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Best Practice

www.bpac.org.nz

Issue 64 October 2014

Polypharmacy: Managing a clinical conundrum

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ACKNOWLEDGEMENT
We would like to acknowledge the following people for their guidance and expertise in developing this edition:
Dr Emma Best, Auckland
Dr Brent Caldwell, Wellington
Dr Marewa Glover, Auckland
Dr Carl Hanger, Christchurch
Associate Professor Andrew Harrison, Wellington
Dr Rosemary Ikram, Christchurch
Dr Peter Jones, Wellington
Dr Jeremy McMinn, Wellington
Dr Hayden McRobbie, Auckland
Dr Diana Purvis, Auckland
Dr Christine Roke, Auckland
Associate Professor Mark Thomas, Auckland
Dr Arlo Upton, Auckland

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Best Practice

Issue 64 October 2014

Best Practice Journal (BPJ)
ISSN 1177-5645 (Print)
ISSN 2253-1947 (Online)

BPJ is published and owned by bpac^{nz} Ltd
Level 8, 10 George Street, Dunedin, New Zealand.

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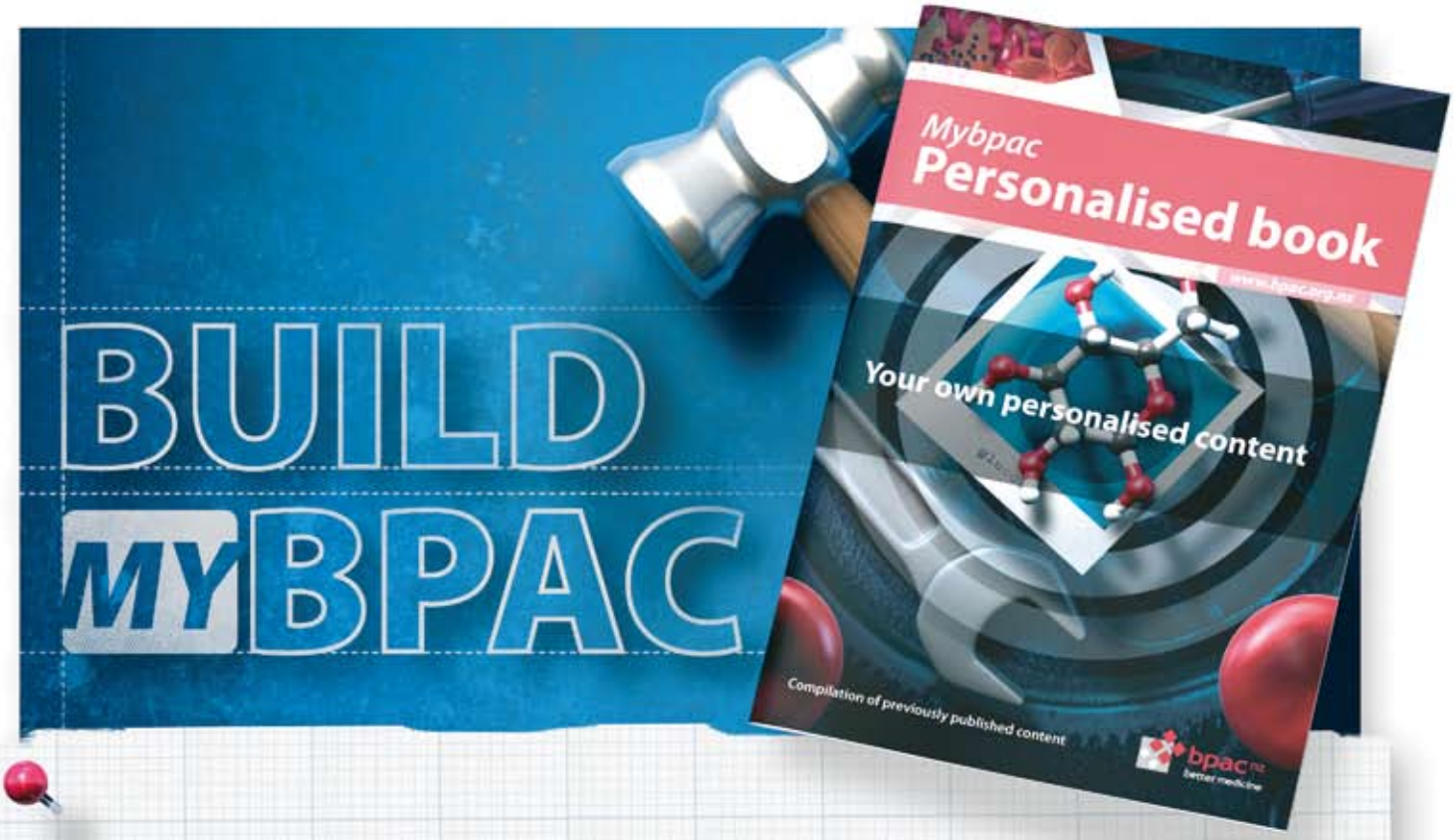

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Polypharmacy in primary care:

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**

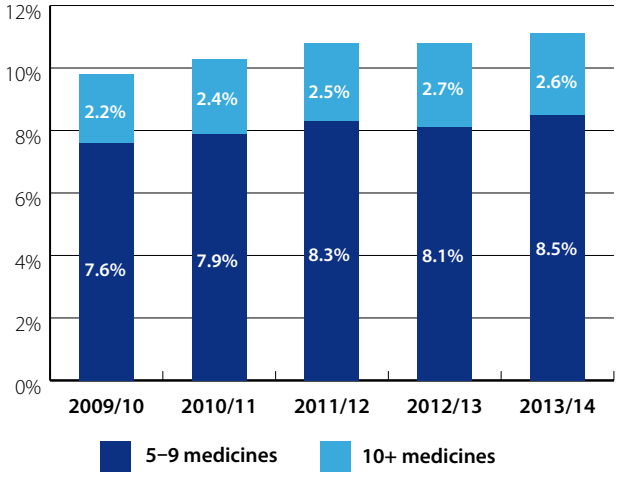

Figure 1: Proportion of the New Zealand population who were continuously prescribed (i.e. three or more dispensings of a medicine in a year) five to nine medicines, or ten or more medicines from 2009 – 2014[4]

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 – 2013[7]

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 oesteoporosis 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 occurring[14]

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 hyper-thyroidism
	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

ACKNOWLEDGEMENT: Thank you to **Dr Carl Hanger**, Consultant Physician/Geriatrician, The Princess Margaret Hospital, Christchurch and Clinical Lecturer, Christchurch School of Medicine, University of Otago, Christchurch for expert review of this article.

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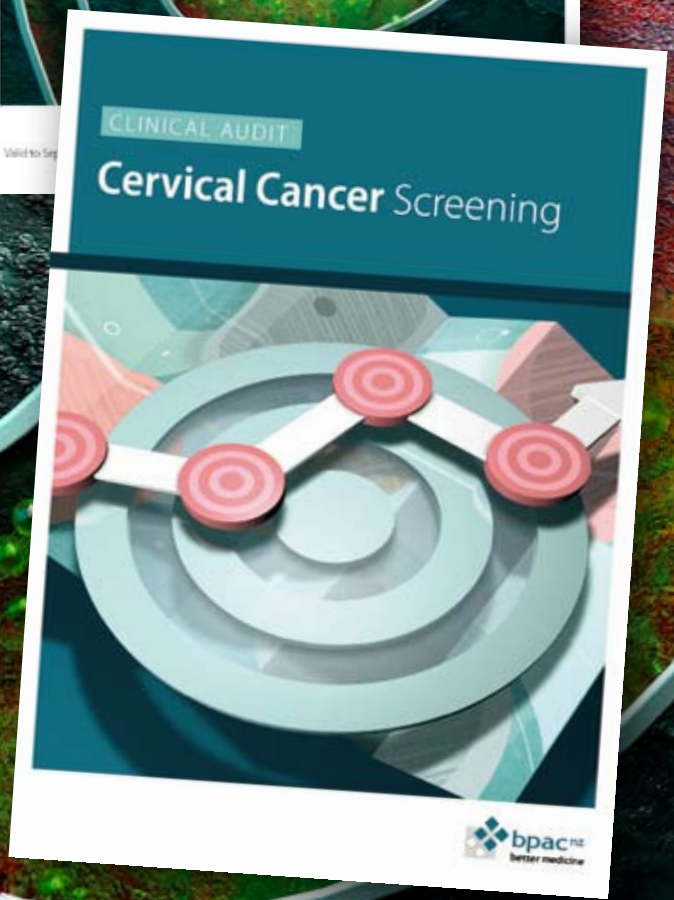

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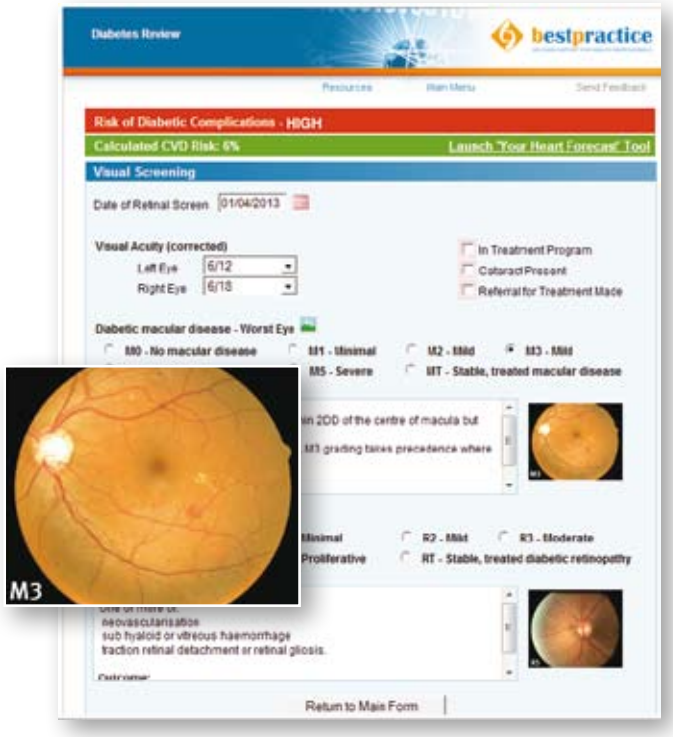

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DECISION SUPPORT FOR HEALTH PROFESSIONALS

Identifying and managing **addiction to opioids**

The increased use of opioid analgesics in recent years, particularly oxycodone, has resulted in misuse and addiction issues associated with prescription opioids becoming more evident in New Zealand. Clinicians need to be aware of what these issues are, and how to identify and manage patients with inappropriate opioid use. All patients with non-malignant pain who have been taking opioids for longer than a few weeks should be reviewed, to consider whether treatment is still appropriate and how adequate controls can be ensured.

There are a number of issues associated with the long-term use of opioid analgesics for the treatment of patients with chronic non-malignant pain, including an unproven efficacy for this use, adverse effects, tolerance, aberrant behaviour and addiction (see: "Definition of terms related to opioid misuse", over page). Patients initially start taking opioids to manage pain, but become increasingly reliant on the opioids, not only for pain relief, but also to manage emerging issues that overlap with addiction. Pain and addiction have inter-related symptoms and are often present at the same time. If one disorder is untreated, effective treatment of the other will not be possible. This adds to the complexity of managing patients with pain and addiction. It also further reinforces that opioids should be a treatment undertaken with considerable caution in patients with chronic non-malignant pain, and subject to careful and ongoing oversight.

The international experience with oxycodone misuse

Although not the only opioid that is misused, the well-documented global experience with oxycodone demonstrates the problems that occur when large volumes of strong opioids are available in the community.

Canada has led the world in publicising the misuse and addiction problems associated with oxycodone. After controlled-release oxycodone (OxyContin) was approved by Health Canada in 1996, and added to the Ontario provincial drug formulary in 2000, it rapidly became widely prescribed and then misused, particularly in Ontario. It soon became evident that the controlled-release characteristics of this formulation of oxycodone could be overcome by chewing or crushing the tablet, therefore making it an attractive medicine to misuse.

Between 2005 and 2011, there was a strong and significant correlation between prescription oxycodone dispensing levels and opioid-related mortality in Ontario. The number of oxycodone-related deaths increased from 0.54 deaths per 100 000 people in 2005 to 1.24 deaths per 100 000 in 2011.[5]

The oxycodone problem readily extended to remote communities and Canada's First Nations People. Some communities in Northwest Ontario have reported addiction rates as high as 70% in their adult populations.[6] In addition to adverse health effects, this has had significant economic implications with single 80 mg tablets selling for $80 – 800.[6]

The problems experienced from 1996 – 2012 resulted in a number of changes to how oxycodone is supplied and prescribed in Canada. Despite the manufacturers replacing OxyContin with the "crush-deterrent" formulation OxyNeo in 2012, legislation was passed in Ontario to delist oxycodone from the province's public drug benefit programme. This was a first for any province to delist a medicine based on addictive properties. The new law prohibits prescriptions for OxyNeo except to certain patients under an Exceptional Access Programme, which includes use for patients in palliative care and patients who have other extenuating circumstances.

At this stage the strategy appears to be working. It has been reported in the media that a year after the change, the number of OxyNeo prescriptions in Ontario was approximately 60% lower than the number of OxyContin prescriptions in the year before it was replaced.

Oxycodone was introduced to Australia in 1999 and, like in Canada, use of this medicine rapidly rose. The number of prescriptions for oxycodone increased by 152% over a five year period, from 3530 prescriptions per 100 000 people in 2002/03 to 8902 per 100 000 in 2007/08.[7] Of the 465 oxycodone-related deaths that were reported during this period, 53% were in patients who had been prescribed oxycodone (as opposed to obtaining it from other sources).[7]

A crush-deterrent tablet formulation of controlled-release oxycodone was released in Australia in April, 2014 and conventional OxyContin formulations were withdrawn, with the aim of reducing the misuse issues associated with oxycodone.[8] It is too early to tell what impact these changes have had, but it is hoped that it will result in positive changes similar to those seen in Canada.

Definitions of terms related to opioid misuse

Aberrant behaviour: any behaviour that raises concerns about addiction in opioid-treated patients, including:[1]

- Recurrent prescription losses
- Undertaking unauthorised dose escalations rather than adhering to scheduled dosing
- Repeated, and often aggressive, requests for higher doses of opioids
- Accessing opioids from other sources, e.g. from friends and relatives, "doctor shopping" and from the street
- Altering the route of delivery, e.g. injecting or snorting oral formulations

Addiction: Characterised by an inability to consistently **a**bstain (from taking opioids), impairment in **b**ehavioural control, **c**raving, **d**iminished recognition of significant problems relating to behaviour and interpersonal relationships, and a dysfunctional **e**motional response; the "ABCDE of addiction".[2]

Dependence: a state of physiological adaptation that can be unmasked by abrupt cessation, rapid dose reduction, decreasing blood levels of the opioid or administration of an opioid antagonist.[1] The terms addiction and dependence are frequently used interchangeably, depending on the medical context. Pain specialists tend to refer to dependence to mean neuroadaption (tolerance and withdrawal) by itself; addiction specialists use the term dependence to mean neuroadaption plus behavioural change.

