and opioid analgesics.
- Use of drugs that have synergistic adverse effects, such as hypotension or sedation.
- Use of drugs from multiple prescribers.
- Recent commencement of new medicine.
- Recent discharge from hospital.
- Unsupervised use of over-the-counter or complementary medicines.
- When a patient cannot communicate effectively, for example because of Alzheimer's disease or intellectual handicap.

A really good recipe for DRP

Rx: Gli anziani cadono

"Elderly people all over New Zealand are falling for this deceptively easy recipe. Its basic ingredients are common in everyday practice as prescribers try to balance the possible benefits of drug therapy with the potential for unfortunate outcomes."

Ingredients

6 or more drugs

12 or more daily doses

2 or more chronic conditions

2 or more prescribers

1 or more of the following:

- high risk drugs
- high risk drug combinations
- high risk drug-condition combinations

Optional

Various herbal or alternative remedies

Any one of these ingredients or several combined can, if left to simmer, produce a surprising concoction that makes elderly people go weak at the knees and makes their heads spin.

To increase the risk of an unfortunate outcome you can leave the mixture to stand, without regular checking, or throw in an additional ingredient without first assessing the effects of the ones already in the pot.

Unlike kitchen recipes you can remove ingredients which don't appear to be working.

Simplifying the recipe, assessing the need for the ingredients, and monitoring their effects are the secrets to achieving the benefits of drug therapy whilst avoiding unfortunate outcomes.

Buona Salute!

Drug related harm; terms and definitions

Drug related problem (DRP) now sometimes referred to as Medicines related problem

An event or circumstance involving a patient's drug treatment (or lack of drug treatment) that actually or potentially interferes with the achievement of an optimal outcome. Adapted from Hepler and Strand, 1990.

DRPs include:

- Untreated indications
- Drug use without a clear indication
- Sub-therapeutic dosage
- Excessive dosage
- Adverse drug reaction
- Drug interaction
- Drug withdrawal reaction
- Medication error
- Non-adherence to drug treatment
- Therapeutic failure

(Adapted from Hanlon et al, 2004)

DRPs cause significant morbidity and mortality in the general population. Some authors have estimated that the economic cost of DRP rank around fourth behind, cardiovascular disease, cancer and diabetes in the developed world (Johnson and Bootman, 1995).

A recent systematic review reported that a median 7.1% (range 5.7–16.2) of hospital admissions result from drug related problems, of which 59% were considered preventable (Winterstein et al, 2002).

Adverse drug event (ADE)

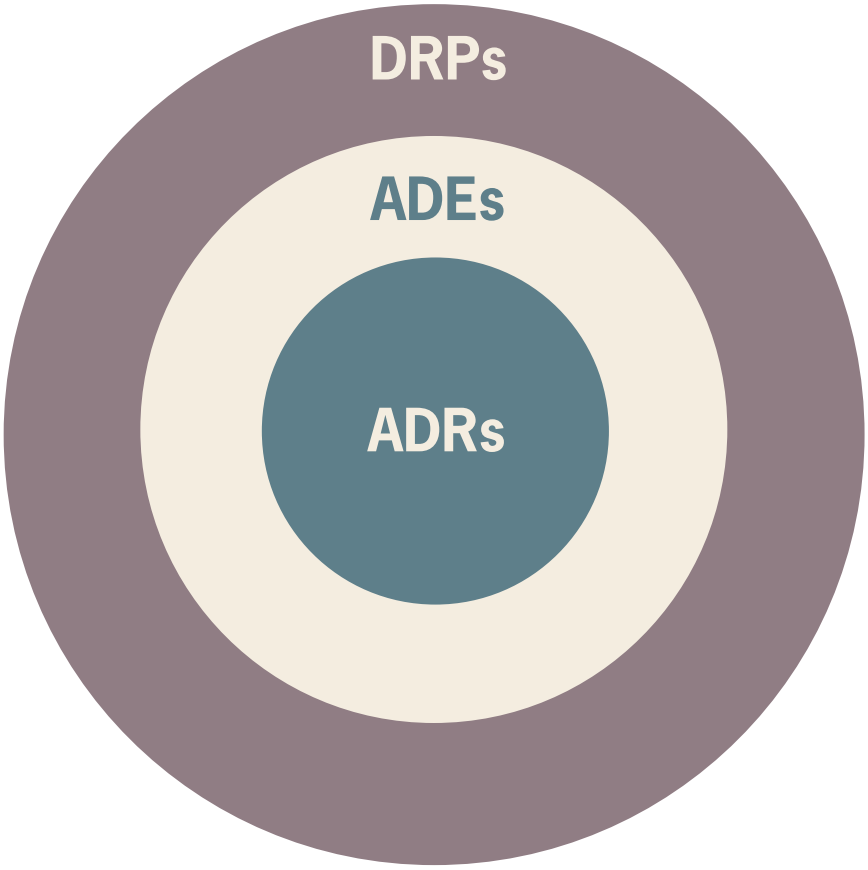
An injury resulting from the use of a drug

