



Polypharmacy in primary care:

Managing a clinical conundrum

Polypharmacy can be appropriate and beneficial for patients. However, polypharmacy also increases the risk of problematic prescribing and is associated with adverse health outcomes. Two “golden rules” which reduce problematic prescribing are to always enquire if patients are taking their medicines as prescribed, and to never assume that all of the medicines a patient is taking are known. Prescribers can take further steps to reduce problematic prescribing by being clear about the goals of care, adopting a systematic approach to new prescribing, being aware of medicines and conditions commonly associated with adverse outcomes and identifying patients at high risk of being affected by problematic prescribing, e.g. patients taking ten or more medicines simultaneously. Medicine reviews should be periodically conducted for all patients with multiple long-term conditions.

The twin faces of polypharmacy

Balancing the potential benefits and harms of prescribing multiple medicines is a challenge that all prescribers face on a daily basis. Among older patients polypharmacy is associated with falls and fractures, dehydration and acute kidney injury (AKI), delirium, hypoglycaemia, malnutrition, hospitalisation and death.¹ However, polypharmacy is not necessarily harmful and for many patients, taking multiple medicines does increase life expectancy and improve quality of life.² For example, in patients with established coronary artery disease the appropriate use of several concurrent medicines, e.g. an angiotensin converting enzyme (ACE) inhibitor, a calcium channel blocker, a diuretic, a statin and an antiplatelet, reduces the risk of a vascular event by between two-thirds and three-quarters.²

The number of people prescribed multiple treatments is continuing to climb (Figure 1) as the age of the population, the number of preventative treatments, and the number of long-term conditions that are diagnosed also increase.

Polypharmacy has traditionally been defined by the number of medicines that a patient is taking simultaneously, typically five or more.³ Defining polypharmacy purely by an arbitrary number of medicines, however, fails to acknowledge that the potential risk of adverse effects of medicines can vary widely. For example, an emollient prescribed for dry skin poses a much lower risk to a patient (if any) compared to prescribing a non-steroidal anti-inflammatory drug (NSAID) or diuretic. Recently, polypharmacy has been further categorised to account for both its positive and negative aspects.²

“Good” and “bad” polypharmacy

Appropriate polypharmacy describes treatment where a patient has multiple morbidities, and/or a complex condition, that is being managed with more than one medicine, where the potential benefits outweigh the potential harms.³ For

example, a patient with heart failure, hypertension and atrial fibrillation will be prescribed a range of cardiac medicines, all of which are likely to improve the quality of the patient’s life.

Problematic polypharmacy describes a patient receiving multiple medicines, where one or more of these medicines have potential harms that outweigh the potential benefits; the patient may no longer need the medicine, the medicine may adversely interact with another medicine in the patient’s regimen, or the patient may not receive the intended benefit of multiple treatments.³ Reducing problematic polypharmacy improves patient safety and quality of life, while also reducing waste.

The Health Quality and Safety Commission atlas of healthcare variation provides a range of prescribing data for older patients in New Zealand by DHB, showing indicators of polypharmacy. It is available at: www.hqsc.govt.nz/assets/Health-Quality-Evaluation/Atlas/polypharmacySF/atlas.html

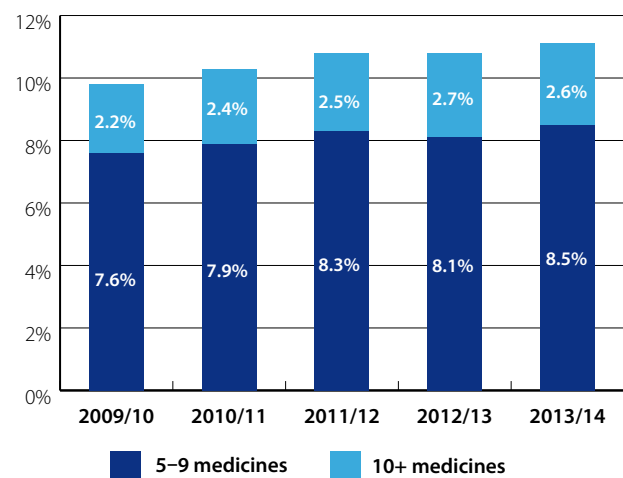


Figure 1: Proportion of the New Zealand population who were continuously prescribed (i.e. three or more dispensings of a medicine in a year) five to nine medicines, or ten or more medicines from 2009 – 2014⁴

