Best Practice

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SCE Issue 1 August 2020

A Special Commemorative Edition of
Best Practice Journal 2020

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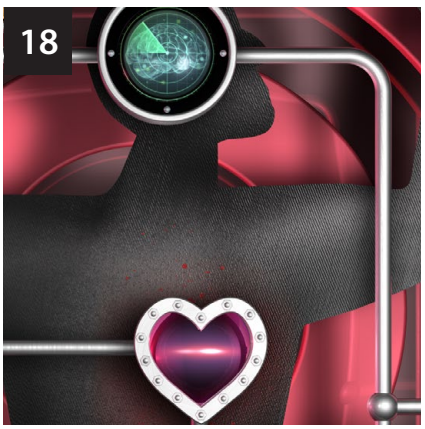

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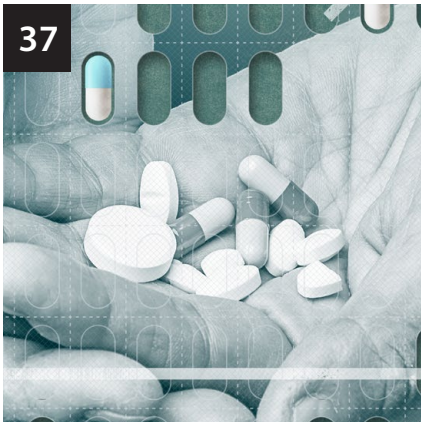

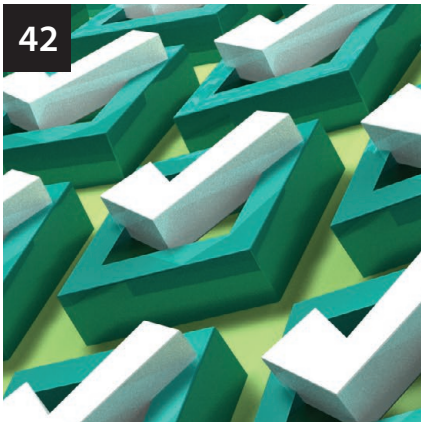

Welcome to your Special Commemorative Edition of Best Practice Journal 2020

We are pleased to offer our readers a curated selection of ten of our most popular and influential articles published in Best Practice Journal, Best Tests and online over the last few years. We have chosen topics to cover a wide range of primary care practice and have edited and updated these articles to include the latest evidence and prescribing data.

These articles reflect some of our major campaigns that our primary care audience have engaged with and supported to translate into meaningful changes in practice. This includes significantly reducing the volume of oxycodone prescribed in the community and halving the number of prescriptions for topical antibiotics.

Many of you have been with us since our first edition of Best Practice Journal, published in 2006. We went on to publish 79 editions over 12 years, with our last edition hitting the presses in 2017. We never said it was over though! So many of you ask us when you will get your next edition of BPJ, so we have delivered. We would like to make this a regular occurrence; online and in print format. We will let you know all the details, after we ascertain our audience's needs and finalise the specifics.

As we move into a new era of publishing, we are also excited to explore future possibilities for optimising the way that primary care receives and interacts with medical information and continuing education. For example, integrating guidance directly into the patient record, to provide an "auto-assist" at the point of care. Any technology advancement will be underpinned by the robust, evidence-based, high-quality guidance that you know, trust and expect from bpac[nz].

We trust that you will enjoy this complimentary edition of Best Practice Journal. If you have any feedback, please email: **editor@bpac.org.nz**

Ngā mihi, best regards
The Publications Team, bpac[nz]

The oxycodone problem: did we fix it?

For more than ten years bpac^nz has been at the frontline of New Zealand's battle against oxycodone overprescribing. We review the oxycodone story, examine how the problem occurred in the first place, and analyse where we are at now. Much of the work is now set in place, but there is never a time to become complacent about this medicine.

An old medicine, but a recent problem

Oxycodone was first synthesised in 1916 in Germany and was available for clinical use in the United States by 1939. A controlled release formulation of oxycodone (OxyContin) was first distributed in 1996. This "new" medicine was regarded by many as an improved opioid analgesic with fewer adverse effects and less of the stigma associated with morphine. Since then, use of oxycodone has increased dramatically and many countries are battling the consequences of widespread misuse, addiction and illegal diversion. For example, in Ontario, Canada, the number of prescriptions for oxycodone increased by 850% between 1991 and 2007.[1] In Australia, the supply of oxycodone increased 22-fold between 1997 and 2012, and oxycodone became the seventh most commonly prescribed medicine in general practice.[2] The adverse effects of overuse are most clearly seen in the United States where an average of 41 people died each day in 2018 from overdoses involving prescription opioids.[3]

Did we fall for the hype?

When it was released, oxycodone was promoted by an intensive marketing campaign. During the first six years that Oxycontin was on the market, Perdue Pharma spent six to 12 times the amount it spent on marketing MS Contin (morphine) and sales increased from $48 million (USD) in 1996 to $1.1 billion (USD) in 2000.[4] A consistent feature of this promotion was a minimisation of the risk of addiction associated with OxyContin. This misrepresentation was costly; Perdue subsequently pleaded guilty to criminal charges and was ordered to pay $634 million (USD) in fines.[4]

The adverse effect profile of oxycodone

The reality, however, is somewhat different. Despite its name, oxycodone is not a version of codeine; it is a strong opioid, approximately twice as potent as morphine. It has a similar adverse effect profile to other opioids and may have even more addiction potential than morphine. Constipation and nausea should be expected in one-quarter to one-third of patients and drowsiness, vomiting and pruritis occurs in 10–15% of patients.[5]

The oxycodone story in New Zealand

Oxycodone was approved by Medsafe in 2001 and controlled and immediate-release oral forms were subsidised in New Zealand from 2005. Prescribing of oxycodone in New Zealand peaked in 2011/12. Since becoming available in New Zealand,

oxycodone has increasingly been used as a drug of abuse. For example, the percentage of injecting drug users who had used oxycodone in the previous six months increased from 9% in 2008 to 17% in 2016.[6]

The bpac^{nz} message has been consistent

In 2009, bpac^{nz} first began urging prescribers to review their use of oxycodone, and since then we have published over 20 articles, prescribing reports, clinical audits and peer group discussions focusing on the following key messages:

- Oxycodone is a strong opioid, approximately twice as potent as morphine
- There are few situations when a strong opioid should be initiated in primary care for the management of acute pain
- Morphine is the preferred first-line option when a strong opioid is indicated
- Oxycodone is rarely preferable to morphine because it has a similar adverse effect profile, is not more effective and may have more addictive potential

Many clinicians have prescribed oxycodone in preference to morphine thinking that oxycodone is safer in patients with renal impairment. Fentanyl or methadone, however, are preferable options in this patient group, because unlike morphine and to a lesser extent oxycodone, neither have significant active metabolites.