Opioid-induced hyperalgesia: occurs when prolonged administration of opioids results in a paradoxical increase in atypical pain that may be unrelated to the original cause of pain.[3] The typical presentation is a patient with increased sensitivity to pain (sometimes at a different location to the original pain site), with different characteristics to the original pain.[4]

Tolerance: occurs when repeated administration of opioids results in a diminished clinical effect.[1]

Withdrawal: physical and psychological symptoms that occur when patients stop taking opioids.[1]

What is happening in New Zealand?

In New Zealand the dispensing rate of oxycodone increased by 249% between 2007 and 2011, before slowing in 2012 – 13.[9] The misuse problems seen in other countries are now starting to become apparent in New Zealand. Obtaining an accurate estimate of the rate of opioid dependence/addiction in New Zealand is difficult as there is limited data available. However, data from a number of sources show that the rate of opioid misuse in New Zealand is increasing. Anecdotally, addiction specialists across the country have raised concerns about the frequency at which oxycodone is found to be a factor, or the driving force, in new patient presentations.

Statistics on oxycodone misuse in New Zealand

The 2014 Global Drug Survey was conducted in 20 countries, with nearly 80 000 respondents, typically aged in their 20s and 30s. It was found that opioid analgesics had been used in the previous year by 8.7% of all respondents. This figure was substantially higher among respondents from New Zealand (19.1%) and second only to the USA (21.5%).[10]

It was estimated in a 2012 study in New Zealand that 0.3% (9100) of people aged 15 – 64 years were dependent on opioids.[11] However, the authors acknowledged that this figure is lower than previous estimates and should be considered as a minimum estimate of opioid dependence.[11]

The results of a 2010 survey that was sent out to a random sample of 300 New Zealand general practitioners, revealed that 66% of respondents had diagnosed at least one patient with prescription drug misuse in the last year.[12] Benzodiazepines and opioids were the most problematic medicine classes. Of the 111 general practitioners who had prescribed oxycodone in the preceding 12 months, 30% reported that they had at least one occasion where they had declined to prescribe oxycodone to a patient or had concerns about prescribing it due to issues of misuse.[12] As was reported in BPJ 62 (Jul, 2014), 72% of prescriptions for oxycodone in New Zealand in 2013 were initiated in secondary care.[9] This means that general practitioners frequently encounter patients discharged from hospital on oxycodone and face the challenge of negotiating withdrawal of oxycodone treatment.

The Illicit Drug Monitoring System (IDMS) is a survey which is conducted annually to provide a snapshot of trends in the use of illicit substances in New Zealand. The latest IDMS results are available from the 2012 survey which involved interviews with 330 frequent illegal substance users from Auckland, Wellington and Christchurch.[13] The report revealed that each

year, oxycodone becomes more widely used for recreational purposes. The proportion of frequent injecting-drug users who had used oxycodone in the previous six months increased from 9% in 2008 to 25% in 2012. The proportion who had used oxycodone at any time increased from 21% in 2008 to 54% in 2012.[13]

The implications of opioid misuse in general practice in New Zealand

The increase in use and misuse of oxycodone and other strong opioids in New Zealand highlights two main points – firstly, that these medicines should be avoided in patients with chronic non-malignant pain, and secondly, that patients who are taking opioids long-term, with no plan for stopping or controls around dispensing should be re-assessed.

The efficacy, tolerability and addictive potential of opioids make them a generally unsuitable treatment option for patients with chronic non-malignant pain. However, prescribing data shows that many patients in New Zealand are receiving strong opioids long term.[9] Clinicians should re-assess opioid use in these patients, and consider whether their pain condition is being ideally managed. This involves first gaining an understanding of the patient's experience of their pain, and the factors that may be contributing to their pain. Chronic non-malignant pain is best managed with a combination of non-pharmacological treatment interventions, e.g. cognitive behavioural therapy, exercise and lifestyle activities, and non-opioid pharmacological treatments. Even optimal pain treatment may need to allow for the continued experience of manageable pain.

 For further information on understanding pain and why opioids are not an appropriate treatment, see: "Helping patients cope with chronic non-malignant pain: it's not about the opioids", BPJ 63 (Sep, 2014).

How to withdraw opioid treatment

Although prevention is better than cure when it comes to opioid misuse and addiction, clinicians should be aware of appropriate treatment pathways when patients need to be withdrawn from opioids. This may be because the patient is showing signs of aberrant behaviour or addiction, or because long-term use of a strong opioid is no longer considered appropriate.

The features of opioid addiction are not always obvious and can be difficult to clearly define. Some signs and symptoms may include:

- Physical symptoms – flushing, vomiting, dizziness and lack of stability resulting in falls, loss of appetite, dry mouth, compromised mental function, breathing difficulties, headaches and migraines, impaired liver function, seizures, decreased blood pressure and sleep apnoea
- Psychological issues – altered perception of reality, anxiety, depression, mood swings, personality shifts, low self-esteem and negative body image, feelings of rage and bursts of anger, confusion, disorientation and paranoia
- Social issues – withdrawal and isolation from friends and family, loss of interest in activities normally enjoyed, damaged relationships with loved ones

Management of patients with addiction issues can be challenging and a decision needs to be made whether to attempt to withdraw the opioid in primary care or refer to a specialist pain or addiction service (see: "When to attempt opioid tapering in primary care", Page 21). Patients taking high doses of opioids for prolonged periods and patients with signs of aberrant behaviour are usually best referred to a specialist service. Other factors to consider are the patient's level of motivation to withdraw from treatment, how amenable they are to dose reduction and the nature of their underlying pain condition, e.g. what other options are available to manage their pain? The decision to refer to specialist services will also be dependent on the general practitioner's expertise in treating addiction.

General practitioners should not be deterred from referring a patient to an addiction specialist (or seeking a second opinion), if they have an aggressive or negative response to withdrawing treatment. It can be explained to patients that opioids cannot continue to be prescribed to them without a review of their case by an addiction specialist, as there would be concern that further prescriptions would contravene the Misuse of Drugs Act. Linking the ongoing prescribing of opioids with the date of the specialist assessment will encourage attendance at the appointment.

Managed opioid withdrawal

The two general approaches to managed withdrawal from opioids are abrupt cessation and gradual dose reduction. The preferred method depends primarily on the dose the patient has been taking and the duration of opioid use.

Abrupt cessation

Patients treated with lower doses of opioids (e.g. morphine 20 – 40 mg/day or oxycodone 10 – 20 mg/day) and for short periods

of time (one to two weeks) can generally stop treatment abruptly without experiencing withdrawal symptoms.[14] This is most likely to be patients discharged from hospital on opioids and patients with acute injuries who have received short-term opioid treatment.

Some patients may prefer not to stop opioid treatment abruptly but to rapidly reduce their dose, e.g. by 25% of their total daily dose per week (this is termed rapid tapering).[15] This approach may also be suitable for patients who have been taking lower doses of an opioid for longer periods of time, e.g. one to two months, who are highly motivated to discontinue the opioid.

Gradual dose reduction (tapering)

Patients who have been receiving higher doses of opioids or long-term opioid treatment are likely to require gradual tapering of the opioid dose. The rate of reduction of the opioid dose depends on a number of factors. These include the length of time the patient has been taking the opioid, their total daily dose, the underlying condition being treated, co-morbidities, e.g. depression and other psychological conditions, and upcoming important events.

Opioid-tapering protocol

Tapering regimens for opioids vary. Discussion with a pain or addiction service is recommended before beginning a taper, particularly if patients are taking high doses of an opioid.

A suggested protocol is as follows:[1]

Set goals prior to initiation of opioid taper

1. Emphasise that the goal is to reduce the pain intensity and improve patient function and mood
2. Have a written clinician/patient treatment agreement that clearly defines the aims and method of opioid tapering. Make sure the patient understands all the conditions documented in the agreement.
3. Recognise that frequent and supportive review will be required. Continuity of care is important and where possible a single clinician should conduct follow up and prescriptions should be collected from the same pharmacy. Formal counselling may not be necessary, but regular contact to "keep the faith" is valuable.

Consider the treatment regimen

1. Have a stabilisation phase of two to four weeks to clarify the daily dose of opioid the patient is taking; this will require an honest and open discussion for the patient to reveal the actual extent of their opioid use – do not assume that the patient's opioid requirements are what has been prescribed to them. Enquire about use of over-the-counter medicines which contain codeine and opioids from friends or family members. Consider a urine drug test and an examination for injection sites.

   N.B. Oxycodone, fentanyl, buprenorphine and tramadol are not included on a standard drug screen – list the medicine(s) you specifically wish to test for on the requesting form.
2. Prescribe scheduled doses. Consolidate long- and short-acting regimens and "as required" use into a set twice-daily regimen.
3. Prescribe frequent dispensing intervals, e.g. daily, alternate days or weekly, depending on what level of control the patient has over their opioid use; do not refill the prescription if the patient runs out and be especially cautious about claims of accidental losses. Addiction services often require that the patient has their opioid dispensed daily during this phase of treatment, and lost or vomited doses are not usually replaced.
4. Do not co-prescribe benzodiazepines – if the patient has been taking benzodiazepines, consider stopping these before withdrawing the opioid. N.B. Specialist advice for withdrawal of benzodiazepines may be required.
5. Discourage use of alcohol and cannabis during the opioid withdrawal.

Be flexible on the rate of taper

1. The rate of taper can vary from a 10% reduction in the total daily dose every day, to a 10% reduction every one to two weeks. The decision on the rate of tapering should be jointly agreed between clinician and patient and can be varied, e.g. with larger dose reductions initially or a slowing of the rate of reduction due to an important upcoming event.
2. As doses are recalculated, they may not be able to be easily made up using available medicine formulations therefore clinical judgement is required in selecting an appropriate dose.
3. A reduction in the total daily dose can be equally divided into the two daily doses although this may only be practical in patients starting their taper from a higher starting dose of opioid. For patients on lower total daily doses, a suggested approach may be to start the taper by reducing the patients' dose at the time of day when their pain is less. For example, in a patient taking 20 mg of oxycodone, twice daily (i.e. total daily dose of 40 mg), reduce the morning dose to 15 mg if this is when their pain is best controlled and leave the evening dose at

20 mg. Although this is slightly more than a 10% dose reduction (12.5%), it represents a practical "patient focused" solution given the available tablet sizes of oxycodone.

4. Slower rates of taper, e.g. 5% dose reductions, may be more appropriate in some patients, e.g. those who have significant co-morbidities, are anxious about tapering or who may be psychologically dependent on opioid treatment.
5. Once the patient has tapered to one-third of their original dose, the taper can be slowed to half or less of the previous rate.
6. Be prepared to hold the dose when necessary, including when the patient experiences reduced function, severe withdrawal symptoms or has a significant worsening in mood or pain (referred to as the neuro-adaptation plateau). Reassure the patient that their symptoms will resolve as neuro-adapation occurs, and the reduction in opioid will then resume.

Regularly monitor the patient during the tapering period

1. Schedule frequent contact, e.g. weekly, during the tapering period. Be aware that the cost of consultations may be prohibitive for some patients. Face-to-face consultation is preferred, but contact by other means, e.g. phone call or text message, can be considered and is often well received by the patient.
2. At each consultation ask the patient about withdrawal symptoms and their functional status (function rather than pain should be the focus) as well as any possible benefits they may be experiencing, e.g. improvements in energy levels, mood or alertness. A return of a more normal emotional range may initially be unsettling to the patient, but can also be very rewarding.
3. Check for injection sites and consider requesting urinary drug testing to assess adherence.

Endeavour to complete the taper

1. Be aware, and advise the patient, that the tapering period can take a variable length of time, e.g. from two weeks to four months.
2. Be prepared to keep patients on low doses of opioids for an extended period if they are unable to complete the taper, as long as their mood and functioning improves and they are willing to follow the opioid withdrawal agreement.
3. Avoid any dose increase, except for a brief return to a previously manageable dose – a "reducing" schedule that is actually oscillating up and down should be re-thought.

When to attempt opioid tapering in primary care

One of the more challenging aspects of withdrawing opioid treatment is deciding whether the patient can be successfully managed in primary care or whether they require more specialised support. In general, it may be worth considering the following broad categories when assessing the most appropriate treatment setting:[16]

1. Patients who can be managed in primary care – no personal or family history of substance use disorder and no major or untreated psychiatric disorders.
2. Patients who can be managed in primary care with specialist support* – a past history of substance use disorder, a significant family history of problematic drug use or a past or concurrent psychiatric disorder, but no active addiction
3. Patients best managed in a speciality pain service – active substance use disorder or major untreated psychiatric disorder

* Specialist support may be formal, i.e. the patient is co-managed in a pain/addiction clinic, or the patient can be referred for reassessment as required.

Managing symptoms during opioid withdrawal

Many of the symptoms classically associated with withdrawal may not be seen in patients who undergo a gradual taper.[17] Symptoms also vary between individuals. Withdrawal from opioids is not considered a life-threatening situation (except in neonates), in contrast to withdrawal from alcohol and benzodiazepines, which can be. The physical symptoms of withdrawal generally resolve within five to ten days after opioid dose reduction/cessation; whereas, psychological symptoms, when present, may take longer to resolve, e.g. weeks to months.[17]

Early symptoms (hours to days after withdrawal) include: restlessness and anxiety, rapid short respirations, sweating, yawning, sniffing, rhinorrhoea, lacrimation, musculoskeletal pain and dilated reactive pupils.[17]

Late symptoms (days to weeks) include: continuation of early symptoms (as above), along with tremor, diffuse muscle spasms and aches, abdominal pain, nausea, vomiting, diarrhoea, tachypnoea, pilo-erection, fever and chills. Patients who rapidly withdraw from opioids may have a transient increase in white blood cell count (although testing WBC is not generally required during opioid withdrawal).[17]

Prolonged symptoms (weeks to months) include: craving, reduced tolerance to stress, irritability, insomnia, fatigue, bradycardia and decreased body temperature.[17]

How to manage withdrawal symptoms

Symptomatic management is important for successful opioid withdrawal, along with compassionate acknowledgement of what the patient is experiencing. The patient can be reassured that their discomfort is temporary and will resolve. The patient's underlying levels of distress during the opioid withdrawal should be monitored and they can be referred for specialist addiction treatment if agitation or anxiety is severe. Involving family members to support the patient during their withdrawal is also recommended – as for any mental health condition, family support enhances the prognosis.

Symptomatic treatments that may be required include:[17]

- Paracetamol and/or NSAIDs for withdrawal aches and pains and general pain
- Topical rubefacients, e.g. menthol + methyl salicylate (Deep Heat) and massage for muscle pain and aches
- Mebeverine for abdominal cramping
- Loperamide for diarrhoea
- Antiemetics, e.g. prochlorperazine or metoclopramide, for nausea and vomiting
- Oral or transdermal clonidine (off-label use) for hot/cold sensations (not routinely required if the taper is gradual), however, be aware that clonidine has misuse potential also. Blood pressure monitoring is required after the first dose and for at least 72 hours or until a stable dose is achieved and then again after discontinuation. Reassess treatment after one week and taper to stop.

