Discontinuation of medications - Deprescribing

Learning objectives:
After completing this activity, pharmacists should be able to:
1. Describe deprescribing principles
2. Prioritise and plan a deprescribing regimen
3. Identify the risks associated with deprescribing
4. Counsel patients on the management of rebound symptoms

The 2010 Competency Standards addressed by this activity include (but may not be limited to): 4.1, 4.2, 6.1, 6.2, 7.1, 7.2.

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Debbie is the Chair of the Australian Association of Consultant Pharmacy (AACP) Board and member of the National Advisory Group of AACP, as well as a Director of the National Prescribing Service (NPS) Board. Debbie is also a Fellow of PSA and the American Society of Consultant Pharmacists (ASCP). Academic appointments include Adjunct Senior Lecturer at University of Queensland and James Cook University. She is also on the Australian & New Zealand Continence Journal Editorial Committee.

Debbie has a special interest in geriatric pharmacotherapy and chronic disease self-management, regularly conducts medication review services as an accredited pharmacist and provides many presentations to pharmacists, nurses, general practitioners, allied health professionals and consumers.

In 2001 Debbie was awarded the PSA Australian Pharmacist of the Year, in 2002 the PSA Qld Bowl of Hygeia and in 2008 was the inaugural recipient of the AACP Consultant Pharmacist Award.

Successful completion of this activity is demonstrated by answering five of the six multiple choice questions correctly.
Introduction
Deprescribing or ceasing unnecessary or harmful medications is an important component of quality use of medicines. An individual approach is needed taking into account the best available evidence, balancing the benefits and risks, patient’s signs and symptoms as well as the patient’s preferences.

French physician and psychiatrist Philippe Pinel stated:

“...in disease of the mind, as well as in all other ailments, it is an art of no little importance to administer medicines properly; but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them”.

Quality use of medicines
Quality use of medicines is one of the four objectives of the National Medicines Policy. To achieve optimum outcomes for consumers, use of medicines must be safe, effective, appropriate and judicious.

Quality use of medicines involves selecting management options wisely, choosing suitable medicines if a medicine is considered necessary, and using medicines safely and effectively.

The World Health Organization defines rational use of drugs as: ¹

When a drug is required, the appropriate drug must be prescribed, it must be available at the right time at a price people can afford, and it must be dispensed correctly. It must be taken in the right dose at the right intervals and for the right length of time. The appropriate drug must be effective, and of acceptable quality and safety. If any of the requirements in this definition are not met the best possible treatment is not being achieved.

There is considerable evidence of inappropriate prescribing in older people and that patient outcomes and quality of life may be enhanced through deprescribing.

Many medications are only intended for short-term use, and continued indefinitely from lack of regular medication review and poor patient health literacy. Classic examples of short-term prescribing include the use of benzodiazepines, NSAIDs, clopidogrel after stent insertion, and proton pump inhibitors (PPIs).

Discontinuation of unnecessary medications can reduce the risk of preventable adverse drug events. In addition, the ongoing benefit of specific drugs must be considered in the medical and social context of the patient.

Pharmacists should consider the need for optimisation of medication regimens during dispensing as well as when conducting professional services such as Medicine Use Reviews (MedsCheck), Home Medicine Reviews (HMRs) and Residential Medication Management Reviews (RMMRs). This rationalisation of therapy through a shared decision making process with the consumer may lead to recommendations for the discontinuation of some medications.

During the medication review process and discussion with the patient and their carers, pharmacists should consider goals of care, treatment targets and the potential risks and benefits of medications, as
well as the patient’s remaining life expectancy and quality of life. The time until benefit also needs to be carefully considered in view of the best available evidence.

**Polypharmacy**
Polypharmacy increases the risk of adverse drug effects and may lead to poor patient outcomes. Older people are often prescribed multiple medications to manage multiple chronic conditions. Recent surveys conducted by NPS: Better choices, Better health have shown that majority (87.1%) of Australians aged 50 years and older take one or more medicines, with almost half (43.3%) taking five or more. Complementary medicines are used by 46.3% of participants used in the past day, and 87.4% of these participants used both conventional and complementary medicines.