An adverse drug event is a broader term which includes adverse drug reactions plus harm from the use of the drug including prescribing, administration, overdoses, dose reductions and discontinuations of therapy (medication errors).

Examples:

1. Severe bronchospasm following use of metoprolol in an asthmatic patient with a history of beta-blocker induced bronchospasm. This is a medication error as the history was not recognised. The metoprolol unmasked and aggravated the bronchospasm rather than causing it directly.
2. Metoprolol stopped suddenly resulting in tachycardia and hypertension. This is also a medication error resulting from abrupt discontinuation of the metoprolol and associated rebound effects. The dose should have been gradually reduced.
3. Severe bradycardia resulting from the administration of three times the intended dose of metoprolol (47.5 mg TID instead of daily). Another medication error which could be due to an incorrect prescription or incorrect reading or interpretation of the prescription.

NB the term adverse drug event does not include situations when a drug is not used when the patient could potentially benefit from it. For example, failure to use a beta-blocker in a patient with stable well controlled COPD and heart failure or post myocardial infarction. This is an "untreated indication".



Adverse drug reaction (ADR)

A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of a disease or for the modification of physiological function.

In other words, harm directly caused by the drug at normal doses. For example, depression caused by a beta-blocker.

Adverse drug reactions fall in to one of two main categories:

Type A reactions are predictable, dose-related reactions where the intensity of the effect increases with dose or reduced clearance of the drug from the body, i.e. increased blood concentrations. For example, the anticholinergic effects (constipation, blurred vision) of amitriptyline will tend to worsen if the dose is increased from 25 mg to 50 mg daily. In addition the patient will tend to become more drowsy and sedated.

Type B reactions are not related to dose and are largely unpredictable (idiosyncratic). These represent many potentially serious adverse reactions such as blood dyscrasias and hepatotoxicity.