Are strong opioids necessary?

Opioids are of little benefit in managing long-term non-malignant pain. Typically, they are associated with a brief reduction in subjective pain before tolerance and hyperalgesia negate the benefit, leaving the patient neuro-adapted to a higher dose. In addition, constipation associated with opioids can be difficult to manage.

Health professionals are recommended to form a treatment contract with patients before prescribing strong opioids. This agreement should cover the expected treatment duration, dose parameters, outcome measures, how to manage adverse effects and dates of review. Outcomes should be measurable by improvements in function, not subjective pain score – pain always eases with a dose increase, but temporarily, just as it always flares with a dose decrease, temporarily.

Further information on the use of strong opioids is available from: "When to consider strong opioids for patients with acute pain", **https://bpac.org.nz/2018/opioids.aspx**

Information on withdrawing strong opioids and detecting potential drug seeking behaviour is available from: "Update on oxycodone: what can primary care do about the problem", **https://bpac.org.nz/bpj/2012/may/oxycodone.aspx**

The Alcohol & Drug Helpline (0800 787 797) can advise on local availability of addiction support services and provides Māori, Pasifika and Youth helplines.

Have we collectively made a difference?

Oxycodone dispensing decreased substantially from 2011 to 2015 and has remained at approximately the same level since then (Figure 1). Over the same time, however, dispensing of morphine increased and plateaued suggesting that while oxycodone may be being prescribed more appropriately, the use of strong opioids in New Zealand has increased.

How prescribing of oxycodone has changed in New Zealand

Prescribing of oxycodone by primary care clinicians has reduced substantially, which will have undoubtedly decreased opioid-related harms in New Zealand communities. Table 1 shows that the proportion of patients initiated on oxycodone

Figure 1: The number of patients in New Zealand dispensed oxycodone hydrochloride and morphine (2011–2019)[7]

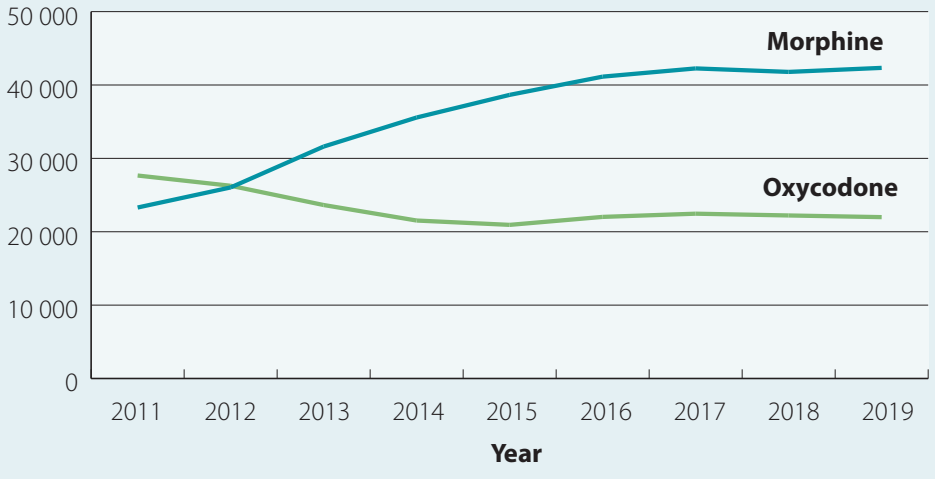

Table 1: The origin of oxycodone prescriptions in New Zealand[7]

Year	Initial prescription in secondary care		Initial prescription in primary care	Total new patients prescribed oxycodone
	Not continued in primary care	Continued in primary care		
2011	52%	17%	31%	22,678
2015	57%	18%	25%	16,144
2019	59%	17%	24%	17,987

in primary care has decreased from approximately one-third to one-quarter. This is mirrored by a reduction of approximately 5,000 in the number of new patients initiated on oxycodone in 2019, compared to 2011. An area where improvements could potentially still be made is the proportion of patients who are initiated on oxycodone in secondary care and their prescriptions continued by primary care prescribers; this percentage has remained similar over the past ten years.

There is still mahi to be done

Despite successfully reducing the amount of oxycodone dispensed in New Zealand, there is still more work to be done. Specifically, there are marked regional differences in oxycodone dispensing (Figure 2). The two DHBs with the highest levels of oxycodone dispensing in 2019 were Waikato DHB with 8.29 patients per 1,000 population, and Bay of Plenty DHB with 7.65 patients per 1,000 population. The Capital and Coast DHB (CCDHB) had the lowest rate of community dispensing of oxycodone in New Zealand in 2019 with 0.84 patients per 1,000 population. The success of CCDHB in reducing oxycodone prescribing may be largely attributed to a programme launched in 2012, with supporting resources from bpac^{nz}, that educated clinicians from both secondary and primary care on the appropriate use of oxycodone; this initiative may be useful as a template for other DHBs.