A short-acting benzodiazepine or zopiclone should only be considered if the patient has insomnia that cannot be managed with non-pharmacological treatments (e.g. "sleep hygiene" and relaxation techniques) and the insomnia is compromising the success of the withdrawal. These medicines have significant misuse potential and should only be used for a short time.

Quinine is no longer used to treat symptoms of withdrawal.

Refer to NZF for dosing instructions for these medicines: **www.nzf.org.nz**

How to manage pain in patients undergoing opioid tapering

During the opioid taper, patients are likely to report that their pain has increased as the opioid dose was decreased. An increase in pain when withdrawing opioids does not mean that the opioid was effective in providing pain relief, only that removing it makes the pain worse for a short period of time. When pain occurs, the rate of taper can be slowed and other pharmacological (e.g. paracetamol, NSAIDs) and non-pharmacological treatments (e.g. exercise, massage, cognitive behavioural therapy) added to maximise pain relief.

Preventing relapse

Naltrexone may be considered for relapse prevention in people who have ceased opioid use. It is approved in New Zealand for this indication, but is only subsidised for the treatment of alcohol dependence. However, the evidence of effectiveness of naltrexone in maintaining opioid abstinence is low, as the majority of patients stop taking it, especially during risk periods. The risk of fatal overdose may then be increased as the patient relapses without any tolerance for opioids. If relapse occurs, or is very likely to occur, a period of opioid substitution (specifically with a long-acting opioid, i.e. methadone or buprenorphine) is the treatment best supported by the evidence.

Opioid substitution treatment (OST) in New Zealand

OST is the evidence-based treatment of choice in patients with opioid misuse and addiction problems who have not achieved opioid withdrawal or for whom tapering is an unsuitable withdrawal method, e.g. due to complex co-morbidities. Substitution with a long acting opioid, i.e. methadone or buprenorphine, allows the patient to move away from the reinforcing effects of shorter acting opioids. The "on-off" effects of opioids with shorter half-lives means that the expected return of pain (or associated opioid withdrawal symptoms) becomes a powerful disincentive to completing a successful taper.

By law (the Misuse of Drugs Act 1975) OST can only be carried out by specialist services in New Zealand and some general practitioners that are trained and authorised by the specialist service to administer OST.

Methadone or buprenorphine can be used for OST

The rationale behind opioid substitution stems from the fact that the majority of patients who have been dependent on opioids for a year or longer, will not be able to remain abstinent from opioids, even with optimal support.

Methadone and buprenorphine are used as opioid substitutes.[18] These medicines both have gradual onsets of effect with longer durations of action than the opioids being misused, e.g. oxycodone and morphine, resulting in more stable serum levels. As a result of this, patients taking methadone or buprenorphine do not experience a "rush" or marked withdrawal symptoms, and have a reduced desire to use other opioids. For patients with pain, this longer action ameliorates the sudden onset and rapid wearing off of pain relief of shorter acting opioids and therefore improves pain cover.

Methadone is the more commonly used substitute, as it is more effective in retaining patients in treatment, has been available for longer and is substantially cheaper than buprenorphine. Buprenorphine is a useful alternative choice, although its partial agonist action means that it may not achieve enough protection against relapse in all patients. In New Zealand, only the buprenorphine combined with naloxone (Suboxone) is funded, subject to Special Authority criteria. The naloxone does not act unless injected – its inclusion in Suboxone is to deter injection (although some drug users will do so anyway).

Long-acting morphine and sustained relapse oxycodone preparation are not effective opioid substitutes.

Treating acute pain in opioid-dependent patients

Using opioids for acute pain in patients who are, or have been, opioid dependent has risks and should be done with caution. If needed at all, opioids should only be prescribed for an acute, clearly defined condition in combination with regular review. The treatment plan should be agreed on with the patient and include regular follow up and a plan to rapidly taper and stop the opioid treatment. Course length will be between three and 14 days, depending on the condition treated. Dispensing safeguards need to be addressed. In patients with a significant risk of relapse or with an active opioid addiction discussion with specialist pain/addiction services is strongly recommended if pain relief is required, and as a courtesy if the patient is undergoing opioid substitution treatment.

Some best practice principles for acute pain management in this patient group include:[18, 19]

- Consult with specialist pain/addiction services and consider early referral for assessment and management
- Maximise the use of non-opioid analgesics and non-pharmacological treatments
- If an opioid is required, it may be best to use it in combination with a non-opioid analgesic to reduce the dose of opioid needed
- If opioid substitution is already in place, the addiction service may suggest a temporary increase of the opioid substitute as a pragmatic solution, with dispensing controls already in place
- Alternatively, patients on opioid substitution who have been stable in treatment for a year or more may find it psychologically easier to separate the opioid prescriptions into the opioid substitute for addiction, and a closely supervised, reducing dose of a shorter acting opioid for pain. This only generally works for short periods of time, i.e. less than 14 days, because of the degree of supervision (dispensing restriction and close review) involved

When patients first begin OST, the opioid substitute is dispensed daily as this becomes an external control that takes the place of the patient's diminished internal control. This phase of treatment may last for three to six months. Dispensing restriction is then gradually relaxed to aid rehabilitation as the patient regains the confidence and ability not to use doses in advance or by injection.

Patients usually require a minimum of two years of opioid substitution for it to be effective, reflecting how profoundly opioid dependence affects individuals. Any duration of treatment less than one year would be considered to represent an opioid detoxification, where the chance of relapse is high. For these reasons alone, prevention of opioid dependence by careful opioid prescribing is far more preferable than having to treat dependence.

Referral of patients to OST services

The decision of whether to refer a patient for OST will depend on a number of factors. OST is offered nationwide and there should not be significant waiting lists for treatment. Patients in rural areas can also access OST, although alternative dispensing procedures may have to be put in place (e.g. involving a district nurse) if the patient has to travel a significant distance to a pharmacy.

Red flags for referral for OST in patients taking opioids include:[18, 19]

- Higher doses of opioids (e.g. greater than oxycodone 60 mg/day or morphine 100 mg/day)
- Signs of aberrant behaviour, e.g. injecting or snorting oral formulations, recurrent prescription losses, accessing opioids from other sources, requests for pethidine
- Repeated failure of opioid tapering
- History of significant psychological and/or substance use disorders
- Aggressive or intimidating behaviour
- Feedback from pharmacies about problem behaviour, including presenting prescriptions from different doctors, intoxicated or intimidating behaviour, or contact with other people with opioid dependence

General care of patients undergoing OST

Most general practitioners will not be involved in the day-to-day administration of OST, but there are a number of potential issues to be aware of when patients receiving OST present in general practice.

Adverse effects

Methadone is associated with a number of significant adverse effects. Patients have an increased risk of methadone overdose in the first two weeks of treatment.[18] Titration to an effective dose of methadone can take two to six weeks, and during this time patients may resort to using alternative supplies, with the potential for fatal misjudgement of dose. Loss of consciousness through cardiorespiratory depression will require emergency treatment with injectable naloxone.

The most troublesome adverse effects associated with methadone include excessive sweating, dental cavities resulting from decreased saliva production, sleep apnoea, constipation, osteoporosis, drowsiness and reduced sexual function through either impotence or loss of libido.[18] In general, these adverse effects can be managed symptomatically or with dose reduction.[18] QT prolongation is a recognised risk of methadone treatment, especially in patients with a family history of QT prolongation, those taking higher doses of methadone and those concurrently taking other QT prolongating medicines, e.g. antidepressants and antipsychotics. The risk of QT prolongation is also increased in females, and with increasing age.[20]

Buprenorphine is not generally associated with overdose, unless the patient is opioid naïve (i.e. inappropriately in OST). Adverse effects include constipation, nausea, reduced sexual function and drowsiness.

Medicine interactions

Methadone and buprenorphine have potentially significant interactions with a number of other medicines such as antibiotics (e.g. ciprofloxacin and erythromycin), antifungals (e.g. fluconazole) and antivirals (e.g. ritonavir).[18]

Refer to the New Zealand Formulary for full details: **www.nzf.org.nz**

Safe storage

Not all patients receiving OST will be given "take away" doses. However, those that do should be educated on safe storage of their medicine. Even small doses of methadone in children can be life-threatening and deaths have been reported in adolescents who have inadvertently taken methadone when looking for an analgesic at home. Pharmacists should dispense all opioids in child-resistant packing whenever possible.

Managing pain

Be aware that methadone and buprenorphine provide little, if any, analgesia for acute pain due to increased opioid tolerance or hyperalgesia. As a result, opioid analgesics are often less

effective in managing acute pain in patients undergoing OST and these patients require higher doses more frequently than usual.[18] If a patient has a need for acute pain relief for a clearly defined condition, discuss appropriate options with their OST provider.

The partial agonist action and high opioid receptor affinity of buprenorphine creates particular challenges for using additional opioids for analgesia. Because stopping the buprenorphine can destabilise the opioid substitution control, prescribers are usually faced with providing sufficient short-acting opioids to achieve analgesia. Given that this may involve substantial doses, inpatient oversight is commonly required.

Further resources

The 2014 New Zealand Practice Guidelines for OST contain practical and evidence-based information for clinicians on the clinical assessment and treatment of people with opioid dependence. This document is available from: **www.health.govt.nz/publication/new-zealand-practice-guidelines-opioid-substitution-treatment-2014**

The Alcohol & Drug Helpline (0800 787 797) and DHBs can advise on local availability of addiction support.

Community and Alcohol Drug Services (CADS) are offered in most main centres around New Zealand. Resources are also available from: **www.cads.org.nz**

Addiction support is also be available through non-government organisations, including the Salvation Army, CareNZ, 12-Step Programmes (e.g. Narcotics Anonymous, Alcohol Anonymous & Al-Anon) and Tranx.

ACKNOWLEDGEMENT: Thank you to **Dr Jeremy McMinn**, Consultant Psychiatrist and Addiction Specialist, Wellington for expert review of this article.

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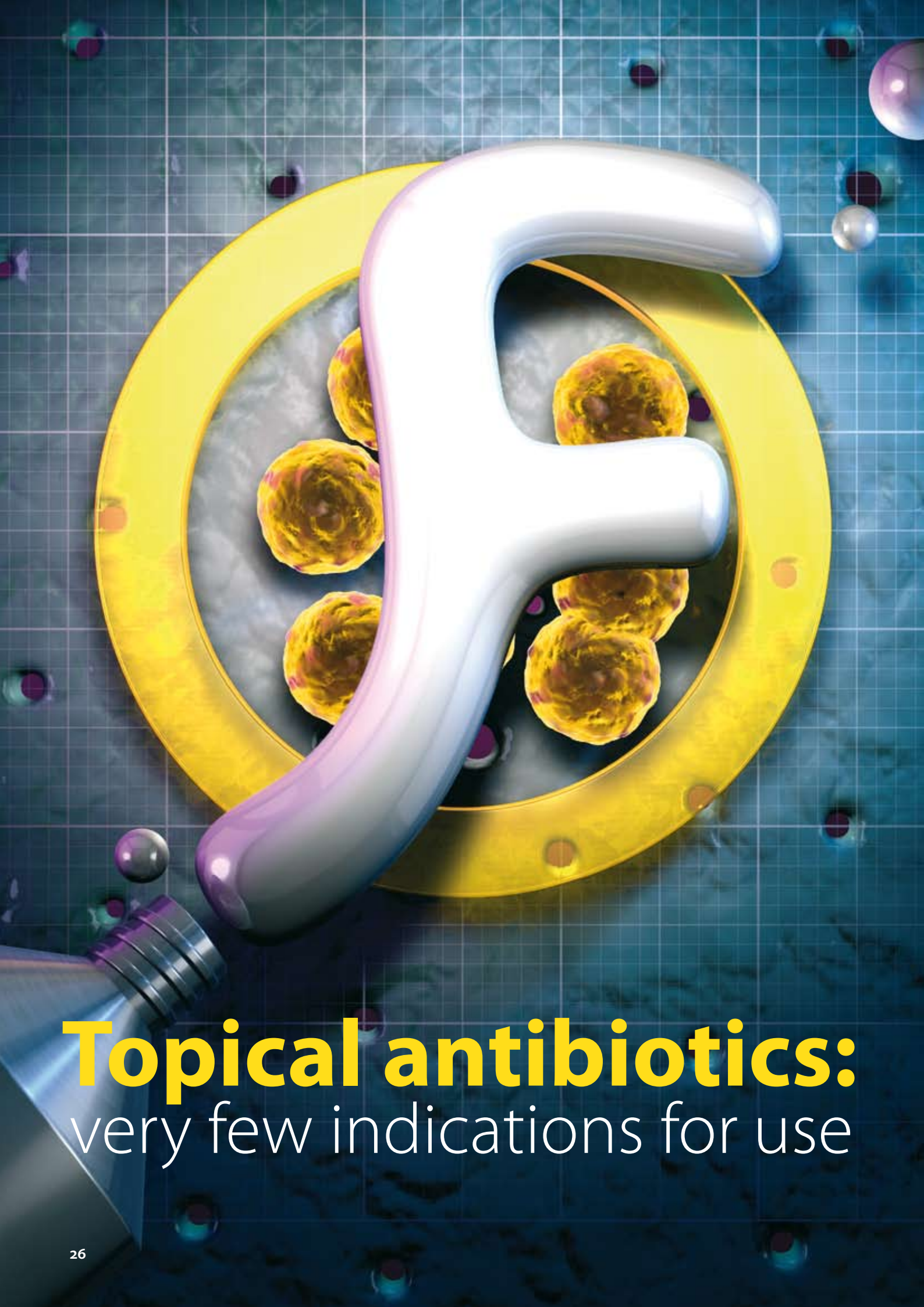


Topical antibiotics: very few indications for use

Topical antibiotics in general have been excessively used in New Zealand in recent years. The increasing prevalence of resistance to fusidic acid in Staphylococcus aureus *means that treatment will often be ineffective. Topical antibiotics may be considered for patients with localised areas of impetigo. Antibiotic treatment, whether given topically or orally, is rarely indicated for the treatment of patients with furuncles (boils) or carbuncles (multiple headed lesions). Oral antibiotics, but not topical antibiotics are indicated for wound infections, cellulitis or other deeper skin infections. It is important to reconsider the use of topical antibiotics in skin infections and reduce inappropriate prescribing.*

The role of topical antibiotics in the treatment of minor skin infections

1. Not all patients with a skin infection require an antibiotic (Table 1)
2. If an antibiotic is required, topical antibiotics are only appropriate for patients with minor, localised areas of impetigo

Most minor skin infections are self-limiting and resolve without the use of an antibiotic (with standard skin hygiene advice). The decision to treat will be determined by several factors, including the extent and severity of infection, the patient's co-morbidities and socioeconomic status (e.g. living environment).

Despite increasing bacterial resistance to fusidic acid, it remains a valid treatment option for patients with localised areas of impetigo caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or other related streptococci.[2] Oral antibiotics are appropriate for patients with more extensive areas of infection or systemic symptoms. Fusidic acid may also be considered for treating patients with small, localised areas of infected eczema, however, oral antibiotics are more likely to be required as infected eczema is often extensive.

