# The prescribing cascade

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## Summary

**A prescribing cascade occurs when a new medicine is prescribed to 'treat' an adverse reaction to another drug in the mistaken belief that a new medical condition requiring treatment has developed. Adverse outcomes associated with prescribing cascades can result when the second drug increases the severity of the adverse reaction to the first drug or when the second drug places the patient at risk of additional adverse drug reactions. The factors that are associated with an increased likelihood of an adverse drug reaction may also lead to prescribing cascades. The elderly, those using multiple medicines, women, and people using high risk medicines are more likely to get adverse drug reactions. The key to preventing prescribing cascades lies in the avoidance and early detection of adverse drug reactions and an increased awareness and recognition of the potential for adverse reactions.**

## In this issue…

This year's top ten drug lists show that thousands of Australians are taking drugs to lower cholesterol. Jane Smith thinks there may be some inappropriate prescribing which may lead to unnecessary adverse effects.

All medicines can cause adverse effects. Sometimes another drug is prescribed to treat these adverse effects and this could result in a prescribing cascade, according to Lisa Kalisch and colleagues. One way to manage a prescribing cascade is to 'deprescribe', and David Le Couteur and his co-authors advise us how to do this.

The new drugs for osteoporosis reviewed by Peter Ebeling have a range of adverse effects. Whether these drugs have long-term advantages over oral bisphosphonates is not yet known.

Key words: adverse effects, polypharmacy.

*(Aust Prescr 2011;34:162–6)*

## Introduction

Adverse events associated with medicines are common and place a significant burden on the healthcare system in terms of both health outcomes and cost. It is estimated that 10% of patients visiting general practices will have had an adverse drug event in the previous six months.[1] This affects more than 1.5 million people per year[2] and results in at least 190 000 hospital admissions annually.[3] Adverse drug events include errors in the way the medicine is used, and adverse drug reactions that result from the pharmacological properties of the drug itself, either alone or in combination with other medicines. Recognising and preventing all types of adverse drug events is therefore a high priority. Failure to recognise an adverse drug reaction has the potential to further compound poor health, particularly when the reaction is mistaken for a symptom of a new health problem. If this is subsequently treated with another drug a prescribing cascade results. This can make the original adverse drug reaction even more difficult to recognise and puts the patient at further risk of adverse reactions.