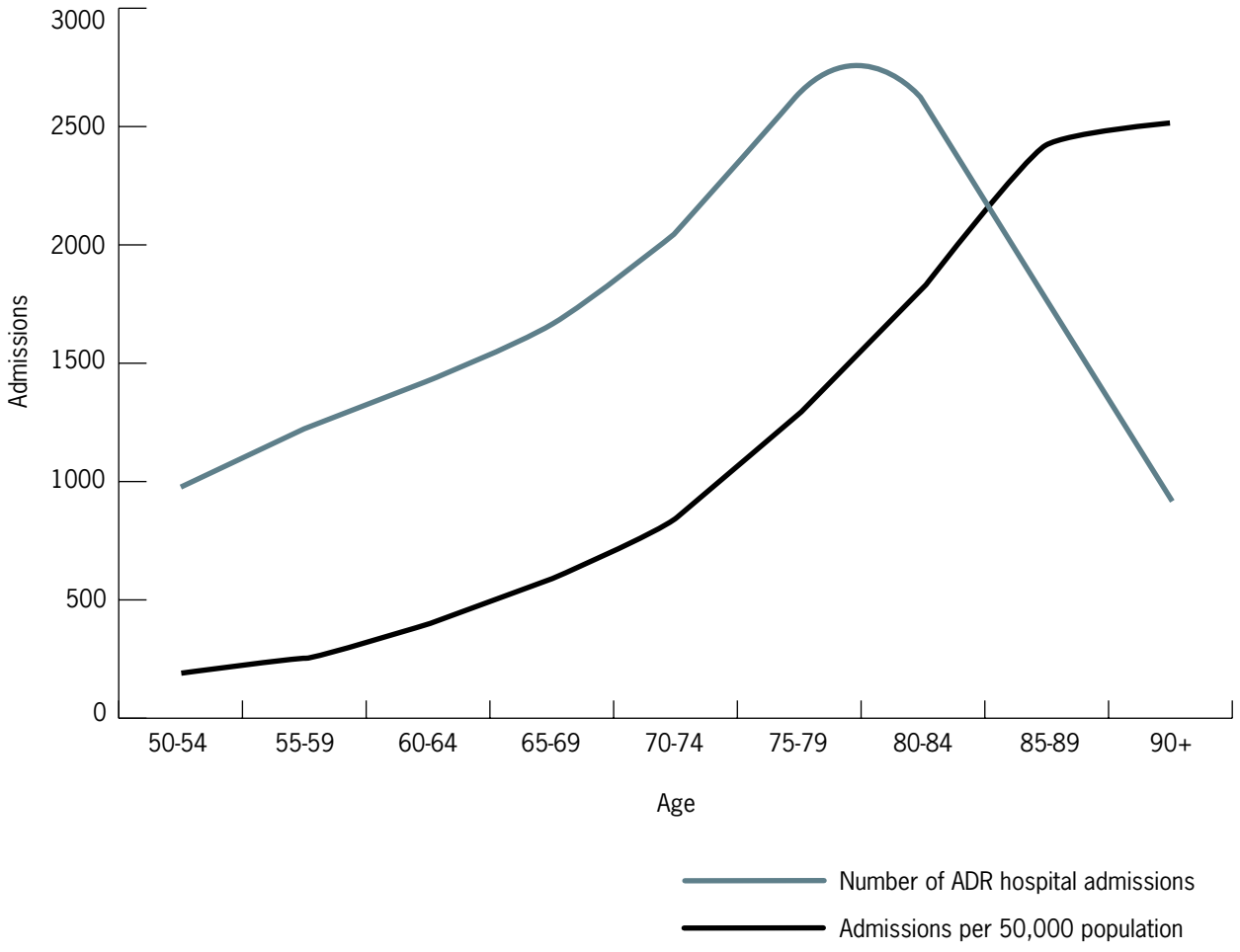
For some adverse drug reactions there appears to be a threshold drug dose or concentration at which a type B reaction becomes more likely. For example, it is difficult to predict who will get confusion due to cimetidine or ranitidine, but the elderly seem to be more susceptible especially if the dose is not reduced according to the decline in renal function. Similarly, the risk of the rare allopurinol hypersensitivity syndrome is increased if the dose is not adjusted in renal impairment.

Hospital admissions for adverse drug reactions

We identified hospital admissions in 2005 for adverse drug reactions in people over 50 years of age by extracting ICD-10 codes and patient demographic data from the Hospital Separation Diagnosis Database. International literature suggests that these data are likely to underestimate the actual number of admissions for adverse drug reactions because of incomplete coding.

Over the year, there were 15,254 admissions for 17,806 adverse drug reactions. There were 146 different adverse drug reactions recorded. Adverse drug reactions increase with age (graph below). Fifty six percent were female. Only 8% of overall admissions for adverse drug reactions were for Māori people although Māori represent approximately 15% of the population. However, in the younger age-bands 50-59, Māori represented a greater proportion of admissions probably due to being on more drugs at a younger age caused by earlier onset of chronic disease.

Hospital admissions for adverse drug reactions increase with age



Anticoagulants were the most frequently implicated drugs followed by diuretics, opioids, non steroidal anti-inflammatory drugs and beta blockers.