Clinicians must balance the risks versus the benefits of polypharmacy

When managing medicines it is vital that concerns over possible problematic prescribing do not lead to under-treatment in patients.² The problem that must be resolved on a case-by-case basis is deciding what constitutes “too many medicines” for an individual patient.² The goal is to avoid or stop problematic prescribing, while continuing treatment where there is a clear benefit to the patient. Clinicians who are skilled at this are able to identify which of the multiple possible treatment options are needed by the individual patient, and which are not. This is where experience and judgement provide invaluable additional information to guidelines and treatment algorithms.


A guiding principle is to first decide on the desired goal of treatment, e.g. immediate pain relief or fracture prevention.⁵ An appropriate treatment target can then be agreed upon with the patient that may vary from primary prevention in order to prolong life, to symptom control for acute illness.⁵ Once treatment has begun the goals and the patient’s treatment targets should be periodically reassessed. Where there is an absence of evidence that a medicine is providing a patient with ongoing benefit, the prescriber should consider withdrawing that treatment.² The two steps of careful prescribing and then de-prescribing should go hand-in-hand.

Systems and considerations to improve patient safety

In an ideal scenario one prescriber would have responsibility for one patient’s medicines. Modern medicine is increasingly moving away from this approach. Levels of specialisation are increasing, meaning there is an ever-growing need for health professionals to share information, and centralised patient records are a response to this need. New Zealand data shows that the average number of medicines a patient is prescribed increases as the number of prescribers involved in their care increases (see: “Managing medicines in older people”, BPJ 47, Oct, 2012). This highlights a risk to patients as the number of prescribers a patient has is also associated with their risk of experiencing an adverse drug reaction.

Regularly asking patients whether they have consulted another health professional can be beneficial, even for younger patients. For example, female patients may have visited a Family Planning clinic and were prescribed oral contraceptives. When prescribing to a patient, who is normally under the care of another clinician, it is good practice to discuss the medicines with the patient when providing repeat prescriptions and

to advise their usual prescriber of any clinically significant changes (both adding and removing a medicine) to the patient’s treatment regimen. Any other information that may improve patient safety should also be passed on.

 **Best Practice Tip:** Avoid writing “as required” or “as needed” on prescriptions and ensure a total daily amount of medicine is specified. If “as required” is written on a prescription then the quantity of medicine to dispense should always be recorded, otherwise a pharmacist will be required to dispense the maximum three-month quantity that could be theoretically taken. For example, paracetamol prescribed without a dispensing quantity as one to two tablets, four times a day, as required for pain, could result in 720 tablets of paracetamol being dispensed.

Adopt a systematic approach to new prescribing

A standardised approach to prescribing means that the most frequent reasons for errors and problematic prescribing can be avoided. This includes a methodical approach to medicine justification and double checking all prescriptions before signing. Prescribers should have a low threshold for double-checking high-risk medicines and medicines that require dosage calculations. Good team work between prescribers, nurses and pharmacists means that errors are more likely to be detected and patient safety improved.

Before prescribing a medicine consider the following:

Could new symptoms be due to an adverse drug reaction?

Withdrawing a medicine for a short period, followed by reintroduction, may be an appropriate way of testing this, e.g. when investigating myalgia in a patient taking a statin (see: “Avoiding prescribing cascades”, Page 8).

What are the goals of treatment? For immediate control of symptoms such as pain, this question is easily answered. This is more complex when considering the magnitude of benefit of preventative treatments in patients with multiple co-morbidities or frailty.

Will this patient benefit from taking an additional medicine?