Further information about how Capital and Coast DHB reduced oxycodone prescribing is available from: "Oxycodone prescribing: New Zealand solutions to a global problem", **https://bpac.org.nz/2016/oxycodone-prescribing.aspx**

The key messages about opioids remain the same

Key messages for considering the role of opioids in the management of non-cancer pain include:

- Optimise appropriate non-pharmacological and non-opioid treatments first
- Strong opioids are only appropriate for moderate to severe pain
- Morphine is the first-line strong opioid unless the patient is intolerant
- Regularly assess patients taking strong opioids and step down to a weaker opioid or paracetamol if a strong opioid is no longer required
- Ensure the patient understands the risks and benefits of opioid treatment
- Avoid prescribing more than three days' supply unless longer term treatment is clearly warranted
- Co-prescribe laxatives if opioids are used for more than a few days
- The concurrent use of paracetamol or a NSAID reduces the dose of opioid required
- Primary care clinicians do not need to repeat the same prescription for patients discharged from hospital
- Prescribe opioids with caution in elderly patients: take renal function into account and prescribe lower doses if necessary
- Ensure the patient understands that opioids can affect their ability to work or drive

Health professionals in primary care have the best understanding of a patient's clinical needs and psychosocial background and are encouraged to promptly revaluate the pain management strategies for all patients who are discharged from hospital; do not simply "go with the flow" in terms of analgesic regimens.

Further information about non-pharmacological interventions for the management of long-term pain is available from: "Helping patients cope with chronic non-malignant pain: it's not about opioids", **https://bpac.org.nz/BPJ/2014/September/chronicpain.aspx**

Further information about managing acute pain is available from: "The principles of managing acute pain in primary care", available from: **https://bpac.org.nz/2018/acute-pain.aspx**

Summary: The price of safety is eternal vigilance

So did we fix it? We have certainly made excellent progress and New Zealand has so far largely avoided the "opioid epidemic" and follow-on consequences seen in other countries. This is, however, no reason for complacency. Prescribers are encouraged to continue to review their use of strong opioids to ensure that it is appropriate and optimal. Non-opioid and non-pharmacological methods of analgesia should be an integral part of any pain management plan.

Further information on prescribing oxycodone in primary care is available from: "Oxycodone use still increasing", **https://bpac.org.nz/BPJ/2011/june/oxycodone.aspx** , "Upfront: A disaster in the making: it's time to take action against misuse of oxycodone" , **https://bpac.org.nz/BPJ/2014/June/upfront.aspx** and "Oxycodone: how did we get here and how do we fix it?" , **https://bpac.org.nz/BPJ/2014/July/oxycodone.aspx**

A clinical audit on oxycodone prescribing is available from: "Appropriate prescribing of oxycodone for non-cancer pain in general practice", **https://bpac.org.nz/Audits/Oxycodone.aspx**

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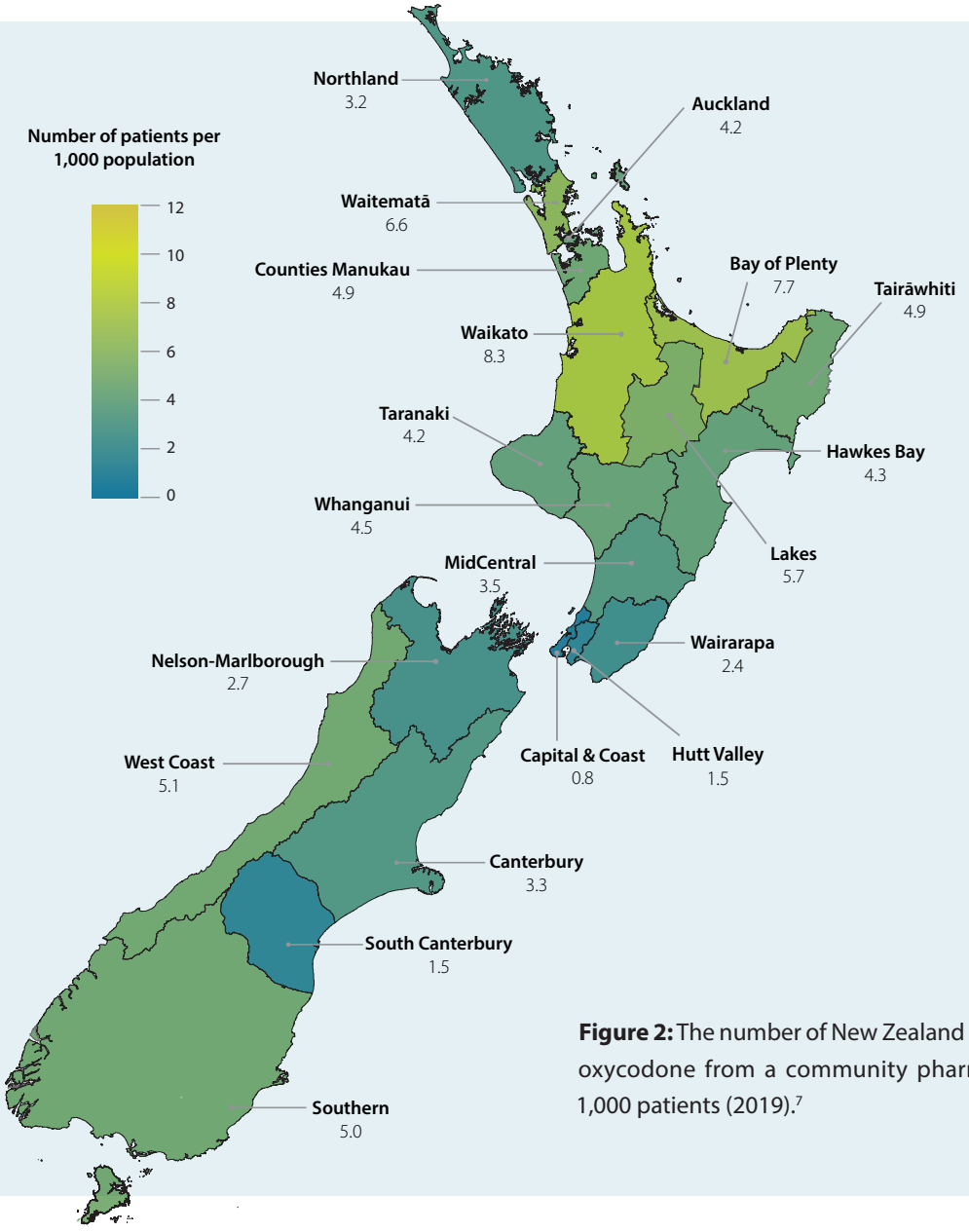

Figure 2: The number of New Zealand patients dispensed oxycodone from a community pharmacy by DHB, per 1,000 patients (2019).[7]

A rising tide of type 2 diabetes in younger people: what can primary care do?