More than 1.5 million people are affected by an adverse reaction to a medicine each year in Australia, and this results in at least 190,000 hospital admissions annually. Australian studies have demonstrated that 2 to 4% of all hospital admissions, and up to 30% for patients >75 years of age, are medication-related; and up to three-quarters are potentially preventable.

A literature review by the NPS found that around 6% of hospital admissions in Australia are associated with adverse drug events, with almost one third of admissions for the elderly associated with adverse events.

In the Australian veterans’ population more than one-quarter (25.7%) had at least one potentially preventable medication-related hospitalisation during a five-year study period of 2004-2008; and 6.6% veterans had two or more potentially preventable admissions.

NPS research has shown that 19% of medicine users reported experiencing a problem with their medicines in the past year.

**Prescribing cascade**
A ‘prescribing cascade’ occurs when a new medicine is prescribed to ‘treat’ side effects to another medicine in the mistaken belief that a new medical condition has developed.

Medication review and clinical interventions may reveal this prescribing cascade, where one drug is prescribed to control the side effects of another.

Examples of this include:
- High dose thiazide leading to gout and prescription of allopurinol or colchicine;
- Extrapyramidal side effects from metoclopramide and treatment with levodopa;
- PPI to reduce the gastrointestinal adverse effects associated with NSAIDs;
- Oxybutynin to manage urinary incontinence caused by cholinesterase inhibitors;
- Levodopa to manage metoclopramide-induced movement disorder; and
- Antihypertensive to treat NSAID-induced hypertension.
**Discriminatory prescribing**

Stopping prescriptions for medicines that patients no longer need is an important part of good prescribing.10 “Unnecessary drug therapy” is one of the 8 medication-related problems first defined by Linda Strand et al in 1990 at the start of pharmaceutical care model.11 Clinical interventions performed by community pharmacists with the purpose of preventing or addressing medication-related problems can be classified under the DOCUMENT system.

The absence of a clear therapeutic rationale and patient benefit can have unintended consequences, including medication-related hospital admissions, preventable adverse effects and cost implications. Discontinuing medications can simplify medication regimens, reduce polypharmacy and the medication burden, reduce the risk of drug interactions, as well as decreasing costs. For many conditions such as depression, generalised seizures or menopause, therapy discontinuation may be appropriate after a specified period.

In the older person and patients in end-of-life care, medicines should be limited to those that are likely to provide benefit, balancing the burden of disease with the burden of medication. Consideration should be given to stopping medications that would not reasonably be expected to give a benefit within the reasonable expectations of a person’s lifespan.12

Pharmacists need to recognise that in older patients with multiple chronic diseases, quality of life is the most relevant outcome; whereas, in younger patients life extension is an important aim of treatment.

Deprescribing should be considered in the following situations:12,13,14.

- Polypharmacy
- High-risk drugs in the older person
- Adverse drug reactions and drug interactions
- Lack of effectiveness
- Diminished benefit
- Falls
- Indications of shortened life expectancy
- Terminal illness, dementia or frailty

There are also good rationales for back-titration of medication dosages in older people.15

**Shifting evidence in primary prevention**

As evidence accumulates through research, guidelines for the primary prevention of diseases may change. This may warrant cessation of medicines previously thought to provide benefit in preventive health care. Recent examples are the shift for the use of aspirin and statin in primary prevention of cardiovascular disease.

The benefit to risk ratio for aspirin therapy among patients with no prior cardiovascular disease needs to be carefully weighed because aspirin increases the risk of bleeding (GI bleeding and, more rarely, haemorrhagic stroke). In a meta-analysis of 9 RCTs with at least 1000 participants each, the authors concluded:16

Despite important reductions in nonfatal MI, aspirin prophylaxis in people without prior CVD does not lead to reductions in either cardiovascular death or cancer.