Consider the patient’s life expectancy (Table 1) and the likely time to benefit from treatments. For example, will a patient with severe chronic obstructive pulmonary disease (COPD) and osteoporosis receive a clinically significant benefit from the prescription of a bisphosphonate which will reduce their risk of experiencing a fracture over the next five years? For some patients it may be appropriate to consider scaling back treatment intensity as the goals of care change, e.g.

reducing the intensity of glycaemic control in older patients with type 2 diabetes lessens the risk of falls.² One way to assess the suitability of a treatment for a patient who is frail, or has a terminal condition, e.g. cancer, is to ask the question, “Would I be surprised if this patient were to die in the next six to 12 months?”⁶ Other signs that may indicate a limited life expectancy include: the use of medicines for symptom control rather than curative purposes, advanced organ failure, advanced co-morbidities causing significant functional impairment and advanced dementia.⁶

Are there any non-pharmacological treatments that are appropriate alternatives to medicines? For example, exercise to improve intermittent claudication, physiotherapy for patients with chronic back pain, or a walking aid for patients with osteoarthritis of the knee.

Table 1: Average expected years of life remaining for older New Zealand male and female populations, 2011 – 2013⁷

Male		Female	
Age (years)	Expected years of life remaining	Age (years)	Expected years of life remaining
65	19.1	65	21.4
70	15.3	70	17.3
75	11.8	75	13.4
80	8.8	80	10.0
85	6.4	85	7.0
90	4.8	90	4.8

Always enquire about treatment adherence before increasing doses

If a patient’s response to a medicine is less than expected, consider if this may be due to treatment non-adherence before titrating the dose upwards. If patients have not been taking medicines regularly then they may experience adverse effects if a structured dosing regimen is introduced due to a change in circumstance. For example, a patient with poorly controlled hypertension due to non-adherence with treatment, may develop hypotension following entry to a care facility once they begin regularly taking their prescribed daily dose of antihypertensives.

Treatment non-adherence is common in older patients and may be due to many reasons from deliberate non-compliance,

to forgetfulness or problems swallowing medicines. It is estimated that approximately 40% of patients taking long-term medicines do not take them as intended.² Open-ended and non-judgemental questioning, e.g. “tell me about any times when you forget to take your medicines”, is useful when exploring treatment adherence with patients.

In patients who experience confusion or who regularly forget to take oral medicines, consider if a medicine organiser or blister pack would be appropriate, although the cost of preparing these packs can vary widely. Once daily, or at most twice daily dosing, makes it easier for patients to remember to take medicines and is the preferred frequency whenever possible.² Building medicine administration into the patient’s daily routine can be useful, e.g. patients taking daily eye drops for glaucoma can associate this activity with brushing their teeth each morning. For patients who need to take medicines weekly, easily remembered schedules such as “methotrexate Mondays” and “folic acid Fridays” may help assist them in maintaining treatment adherence. Technology can also be used to support dosing regimens, e.g. patients who are at risk of vitamin D deficiency could use their mobile phone to automatically provide a reminder on the first of every month to take a cholecalciferol tablet.

Substituting medicines may be appropriate for patients with issues of adherence, e.g. recommending a combination alendronate with cholecalciferol tablet for patients with osteoporosis who are taking a bisphosphonate and forget to take cholecalciferol monthly.

Be aware of medicines associated with adverse drug reactions

The risk of adverse drug reactions and harmful interactions between medicines increases as patients are prescribed more medicines, e.g. the combination of NSAIDs, ACE inhibitors and diuretics.² For patients taking two medicines, the risk of an adverse drug reaction is reported to be 13%, which rises to 58% when five medicines are prescribed, increasing to 82% when seven or more medicines are prescribed.⁸

An awareness of which medicines are most likely to cause adverse drug reactions in patients is important, not only so they can be monitored appropriately, but also so patients can exercise informed consent.² Medicines that are commonly associated with adverse drug reactions because of their mode of action and/or frequency of use include:^{9, 6, 15–17}

- NSAIDs
- Diuretics
- ACE inhibitors

Avoiding prescribing cascades

When multiple medicines are prescribed the risk of a prescribing cascade ensuing is increased. This occurs when a clinician prescribes a medicine to a patient to treat an adverse effect that is caused by another medicine. Table 2 shows commonly prescribed medicines that are known to be involved in prescribing cascades. An example of a prescribing cascade

is the treatment of dizziness with prochlorperazine in patients taking antihypertensives. Prochlorperazine can cause further sedation and postural hypotension which exacerbates the patient's original symptoms and may result in other adverse effects such as falls.¹² The incidence of hip fracture in older patients has been shown to be increased by 50% following the initiation of prochlorperazine.¹³