Topical mupirocin should be reserved for treating patients with localised mild skin infections (impetigo or infected eczema), that are resistant to fusidic acid and have sensitivity to mupirocin.

Antibiotic management of impetigo

Topical treatment with fusidic acid may be considered for a patient with no more than three areas of impetigo or an area of infection of less than 5 cm^2.[2] Response to treatment should be regularly assessed, and a switch to oral antibiotics considered if the infection is not resolving or is worsening. A swab for culture and sensitivity will help to guide treatment in this case.

Table 1: General guidance for use of antibiotics for skin infections most commonly seen in general practice[1]

Antibiotics (topical or oral) rarely required	Topical antibiotics may be considered	Oral antibiotics (not topical) usually indicated
Furuncles (boils) Carbuncles (multiple headed lesions) N.B. In most cases these can be treated with incision and drainage	Impetigo (small, localised patches) Occasionally considered for infected eczema (small, localised patches, not improving with standard care)	Infected wounds, including bites Cellulitis Widespread impetigo or infected eczema Mastitis

The history of fusidic acid use in New Zealand

Fusidic acid is a relatively narrow-spectrum antibiotic, active against Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus spp*. It is most commonly used in topical form. Fusidic acid belongs to the fusidane class (a fungal derivative), with a chemical structure similar to corticosteroids, although it does not have anti-inflammatory properties.[8]

Fusidic acid has been available for many years in New Zealand, however, use has increased significantly over the past decade. This occurred after restrictions were placed on another topical antibiotic, mupirocin, which has similar activity to fusidic acid. Mupirocin was available as an "over-the-counter" medicine from 1991, however, its status reverted to a prescription only medicine in 2000. This was due to concerns over increasing bacterial resistance, particularly in methicillin-resistant *Staphylococcus aureus* (MRSA). This resulted in a significant reduction in dispensing of mupirocin, but at the same time, dispensing of fusidic acid increased as topical antibiotics continued to be widely prescribed.[9]

The total number of community-dispensed prescriptions of topical fusidic increased from approximately 146 000 in 2008 to approximately 220 000 in 2013 (Figure 1).[10] The incidence of *S. aureus* skin infections in New Zealand has increased by approximately 5% each year over the last decade,[11] which may account for some of the additional use of topical antibiotics.

This change in prescribing also had an effect on bacterial resistance to both fusidic acid and mupirocin. The prevalence of resistance in *S. aureus* to mupirocin, which was 28% in 1999 (based on a national survey of isolates from community and hospital laboratories),[12] had fallen to 11% in 2013 (based on a survey of isolates from an Auckland community laboratory).[9] In contrast, the increased level of prescribing of fusidic acid over recent years resulted in a rapid rise in the prevalence of resistance, from 17% in 1999,[12] to 29% in 2013.[9]

Latest antibiotic resistance surveillance data from ESR (from both community and hospital laboratories) show that in 2012, 15% of all sampled *S. aureus* isolates were resistant to fusidic acid, compared to 8% resistant to mupirocin.[13] Of those isolates which were methicillin-resistant (i.e. MRSA), 37% were resistant to fusidic acid and 10% resistant to mupirocin.[13]

It appears that the increased and widespread use of fusidic acid has rapidly resulted in it becoming a much less effective antibiotic treatment for the skin infections it is indicated for, i.e. localised areas of impetigo.

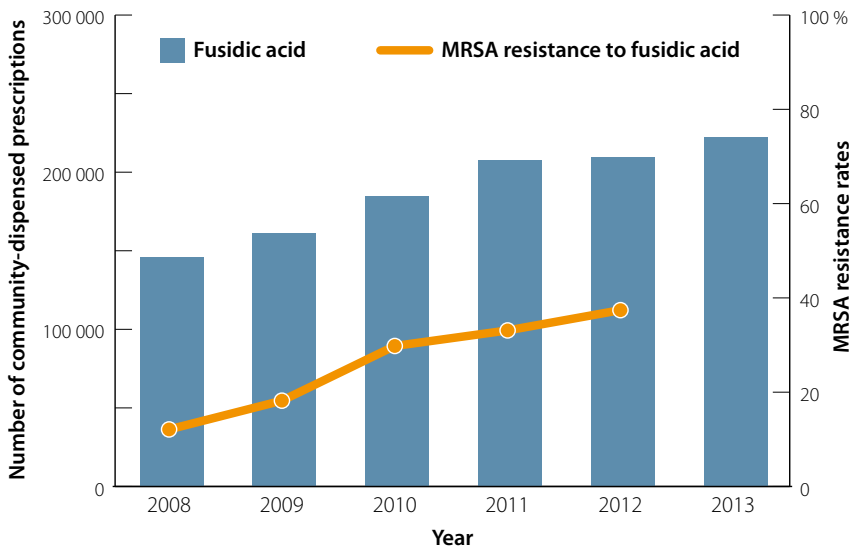


Figure 1: Number of community-dispensed prescriptions for fusidic acid between 2008 – 2013, and MRSA resistance rates to fusidic acid[10, 14]

Advise the patient/carer to remove crusted areas on lesions, with warm water and a soft, clean cloth.[3] Apply fusidic acid 2% ointment or cream to lesions three times daily, for seven days.[1, 2]

Oral antibiotics are more appropriate than topical treatment for patients with widespread lesions or if systemic symptoms are present. The recommended oral antibiotic treatment is flucloxacillin:[1]

- Child – 12.5 mg/kg/dose, four times daily,* for five to seven days
- Adult – 500 mg, four times daily, for five to seven days

* If compliance is an issue, an alternative regimen is flucloxacillin 10 – 25 mg/kg/dose, three times daily (maximum 500 mg per dose) for five to seven days.[2] To optimise absorption, oral flucloxacillin is ideally taken on an empty stomach.

Cephalexin has been recommended as an option for children who find flucloxacillin syrup unpalatable,[2] however, consideration should be given to the disadvantages of using an unnecessarily broad spectrum antibiotic and the effect on the spread of antimicrobial resistance (see: "Antibiotic resistance in New Zealand, Page 24). Erythromycin is an alternative for patients with penicillin allergy. If MRSA is found to be present, the recommended treatment is oral co-trimoxazole (see: New Zealand Formulary or the bpac^{nz} antibiotic guide for recommended doses of these medicines).

In children with impetigo, the affected area should be kept covered and the child excluded from day-care or school until 24 hours after antibiotic treatment has been initiated.[3]

Information and resources for families about impetigo are available from: **www.kidshealth.org.nz/impetigo-school-sores**

Antibiotic management of infected eczema

A topical antibiotic may be considered for patients with a small area of infected eczema (a single patch < 5 cm^2), that is not resolving with usual eczema management (including antiseptic baths).[4, 5] Advise the patient/carer to apply fusidic acid 2% ointment or cream to the infected area three times daily, for seven days. A combination fusidic acid/corticosteroid product is also an option (see opposite).

Oral antibiotics are appropriate when the infection is more widespread (i.e. > 5 cm^2), if there is more than one area of infection or if systemic symptoms occur.[5] The same oral antibiotic regimen as recommended for impetigo can be used.

Where possible, topical emollients and medicines should be provided in a tube or pump dispenser to reduce the risk of contamination. Emollients in a tub should be scooped out for application to skin using a spoon or ice-cream stick. After an infection patients/carers should be advised to discard and renew topical medicines in tubs, as they may have become contaminated.[4, 5]

Recurrently infected eczema is usually due to under-treatment of the eczema. Factors such as adherence should be addressed, and a referral made to dermatology if eczema persists despite primary care intervention.

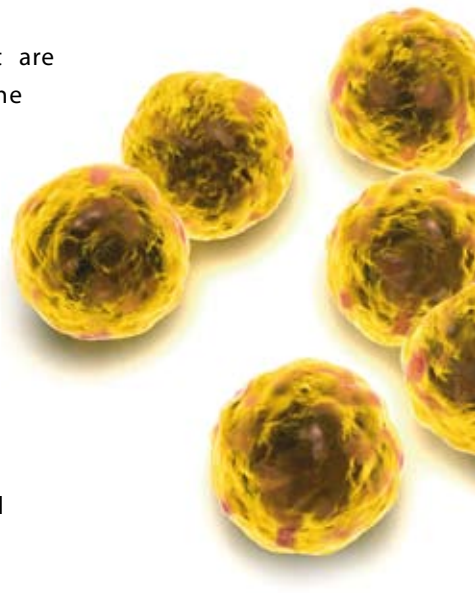
Combination topical antibiotic + corticosteroid

Several topical combination antimicrobial/corticosteroid products are available in New Zealand. Fusidic acid is combined with betamethasone in Fucicort (partly subsidised). Pimafucort contains hydrocortisone, natamycin and neomycin (fully subsidised).[6]

These products are best reserved for treating small areas of localised infection in patients with an underlying inflammatory skin condition that will respond to a corticosteroid.[6] For example, Fucicort may be considered for a patient with a small area of eczema (in which a corticosteroid is part of the treatment regimen) with a secondary bacterial infection (for which fusidic acid may be appropriate). Pimafucort may, for example, be considered for the treatment of a patient with superficial skin lesions that will respond to corticosteroids, complicated by a secondary candidal infection.[6]

It is recommended that these combination products are used regularly, for a short time period, e.g. twice daily, for seven days.[6]

Fucicort and Pimafucort are not appropriate for the treatment of acne vulgaris. Topical antibiotics (e.g. clindamycin, erythromycin) are no longer funded for the treatment of acne but may be used for patients with mild inflammatory acne which does not respond to topical retinoids or where topical retinoids are not tolerated.[7]



The emergence of MRSA

Penicillin was first used to treat *S. aureus* infections, but now approximately 90% of isolates in New Zealand are resistant.[13] Methicillin (a semi-synthetic penicillin) and other closely related antibiotics, such as flucloxacillin, dicloxacillin and cloxacillin, were then used to treat *S. aureus* infections, but this led to the "super bug" methicillin-resistant *S. aureus* (MRSA) which became endemic in many hospitals in New Zealand in the 1990s.[12] Measures were implemented to control MRSA, and levels in New Zealand hospitals are now lower than in many other countries, such as the United States.[15] In 2013, the national rate of MRSA in New Zealand was 23.9 cases per 100 000 people,[16] however, there are significant geographical variations in incidence. The DHB regions with the highest MRSA incidence rates per 100 000 people in 2013 were Northland (60.5), Counties Manukau (54.9) and Tairawhiti (53.5).[16]

Preventing recurrent skin infections

S. aureus skin infections in New Zealand have increased significantly over the past decade.[11] More people are being hospitalised with skin infections, and there is an increase in the number of infections being reported in the community.[11] The incidence rate of patients hospitalised with *S. aureus* skin infections in the Auckland DHB region increased from 81 cases per 100 000 people in 2000 to 140 cases per 100 000 people in 2011, which represents an increase of approximately 5% per year.[11] Māori and Pacific peoples, adults aged over 75 years, children aged under five years and people living in more deprived areas have been found to have a higher incidence of hospitalisation for *S. aureus* infection.[11] Factors contributing to the high rates of *S. aureus* infections in New Zealand are thought to include delayed access to health care, increasing overcrowding in households and declining socioeconomic circumstances in some population groups.[11]

With the high rates of *S. aureus* skin infections in New Zealand and the increasing emergence of resistant strains, it is important that measures are put in place to reduce the risk of recurrent infections, especially among households. This primarily involves educating patients and their families about infection control measures and the principles of good hygiene. A formal decolonisation regimen, using topical antibiotic and antiseptic techniques, is not necessary for all patients, but may be appropriate for those with recurrent staphylococcal abscesses.

General messages for preventing skin infections

General lifestyle and hygiene measures can be discussed with families to reduce the likelihood of skin infections.

These include:[17]

- Use an emollient to treat dry skin
- Ensure that skin conditions such as dermatitis or eczema are optimally managed
- If skin is dry or damaged, avoid soaps which can irritate the skin, and prolonged exposure to hot water
- Where possible, store and use skin products from pump or pour bottles, rather than jars
- Keep fingernails and toenails trimmed and clean
- Do not share personal hygiene items such as hairbrushes, razors, facecloths and towels, and regularly clean these items
- Wash and dry hands after using the toilet and before eating

- Wash clothes, towels and sheets regularly; if a family member has a skin infection, ideally use hot water and dry items in a hot clothes dryer (although acknowledging that this is often not affordable for families). A hot iron can be used after clothes are dry.
- Regularly wash toys using a mild disinfectant – hard toys can be washed in a dishwasher, soak soft toys prior to washing; there is no evidence that freezing soft toys reduces bacterial contamination[18]
- If a skin injury occurs, clean and cover it to help prevent infection and regularly change the dressing
- Avoid scratching skin lesions
- Avoid sharing bath/cleaning water when a member of the family has a skin infection
- Avoid swimming in unclean/untreated water if an open wound is present

Information for families is available from: **www.health.govt.nz/system/files/documents/publications/looking-after-your-childs-skin-treating-skin-infections-guide-parents-caregivers-nov-13.pdf**

Decolonisation of *S. aureus* in patients with recurrent abscesses

Patients presenting in primary care with recurrent staphylococcal abscesses (furuncles or carbuncles) are likely to be carrying a high bacterial load of *S. aureus* (some with MRSA), which is causing multiple re-infections when skin becomes damaged, e.g. through scratching or injury. The most common site of staphylococcal colonisation is inside the nostrils. Other frequently colonised sites include the groin, perineum, axillae and pharynx. There is conflicting evidence as to whether undergoing staphylococcal decolonisation results in fewer skin infections (see: "Evidence of effectiveness of decolonisation measures", over page). However, if a patient with recurrent staphylococcal abscesses (or their parents/carers) is likely to be compliant with a decolonisation regimen, it is reasonable to try this. Treatment to eliminate *S. aureus* colonisation in the most affected member of the household is usually all that is required to prevent recurrences in all household members.

Decolonisation should only begin after acute infection has been treated and has resolved.

The first step is to take a nasal swab to determine whether the patient has *S. aureus* nasal colonisation and if so, whether the *S. aureus* colonising the patient is sensitive to fusidic acid or mupirocin:

- **If *S. aureus* is present and the isolate is sensitive to fusidic acid** the patient should be treated with fusidic acid 2% cream or ointment, applied inside each nostril (with a cotton bud or finger), twice daily, for five days.
- **If *S. aureus* is present and the isolate is resistant to fusidic acid, but sensitive to mupirocin**, the same treatment regimen should be undertaken, but with mupirocin 2% ointment.
- **If *S. aureus* is not present or if the isolate is resistant to both fusidic acid and mupirocin**, topical treatment is not indicated. Systemic antibiotics may be required in some patients with particularly resistant strains of *S. aureus*;[17] discuss this with an infectious diseases specialist.

Bleach baths or antiseptic washes should also be used

To help reduce the bacterial load, patients undergoing *S. aureus* decolonisation should also be advised to shower or bathe for one week using an antiseptic.