KEY PRACTICE POINTS:

- The incidence of type 2 diabetes in younger adults and adolescents in New Zealand is increasing; people of Māori, Pacific and South Asian ethnicities are particularly at risk
- Preventing, or delaying, onset of type 2 diabetes is paramount to reducing the burden of diabetes complications; this may be possible with careful management
- Test HbA_{1c} levels in patients at high risk, regardless of their age, so that patients can be supported to make lifestyle changes before they develop diabetes
- The management of type 2 diabetes in younger people is essentially the same as for older people, i.e. lifestyle interventions and metformin first-line, but treatments need to be more assertive, e.g. pharmacological treatment escalated sooner
- If an additional pharmacological treatment is required, clinicians and patients can choose between adding vildagliptin, a sulfonylurea or pioglitazone to metformin, or using one of these alone if metformin is contraindicated or not tolerated; insulin should be initiated if further intensification is required
- A high degree of patient engagement is crucial to maximise the benefits of lifestyle changes and ensure patients take their medicines as prescribed

Early onset type 2 diabetes: increasingly common and associated with higher risks

New Zealand has a diabetes problem, fuelled in part by one of the highest rates of obesity in the world.[1] Approximately 6% of the total population has diabetes. The prevalence of diabetes is highest in older age groups, reaching approximately 15–20% in people aged over 65 years; however, prevalence is increasing in younger people in New Zealand.[2] People of Māori, Pacific and South Asian ethnicity, and people who are socioeconomically disadvantaged, bear a disproportionate burden of obesity and type 2 diabetes.

Many young people are at high risk of developing type 2 diabetes

People with HbA_{1c} levels of 41–49 mmol/mol are classified as having "pre-diabetes", which is associated with an increased risk of cardiovascular disease and progression to type 2 diabetes. Data from the most recent national nutrition survey identified that 16% of the population aged under 45 years had pre-diabetes.[3] It is estimated that in the Auckland region, over 40% of people of Māori, Pacific or Indian ethnicity aged 35–39 years have pre-diabetes.[2]

Early onset results in worse health outcomes

Younger people diagnosed with type 2 diabetes, e.g. before the age of 40 years, have a higher risk of early mortality, cardiovascular disease, chronic kidney disease and retinopathy than older adults diagnosed with type 2 diabetes or people with type 1 diabetes at a similar age.[4–6] This is largely because people diagnosed younger have diabetes for longer and are therefore exposed to more risk, but also because glycaemic control tends to be worse and younger people are more likely to have sporadic contact with health care services.[4, 7]

Test people at high risk

HbA_{1c} should be tested in people at high risk of type 2 diabetes of any age to aid early detection and therefore reduce their risk of future cardiovascular and renal complications. As type 2 diabetes is not necessarily associated with any symptoms, patients may not even recognise that they are at risk.

Identifying people at elevated risk

Ministry of Health guidelines recommend HbA_{1c} testing in people with **any** of the following risk factors:[2]

- A BMI of ≥ 27 kg/m^2 for people of Māori, Pacific or South Asian ethnicities, or ≥ 30 kg/m^2 for people of other ethnicities*
- A first-degree relative who developed type 2 diabetes at an early age, e.g. < 40 years
- Long-term use of oral corticosteroids
- Females with a personal history of gestational diabetes
- Females with polycystic ovary syndrome
- Severe mental illness, particularly those on long-term antipsychotic treatment
- Known ischaemic heart, cerebrovascular or peripheral vascular disease

Children and adolescents (aged > 10 years or at onset of puberty, whichever occurs earlier) who are overweight or obese (BMI ≥ 85th percentile or BMI ≥ 95th percentile, respectively) should be tested if there is a family history of early onset type 2 diabetes, a maternal history of diabetes or gestational diabetes, or if they are of Māori, Pacific or Indian ethnicity.[2, 8]

* A lower BMI threshold is recommended for people of Māori, Pacific or South Asian ethnicities due to the higher risk people of these ethnicities have of developing type 2 diabetes.[2] South Asian ethnicities include Indian, Fijian Indian, Sri Lankan, Afghani, Bangladeshi, Nepalese, Pakistani and Tibetan.

A specific opportunity to incorporate HbA_{1c} testing into routine practice is the cardiovascular risk assessment; the age at which to start assessments is now recommended as:[9]

- 45 years for males and 55 years for females with no known risk factors
- 30 years for males and 40 years for females of Māori, Pacific or South Asian ethnicity
- 35 years for males and 45 years for females with known cardiovascular risk factors or at high risk of developing diabetes†

† Further information on family and personal risk factors is available at: www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care

Consider the possibility of type 1 diabetes or a monogenic form of diabetes in younger adults with elevated HbA_{1c} without obesity, family history or other typical features such as hypertension, dyslipidaemia or non-alcoholic fatty liver disease.

Lifestyle change is a cornerstone of managing and reducing the risk of type 2 diabetes

One of the most important points to convey to people who have type 2 diabetes or pre-diabetes is that the course is modifiable. Changes to their lifestyle, i.e. ensuring a healthy, balanced diet and engaging in regular physical exercise, may be difficult at first, but they can substantially improve their future health. The patient will have to take the lead role in making those changes, but with support from their primary care team. Setting small, incremental goals can be helpful if patients are feeling overwhelmed by the extent of changes recommended.[10]

Weight loss has the potential to induce remission of type 2 diabetes in people who are overweight or obese, i.e. to achieve an HbA_{1c} < 50 mmol/mol without the use of medicines,[11] and should be regarded as a core focus of treatment.


For further information on weight loss, see: **www.bpac.org.nz/2019/weight-loss.aspx**

Lifestyle change in people with pre-diabetes reduces their chance of developing diabetes by approximately 50–60% over three years and 27% over 15 years.[12, 13] This includes aiming for a 7% weight loss, 2.5 hours per week of moderate intensity physical activity and following healthy diet recommendations.