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mortality. Because the benefits are further offset by clinically important bleeding events, routine use of aspirin for primary prevention is not warranted and treatment decisions need to be considered on a case-by-case basis.

The U.S. Preventive Services Task Force recommends use aspirin in women 55 to 79 years of age, when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal haemorrhage. In men 45 to 79 years of age, aspirin is used when the potential benefit of a reduction in myocardial infarction outweighs the potential harm of increase in gastrointestinal haemorrhage.\(^{17}\)

In contrast, individuals with a history of cardiovascular events who stop taking low dose aspirin are at increased risk of non-fatal myocardial infarction compared with those who continue treatment.\(^{18}\)

Recent evidence does not support prescribing statins in primary prevention in patients with low cardiovascular risk.\(^{19}\) Current data support only a modest mortality benefit for statin primary prevention when assessed in the short term (>5 years).\(^{20}\) Statins for primary prevention are more likely to benefit patients with intermediate to high life-time risk of developing coronary heart disease.

**Medication withdrawal**

Discontinuation is often done empirically, not guided by controlled studies. Hence the only evidence may be case reports of adverse outcomes of discontinuation. However there are a number of published trials on the outcomes of discontinuation of medications.\(^{21}\)

A systematic review of 31 clinical trials in older people (≥65 years) showed adverse events from medication withdrawal was infrequently encountered.\(^{22}\) Between 20% and 100% of patients can be withdrawn from their medications from periods of 4 to 52 weeks without clinically significant adverse effects or withdrawal symptoms.\(^{22}\) After withdrawal of antihypertensive therapy, many patients (20-85%) remained normotensive and did not require therapy for between 6 months and 5 years, with no increase in mortality.\(^{22}\) Thiazide diuretics were stopped in between 51% and 100% of patients for a period of 6-52 weeks, with no withdrawal syndromes observed.\(^{22}\)

Evaluations of the use of medications in 190 geriatric patients led to discontinuation of 322 drugs in 119 patients (63%) (average 2.8 drugs per patient) with no significant adverse effects after 12 months.\(^{23}\) Drugs discontinued with no adverse effects included NSAIDs, analgesics, statins, oral hypoglycaemics, carbamazepine and digoxin. Discontinuation of H\(_2\) blockers did not cause upper gastrointestinal symptoms in 94% of patients. Discontinuing antihypertensive drugs did not cause an increase in blood pressure in 82% of patients.

The authors of this study concluded that in this sub-population the well accepted guideline of “start low, go slow”, should be changed to “stop most, reduce dose”.

In another study of elderly outpatients 60% had therapy with 1 or more medications discontinued successfully.\(^{24}\) For 124 patients a total of 238 medications (1.92 per patient) were discontinued. The reasons for discontinuing use included patient compliance, patient at risk or experiencing an ADR, no indication, or chronic medical condition stable.

The Australian national blood pressure study demonstrated that 37% of participants remained normotensive one year after drug withdrawal.\(^{25}\) Indicators for patients who may successfully stop taking their antihypertensive drugs include:...
Younger age (65-74 years)  
Relatively low on-treatment systolic blood pressure  
Higher waist:hip ratio (dietary interventions more likely to be effective)  
Single drug treatment

Patients most likely to have maintained normal blood pressure were aged under 75, with blood pressure well controlled by treatment with one drug. The authors cautioned that discontinuation should only be trialed in patients without cardiovascular disease or comorbidity for which the treatment is also needed.

PPI rebound

The NPS Prescribing Practice Review 45: Proton pump inhibitors: step-down to symptom control recommends stopping PPI therapy when appropriate (or using PPIs for the shortest time and at the lowest effective dose) as the benefit can be preserved and the risk of serious adverse effects reduced.26

Systematic review of rebound acid hypersecretion after discontinuation of proton pump inhibitors found contradictory results.27 Five studies (including four randomized studies) did not find any evidence of rebound acid hypersecretion, whilst 3 studies suggested that rebound acid hypersecretion may occur in H. pylori-negatives after 8 weeks of PPIs.