For a bleach bath, add 1 mL of plain unscented 5% bleach per 1 L of bathwater (or 2 mL of 2.2% bleach per 1 L of water). Products that contain added detergent (e.g. Janola) are not recommended. N.B. A regular-sized bath filled to a depth of 10 cm contains approximately 80 L of water and a baby's bath holds approximately 15 L of water.[19]

After immersing in the bath water for 10 – 15 minutes, rinse with fresh water. The bleach bath should be repeated two to three times within the week.

A patient/carer handout on instructions for a bleach bath is available from: **www.kidshealth.org.nz/sites/kidshealth/files/pdfs/bleach_bath_handout.pdf**

Alternatively, patients may shower daily for one week, using triclosan 1% or chlorhexidine 4% wash. The wash can be applied with a clean cloth, particularly focusing on the axillae, groin and perineum. Although difficult in a showering situation, the antiseptic should ideally be left on the skin for at least five minutes before being rinsed off. Hair can be washed with the antiseptic also.[17]

Bleach baths or antiseptic washing can be carried out intermittently after the initial decolonisation period, to help prevent recurrence of infection.[17] This can also be recommended for patients with recurrent skin infections who have not undergone formal decolonisation.[17]

Mouth gargle

As *S. aureus* can also colonise the pharynx, an antiseptic throat gargle (e.g. chlorhexidine 0.2% solution, three times daily) is also recommended for the duration of formal decolonisation treatment.[17]

Linen and clothing can also be decolonised

To support the decolonisation regimen, potentially contaminated clothing, towels, facecloths, sheets and other linen in the household should be washed then dried on a hot cycle in a clothes dryer, or dried then ironed. Clothing and linen that is white or colourfast can be washed with diluted household bleach. Washing is recommended twice within the one week decolonisation period.[17]

Ideally, the household should also replace toothbrushes, razors, roll-on deodorants and skin products. Hair brushes, combs, nail files, nail clippers can be washed in hot water or a dishwasher.[17]

Surfaces that are touched frequently, such as door handles, toilet seats and taps, should be wiped daily, using a disinfectant, e.g. alcohol wipes, bleach.[17]

Soft furnishings that cannot easily be cleaned, e.g. couches and arm chairs, can be covered in a sheet or blanket that is regularly washed.

Evidence of effectiveness of decolonisation measures

There is mixed evidence of the effectiveness of formal decolonisation regimens in reducing recurrent infections in patients with persistent carriage of *S. aureus*. A 2003 Cochrane review of six randomised controlled trials did not find evidence to support decolonisation of patients with MRSA, with either topical or systemic methods.[20] However, further trials have subsequently been published, some with more positive results.

A recent United States-based study randomised patients with *S. aureus* colonisation to receive hygiene education only, education + 2% mupirocin ointment applied inside the nostrils, twice daily for five days; education + mupirocin + chlorhexidine 4% body wash daily; or education + mupirocin + bleach bath daily.[21] After one month, the rate of *S. aureus* nasal colonisation in patients who received mupirocin (27%), mupirocin + chlorhexidine (26%) and mupirocin + bleach (17%) was approximately half that in patients who received education alone (46%).[21] However, after four months, only the group who received mupirocin + bleach had significantly lower rates of *S. aureus* nasal colonisation (15%) compared to those who received education alone (50%). The group who received mupirocin + chlorhexidine had a significantly lower rate of recurrent skin infections after one month (11%) compared to the group who received education alone (26%). However, there was no effect on the rate of skin infections at either four or six months after the intervention.[21]

The eradication of *S. aureus* was thought to be more successful in the group who used mupirocin + bleach compared to other groups, because soaking in the bleach bath allowed fuller body exposure to the antiseptic and a longer period of contact, therefore increasing the antimicrobial effect of the intervention.[21]

As the effect of the initial interventions was not sustained over time it may suggest that decolonisation regimens should be repeated regularly to successfully eradicate *S. aureus*. However, there is currently no evidence to support the efficacy of this approach.

N.B. Mupirocin was used in this study, but is only recommended in New Zealand if colonisation with *S. aureus* that is resistant to fusidic acid and sensitive to mupirocin has been confirmed.

The role of topical antiseptics in treating skin infections

Antiseptics slow or stop the growth of micro-organisms on external surfaces of the body, i.e. the skin and mucus membranes, and help to prevent infections.[22] Antiseptics have broad-spectrum bactericidal activity and can also act against fungi, viruses and protozoa.[23] There has been recent interest in the use of antiseptics for treating skin infections, to help to reduce the use of topical antibiotics. Antiseptics contribute to bacterial resistance to some degree, but not to the extent that antibiotics do. This is because antiseptics generally eliminate or inhibit all bacteria, whereas antibiotics act only on susceptible bacteria.[23]

There is currently a lack of evidence to support the use of topical antiseptics in the treatment of minor skin infections. However, they do have a role in preventing infection in wounds.[24] Like topical antibiotics, antiseptics only work on external surfaces of the body and do not have any effect on systemic infections.[22]

In general, antiseptics may be used for:[22]

- Cleaning cuts, abrasions and other minor injuries to help prevent infection from occurring
- Hand washing to prevent cross-contamination
- Prior to surgical procedures to reduce resident skin flora
- In the prevention of recurrent skin infections to reduce bacterial load on the skin (Page 31)

N.B. Antiseptic solutions can cause irritation or contact dermatitis in some people, and some products may stain the skin.[22]

Most antiseptics reduce bacterial load: the clinical significance of this is uncertain

Much of the evidence about antiseptics is in regards to their use in dressings for preventing infection in open wounds rather than as a treatment for minor skin infection.[24] Many antiseptics do reduce bacterial load in a wound, but the clinical significance of this is uncertain. Bacterial load is also not the only predictor of infection – other predictors include the presence of foreign bodies in the wound, the patient's co-morbidities and the virulence of the bacteria present.[23] There is evidence that some antiseptics can be toxic to human cells important in the healing process, e.g. fibroblasts, keratinocytes and leukocytes, however, this is usually only when antiseptics are used at high concentrations.[23, 24]

Povidone iodine is one of the more frequently used antiseptics. It has been shown to reduce the bacterial load in wounds and not to impede healing, however, there is no evidence that it increases the rate of wound healing.[23]

Hydrogen peroxide does not negatively affect wound healing, but it is thought to be ineffective at reducing bacterial count.[23] It may be useful as a chemical debriding agent.[23]

Chlorhexidine does not adversely affect wound healing, and is likely to be useful as a rinse, but it is uncertain how effective it is in preventing infection in open wounds.[23]

Antiseptics are not usually associated with bacterial resistance

Although there have been isolated reports of bacterial resistance to povidone iodine, the consensus is that iodine-resistant strains of micro-organisms have not yet emerged, after over 150 years of use of iodine-containing antiseptics.[25] There have been no reports of bacterial resistance to hydrogen peroxide. Some bacterial resistance has been reported to quaternary ammonium antiseptics (P*seudomonas aeruginosa*), chlorhexidine (staphylococci) and triclosan (*P. aeruginosa*).[25, 26]

Refer to the New Zealand formulary for available antiseptics and subsidy details

Take home messages

- Antibiotics are not required for all skin infections; only use them when they are clinically indicated
- Use topical antibiotics for small areas of localised impetigo and oral antibiotics for more extensive infections
- If a topical antibiotic is the most appropriate treatment option, use fusidic acid as first-line treatment, but be alert to the relatively high prevalence of resistance in *S. aureus*. Reserve the use of mupirocin for the treatment of infections that are resistant to fusidic acid and susceptible to mupirocin.
- In patients with recurrent skin abscesses, investigate for carriage of *S. aureus* and decolonise if present
- Prevention is better than cure, so educate patients about the importance of good hygiene and keeping their skin healthy

Antibiotic use and resistance rates in New Zealand

New Zealand has one of the highest levels of antibiotic use in the world.[27] Microbial resistance is directly related to the amount of an antimicrobial medicine that an organism is exposed to. Therefore the high rate of consumption of antibiotics in New Zealand means that we also have increasing rates of antibiotic resistance.[27]

Antibiotic use is standardised in studies by reporting results as defined daily doses (DDD). The DDD is the amount of medicine that is internationally agreed as the standard daily dose when treating an otherwise healthy adult, e.g. the DDD of oral amoxicillin is 1 g.

In a recent New Zealand study it was calculated that the annual per capita consumption of antibiotics in New Zealand in 2012 was approximately 25 DDDs/1000 people/day (i.e. an average over the year of 25 daily treatment doses of an antibiotic, per 1000 people in New Zealand, per day).[27] Compared to European countries, the volume of antibiotic consumption in New Zealand was higher than in the United Kingdom, Spain, the Netherlands, Scandinavia, the Czech Republic, Austria and Germany, and only lower than in Greece, Belgium, France and Italy.[27]

Use of broad-spectrum antibiotics is a contributing factor to antibiotic resistance and narrow-spectrum antibiotics should be used where possible. In 2012, narrow-spectrum penicillins represented only 21% of the total number of DDDs of various penicillins consumed by patients in the community in New Zealand.[27]

There are still relatively effective treatments for most antibiotic-resistant bacteria seen in New Zealand, although these treatments are not necessarily cost effective, and can be associated with significant adverse effects. However, some strains of treatment-resistant *Escherichia coli* and *Klebsiella pneumoniae* are now beginning to be seen in New Zealand.

If these resistant strains become prevalent, this will have serious consequences for the provision of surgical treatments, such as implantation of prostheses or organ transplant, where the risk of fatal infection and increased morbidity from failed procedures would be high.[27]

So what can we do?

The use of all antibiotics, including topical antibiotics, is contributing to the increasing rates of antimicrobial resistance in New Zealand and the rest of the world. Some things that health care professionals can do to help preserve usefulness of antibiotics include:[27]

- Do not prescribe an antibiotic when it is not required, e.g. for a viral upper respiratory tract infection, sinusitis, self-limiting cases of otitis media and conjunctivitis (which is often viral), boils (unless co-morbidities) and most diarrhoeal illnesses
- Use an antibiotic appropriate for the infection, and where possible avoid broad spectrum antibiotics, e.g. prescribe flucloxacillin for a *S. aureus* infection instead of cephalexin or amoxicillin clavulanate
- Prescribe antibiotic treatment for the recommended duration and advise patients to complete the full course; avoid prolonged or repeated courses without a strong clinical justification
- Prioritise consideration of antibiotic resistance, over palatability and convenience for the patient, when deciding which antibiotic to prescribe

Patient education is also important in reducing the inappropriate use of antibiotics. This includes:

- Inform the patient about the problems associated with the increasing rates of antimicrobial resistance
- Ensure the patient understands what the antibiotic is being prescribed for, what dose to take and how often
- Educate the patient about the importance of completing the full course of antibiotic treatment
- Encourage the patient to appropriately dispose of any antibiotic that may be left over after completion (e.g. unused topical antibiotic) or cessation of treatment (e.g. antibiotic changed due to susceptibility), and not to use it for a subsequent infection
- Ensure the patient is aware that the antibiotic being prescribed is for them only and should not be used by family members or friends
- Educate the patient that the antibiotic should only be used for the condition it was prescribed for and should not be used for other conditions, e.g. topical antibiotics should not be applied to minor cuts and abrasions

ACKNOWLEDGEMENT: Thank you to **Dr Emma Best**, Paediatric Infectious Diseases Consultant, Starship Children's Health and Senior Lecturer, Paediatrics, University of Auckland, **Dr Rosemary Ikram**, Clinical Microbiologist, Christchurch, **Dr Diana Purvis**, Paediatric Dermatologist, Starship Children's Health, **Associate Professor Mark Thomas**, School of Medical Sciences, University of Auckland and Infectious Diseases Specialist, Auckland DHB and **Dr Arlo Upton**, Clinical Microbiologist Labtests Auckland and Infectious Diseases Specialist, Auckland DHB, for expert review of this article.

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SMOKING CESSATION BEYOND THE ABC:

Tailoring strategies to high-risk groups

Smoking rates are declining in New Zealand as more and more people are successfully quitting. However, rates remain unacceptably high among deprived communities, Māori and Pacific peoples and in people with mental health disorders. It is often helpful to think of smoking as a chronic relapsing disease, thereby acknowledging the difficulties of smoking cessation and the likelihood of relapse. Ideally, health professionals should be providing smoking cessation support in the ABC format to every patient who smokes, at every consultation. It is also important to individualise cessation support by understanding why a patient's previous quit attempts have failed and encouraging a wave of social support for future attempts, particularly in groups with high rates of smoking. Health professionals who are able to do this increase the chances that patients will be able to stop smoking long-term.

Identifying groups with high rates of smoking

In New Zealand, smoking rates are falling; daily smoking among all adults was 18.3% in 2006/07, 16.4% in 2011/12 and most recently, 15.5% in 2012/13.[1] However, smoking is analogous to a chronic disease with frequent relapses, and ongoing work is required to continue this downward trend in the number of people who smoke.

Smoking rates are substantially higher than the national average, and particularly concerning in:

- People who live in highly deprived areas
- Māori and Pacific peoples
- People with mental health disorders

The good news is that many people who smoke also frequently think about quitting, regardless of their background. When surveyed, approximately 40% of people who smoke reported attempting to quit in the previous 12 months.[2] However, most attempts to quit do not succeed, and long-term success, e.g. remaining smokefree for at least six months, is only achieved in 3 – 5% of attempts without the support of a health professional.[3]

There are two strategies that health professionals can pursue in order to increase the number of people who quit smoking long-term:

1. Increase the number of people who attempt to quit smoking
2. Increase the success rate of quit attempts

Brief advice to stop smoking and, most importantly, an offer of cessation support by a health professional can increase the number of people who attempt to stop smoking by 40 – 60%.[4] This means that one extra person can be expected to attempt to give up smoking for every seven people who are advised to do so and offered support in their attempt.[4]

Tailoring support to patients by understanding their quit-history and circumstances means that health professionals can increase the chances of the patient's next attempt succeeding. It is important to let patients who are quitting know that it is likely that they will lapse. However, behavioural support, e.g. Quitline, and pharmacological smoking cessation aids, do help prevent a lapse in abstinence becoming a return to regular smoking.