Referral for bariatric surgery may be appropriate for some people with a BMI between 35–55 kg/m^2 to assist with weight loss.[10] Bariatric surgery can reduce the likelihood of developing type 2 diabetes, and in those who already have type 2 diabetes, can induce remission, as well as reduce the risk of diabetes complications, cardiovascular disease and some cancers.[10, 14]


For further information on bariatric surgery, see: **www.bpac.org.nz/2018/diabetes.aspx#bariatric**

Managing cardiovascular and renal risk

Cardiovascular and renal diseases are the main causes of early mortality in people with type 2 diabetes, and preventing the onset or progression of these conditions in young people should be a focus of management.[15] Lifestyle changes can improve markers of cardiovascular risk, such as blood pressure and lipid levels, however, pharmacological treatment should be initiated if lifestyle changes result in insufficient improvements, or if the patient's risk is high.

For further information on managing cardiovascular and renal risk in patients with type 2 diabetes, see: **www.health.govt.nz/publication/cardiovascular-disease-risk-assessment-and-management-primary-care**

An online calculator for determining the risk of cardiovascular and renal disease in patients with type 2 diabetes is available at: **www.nzssd.org.nz/cvd_renal/**

Engaging people to make changes

Identify what motivates people. People can have very different reactions to a diagnosis of type 2 diabetes, or being told they are at high risk. Motivational strategies should be individualised, but a key message is that it is never too late to "step back from the edge" and their course of type 2 diabetes is not pre-determined.

Avoid stigma and blame. Discussing lifestyle changes can be challenging, as the advice required often carries an unspoken implication that the person has brought the disease on themselves. Conveying that the risk of type 2 diabetes and obesity is influenced by factors which are out of a person's control, e.g. genetics, exposures *in utero* or early childhood, or factors in the environment, may help alleviate some of the stigma and embarrassment associated with obesity and type 2 diabetes. Advice on language that can help avoid blame when discussing type 2 diabetes is provided in Table 1 of the original article, available here: **www.bpac.org.nz/2018/diabetes.aspx**

Regular follow-up is essential. Develop an agreed plan that can be used to track progress, e.g. appointment with a practice nurse, providing advice or support via telephone or text message. Encourage patients to make one change at a time with subsequent goals added at follow-up appointments; focus on the changes that will bring the greatest benefit, e.g. weight loss or smoking cessation.

Connect patients to services that can assist with lifestyle changes, including referring patients to a dietitian, providing them with a Green Prescription, or referring to programmes offered by a local PHO, DHB or Māori health provider.

Pharmacological management of people with early onset type 2 diabetes

The approach to pharmacological management of patients with early onset type 2 diabetes is essentially the same as for older patients with type 2 diabetes, i.e. metformin first-line, followed by other oral hypoglycaemic medicines and insulin, as appropriate. However, faster escalation of treatments may be required and lower targets for glycaemic control are justified.[16] Patients with early onset type 2 diabetes can have a more rapid increase in HbA_{1c} levels, despite treatment, and are likely to require more frequent dose increases, use of multiple oral medicines or earlier addition of insulin than older patients with type 2 diabetes.[17] Effective communication and engagement with patients in regards to the importance of adhering to their prescribed medicines is of particular importance in this age group.

Despite being young, patients may already have complications and should have their retinal, foot, renal and cardiovascular health fully assessed and managed at diagnosis. Also consider associated co-morbidities, such as sleep apnoea or non-alcoholic fatty liver disease.

For further information on setting a HbA_{1c} target and prescribing glucose-lowering medicines for patients with type 2 diabetes, see: **https://bpac.org.nz/2019/hba1c.aspx**

Metformin for patients with "pre-diabetes"

Metformin can be prescribed (unapproved indication) to reduce the risk of developing type 2 diabetes in patients at high risk (e.g. HbA_{1c} of 46–49 mmol/mol), but should be considered an adjunct treatment in addition to changes in diet and activity levels.[12] Metformin reduces the risk of developing type 2 diabetes by approximately one-third after three years, and approximately 20% after ten years, compared to a placebo medicine in patients at high risk.[18]

Dual therapy: adding a second anti-diabetic medicine

If a sufficient reduction in HbA_{1c} levels is not achieved with metformin, treatment is typically escalated by reinforcing the importance of diet and exercise, and adding a second pharmacological treatment.

Options include:

- Vildagliptin (oral, funded), taken either as separate metformin and vildagliptin tablets, or a combination vildagliptin + metformin formulation
- A sulfonylurea (oral, funded), such as gliclazide or glipizide
- Pioglitazone (oral, funded)
- A sodium-glucose co-transporter 2 (SGLT-2) inhibitor (oral, not funded*)

- A glucagon-like peptide 1 (GLP-1) receptor agonist (injectable, not funded*)

* Update September, 2020: PHARMAC is currently consulting on a proposal to fund a sodium-glucose co-transporter 2 (SGLT2) inhibitor, empagliflozin (with and without metformin) and an injectable glucagon-like peptide 1 (GLP-1) receptor agonist, dulaglutide. If the decision is made to fund these medicines, empagliflozin would be available from 1 December, 2020 and dulaglutide available as soon as it receives Medsafe approval; it is proposed that Special Authority criteria would need to be met to be eligible for funded access to these medicines.

Clinicians and patients can jointly decide which of these medicines to use, taking into account any contraindications, cardiovascular comorbidities, risk of hypoglycaemia, effects on weight, medicines interactions, adverse effects and cost (Table 1).[19] A SGLT-2 inhibitor or GLP-1 receptor agonist is the preferred second-line pharmacological treatment in international guidelines for people with type 2 diabetes who are at high risk or have established CVD, chronic kidney disease or heart failure, or where there is a need to minimise weight gain or promote weight loss.[19, 20] However, these medicines are not currently funded in New Zealand.