Table 2: Examples of medicines known to increase the likelihood of a prescribing cascade occurring¹⁴

First medicine	Adverse drug reaction	Second medicine prescribed to treat adverse drug reaction
Digoxin, nitrates, loop diuretics, ACE inhibitors, oral corticosteroids, antibiotics, NSAIDs, opioids, methylxanthines, e.g. theophylline	Nausea	Antiemetic, e.g. metoclopramide
Antiepileptic medicines	Nausea	Antiemetic, e.g. metoclopramide
	Rash	Topical corticosteroids
Vasodilators, diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, NSAIDs, opioids, sedatives, statins	Dizziness	Prochlorperazine
Cholinesterase inhibitors, e.g. donepezil	Incontinence	Anticholinergics, e.g. oxybutynin
NSAIDs	Hypertension	Antihypertensives
	Gastrointestinal symptoms	Proton pump inhibitors
Aspirin	Gastrointestinal symptoms	Proton pump inhibitors
ACE inhibitors	Cough	Cough suppressants and/or antibiotics
Thiazide diuretics	Hyperuricaemia, gout	Allopurinol, NSAIDs, colchicine
Paroxetine, haloperidol	Tremor	Levodopa-carbidopa
Antipsychotics	Extrapyramidal adverse effects	Anticholinergics, levodopa

- Beta blockers
- Medicines that affect the central nervous system, e.g. antidepressants (particularly tricyclic antidepressants), antipsychotics, benzodiazepines, opioids and other analgesics
- Dihydropyridines, e.g. nifedipine
- Digoxin in doses over 250 micograms, daily
- Anticholinergics
- Phenothiazines, e.g. prochlorperazine

Long-term conditions associated with adverse drug reactions

Being able to identify patients, in whom serious adverse drug reactions are more likely to occur, allows for recommendations to be made so patients can reduce their risk of hospital admission, e.g. advising patients with chronic kidney disease (CKD) to temporarily withdraw potentially nephrotoxic treatment (e.g. furosemide) if they become acutely unwell with diarrhoea. This anticipatory planning can significantly reduce morbidity and could even be life-saving.

Conditions that are associated with an increased risk of recurrent adverse drug reactions include:¹¹

- CKD
- Diabetes with long-term complications
- Malignancy
- Liver disease
- Congestive heart failure
- Peripheral vascular disease

An Australian study followed over 28 500 patients aged over 60 years, who had been admitted to hospital for an adverse drug reaction. It was found that the likelihood of being readmitted for another adverse drug reaction in the next three years ranged from a 1.27 times increased risk for patients with peripheral vascular disease to a 1.91 times increased risk for patients with diabetes with long-term complications and a 1.93 times increased risk for patients with CKD.¹¹

Consider if a trial of treatment is appropriate

Initiating a medicine for a patient as a time-limited trial is a good way to set an expectation that treatment may not be needed indefinitely; making it easier to discuss dose adjustments or de-prescribing at a later date. For example, when considering the use of a PPI the patient could be offered a four to six week course of omeprazole 20 mg, daily, with the suggestion that the dose be reduced to omeprazole 10 mg, daily, or “as required”, if treatment is successful. Practice

nurses can assist in monitoring treatment efficacy by routinely asking patients about symptoms. It is also important when considering a trial of a medicine that clearly defined criteria for treatment success and failure be established before treatment is initiated. All medicines that are started as trials should be reviewed against the trial criteria, and stopped if the original goals of treatment are not being achieved.

Document the indications for each medicine

When an additional medicine is added to a patient’s treatment plan, the reason for making the treatment decision should also be recorded in the patient’s notes.² This makes it clear to other members of the primary care team why the patient is taking the medicine, while also suggesting when it would be appropriate to withdraw the medicine, i.e. if the indication for treatment resolves, or the balance of risk versus benefit changes. Writing the patient’s indication for treatment on the prescription, e.g. one a day for hypertension, is also a useful reminder for medicines that are indicated for more than one condition, e.g. beta-blockers.