Current smoking is associated with poverty

Deprivation is strongly associated with smoking in New Zealand (Figure 1, over page). After adjusting for age, sex and ethnicity, a person from one of the most deprived communities in New Zealand (Decile 10) is over three time more likely to be a current smoker, compared with a person from one of the least deprived communities (Decile 1).[1] Women who live in lower socioeconomic areas are also more likely to smoke during pregnancy (17%) compared with pregnant women in the general population (11%).[5]

Smoking rates in Māori and Pacific peoples must be reduced further

Almost one-third (32.7%) of Māori smoke, a rate more than twice as high as New Zealanders of European descent, and more than one-third of Māori women smoke during pregnancy.[5, 7] Death rates due to lung cancer and smoking-related diseases are three times higher in Māori than non-Māori.[7] However, it is encouraging to know that most Māori who smoke do want to quit. During the five-year period between 2006 and 2011, it was estimated that almost two-thirds (62%) of Māori who

smoked made at least one quit attempt.[7] It is important that these previously unsuccessful attempts be acknowledged and lessons learnt when future attempts to quit smoking are made. It is also good news that the number of Māori youth who have never smoked is increasing: for boys from 58% in 2006/07 to 75% in 2013/14, and for girls from 52% in 2006/07 to 72% in 2013/14.[7] Relative to their population size, Māori also tend to use smoking cessation support services more than non-Māori; from April to June 2014 Māori accounted for almost one in five Quitline caller registrations.[8]

Māori who do not smoke are exposed to second-hand smoke more (11.4%) than non-Māori who do not smoke (6.4%).[7] This increases the severity of the negative health effects of smoking on Māori children. More than 20% of Māori households with one or more child have at least one person who smokes inside the home, compared to under 8% in non-Māori households.[7]

The overall rate of smoking among Pacific peoples is 23%, although this varies greatly depending on sub-ethnicity; it is reported that 32% of Tokelauan and 30% of Cook Island people were classified as regular smokers in the 2013/14 New Zealand census, while 13% of people who identified as Fijian were regular smokers.[9] Encouragingly, rates of smoking are reported to be declining among Pacific youth. Regular smoking among Pacific boys aged 15 – 19 years dropped to 13.6% in 2013/14 (from 20.1% in 2006/07), and regular smoking among Pacific girls of the same age fell to 10.3% in 2013/14 (from 21.4% in 2006/07).[9]

Smoking prevalence increases with severity of mental health disorders

People with a mental health disorder are approximately twice as likely to smoke as people who do not have a mental health disorder and generally, the level of nicotine dependence increases with the severity of the illness.[10] Many people with mental health disorders who smoke will require additional support from health professionals to achieve long-term abstinence.[10]

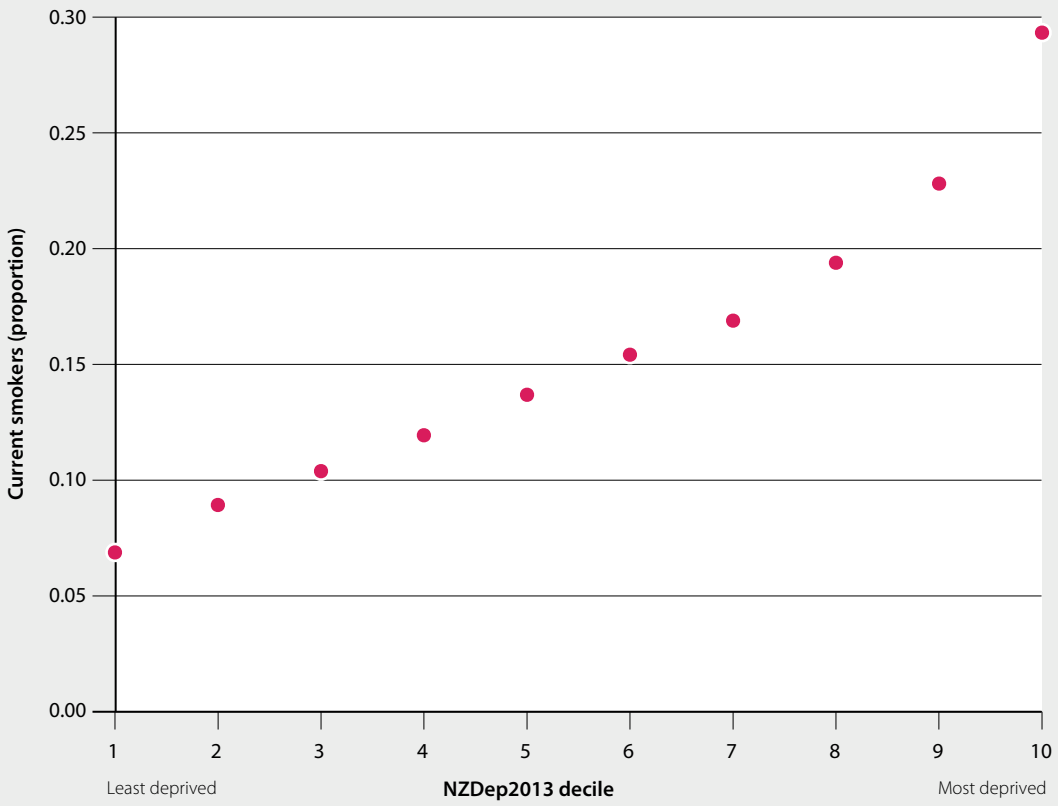


Figure 1: Proportion of people living in New Zealand communities, by deprivation status, who are current smokers, adapted from NZDep2013[6]

Adapting the ABC to different patient groups

General practitioners are encouraged to **A**sk about smoking, **B**riefly advise to quit and offer **C**essation support (ABC), to all patients who smoke, at every consultation.[11] Some health professionals may be reluctant to persistently advise people to quit smoking due to concerns that their relationship with patients may be damaged. However, it should be remembered that most people who smoke are open to the idea of quitting;[12] 80% of current smokers report that they would not smoke if they had their life over again.[11]

"When was the last time you smoked a cigarette?" is a non-judgemental way of enquiring about smoking status in patients who are known to be smokers.

Understand the barriers before you start

Understanding why the patient relapsed into smoking following attempts to quit allows health professionals to provide individual strategies, e.g. encouraging the patient's partner to also take part in the quit attempt if the partner is influencing the patient's smoking status. Having a partner who continues to smoke during pregnancy is said to "almost universally predict" a return to smoking among women who are pregnant.[13]

Fear of consequences can encourage smoking

For people whose social life is restricted to family/whanau and neighbours, a fear that quitting smoking can result in being "left-out" socially is a barrier to quitting.[12] Concerns that giving up smoking will cause illness are also not uncommon, e.g. coughing or chest infections following quitting. Other barriers to quitting smoking that are frequently reported include: fear of weight gain, boredom and the timing of a quit attempt being problematic.[12] A patient's individual concerns about quitting need to be addressed when discussing smoking cessation.

Viewing smoking as a stress-reliever can be a barrier to quitting

People who smoke often view it as a stress-relieving activity, therefore do not want to quit.[12, 14] There may also be concern that quitting smoking will worsen mood in people with a mental health disorder.[14] In fact the opposite is more likely to be the case: smoking cessation has been shown to have beneficial effects on mood disorders, with an effect size equal to, or larger than, treatment with antidepressants.[14] Health professionals should acknowledge that a patient's mood may improve in the minutes after smoking a cigarette. However, this is an opportunity to explain to the patient that the reason

Why does quitting smoking improve mental health?

A meta-analysis of 26 studies found consistent evidence that smoking cessation is associated with improvements in depression, anxiety, stress, quality of life and positive affect.[14] This benefit was similar for people in the general population and for those with mental health disorders.[14]

The fallacy that smoking improves mental health can be understood when the neural changes that long-term smoking causes are considered. Over time, smoking results in modification to cholinergic pathways in the brain, resulting in the onset of depressed mood, agitation and anxiety during short-term abstinence from tobacco, as levels of nicotine in the blood drop.[14] When a person who has been smoking long-term has another cigarette their depressed mood, agitation and anxiety is relieved. However, as a person continues to abstain from smoking the cholinergic pathways in the brain remodel and the nicotine withdrawal symptoms of depressed mood, agitation and anxiety are reduced through abstinence from nicotine. The process whereby people relieve withdrawal symptoms with a drug, i.e. nicotine, which then reinforces these symptoms is referred to as a withdrawal cycle and it may also be associated with a decline in mental health.[14]

The effects of smoking cessation on patients with mental health disorders

Hydrocarbons and tar-like products in tobacco smoke are known to induce the cytochrome P450 enzyme CYP1A2.[15] When patients taking other medicines that are metabolised by this enzyme stop smoking there may be an initial rise in medicine levels in their blood as enzymatic activity falls to normal levels. There may be some instances where stopping smoking in a patient taking certain antipsychotics (e.g. clozapine, olanzapine, chlorpromazine, haloperidol) or insulin causes clinically significant changes in serum concentrations.[15] Patients with insulin-dependent diabetes who stop smoking should be alert to the symptoms of hypoglycaemia and increase their frequency of blood glucose monitoring.[16]

they feel better is because they are addicted to nicotine, and that every puff continues this cycle (see: "Why does quitting smoking improve mental health?", previous page). The patient can then be reassured that all people who break the cycle of smoking addiction will experience mental health benefits.[14] N.B. The doses of antipsychotics used to treat some mental health disorders (and insulin) may need to be adjusted if abrupt cessation occurs in a person who is heavily dependent on cigarettes (see: "The effects of smoking cessation on patients with mental health disorders: previous page).

From talking to quitting

Motivational interviewing can increase the likelihood that a patient will attempt to quit smoking and increase the chances of them succeeding.[10]

The general techniques of motivational interviewing include:[10]

1. Expressing empathy

   e.g. "So you've already tried to give up smoking a couple of times and now you're wondering if you will ever be able to do it?"

2. Developing the discrepancy between the goal of being smokefree and the behaviour of smoking

   e.g. "It's great that your health is important to you, but how does smoking fit with that for you?"

3. Rolling with resistance

   e.g. "It can be hard to cope when you're worried about your mother's health and I realise that smoking is one of the ways that you've used to give yourself a break. What other ways do you think you could use? "

4. Encouraging self efficacy

   e.g. "Last time you didn't think you'd be able to manage without smoking at all – and you've actually gone all week with only two cigarettes – what did you do differently this time to make that happen?"

A goal of care when consulting with patients who are current smokers is to negotiate a firm quit date and to agree on "not one puff" from that point onwards.[10]

Cessation support is the most important aspect of the ABC approach

It is important that cessation support, e.g. referral to smoking cessation service, should be offered to all people who smoke without assessing their readiness to stop smoking. Only offering cessation support to people with a stated desire to quit smoking is a missed opportunity for positive change. Also see: "A review of pharmacological smoking cessation aids", Page 42.

A meta-analysis of the effect of cessation support found that offers of cessation support by health professionals, e.g. "If you would like to quit smoking I can help you do it", motivated an additional 40 – 60% of patients to stop smoking within six months of the consultation, compared to being advised to quit smoking on medical grounds alone.[4] It is important to note that the motivation of patients to stop smoking was not assessed before offers of cessation support were made.

Referral to a smoking cessation service is recommended

Quitline is a smoking cessation service which offers phone-based support, six days a week (Monday – Friday 8 am – 9.30 pm, Sunday 10 am – 7.30 pm on 0800 778 778) to all people who want to quit smoking. People can self-refer to Quitline or they can be referred by a health professional. Patients can also be referred electronically if the relevant feature is enabled on the practice management system. Txt2Quit support is available from Quitline directly to mobile phones.

For further information go to: **www.quit.org.nz**

Aukati Kai Paipa is a free smoking cessation service that delivers face-to-face coaching for Māori from over 30 centres around New Zealand.

To find your closest provider go to the Aukati Kai Paipa website at: **www.aukatikaipaipa.co.nz/contact-us**

Smokefree Communities offers smoking cessation services to people living in the North Shore, Waitakere and Rodney areas. Programmes focus on reducing rates of smoking among women who are pregnant and their whanau/family, Asian people and their families, and all families with children aged under 16 years. Smokefree Communities provides support in Chinese, Korean, Burmese and Hindi/Fiji Hindi languages.

To find out more about Asian Smokefree services go to: **www.comprehensivecare.co.nz/services-and-programmes/addictions/asian-smokefree-services/**

Preventing smoking relapses

Health professionals can discuss strategies with patients to help manage triggers where there is extra pressure to smoke. For example, focus on something that is important to the

patient and incorporate it into a response that they use to decline an offer to smoke, e.g. "No thanks, my daughter has asthma – our home is now smokefree to help her breathing get better".

Creating a wave of social support

Encourage the person quitting to reach out for assistance from anyone they know who has previously quit smoking. Peer support for people who are attempting to quit smoking can take many forms. The rationale is that a person with similar life experiences to the person who wants to stop smoking can provide practical tips that fit with their lifestyle. A friend or family member is also more likely to have regular contact with the person attempting to quit. Examples of peer support might be having a coffee or tea together each morning to discuss any difficulties or temptations, or attending situations together where there may be a strong temptation to smoke, e.g. the pub.

There is some evidence that peer support may be more successful when people in deprived communities attempt to quit smoking, compared with people in the general population.[17] Some maraes in New Zealand have also run competitions that both challenge people who are quitting smoking to stay smokefree while also supporting each other's quit attempts.

The Quitline Blog is the most popular online smoking cessation peer support forum operating in New Zealand. People who are attempting to quit smoking can be encouraged to access this forum to receive support at any time of the day or night. Social networking platforms, e.g. Facebook, can also be used to provide a substitution for social situations where the person has previously found it difficult to resist the temptation to smoke. Social networking is more likely to be used by younger people who smoke and have regular access to the internet.

The Aukati KaiPaipa Facebook page is available at: **www.facebook.com/tkha.akp**

Children are a positive and motivating influence

The health-related and financial benefits that the children of people who smoke gain when their parents quit smoking is a powerful motivating factor.[12] In particular, prospective parenthood can provide additional motivation to stop smoking. Having a smokefree pregnancy and then maintaining a smokefree household means that children are less likely to develop middle ear infections, or to have lower respiratory illness, asthma or abnormal lung growth, and have a lower incidence of sudden unexplained death in infancy.[11]

Incentives to smokefree pregnancies

Incentive programmes have recently been launched to encourage pregnant women to quit smoking in some North Island areas, including Waikato, Counties Manukau and Northland DHBs. As part of the Waikato programme, vouchers to a total value of $250 are given to Māori or Pacific women who are up to 28 weeks pregnant, at one, four, eight and 12 weeks after they have quit smoking.[19] Vouchers are intended to be spent on items such as groceries or petrol; they cannot be exchanged for cash or spent on cigarettes or alcohol.[19] The smokefree status of the women participating is measured by testing exhaled carbon monoxide levels. It was reported that this was a positive influence on quit attempts as it provided accountability.[20] The Counties Manukau programme resulted in a 65% quit rate at four weeks and a 60% rate at 12 weeks.[20]

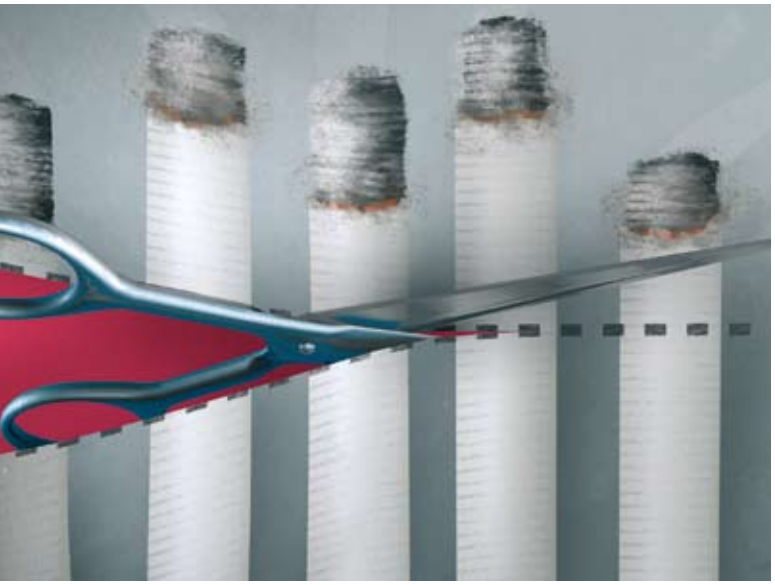
The cost of smoking just keeps going up

Cost increase is a recognised method for decreasing cigarette consumption. As part of the drive to create a smokefree New Zealand by 2025, it is government policy that an average pack of 20 cigarettes will cost more than $20 by 2016, with future price increases beyond this highly likely.[18] This policy is supported by the Royal New Zealand College of General Practitioners.[11]

At a cost of $20, a pack-a-day smoker would be spending $140 a week, or more than $7000 per year on cigarettes. The money that a family/whanau can save by quitting smoking can, and should, be used to create goals that unite families in their desire to be smokefree. For example, as well as spending the extra money on essentials such as clothing, a small weekly treat such as going to the local swimming pool can provide an ongoing and tangible incentive to being smokefree. Longer term goals such as saving for a family holiday can also create family "buy-in" and may help parents remain abstinent from smoking in the months following their quit date.