In a double-blind randomised controlled trial (RCT) of 120 healthy volunteers with no history of heartburn or dyspepsia, participants received either 12 weeks placebo or 8 weeks esomeprazole (40mg daily) followed by 4 weeks placebo.28 During the weeks 9 to 12, participants assigned the PPI therapy reported more symptoms of reflux, suggesting a rebound effect.

Pharmacists need to provide advice for patients to manage possible rebound symptoms:

- Warn about possible rebound effects  
- Taper dose reduction  
- Manage with antacids

End of life issues

Prioritisation and discontinuation of medications becomes important when a patient approaches the end of life and goals that were previously curative become palliative.29

At end of life, patients often continue to take medications that no longer provide clinical benefits based on the patient’s remaining life expectancy and the medication’s expected time until benefit.30

Holmes et al described a model for appropriate prescribing for patients late in life as a delicate balance between remaining life expectancy, time until benefit, goals of care and treatment targets.31 They suggested that efforts should be made to discontinue use of medications identified according to these components as inappropriate for patients late in life.

Discontinuation benefits

The evidence for benefits of medication withdrawal has been shown mainly in trials with psychotropic medications.22

Withdrawal of psychotropic medications is associated with a reduction in falls and improved cognition.22 Benzodiazepine withdrawal is often associated with an improvement in daily function and with improvements in several cognitive and psychomotor tasks.22 Benzodiazepines must be weaned over a period of several weeks.
For many chronic diseases with maintenance therapies, persistence of benefit may be present after stopping the medication. The FLEX study showed that after 5 years of treatment, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk.\textsuperscript{32}

The benefits of statins may continue long after discontinuation. Data from a long-term follow-up of patients in the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm (ASCOT-LLA) indicates a continuing mortality benefit in those assigned to statin. Eight years after the trial officially stopped, results showed that treatment with atorvastatin 10mg reduced all-cause mortality by 14\% compared with placebo, mainly through a reduction in noncardiovascular deaths.\textsuperscript{33}

**Discontinuation risks**

Many medications can be successfully stopped without causing any adverse effects or withdrawal effect. However, in some situations cessation of medicines may lead to recurrence or worsening of the condition. Stopping some medications may be associated with significant withdrawal syndromes e.g. opioids, β-blockers, levodopa and corticosteroids.

Some medications may be associated with rapid symptomatic decline if stopped and therefore need a stepwise withdrawal after careful consideration of the expected benefits and harms of discontinuation.\textsuperscript{12}

- ACE inhibitors in heart failure
- Diuretics in heart failure
- Steroids
- Drugs for heart rate or rhythm (e.g. β-blockers, digoxin)

The 2 most common classes associated with adverse drug withdrawal events are cardiovascular and CNS drugs.\textsuperscript{24} Psychotropic and anti-epilepsy drugs need to be slowly tapered over several weeks to avoid withdrawal effects.

**Psychotropic medications**

Therapeutic Guidelines provides the following information on discontinuation of treatment on psychotropic medications:\textsuperscript{34}

- After the discontinuation of antipsychotics, a number of nonspecific symptoms can follow for several weeks, eg nausea, vomiting, restlessness and mild flu-like symptoms. A cholinergic discontinuation syndrome (hypersalivation, coryza, abdominal cramping, diarrhoea, sleep disturbance) may follow cessation of antipsychotic drugs that have significant anticholinergic effects.
- Cessation of tricyclic antidepressants (TCAs) can result in symptoms of cholinergic discontinuation syndrome, insomnia, increased dreaming and daytime agitation. Cessation of the other antidepressants, except fluoxetine, moclobemide and reboxetine, can cause flu-like symptoms, paraesthesiae, anxiety, agitation, tremor and electric shock–like sensations.
- Seizures may occur with rapid discontinuation of antiepileptics used as mood stabilisers.
- Benzodiazepine discontinuation syndrome is highly variable. Common symptoms include anxiety, insomnia, irritability, palpitations, hallucinations and sensory disturbances. Abrupt discontinuation in patients taking high doses may be accompanied by seizures.
Cardiovascular medications
Alpha-blockers such as prazosin may cause rebound hypertension and agitation with sudden cessation. Similarly beta-blockers can cause rebound tachycardia, palpitations and a re-emergence of angina. These medications should be reduced gradually, monitoring for symptoms.