Medicine reviews reduce problematic prescribing

Patients often take medicines for longer than required to gain the optimal benefit.² This is partially because prescriptions are often repeated, without clinical review. Medicine reviews ensure prescribers have all the relevant information available and promote care according to best practice, as evidence and treatment guidelines change. As many as one-third of patients may be taking medicines that the treating clinician is unaware of at the time of prescribing.²

It is important to recognise that some patients may not feel comfortable telling a health professional about all of their medicine use. A good rapport and direct questioning may be required for some patients to disclose the practice of medicine sharing. Surveys suggest that 13 – 20% of older patients share medicines with other people.¹⁵ If patients report sharing medicines, or receiving them from other people, it is recommended that the discussion about the risks of this practice be conducted in a non-judgemental way and recorded in the patient’s notes. A non-judgemental approach also increases the likelihood that a patient will report treatment non-adherence, e.g. not taking metformin due to diarrhoea, or the use of alternative therapies such as the use of Rongoā rākau (native fauna herbal preparations).

It can be difficult to find the time to perform a medicine review and it may be necessary to offer a dedicated consultation for

this purpose, although the cost of this may be prohibitive to some patients.² Pharmacists can improve the quality of medicine reviews as well as reducing the amount of work required for general practitioners (see: "Pharmacist assessments reduce polypharmacy", opposite). There are several levels of pharmacist involvement. Community pharmacists can provide medicine reconciliations and are well placed to tell if a patient is not picking up all the medicines they are being prescribed, as well as being more likely to know if a patient is taking OTC products. Clinical pharmacists can provide more specialised assistance and their role in medicine reviews in primary care is increasing.

How to perform a medicine review

Medicine reviews should be conducted systematically and involve the following steps:

1. Record all known medicine intolerances and previous treatment withdrawals
2. Ask the patient to bring all their medicines, including OTC and alternative products, to the consultation. Establish which ones are being taken, and list each medicine with the regimen, route of administration and size of the last dose.¹⁶
3. Discuss each medicine with the patient and the need for continued treatment; agreement with the patient should be reached via a shared-decision making approach. Frame this discussion as an attempt to optimise care and improve quality of life, otherwise the patient may feel abandoned by the withdrawal of treatments. A printed medicine datasheet (available from: www.nzf.org.nz) can be a useful aid for these discussions. Offering to dispose of unwanted medicines ensures that medicines are not stored and used inappropriately later.

A medicine review is also an opportunity to discuss any concerns the patient has with their care, including adherence to medicines.

Identifying patients likely to benefit from a medicine review

Periodic medicine reviews are recommended in patients who are at high-risk of problematic prescribing. This includes patients who are:²

- Taking ten or more medicines continuously
- Taking between four and nine medicines and have at least one criteria for potentially inappropriate prescribing (Table 3, over page)

- At risk of a recognised adverse drug interaction or have a clinical contraindication to a medicine
- Known to have problems taking medicines, including with adherence
- Receiving palliative care
- Known to have multiple prescribers managing their care, e.g. patients who attend several specialist clinics

Patients experiencing adverse effects of medicines

A medicine review is recommended when patients experience an adverse medicine reaction or interaction. Classic features of problematic prescribing include:¹⁷

- Dizziness
- Confusion
- Nausea
- Constipation
- Incontinence
- Falling

Following hospital discharge

It is useful to perform a medicine review after patients have been discharged from hospital as this is associated with an increased risk of prescribing errors occurring. General practitioners should be provided with a complete and accurate list of all the medicines that a patient is taking when they are discharged from hospital, along with the rationale for any changes in treatment. However, this does not always occur and summaries are not always accurate or complete. Over 80% of general practitioners surveyed in the United Kingdom reported that discharge summaries are either inaccurate or incomplete "all of the time" or "most of the time".² A New Zealand study of 100 consecutive general medical and general surgical patients found that there were on average 0.8 recording errors per surgical discharge summary and 1.42 recording errors per general medical discharge summary.¹⁸

Following discharge from hospital a medicine review may detect medicines that have been erroneously omitted, e.g. medicines that secondary care clinicians have decided are no longer providing benefit or are no longer necessary. Equally, general practitioners may identify medicines that were initiated in hospital which had previously been trialled and withdrawn in the community, e.g. oxybutynin for urinary incontinence in hospital, but managed successfully at home without medicines.