What to do if the patient does have another cigarette?

If a patient who is attempting to quit reports that they have had a brief smoking lapse then it is important that they do not see this as a failure. Support is required to help them avoid feelings of guilt and loss of control that can undermine their quit attempt. Remind patients that many people who quit experience lapses. Encourage the patient to continue to use NRT and any other smoking cessation medicines that have been prescribed. Ask the patient to again commit to "not one puff" onwards and to ensure that cigarettes, lighters and ashtrays have been discarded.



A review of pharmacological smoking cessation aids

Pharmacological aids for smoking cessation can reduce nicotine cravings and lessen withdrawal symptoms. An offer of medical assistance may embolden people who have previously attempted to quit smoking without support to try again. Pharmacological aids also reduce the likelihood of a lapse in abstinence becoming a return to long-term smoking.

The important factors to consider when discussing smoking cessation treatment options are the patient's preferences and previous experience of smoking cessations aids, the patient's likely adherence to treatment and the possibility of any adverse effects.

Nicotine replacement therapy

The use of NRT approximately doubles the likelihood of a person being able to quit smoking long-term; one in 14 people who would not otherwise have stopped smoking will do so for at least six months following a course of NRT.[15] Several studies suggest that in people who are unmotivated to quit within the next month, the use of NRT results in an increased number of quit attempts and marginally higher rates of abstinence.[21] NRT may therefore act as a quit catalyst for patients who smoke and who report that they are not yet ready to stop.[21] Offering patients who smoke the opportunity to trial different forms of NRT before they attempt to quit may also improve their choice of NRT and result in better treatment adherence.

Most people who are attempting to quit smoking do not use enough NRT.[22] Patients who are heavily dependent on cigarettes may gain benefit from increasing the dose of nicotine, e.g. wearing two patches, to replicate the levels of nicotine that reach the brain when they are smoking. Combining NRT products, e.g. using a nicotine patch and nicotine gum, is more effective than using a single NRT product.[15] If patients begin to feel nauseous when using NRT they can be advised to reduce the frequency or dose of the product.[22]

Subsidised NRT can be prescribed by general practitioners and registered Quit Card Providers. Subsidised supplies of NRT may also be obtained by general practices using a Practitioner Supply Order. Pharmacists can supply subsidised NRT that is prescribed on a normal prescription (maximum quantity 12 weeks) or a Quit Card (maximum quantity 8 weeks) at a cost of $5; these will be dispensed in four-week quantities. Pharmacists are not able to prescribe subsidised NRT unless they are part of a special regional programme, e.g. Canterbury DHB.

Nicotine replacement therapy should be continued for at least eight weeks; the normal treatment course is 12 weeks.[23] Patients who feel they are still gaining benefit from treatment can continue to use NRT for longer periods.[23] If patients wish to use NRT as a way of reducing cigarette consumption, prior to quitting, then cigarette use should be reduced to half at six weeks and completely stopped at six months.[23]

In order to determine an appropriate NRT regimen, New Zealand guidelines recommend combining the time until the first cigarette with the total number of cigarettes a person smokes each day (Figure 2). The amount of time that passes after waking until a person smokes their first cigarette is a useful guide when assessing nicotine dependence; New Zealand guidelines use smoking within an hour of waking as a sign of high tobacco dependence,[22] smoking within five minutes of waking is a sign of severe dependence.[10]

Nicotine patches are fully subsidised in New Zealand and available in 7mg, 14 mg and 21 mg patches. These should be pressed in place on dry, clean and hairless skin, and replaced daily.[22] Patches may cause some dermal erythema.[22] If patients report disturbed sleep while using nicotine patches then they should be removed at night.

Nicotine gum is available in 2 mg and 4 mg formulations. It is recommended that nicotine gum be used regularly by people who are attempting to quit smoking.[22] The 4 mg formulation is indicated for people who are highly dependent on tobacco, i.e. smoking within an hour of waking. The gum should be bitten to liberate a peppery flavour. The gum should not be chewed continuously as swallowed nicotine can result in gastrointestinal disturbance. It can be placed between the cheek and gum and chewed again when the taste fades, and disposed of after 30 minutes.[22, 23]

Nicotine lozenges are available in 1 mg and 2 mg formulations. It is recommended that lozenges be used regularly when nicotine cravings occur.[22] The 2 mg formulation is indicated for people who are highly dependent on tobacco, i.e. smoking within an hour of waking.

All people who wish to quit smoking can use NRT, including people with cardiovascular disease and women who are pregnant or breastfeeding, if they would otherwise continue to smoke.[22] When discussing the use of NRT with a woman who is pregnant or breastfeeding perform a risk assessment and consider "Can she quit without NRT?" If not, NRT is safer than smoking. A study involving over 1700 pregnant women who used NRT found no significant association between NRT use and decreased infant birth weight.[24] Pregnant women who are using nicotine patches should remove them overnight.[22] Adolescents aged 12 years or over can also be prescribed NRT,[22] however, the use of NRT alone is unlikely to address the reasons why an adolescent has begun, and continues to smoke.

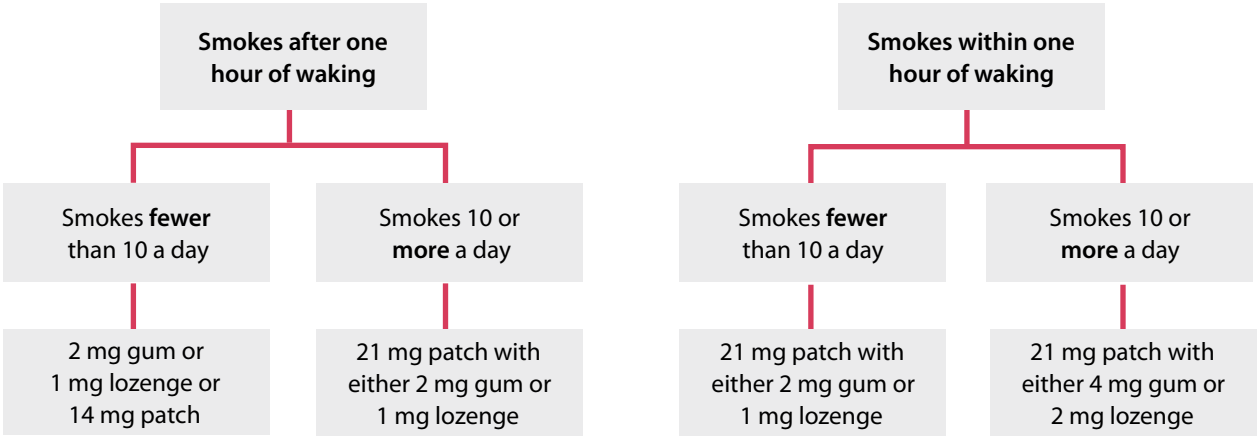


Figure 2: Nicotine dependence assessment algorithm for determining an appropriate NRT treatment regimen, adapted from "Guide to prescribing nicotine replacement therapy (NRT)"[22]

Table 1: Comparison of smoking cessation medicines that are subsidised in New Zealand[23]

	Bupropion	Nortriptyline	Varenicline
Funding status*	Fully subsidised	Fully subsidised	Fully subsidised with Special Authority approval for people who have tried previously to quit smoking with other medicines†
Efficacy	Almost doubles a patient's chances of quitting smoking long-term[15]	Almost doubles a patient's chances of quitting smoking long-term[15]	Approximately triples a patient's chances of quitting long-term[15]
Mechanism of action	Atypical antidepressant which aids smoking cessation independently of its antidepressant action[15]	Tricyclic antidepressant which aids smoking cessation independently of its antidepressant action[15]	Stimulates nicotine receptors less than nicotine, i.e. is a partial agonist, thereby reducing cravings, and, at the same time, reduces the rewarding sensation of smoking, i.e. antagonist effect.[10]
Contraindications	Lowers seizure threshold and should not be taken by patients with acute alcohol or benzodiazepine withdrawal, CNS tumour, eating disorders, bipolar disorder, use of monoamine oxidase inhibitors (MAOI) in the last 14 days, and in patients with severe hepatic cirrhosis.	Should not be taken by patients: who are acutely recovering from a myocardial infarction, with arrhythmias, during manic phases of bipolar disorder, with acute porphyria, who are breast feeding, or who have used a MAOI in the last 14 days	None, however, patients and their family/whanau should be vigilant for changes in behaviour, thinking or mood, in particular depression and suicidal ideation. If this occurs cease taking the medicine and seek medical advice immediately.
Adverse effects	In general, bupropion is considered to be a safer medicine than nortriptyline. One in a thousand patients are expected to have a seizure over the course of treatment.[25] Use with caution in patients taking antipsychotics due to increased seizure risk. Skilled tasks, such as driving, may be impaired.	Has the potential to cause more harm than bupropion and can be fatal in overdose.[15] Adverse effects include: dry mouth, constipation, nausea, sedation (which can affect driving ability) and headaches. Advise patients to avoid alcohol as sedation may be worse.[10]	Nausea may occur in approximately one-third of patients, but this is generally mild and will only be intolerable in a few patients.[10]
Women who are pregnant	Avoid during pregnancy	Should only be taken during pregnancy when the benefits outweigh the risks	Avoid during pregnancy

	Bupropion	Nortriptyline	Varenicline
Patients with mental health issues	May cause levels of citalopram to be raised in some patients	In general, nortriptyline should be used with caution in patients thought to be at an increased risk of suicide, or who have a history of psychosis. Levels of nortriptyline can be increased by two to four-fold, or occasionally more, by the concurrent use of fluoxetine; in this situation nortriptyline dose reductions of 75% have been suggested.	See contraindications
Dosing	Initiate one to two weeks before quit date with one 150 mg bupropion tablet, daily, for three days, then 150 mg, twice daily. The maximum single dose is 150 mg bupropion, and the maximum daily dose is 300 mg bupropion. Treatment is usually for seven weeks. For people with risk factors for seizures or in elderly patients the maximum daily dose is 150 mg bupropion.	Initiate ten to 28 days before the agreed quit date with nortriptyline 25 mg, daily, gradually increase over ten days to five weeks to 75 – 100 mg nortriptyline daily, for up to three to six months. The dose should be slowly tapered while treatment is withdrawn.	Initiate one to two weeks before the quit date, at 500 micrograms varenicline, daily, for three days, increased to 500 micrograms varenicline, twice daily, for four days, then 1 mg twice daily for 11 weeks. The 1 mg dose can be reduced to 500 micrograms if it is not tolerated. This course can be repeated to reduce the risk of relapse.

* Subsidy status correct at the time of printing. Check the New Zealand Formulary for latest information.

† Varenicline is fully subsidised with Special Authority approval for people who have tried previously to quit smoking with other medicines and have not used varenicline in the preceding 12 months. In order to qualify for subsidy patients must:

- Indicate that they are ready to cease smoking; and
- Have enrolled, or about to enrol in a smoking cessation programme that includes prescriber or nurse monitoring; and
- Have trialled and failed to quit smoking previously using bupropion or nortriptyline; or tried but failed to quit smoking on at least two separate occasions using NRT, with at least one of these attempts including the patient receiving comprehensive advice on the use of NRT; and
- Not have used subsidised varenicline in the last 12 months; and
- Agree not to use varenicline in combination with other pharmacological cessation medicines; and
- Not be pregnant; and
- Not be prescribed more than three months funded varenicline

Electronic-cigarettes – the jury is still out

Electronic-cigarettes are a topic in smoking cessation that is evolving rapidly, both in terms of device design and evidence of effectiveness. The devices electronically vaporise a solution made up of propylene glycol and/or glycerol, nicotine and flavourings, that users inhale rather than burning tobacco leaves.[26] The solution is held in cartridges that are inserted into the device.[26] These devices are different to nicotine inhalators.

The body of research on electronic-cigarettes is small, but growing quickly, and opinion is divided as to the potential harms or benefits to personal or public health.[27] Currently, no electronic cigarette products have been approved under the Medicines Act for sale or supply in New Zealand and therefore it is illegal to sell an electronic-cigarette that contains nicotine.[26] It is also illegal for electronic-cigarettes, with or without nicotine, to be sold as smoking cessation aids, or for an electronic-cigarette that resembles a tobacco product to be sold to a person under the age of 18 years.[26] However, electronic-cigarettes are available on international websites as smoking cessation aids and many people who smoke are interested in using them for that purpose.