Sudden withdrawal of nitrates may lead to re-emergence of angina symptoms; so gradual tapering is advised.

In patients with heart failure, a reduction and cessation of frusemide may precipitate an exacerbation of heart failure.

Discontinuation steps
Deprescribing usually involves stepwise tapering of a dose to determine whether symptoms, conditions, or risks can be managed using a lower dose or whether the medications can be discontinued.14

Australian geriatrician Michael Woodward described 4 distinct steps associated with discontinuing medications:35
- Recognizing an indication for discontinuing a medication
- Identifying and prioritising the medication(s) to be targeted for discontinuation
- Discontinuing the medication along with proper planning, communication and coordination
- Monitoring the patient for beneficial or harmful effects.
Communication
Once a medication is initiated, especially if the patient was told to take the medication ‘for the rest of their life’, it may be difficult to stop.

Patients and family resistance to change can be a significant barrier. Medical practitioners may be reluctant to cease a medication commenced by another prescriber, especially specialists. Pharmacists can assist by providing evidence of potential benefit through shared-decision making. HMRs and RMMRs can provide information on how to taper or discontinue a medication.

Shared decision making is particularly important in areas with greater uncertainty or risk. It is important that patients and their carers are including in the stopping process.

Summary
The process of rationally discontinuing medications is an integral part of a pharmacist role, not just during comprehensive medication reviews. The ongoing benefit of medicines needs to be considered in a clinical and social context. Ceasing medications that do not confer a therapeutic benefit or when the balance of risks and benefits shifts is an important component of quality use of medicines.
There is sufficient evidence to suggest that ceasing medications in certain patient populations does not worsen outcomes, decreases the risk of adverse drug reactions, and reduces costs attributable to medications. Education and strategies to improve discontinuation of medications should be integrated into dispensing and medication review practice.

Consistent with patient-centred care, the patient and the carer should be fully informed of the discontinuation process, including follow-up.
MCQs

1. Clues that deprescribing might be useful include:
   a. Falls in older people
   b. Five or more medications
   c. Changes in treatment goals due to frailty
   d. All of the above

2. Some medications require gradually weaning when the decision is made to cease. Which of the following medications requires gradual tapering after long-term use?
   a. Beta-blockers
   b. Alpha-blockers
   c. Levodopa
   d. All of the above

3. Which of the following statements is incorrect?
   a. Sudden cessation of long-term benzodiazepines may cause hallucinations
   b. Withdrawal of beta-blockers may cause rebound hypertension
   c. Rapid discontinuation of antiepileptics used as mood stabilisers may cause seizures
   d. Cholinergic rebound with GI disturbances and headache can occur when ceasing tricyclic antidepressants

4. In a patient at the end of life, which of the following considerations is most significant when considering the need to continue treatment?
   a. Safety, efficacy and time to benefit
   b. Cost of medications
   c. Number of medications
   d. Duration of therapy

5. Which of the following scenarios best describes a prescribing cascade?
   a. Prochlorperazine for drug-induced dizziness
   b. Calcium and vitamin D for osteoporosis
   c. Allopurinol for gout
   d. Folic acid with methotrexate

6. Which of the following statements regarding the use of aspirin in persons aged 55 to 79 years of age for primary prevention of cardiovascular disease is most appropriate?
   a. Use aspirin in men when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal haemorrhage
   b. Use aspirin in women when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal haemorrhage
   c. Use aspirin in women when the potential benefit of a reduction in myocardial infarction outweighs the potential harm of increase in gastrointestinal haemorrhage
References


or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA. 2006;296(24):2927-38.