People who have contraindications to using metformin, or who trial metformin but are unable to continue use due to adverse effects, can initiate any of these other options alone.[20]

Triple therapy: insulin is typically initiated if treatment with two oral medicines is insufficient

If further escalation of treatment is required, insulin can be initiated or three oral medicines used in combination. The addition of insulin is the typical course of action and should be considered for patients with a HbA_{1c} level > 65 mmol/mol despite lifestyle interventions and treatment with two oral anti-diabetic medicines.[22] N.B. A GLP-1 receptor agonist is preferred to insulin for treatment intensification in international guidelines.[19]

Vildagliptin: the new kid on the block

Vildagliptin is an oral dipeptidyl peptidase (DPP-4) inhibitor approved for the treatment of type 2 diabetes. Vildagliptin has been fully funded in New Zealand since 1 October, 2018. Since it was funded, 45,662 people in New Zealand have been dispensed this medicine. Vildagliptin prescribing increased steadily through 2019 and the first half of 2020; it is likely to match the rate of prescribing for sulfonylureas later in 2020.

N.B. The spike in dispensings in March 2020, followed by the drop in April, 2020, reflects New Zealand moving into COVID-19 pandemic Level 4.

N.B. Liver function should be assessed before initiating vildagliptin treatment and monitored every three months for the first year.[21]

For further information on prescribing vildagliptin, see: **https://bpac.org.nz/2018/vildagliptin.aspx**

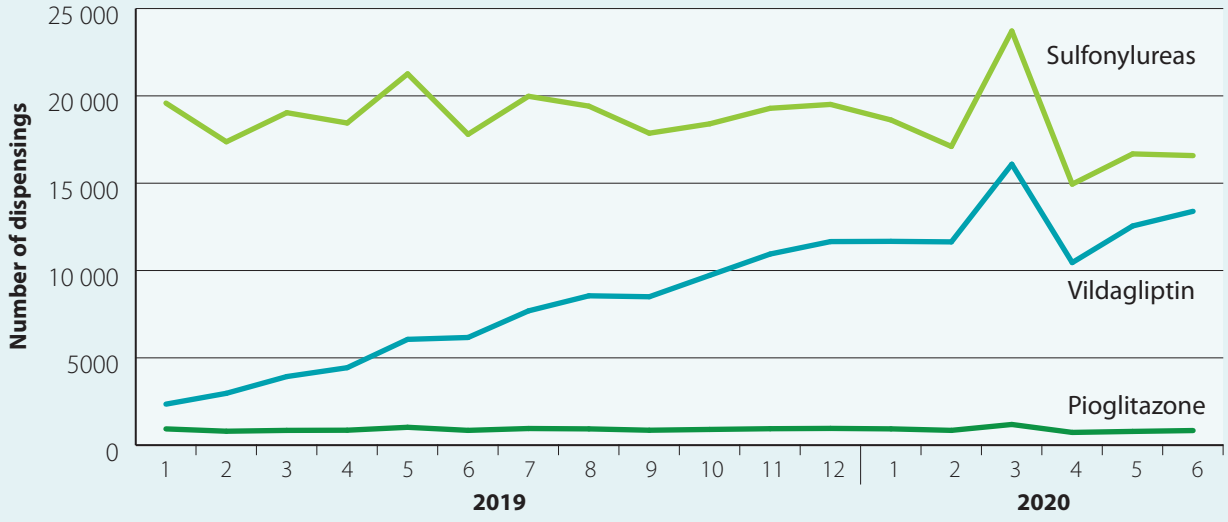

Figure 1: The number of dispensings of vildagliptin (and formulations), sulfonylureas (glibenclamide, gliclazide and glipizide) and pioglitazone dispensed from community pharmacies in New Zealand from January, 2019 to June, 2020.

At diagnosis:

Discuss non-pharmacological treatment:

- Lifestyle changes are the cornerstone of management
- Emphasise the importance of diet and exercise approaches regardless of which medicines are used
- Support and encourage patients to make lifestyle changes throughout follow-up
- Refer patients to support services, e.g. a Green prescription or dietitian, to assist with lifestyle changes

Prescribe an appropriate medicine regimen based on the extent of hyperglycaemia:

- **Initiate metformin at, or soon after, diagnosis** for all patients with type 2 diabetes
  - If patients have contraindications to using metformin, initiate one of the anti-diabetic medicines under "Dual therapy"
- Consider prescribing two oral medicines or initiating insulin if patients have high HbA_{1c} levels at diagnosis, e.g. > 75 mmol/mol

Determine an appropriate HbA_{1c} target

Escalating treatment

If patients do not have a sufficient reduction in HbA_{1c} levels

Dual therapy:

Initiate one of the following medicines **in combination with metformin**:

- Vildagliptin*
- A sulfonylurea
- Pioglitazone
- A SGLT-2 inhibitor†
- A GLP-1 receptor agonist†

Prescribe one of these medicines instead of metformin if patients have intolerable adverse effects while using metformin or contraindications

Triple therapy:

Discuss initiating insulin for patients with an HbA_{1c} > 65 mmol/mol despite lifestyle and oral pharmacological approaches

Or consider a combination of:

- Three oral hypoglycaemic medicines
- Two oral hypoglycaemic medicines + a GLP-1 receptor agonist

For further information on initiating insulin, see:

www.bpac.org.nz/BPJ/2015/December/diabetes.aspx#3

* Vildagliptin can be prescribed with metformin either as separate metformin and vildagliptin tablets or in combination metformin + vildagliptin formulations

† Not funded

Figure 2: An overview of management of patients with type 2 diabetes.[19, 20, 23]

Table 1: Effects of diabetes medicines (excluding insulin) on HbA_{1c}, cardiovascular co-morbidities, progression of kidney disease, weight and risk of hypoglycaemia. Adapted from the American Diabetes Association (2020)[19]

Medicine	Efficacy for lowering HbA_{1c}	Cardiovascular effects		Renal effects: progression of chronic kidney disease	Effects on weight	Risk of hypoglycaemia
		CVD	HF			
Metformin	High	Potential benefit	Neutral	Neutral	Neutral with potential for modest loss	Low
Sulfonylureas	High	Neutral	Neutral	Neutral	Gain	High
Pioglitazone	High	Potential benefit	Increased risk	Neutral	Gain	Low
Vildagliptin	Intermediate	Neutral	Neutral	Neutral	Neutral	Low
SGLT-2 inhibitor*†	Intermediate	Benefit: empagliflozin, canagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	Benefit: empagliflozin, canagliflozin, dapagliflozin	Loss	Low
GLP-1 receptor agonist*†	High	Benefit; lixisenatide is neutral	Neutral	Benefit: liraglutide	Loss	Low

* Not funded

† Preferred choice to add to metformin in patients with cardiovascular disease, heart failure or chronic kidney disease[19]

When to seek further advice

Consider discussing patients with a diabetes specialist if appropriate management and adherence to treatment is ineffective in controlling progression of disease, e.g. HbA_{1c} > 75 mmol/mol, declining renal function, significant albuminuria or other uncontrolled diabetes or cardiovascular complications.