Electronic-cigarettes are considered by experts to be less harmful than conventional cigarettes, however, short-term adverse effects have been attributed to exposure to propylene glycol including eye and respiratory irritation.[28] The aerosol that electronic-cigarettes produce contains a number of cytotoxic and carcinogenic chemicals that may pose long-terms risks to women who are pregnant.[28] These compounds are present at levels one to two orders of magnitude lower than is present in tobacco smoke, but at higher levels than is found in nicotine inhalers.[28]

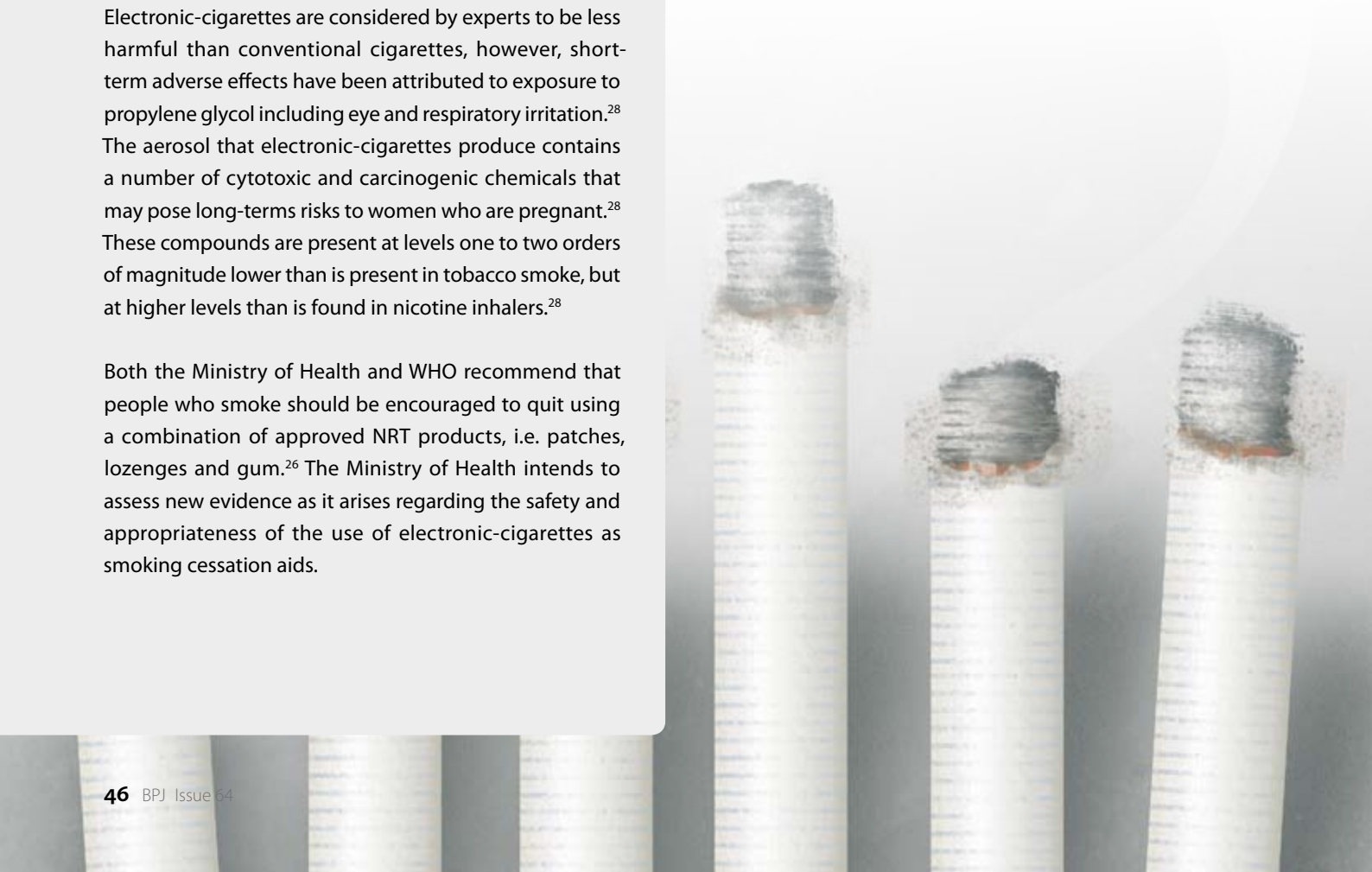
Both the Ministry of Health and WHO recommend that people who smoke should be encouraged to quit using a combination of approved NRT products, i.e. patches, lozenges and gum.[26] The Ministry of Health intends to assess new evidence as it arises regarding the safety and appropriateness of the use of electronic-cigarettes as smoking cessation aids.

Nicotine inhalators (15 mg nicotine cartridges) and nicotine mouth spray (1 mg nicotine per dose) are available as unsubsidised NRT products. Nicotine inhalators can be puffed on for 20 minutes every hour, and the cartridge replaced after three hours.[22] One cigarette puff is equivalent to approximately ten inhalator puffs.[22] Nicotine mouth sprays are also recommended for regular use, or for when cravings occur.[22] After priming the pump, direct one spray to the inside of each cheek. Advise patients to resist swallowing for several seconds after application to achieve best results.[22]

For further information see the "Guide to prescribing nicotine replacement therapy (NRT)" available from: **www.health.govt.nz**

Medicines to aid smoking cessation

Medicines for smoking cessation should be prescribed in combination with behavioural support, e.g. Quitline, to improve their effectiveness.[10] Table 1 (previous page) provides a comparison of smoking cessation medicines subsidised in New Zealand. In general smoking cessation medicines should not be used by women who are pregnant because the potential risk to foetal development cannot be balanced against the known benefits of smoking cessation.[15] Some smoking cessation medicines may not be appropriate for patients with a history of mental disorders.



ACKNOWLEDGEMENT: Thank you to **Dr Brent Caldwell**, Senior Research Fellow, Department of Medicine, University of Otago, Wellington, **Dr Marewa Glover**, Director of the Centre for Tobacco Control Research, University of Auckland and **Dr Hayden McRobbie**, Senior Lecturer, School of Public Health and Psychosocial Studies, Auckland University of Technology, Consultant, Inspiring Limited for expert guidance in developing this article.

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Safer prescribing of high-risk medicines

Methotrexate: potentially fatal in overdose

Low-dose methotrexate is commonly used in the treatment of patients with rheumatoid arthritis and other rheumatologic diseases, as well as severe psoriasis. It is prescribed as a weekly dose and is a preferred option due to its effectiveness, predictable adverse effect profile and low cost. However, it can also be highly toxic and even fatal. Although toxicity is more likely to occur in patients taking high doses, any dosing regimen may induce toxicity.[1]

While methotrexate is usually initiated in secondary care, many patients taking methotrexate will be monitored by their general practitioner, and receive repeat prescriptions in primary care. In 2013, 23.3 prescriptions for methotrexate were dispensed per 1000 patients registered in general practice in New Zealand.[2] General practitioners therefore need to be aware of strategies for safe prescribing of this potentially toxic medicine and be familiar with the symptoms and signs of methotrexate toxicity.

The mechanisms behind the anti-inflammatory effect of methotrexate in rheumatoid arthritis are not certain, but are thought to include suppressing DNA synthesis in inflammatory cells, reducing auto-antibody levels, anti-inflammatory effects of adenosine release, and reducing cytokine levels in synovial fluid to bring about a reduction in inflammatory disease activity and joint damage.[3, 4] Methotrexate acts as an inhibitor of the enzyme dihydrofolate reductase, which interferes with folic acid metabolism. As the adverse effects (but not the anti-inflammatory effects) of methotrexate are mediated via the metabolism of folates, it is given with folic acid supplementation.

Adverse and toxic effects of methotrexate

Adverse effects of methotrexate can occur at therapeutic levels and include headache, malaise, mouth ulcers and hairfall.[5] In overdose, vomiting, diarrhoea and gastrointestinal bleeding may occur, as well as severe bone marrow suppression and disturbance of liver function. Long-term liver injury, normally accompanied by elevations of ALT and AST, can result in hepatic fibrosis. Liver toxicity is more likely in patients with pre-existing risk factors for liver disease, and in patients taking methotrexate for the treatment of psoriasis than those taking it for the treatment of rheumatoid arthritis.[6]

Methotrexate can induce acute pneumonitis, which can be fatal. Patients may present with acute shortness of breath and a dry, persistent cough, possibly with fever.[7] A chest x-ray prior to initiating methotrexate is recommended to facilitate the diagnosis of potential lung disease at a later date.

Co-administration of folic acid, typically given as 5 mg weekly, a few days after each weekly methotrexate dose, has been shown to reduce the risk of adverse effects such as abdominal pain and nausea, abnormal serum transaminase levels, and increases adherence with a methotrexate regimen.[8]

Methotrexate can be fatal

There have been documented cases of death attributable to methotrexate use in New Zealand and around the world. These have often involved patients taking methotrexate as a daily, rather than weekly dose due to patient, clinician and/

or pharmacy error. In New Zealand, fatal cases have occurred most recently in 2012 and 2006.[9, 10] In the United Kingdom, the National Patient Safety Authority released a report in 2004 on methotrexate prescribing after 25 deaths and 26 incidents of serious harm in the preceding decade.[11] In some of these cases, even once the error was identified, patients died due to ongoing deterioration after methotrexate withdrawal.

The usual cause of methotrexate-related mortality is pneumonitis, which can occur idiosyncratically (i.e. it is not dose related), even after one dose. Bone marrow suppression is another cause of mortality, with multiple organ failure and gastrointestinal bleeding occurring secondary to this.

Recommendations for managing risk

A number of common sense steps can be taken by clinicians, including pharmacists, to minimise the risk of methotrexate toxicity and potential accidental overdose. Given the number of documented fatalities which have arisen from simple errors in medicine dosing frequency, the most important lesson is to emphasise that **methotrexate should be taken as a weekly dose** and to put in place procedures, safeguards and reminders to ensure this dosage is followed by doctors, pharmacists and patients.

Steps during patient consultation to ensure weekly administration:

- Avoid writing "as directed" on prescriptions – give the specific dose and state this in mg.
- Write the day the medicine is to be taken in full on the prescription (one case of fatality occurred when a patient interpreted "Mon" as morning, resulting in a daily as opposed to weekly dose).[12]
- Highlight differences in the appearance of 2.5 mg and 10 mg tablets, especially when a patient is transferred from one tablet size to another. Prescribe only one strength of tablet at a time in order to avoid accidental ingestion of 10 mg tablets in place of 2.5 mg tablets.[12]
- Emphasise to the patient the differences between methotrexate and folic acid – cases have occurred where the two dosing regimens were inadvertently swapped by the patient.[11] A simple mnemonic tool is "Methotrexate for Monday", "Folic acid for Friday" as a means of ensuring once weekly dosing for each on different days.
- Maintain contact with the secondary care team and patient contact with rheumatology and practice nurses. Research conducted in New Zealand found significantly higher levels of patient awareness of signs and symptoms of methotrexate toxicity and awareness of weekly dosing in patients who had seen a rheumatology nurse.[13]
- If the patient has a carer, ask that they be present at consultations or that the need for accurate intake of medicines is discussed with them (with patient consent).
- In follow-up appointments specifically question patients on their medicine intake – How many tablets of methotrexate do you take? When do you take them?

Be vigilant for adverse effects, and ensure patients understand what these could be:

- Patients should be advised of key symptoms of methotrexate toxicity such as a sore throat, mouth ulcers, fever, dry persistent cough, vomiting or diarrhoea, and to report if any of these occur.
- Ensure that patient reports of adverse effects while taking methotrexate are relayed by practice staff to the patient's usual clinician.[9]

Practice steps to ensure weekly administration:

- Check that prescribing software automatically defaults to weekly prescriptions for methotrexate.[9]
- Flag the patient's notes to alert other practice staff to report any potential features of methotrexate toxicity.[9]
- Consider a short education session for practice staff on methotrexate risks and symptom awareness, and put processes in place so that methotrexate adverse effects can be reported to the treating clinician.
- Be aware of failures to report for appointments by patients taking methotrexate, and double check the reasons why.

Laboratory monitoring is essential (also see Table 1, over page):

- A full blood count, liver and renal function tests should be carried out before starting methotrexate, and repeated every two to four weeks initially, then every month to three months if results have been normal and the dose is stable.
- Ensure tests have been done within the last six weeks prior to writing repeat prescriptions.[12]
- Results showing decreased white blood cell counts or increased transaminase levels may indicate methotrexate toxicity. Discuss any abnormal results with the rheumatologist/dermatologist. See Table 1 for further details.

- Procollagen 3 (type III procollagen amino terminal propeptide, or PIIINP) may be used to monitor liver safety in patients with psoriasis. This is available as a Tier two test in the National Laboratory Test Schedule and will be arranged by a specialist. Liver biopsies may also be performed.

Check concurrent medicine and alcohol use:

- Impaired renal function can reduce the excretion of methotrexate and patients should report any use of medicines such as NSAIDs which reduce methotrexate excretion.[5]
- Alcohol intake should ideally be no more than one to two standard drinks twice per week,[5] although many patients admit to higher amounts without developing evidence of liver problems.
- Co-trimoxazole and trimethoprim should be avoided in patients taking methotrexate due to a theoretical increase in risk of bone marrow suppression.[5, 14]

Pharmacy steps to avoid weekly dosing errors:[9]

- Ensure that methotrexate labels state that dosing is weekly and give the day of the week, written in full, that the medicine is to be taken.
- Ensure software alerts are given appropriate attention.
- Contact the prescribing clinician with queries or to check that dosing is appropriate when there is doubt.
- Place prepared scripts for medicines with alerts in a different area to general, non-high risk, medicines so that alerts can be appropriately checked and addressed before handing medicines to patients.
- Where prescriptions are manually entered into a pharmacy computer system, double check that entry is correct. When filling repeats, refer back to original script rather than computer system to ensure any errors which may occur when entering prescription details into computer software are not perpetuated.
- Be wary of needing to order stock to fill a script for high risk medicines; as this may indicate that a prescribing error has occurred.
- Have a system for recording "near miss" events, as these can identify sources of error.

A Methotrexate Patient Guide is available from: **www.saferx.co.nz/methotrexate-patient-guide.pdf**

ACKNOWLEDGEMENT: Thank you to **Associate Professor Andrew Harrison**, Rheumatologist, Clinical Head of Department, Wellington Regional Rheumatology Unit and Wellington School of Medicine, University of Otago, Wellington and **Dr Peter Jones**, Rheumatologist and Chief Advisor, Sector Capability

Methotrexate is contraindicated in women who are pregnant or breast feeding

Care must be taken to avoid the use of methotrexate in women who are pregnant as it is an abortifacient and can exert teratogenic effects on the developing foetus.[15] If female patients of reproductive age are prescribed methotrexate, discuss appropriate contraception and delaying pregnancy plans. International treatment guidelines also recommend the use of contraception for male patients taking methotrexate,[14] although recent evidence suggests that paternal use of methotrexate does not increase the risk of miscarriage or birth defects.[16]

Table 1: Recommended monitoring for patients taking methotrexate, adapted from Chakravarty et al, 2008[14]

Laboratory monitoring	Frequency	What to look for	What to do
Full blood count (FBC)	Baseline Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	WBC $<3.5 \times 10^9$/L Neutrophils $<2.0 \times 10^9$/L Platelets $<150 \times 10^9$/L	Discuss with specialist team immediately.
		MCV > 105 fL	Check vitamin B12, folate and TSH. If abnormal, treat any underlying abnormality.
Liver function tests (LFTs)	Baseline Every two to four weeks initially, then every month to three months if results have been normal on a stable dose.	AST, ALT > twice the upper limit of reference range.	Withhold until discussed with specialist team. Other factors to consider: • Check alcohol intake. • Review medicines which may cause liver dysfunction, e.g. NSAIDs
Serum creatinine	Baseline Often performed at same time as LFT and FBC monitoring during dosing changes. Every three months for patients on stable treatment.	Significant deterioration in renal function	Reduce dose
Chest X-ray	Baseline		Repeat if respiratory symptoms occur (see below)

Symptoms	What to do
Rash or oral ulceration	Withhold methotrexate until discussed with specialist team. Folic acid mouth wash may help with mucositis.
Nausea and vomiting, diarrhoea	Giving methotrexate by subcutaneous injection is often a good way of avoiding nausea
New or increasing dyspnoea or dry cough (pneumonitis)	Withhold and discuss URGENTLY with specialist team. Arrange chest x-ray and respiratory function tests
Severe sore throat, abnormal bruising	Request immediate FBC and withhold until results available. Discuss any unusual results with specialist team

and Implementation, Ministry of Health for expert review of this article.

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