Number of admissions for ADR by drug group

Main drug group	Admissions	Sub-group	Admissions
Cardiovascular (43.3%)	7711	anticoagulants	1779
		diuretics	1552
		beta-blockers	1023
		ACE inhibitors	810
		antiarrhythmics	703
		vasodilators	577
		calcium channel blockers	434
		antihypertensive	288
		aspirin	230
		α-adrenoceptor blocker	155
		lipid-lowering	153
		other	7
Nervous system (17.4%)	3107	opioids	1289
		antidepressants	424
		antipsychotics	362
		anaesthetic	180
		benzodiazepines	159
		antiepileptics	143
		analgesics	121
		other	429
Anti-inflammatory (11.6%)	2074	NSAIDs	1124
		corticosteroids	950
Anti-infectives (10.3%)	1826	penicillin	698
		cephalosporin	192
		other	936
Oncology agents (6.4%)	1139	anti-neoplasm	978
		immunosuppressant	152
		other	9
Alimentary tract (4.5%)	805	insulin & oral hypoglycaemics	440
		other	365
Other (6.4%)	1144	musculo-skeletal	178
		hormone preparations	106
		respiratory	81
		topical	38
		sensory system	25
		vaccine	13
		other	703
TOTAL	17806		

Commonly reported adverse drug reactions

The Centre for Adverse Reactions Monitoring (CARM) has identified some commonly reported adverse drug reactions in the last 10 years occurring in patients aged 65 years and older and often resulting from interacting medicines.

Hyponatraemia is an adverse reaction that can be serious and is reported most often in the elderly with fluoxetine, paroxetine and bendrofluazide individually or in combination. In a series of 11 patients aged 65 years and older with hyponatraemia attributed to bendrofluazide, four were taking other medicines also likely to cause hyponatraemia, these were frusemide, fluoxetine and paroxetine, and in one case both frusemide and fluoxetine. Presenting symptoms were sometimes vague and included lethargy, confusion and nausea. One younger patient developed convulsions. Six of the eleven patients required hospital admission and in one case the condition was life-threatening. One patient was also taking quinine and developed atrial fibrillation, probably an adverse effect of quinine made more likely because of the electrolyte disturbance. The patient taking bendrofluazide, frusemide and fluoxetine also took enalapril and rofecoxib and, as well as hyponatraemia, developed acute renal failure due to the combination of diuretics, ACE inhibitor and a non steroidal anti-inflammatory agent (bpac^{nz}, ACE Inhibitors).

Interactions with simvastatin are also commonly reported. Myalgia occurs frequently with simvastatin but high doses or co-prescription of fibrates or medicines that inhibit simvastatin metabolism can lead to myopathy, including on rare occasions, rhabdomyolysis which is often fatal. Reports have been received of such reactions when other potent inhibitors of hepatic CYP3A4 isoenzymes have been prescribed such as azole antifungals, erythromycin and ciclosporin. Of note is that diltiazem, a weak inhibitor of CYP3A4, appears to have precipitated rhabdomyolysis when given with high doses (80 mg daily) of simvastatin or at lower doses where there were a number of co-morbidities. These interactions also affect atorvastatin (Savage, 2006).

Interactions with warfarin continue to be commonly reported. There are a number of recent reports of roxithromycin increasing the effect of warfarin. This is likely to be to a lesser degree than with erythromycin but the product information for roxithromycin indicates that the effect may be clinically significant in patients receiving polytherapy or in the elderly (Medsafe, 2006). The interaction between miconazole and warfarin is well-recognised but reports to CARM, some serious, indicate that it is not always recognised that miconazole oral gel will also interact.

Reports to CARM of **hypotension in the elderly** demonstrate in particular that the addition of psychoactive medicines that lower blood pressure to an antihypertensive regime may mean that some antihypertensive medicines need to be discontinued or the dose lowered if the psychoactive medication is considered necessary. A combination of trifluoperazine, atenolol and amlodipine in one patient led to ataxia, hypotension and syncope. A patient with bradycardia and heart block probably due to the combination of diltiazem and metoprolol, was also taking donepezil and this may have contributed to the dizziness and hypotension the patient also experienced. A patient taking nortriptyline, timolol, nifedipine, captopril and hydrochlorothiazide developed hypotension and syncope and recovered when nortriptyline and nifedipine were withdrawn.

Where the prescription of potentially interacting medicines is unavoidable, careful follow up for indicators that an unwanted outcome is developing is essential.

CARM
Centre for Adverse Reactions Monitoring

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