For the original and extended version of this article see: "A rising tide of type 2 diabetes in younger people: what can primary care do" (available at: **https://bpac.org.nz/2018/diabetes.aspx**)

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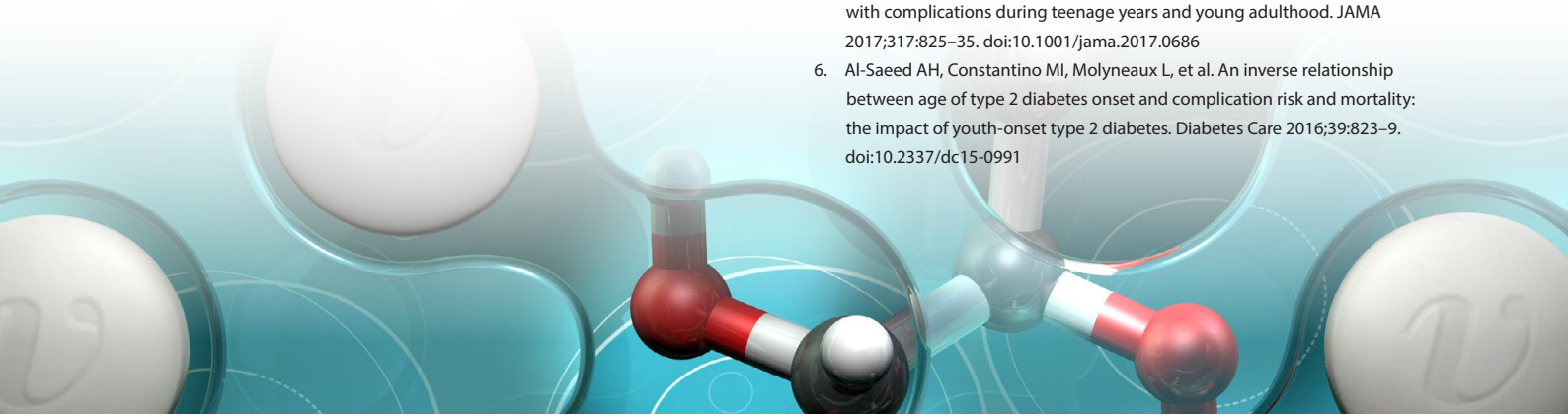

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Topical antibiotics: keep reducing use

Encouraging progress has been made by prescribers in New Zealand in reducing the use of topical antibiotics such as fusidic acid; however, the challenge is to maintain this momentum and reduce use even further as there are very few indications for prescribing these medicines.

KEY PRACTICE POINTS:

- Dispensing of topical antibiotics has continued to reduce over recent years, but further reductions may be possible given the very few indications for use
- Good skin hygiene measures (e.g. "clean, cut and cover") and the use of topical antiseptics such as hydrogen peroxide or povidone iodine are recommended for treating localised or minor skin infections, including impetigo
- If antibiotic treatment is indicated for a skin infection, oral antibiotics are almost always the most appropriate choice
- Topical antibiotics are not required following minor invasive procedures, e.g. removal of benign skin lesions

Topical antibiotics are associated with increasing bacterial resistance

Over the last few years there has been a focus on the high rates of topical antibiotic use in New Zealand and increasing antibiotic resistance. bpac^{nz} has addressed this topic several times with guidance highlighting that many patients with mild bacterial skin infections do not require antibiotics and emphasising the problems associated with topical antibiotic use in New Zealand:

- Increasing resistance leads to ineffective treatment; the most recent available data from 2017 show that approximately 19–51% of *Staphylococcus aureus* samples isolated from skin and soft tissue infections are resistant to fusidic acid[1]
- The use of topical fusidic acid can result in the emergence of *S. aureus* strains which are also resistant to methicillin;[2] methicillin-resistant *S. aureus* (MRSA) is resistant to all beta-lactam antibiotics and can cause severe infections and outbreaks in healthcare settings and the community.[3]
- Increasing resistance to topical fusidic acid threatens the effectiveness of oral formulations of fusidic acid, which has a role in the treatment of invasive infections of bones and joints.

Hydrogen peroxide is increasingly prescribed in place of topical antibiotics

Since 2014, dispensing of topical fusidic acid has dropped by approximately 50%: from 62.3 dispensings per 1,000 population to 31.8 per 1000 in the first half of 2020 (Figure 1). Use of topical mupirocin (partially subsidised) has reduced markedly since 2014 when there were 19.3 dispensings per 1000; the current rate is 5.9 per 1,000. N.B. supply issues are reflected as dips in the graph. Dispensing of topical hydrogen peroxide has increased significantly since 2014 and dispensing of topical iodine has slightly increased.

The decrease in dispensing of topical antibiotics is a positive change and reflects informed prescribing behaviour. However, there are very few situations in which the use of topical antibiotics is warranted therefore it is possible for prescribing rates to be further reduced.

Are topical antiseptics an acceptable alternative?