Medicine review at other times of transition of care is also useful, e.g. patients entering residential care or patients transferring to new practices or clinicians.

Summary: Practical tips to optimise prescribing

1. Adopt a systematic approach to new prescribing and always consider:
 - Are the patient's symptoms due to an adverse drug reaction?
 - What are the goals of treatment?
 - Is the patient likely to live long enough to receive a benefit from treatment?
 - Is the patient likely to receive a net benefit from treatment, and if so, what is the magnitude of this benefit?
 - Are there non-pharmacological treatments that can be considered instead of a medicine?
2. Be aware of medicines and conditions that are often associated with adverse drug reactions
3. Consider if a trial of treatment is appropriate and de-prescribe medicines if they are not as effective as expected
4. Do not assume that you know all of the medicines that a patient is taking - remember to ask about over-the-counter products, traditional medicines and home remedies
5. Always document the reasons for a treatment so they are clear for other health professionals
6. Perform periodic medicine reviews for patients at risk of problematic prescribing, especially patients taking ten or more medicines simultaneously, and in patients following hospital discharge
7. Always check prescriptions for errors before signing. Each prescription should:
 - Include the condition that the medicine is intended to treat
 - Provide specific instructions rather than "as required" or "take as directed"
 - Specify once or twice daily prescribing wherever possible
8. Consider seeking the assistance of a pharmacist for medicine reviews, helping to address patient adherence issues and creating medicine management plans

Pharmacist assessments reduce polypharmacy

In the Canterbury DHB, a Medication Management Service has been introduced that focuses on improving medicine adherence and patient knowledge about medicines. This involves an initial 30 – 45 minute consultation between the patient and a trained community pharmacist, with three quarterly follow-ups to check on progress and provide support (Medicine Use Reviews). The Medication Management Service does not involve a clinical medicine review.

 For further information see: www.ccnweb.org.nz

From September 2011 to August 2013, the Hawke's Bay DHB employed two half-time clinical pharmacist facilitators to work in each of the three general practices, specifically to reduce the amount of problematic prescribing in patients aged over 65 years. Comprehensive Medicine Therapy Assessments were performed by multidisciplinary teams; independently from the Medicine Use Reviews performed by community pharmacists.²⁰ The long-term goal was to encourage changes in prescribing practice through general practitioner education. General practitioners were involved in forming strategies and identifying patients for pharmacist focus.

In one practice 76 Medicine Therapy Assessments were performed resulting in over 500 recommendations, over three-quarters of which were accepted by general practitioners; 83 medicines were stopped in these patients.²⁰ Feedback from primary care health professionals was that:²⁰

- The advice provided was of high quality
- The workload of general practitioners was reduced
- Patient satisfaction was increased
- Working with the clinical pharmacist facilitator provided opportunities to learn
- The increased access to a clinical resource was appreciated

Over a one-year period the estimated savings in the cost of community pharmaceuticals from the Medicine Therapy Assessments programme was more than \$500 000, and 64 fewer falls were recorded in the community than in the previous year resulting in an estimated cost avoidance of almost \$150 000.²⁰

Table 3: Indicators of potentially unsafe prescribing, adapted from Avery *et al*, (2011)¹⁹ *