## What is a prescribing cascade?

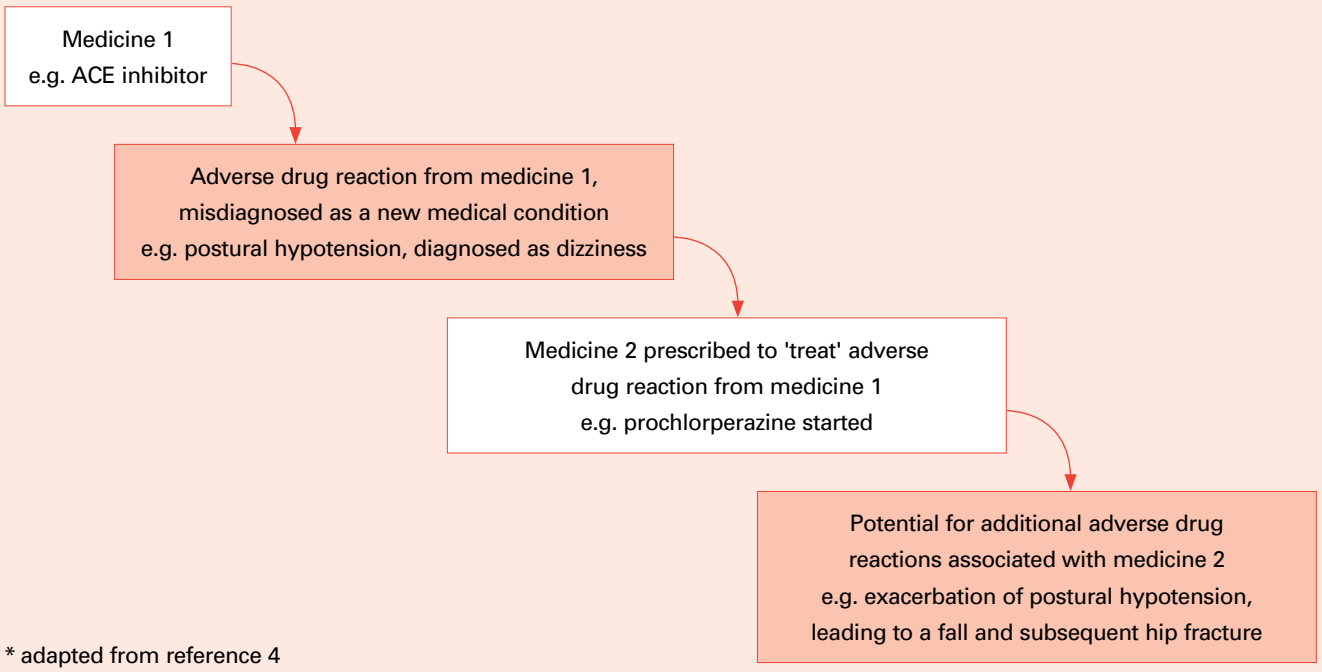
A prescribing cascade occurs when a new medicine is prescribed to 'treat' an adverse drug reaction associated with another medicine, in the mistaken belief that a new medical condition requiring treatment is present (Fig. 1).[4] Prescribing cascades may also occur when an adverse drug reaction is anticipated. An example is the prescription of a proton pump inhibitor to reduce gastrointestinal adverse effects associated with non-steroidal anti-inflammatory drugs (NSAIDs). Prescribing cascades resulting from both unrecognised and recognised adverse reactions put the patient at further risk of harm.

## Drugs commonly involved in prescribing cascades

Many frequently prescribed drugs have been implicated in prescribing cascades. They include drugs for dementia, antihypertensives, sedatives, opioids, NSAIDs, antiepileptics,

*Fig. 1*

**The prescribing cascade** *




* adapted from reference 4

antibiotics, and medicines for nausea. Table 1 shows some of the prescribing cascades reported with these medicines. The cascades include the prescription of prochlorperazine to counteract drug-induced dizziness, antihypertensives to treat NSAID-induced hypertension and levodopa to manage metoclopramide-induced movement disorder. Many other medicines may be involved in prescribing cascades, but many adverse drug reactions go unrecognised and unreported.

## Potential for harm

Prescribing cascades can exacerbate the harmful effects of an unrecognised adverse drug reaction. A study conducted in Australian veterans found an increased rate of prochlorperazine prescription following the prescription of drugs which cause dizziness, such as antihypertensives.[5] Prochlorperazine itself is associated with postural hypotension which may exacerbate any hypotensive effect. This may account for the increased rate of hospitalisation for hip fracture which was observed after patients started prochlorperazine.[5] Although the absolute risk of hip fracture was small, the relative risk of having a hip fracture after starting prochlorperazine increased by nearly 50%.[5] Hip fracture is associated with increased morbidity and mortality,[6] highlighting the potential for serious harm associated with this prescribing cascade.

A published report illustrates the potential for harm arising from a prescribing cascade, involving an antihypertensive drug.[7] An elderly woman developed a cough, which was not recognised as being caused by the ACE inhibitor she was taking, so she was given a codeine-based cough suppressant. When the cough persisted an antibiotic was started. The prescribing cascade went further, when the antibiotic caused *Clostridium difficile* diarrhoea. This prescribing cascade culminated in the patient being hospitalised for delirium and severe diarrhoea.[7]

## What are the contributing factors?

Although factors specifically contributing to prescribing cascades have not been studied, the factors which are associated with adverse drug reactions, that may lead to prescribing cascades, are well known.

The elderly, those using multiple medicines, women, and people using 'high risk medicines', including cardiovascular drugs, NSAIDs, anticoagulants and antibiotics, are at higher risk of adverse drug reactions.[1,8,9]

In the elderly, specific drug classes – anticholinergics, antipsychotics, benzodiazepines, hypnotics and sedatives – increase the risk of adverse drug reactions.[9] Elderly people may be at higher risk of prescribing cascades than younger people because the adverse drug reaction is more likely to be misinterpreted as the onset of a new medical condition.[4] For example, a movement disorder induced by metoclopramide may be misinterpreted as Parkinson's disease, but this misinterpretation would be less likely in a young person as Parkinson's disease is less prevalent in younger people.[4]

Patients are at the highest risk of having an adverse drug reaction soon after starting a medicine. Approximately 90%

*Table 1*

**Medicines implicated in the prescribing cascade**

| Medicine | | Adverse drug reaction | | Second medicine prescribed to treat adverse drug reaction of first medicine |
|---|---|---|---|---|
| Cholinesterase inhibitor[17] | → | Incontinence | → | Anticholinergics (e.g. oxybutynin) |
| Vasodilators, diuretics, beta blockers, calcium channel blockers, ACE inhibitors, NSAIDs, opioid analgesics, sedatives, statins[5] | → | Dizziness | → | Prochlorperazine |
| NSAIDs[4] | → | Hypertension | → | Antihypertensives |
| Thiazide diuretics[4] | → | Hyperuricaemia, gout | → | Allopurinol or colchicine |
| Metoclopramide[4] | → | Movement disorder | → | Levodopa |
| ACE inhibitor[7,18] | → | Cough | → | Cough suppressant and/or antibiotic |
| Paroxetine, haloperidol[19] | → | Tremor | → | Levodopa-carbidopa |
| Erythromycin[20] | → | Arrhythmia | → | Antiarrhythmics |
| Antiepileptic medicines[21] | → | Rash | → | Topical corticosteroids |
| Antiepileptic medicines[21] | → | Nausea | → | Metoclopramide, domperidone |
| Digoxin, nitrates, loop diuretics, ACE inhibitors, oral corticosteroids, antibiotics, NSAIDs, opioid analgesics, methylxanthines (e.g. theophylline)[22] | → | Nausea | → | Metoclopramide |
| Antipsychotics[23] | → | Extrapyramidal adverse effects | → | Levodopa, anticholinergics |

NSAIDs non-steroidal anti-inflammatory drugs ACE angiotensin converting enzyme

of patients who experience an adverse drug reaction report it within four months of starting a new drug, with 75% of these patients experiencing the adverse drug reaction within one month.[10] Many adverse drug reactions are dose related, and starting therapy at high doses is associated with an increased risk of adverse drug reactions in the elderly.[11] Adverse drug reactions may also occur following dose increases.

Patients may not tell their doctor or pharmacist when they experience an adverse drug reaction. Approximately 15% of patients will stop treatment because of an adverse drug reaction without advising their doctor.[12] A quarter of patients report that they are not provided with information about the potential adverse effects of their medicine,[13] meaning that they do not have the knowledge or awareness to identify adverse drug reactions. Poor communication between health professionals and patients increases the risk of adverse drug reactions,[9] so multiple care providers may contribute to the prescribing cascade. With the increase in non-medical prescribing, effective communication and reconciliation of all of the medicines prescribed by the different health professionals caring for a patient is important to avoid the prescribing cascade. The interface between hospital and community care is also a high risk area if timely handover does not occur.

## Preventing the prescribing cascade

Quality use of medicines is the judicious selection of management options, appropriate choice of medicines when a medicine is considered necessary, and safe and effective use

of medicines. These principles can be applied in preventing the prescribing cascade (see Box).

Adverse drug reactions precipitate the prescribing cascade, so the key to preventing prescribing cascades is the avoidance and early detection of adverse drug reactions. Since many adverse drug reactions in the elderly are dose related, starting treatment at low doses and titrating to effect will reduce the risk of adverse drug reactions. Most adverse drug reactions occur within a few months of starting a medicine, so health professionals should consider the potential for an adverse drug reaction to be the cause of any new symptoms, particularly if a drug has been recently started or changed. Health professionals should remember to ask patients about new symptoms, because many patients do not report adverse drug reactions.