Category	Medicine/Patient	Rationale
Cardiovascular and respiratory disease	Beta-blocker (non-selective) in a patient with asthma	Risk of bronchoconstriction
	Digoxin > 125 micrograms, daily, to a patient with renal impairment, e.g. CKD stage three or worse	Risk of digoxin toxicity recognised by persistent nausea, with or without vomiting
	Diltiazem or verapamil in a patient with heart failure	Depression of cardiac function may cause heart failure symptoms to return
	Long-acting beta-2-agonist (LABA) inhaler in a patient with asthma who is not also taking an inhaled corticosteroid	The underlying cause of the asthma must be treated during LABA therapy (deaths have occurred)
	Aspirin > 75 mg, daily for ≥ one month in a patient aged over 65 years. N.B. in New Zealand the standard, fully subsidised dose is 100 mg	Risk of gastric perforation with other medicines that affect prostaglandin protective effect or increase the risk of bleeding
	Aspirin to a child aged ≤ age 16 years	Association of aspirin with Reye's syndrome when taken during a viral illness
Central nervous system	Benzodiazepine or zopiclone for ≥ 21 days	Risk of dependence and need for planned withdrawal programme. Dizziness, falls and impaired cognition are also known adverse effects of these medicines. CNS depression may worsen depressive illness in patients with pre-existing mental health conditions.
	Metoclopramide or prochlorperazine to a patient with Parkinson's disease	Likely to aggravate Parkinson's symptoms
Analgesics	NSAID in a patient with heart failure	Sodium and fluid retention may cause heart failure symptoms to return
	NSAID in a patient with renal impairment, e.g. CKD stage three or worse	NSAID effects on kidneys may worsen renal function
	NSAID (>28 days) (except for naproxen ≤ 1000 mg or ibuprofen ≤ 1200 mg daily) in a patient > 65 years	Risks to renal function, gastrointestinal tract and cardiovascular system are more likely to occur, and to have more significant consequences, in older people
	NSAID long-term without co-prescription of a gastro-protective medicine	Risk of peptic ulceration
	NSAID in combination with warfarin	If gastric perforation occurs, bleeding consequences will be more serious
Interactions and allergies	Penicillin or penicillin-type antibiotic to a patient with a history of sensitivity	Risk of allergy symptoms and anaphylaxis
	Potassium salt or potassium-sparing diuretic, (excluding aldosterone antagonists, e.g. spironolactone) to a patient who is also receiving an ACE inhibitor or angiotensin-II receptor blocker (ARB)	Risk of hyperkalaemia

Interactions and allergies (continued)	Verapamil to a patient who is also taking a beta-blocker, including using a beta-blocker eye-drop preparation	Cardiac depressant effects of verapamil and beta blockers are additive, with risk of bradycardia, hypotension, asystole and sinus arrest – use these together only if patient can be closely monitored when starting treatment
	Phosphodiesterase type-5 inhibitor (e.g. sildenafil) to a patient who is also receiving a nitrate or nicorandil	Additive effects lead to a significant risk of severe hypotension and possibly death
	Erythromycin or clarithromycin to a patient who is also taking simvastatin	Marked increase in simvastatin exposure – cases of rhabdomyolysis have been reported. Temporarily withhold simvastatin if a macrolide antibiotic is required.
Laboratory testing	Lithium without a serum lithium level being measured in previous six months	Lithium has a narrow therapeutic window, and its clearance is affected by renal function, hydration status, and use of NSAIDs and diuretics
	Warfarin without a recorded INR during previous 12 weeks	Risk of high INR and bleeding complications
	Methotrexate without a full blood count or liver function test being performed in previous one to three months	Methotrexate can be hepatotoxic, especially at higher doses or with prolonged therapy, and with hepatotoxic agents including alcohol. One to two standard drinks of alcohol once or twice a week is unlikely to cause a problem, however, drinking more than four standard drinks on one occasion should be strongly discouraged. Advise patients to be alert for any symptoms suggestive of methotrexate toxicity and to report these to their doctor without delay.
	Methotrexate with trimethoprim or co-trimoxazole	Trimethoprim and co-trimoxazole significantly increase the risk of bone marrow aplasia
	Amiodarone without a recorded liver and thyroid function test in previous six months	Amiodarone is associated with severe hepatotoxicity, and with hypo- or hyperthyroidism
	Initiation of an ACE inhibitor or ARB without renal function and electrolytes being measured prior	ACE inhibitors and ARB medicines can reduce renal perfusion and cause potassium to be retained in the body leading to hyperkalaemia
Women's health	Combined hormonal contraceptive in a female with a history of venous or arterial thromboembolism	Risk of recurrence of thromboembolism increased
	Combined hormonal contraceptive to a woman with body mass index ≥ 40	Risk of thromboembolism increased
	Oral or transdermal oestrogens to a woman with a history of breast cancer	Breast cancer may reoccur
	Oral or transdermal oestrogen without progesterone for greater than one year in a woman with an intact uterus	Progesterone reduces the risk of endometrial cancer developing

* Indicators were compiled from a variety of sources including Beers criteria, British National Formulary, Medication Appropriateness Index, PINCER trial indicators, Quality and Outcomes Framework and STOPP/START criteria

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