When drug reactions occur, non-drug treatment strategies are likely to be the most appropriate first-line management, rather than starting a second medicine to counteract adverse effects. Reducing the dose of the medicine causing the adverse drug reaction is appropriate if the reaction is dose related. Trying a different drug with a similar effect, but less risk of causing the adverse drug reaction, may be another way to avoid the prescribing cascade. For example, a patient using metoclopramide for the relief of nausea and vomiting who develops extrapyramidal adverse effects, could be changed to domperidone therapy, with reduced risk of movement disorder. Reconsidering the need for the medicine causing the adverse drug reaction is also an appropriate management strategy. If the risks associated with continuing to use the medicine outweigh the benefits, then stopping it may be appropriate. The decision to prescribe a second medicine to counteract an adverse drug reaction from a first medicine should only occur after careful consideration. The benefits of continuing therapy with the first medicine must outweigh the risks of additional adverse drug reactions from the second medicine.

Patients should be provided with the skills and information they need to help them identify adverse drug reactions to avoid prescribing cascades. This includes information that outlines the drug's possible adverse effects and what to do when adverse drug reactions occur. This information is available in Consumer Medicines Information and should be provided to patients whenever a medicine is started or the dose changed. Home medicines reviews should also be considered for patients who are at risk of adverse drug reactions, and therefore at risk of prescribing cascades. These reviews increase the identification and resolution of medicine-related problems,[14] and reduce medicine-related hospitalisations.[15,16]

## Conclusion

Prescribing cascades have the potential to result in serious harm to patients. Prescribers need to be mindful of the potential for drugs to cause adverse events, particularly in the elderly or patients using medicines commonly associated with adverse drug reactions. An increased awareness and recognition of the potential for adverse drug reactions to lead to prescribing cascades is required. Home medicines reviews should also be considered for those patients at risk of prescribing cascades.

*Box*

**Preventing a prescribing cascade**

Begin new medicines at low doses and tailor the dose to reduce the risk of adverse reactions

Consider the potential for any new symptoms to be caused by an adverse reaction, particularly if a medicine has been recently started or the dose changed

Ask patients if they have experienced any new symptoms, particularly if a medicine has been recently started or the dose changed

Provide patients with information about possible adverse effects of medicines and what to do when adverse drug reactions occur, e.g. in the form of Consumer Medicines Information

The decision to prescribe a second medicine to counteract an adverse drug reaction from a first medicine should only occur after careful consideration, and where the benefits of continuing therapy with the first medicine outweigh the risks of additional adverse reactions from the second medicine

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*Conflict of interest: none declared*

# Letters

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. Letters are usually published together with their responses or comments in the same issue. The Editorial Executive Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. The Committee's decision on publication is final.

## Hyperferritinaemia without positive HFE gene mutation

Editor, – I read the article about testing for HFE-related haemochromatosis with interest (Aust Prescr 2011;34:73-6). Over the last 10 years I have ordered ferritin tests in over 1211 individual patients – 229 of them were found to have abnormally elevated ferritin levels. Haemochromatosis gene testing was ordered for 120 of them and there were 47 positive results. This means a significant cohort of patients with elevated ferritin do not have a positively identified mutation. My casual observation seems to give the impression that a significant number of these patients are Asian people.

Anecdotally, diabetes and lipid control in many of these patients improved when they started donating blood regularly.

My hypothesis is that:

- there are more genotypes yet to be discovered which are responsible for elevated ferritin levels in Asian people
- this (undetected and untreated) elevated ferritin may deposit in the pancreas and liver, and to some extent contributes to the high rate of diabetes and fatty livers that are so prevalent in Asian people.

Unfortunately, this is just a hunch and I do not have the detailed breakdown of these tests.

Chenault Doug Lee
General practitioner
Erindale Medical Practice, ACT