The use of topical antiseptics to treat patients with minor skin infections has long been proposed as a potential solution to the problem of increasing resistance to topical antibiotics. However, much of the evidence surrounding the use of topical antiseptics relates to the prevention of infection in wound management rather than as treatment for established skin infections. In 2020, there remains a lack of randomised controlled trial data and no head-to-head comparisons between topical antibiotics and topical antiseptics, therefore most authors conclude only that further research is required.[5, 6]

For further discussion about the role of topical antiseptics, see: **https://bpac.org.nz/BPJ/2015/June/topical.aspx**

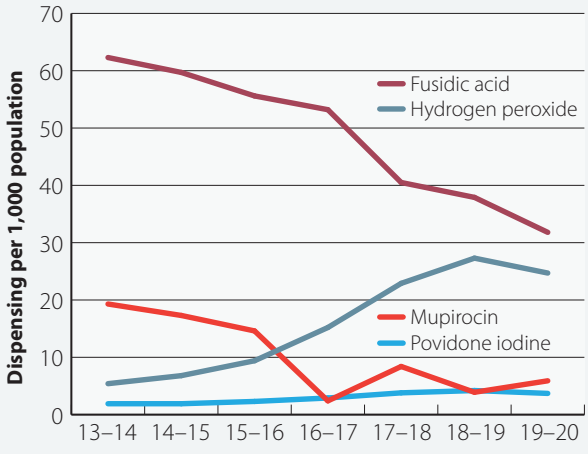

Figure 1: Dispensing of topical antibiotics and antiseptics 2014–2020.[4] N.B. the "dips" in mupirocin dispensing were related to a lack of supply.

Managing skin infections without antibiotics

Most localised or minor skin and soft tissue infections can be treated without antibiotics.

Impetigo is typically self-limiting, and patients or caregivers can be advised to follow simple skin hygiene advice; the "clean, cut (nails) and cover" strategy. Topical antiseptics* can be used for small, localised areas of infection (three or less lesions/clusters) and oral antibiotics considered if infection is more widespread; flucloxacillin is first-line. If a patient with localised infection has not improved after treatment with topical antiseptics, the lesions remain localised and an oral antibiotic is not considered appropriate, then topical fusidic acid may be considered.

For further information for parents and caregivers, see: "What to do about school sores in children", **https://www.kidshealth.org.nz/what-do-about-school-sores-children**

* Subsidised options are hydrogen peroxide cream 1% (available in 15g or 25g tubes) or povidone-iodine ointment 10% (to a maximum of 130g per prescription), other options available over-the-counter

Infected eczema can often be managed by optimising use of topical corticosteroids and emollients.[7] Oral antibiotic treatment can be considered for patients with worsening or severe infection; prescribe an oral antibiotic based on local resistance patterns with appropriate coverage for *S. aureus* and *Streptococcus pyogenes* (Group A ß haemolytic streptococcus). There is no role for topical antibiotic treatment in patients with infected eczema.

For further information on managing eczema, see: "Childhood eczema: improving adherence to treatment basics": **https://bpac.org.nz/2016/childhood-eczema.aspx** and "Topical corticosteroids for childhood eczema: clearing up the confusion", **https://bpac.org.nz/2016/topical-corticosteroids.aspx**

Other skin and soft tissue infections, such as furuncles, carbuncles or folliculitis typically do not require topical antibiotic treatment. Furuncles and carbuncles can be treated with incision and drainage. Folliculitis can be due to bacterial infection but also viral or fungal infection, or sterile folliculitis due to occlusion with adhesive dressings or emollients.

Management should focus on effective skin hygiene, avoiding or treating any underlying cause and topical antiseptics.[8] If the skin lesions are spreading or are in a site associated with complications, e.g. the face, or patients have fever or co-morbidities which place them at higher risk, e.g. diabetes, an oral antibiotic such as flucloxacillin can be prescribed.

Erythromycin can be used for patients with flucloxacillin allergy. Infections that are severe, persistent or recurrent usually require oral antibiotics.[8]

Routine use of oral antibiotics for uncomplicated abscess does not improve treatment outcomes compared to incision and drainage alone.[9] There have been two randomised controlled trials (RCTs) recently that have challenged this recommendation, suggesting that oral antibiotics may provide a modest benefit to patients.[10,11] Two subsequent meta-analyses, which included data from these RCTs, have therefore also concluded that the use of antibiotics in patients with uncomplicated abscesses may improve cure rates.[12, 13] However, there has also been critique of these conclusions given the global issues with antibiotic resistance and that antibiotics can result in significant adverse effects for individual patients.[14] A pragmatic compromise has been suggested where antibiotics are only prescribed for patients who are considered high risk, e.g. those who are immunocompromised, have methicillin-resistant *Staphylococcus aureus* (MRSA) or a history of MRSA, systemic symptoms or who have limited access to follow-up.[14]

For further information for parents and caregivers, see: "Boils in children", **https://www.kidshealth.org.nz/boils-children**

Topical antibiotics are not required for **preventing infection following minor invasive procedures**, e.g. removal of benign skin lesions. People aged over 75 years have one of the highest rates of topical fusidic acid use in New Zealand, and it is thought that using topical antibiotics as a preventative measure following the removal of benign skin lesions contributes to this high use.[15, 16]

When should topical antibiotics be used?

The main clinically appropriate use for topical antibiotics in New Zealand is the eradication of nasal carriage of *S. aureus* in patients with recurrent skin and soft tissue infections, or the eradication of MRSA, with the choice of topical antibiotic determined by susceptibility testing. However, the initial focus should be on optimising skin hygiene, e.g. antibacterial washes, avoiding sharing personal care items, and environmental decolonisation, e.g. frequent washing of linen and cleaning of regularly touched surfaces.

If topical antibiotics are prescribed, include the intended duration of use so this will appear on the prescription label and prescribe just enough volume for the current condition. Encourage patients to discard the remainder of any tubes once treatment is completed, rather than keeping an unfinished tube for use on other occasions or by other household members.

Further reading: two-part series on topical antibiotic use in New Zealand –

"Topical antibiotics for skin infections: should they be prescribed at all", available from: **www.bpac.org.nz/2017/topical-antibiotics-1.aspx**

"Topical antibiotics for skin infections: when are they appropriate?", available from: **www.bpac.org.nz/2017/topical-antibiotics-2.aspx**

Patient information

"Looking after your child's skin": a guide for parents and families, available from: **www.health.govt.nz/system/files/documents/publications/skin-infections-booklet-nov13v2.pdf**

Kids Health skin infection resources, including information on specific conditions and resources in Māori, Samoan and Tongan languages, available from: **www.kidshealth.org.nz/tags/skin**

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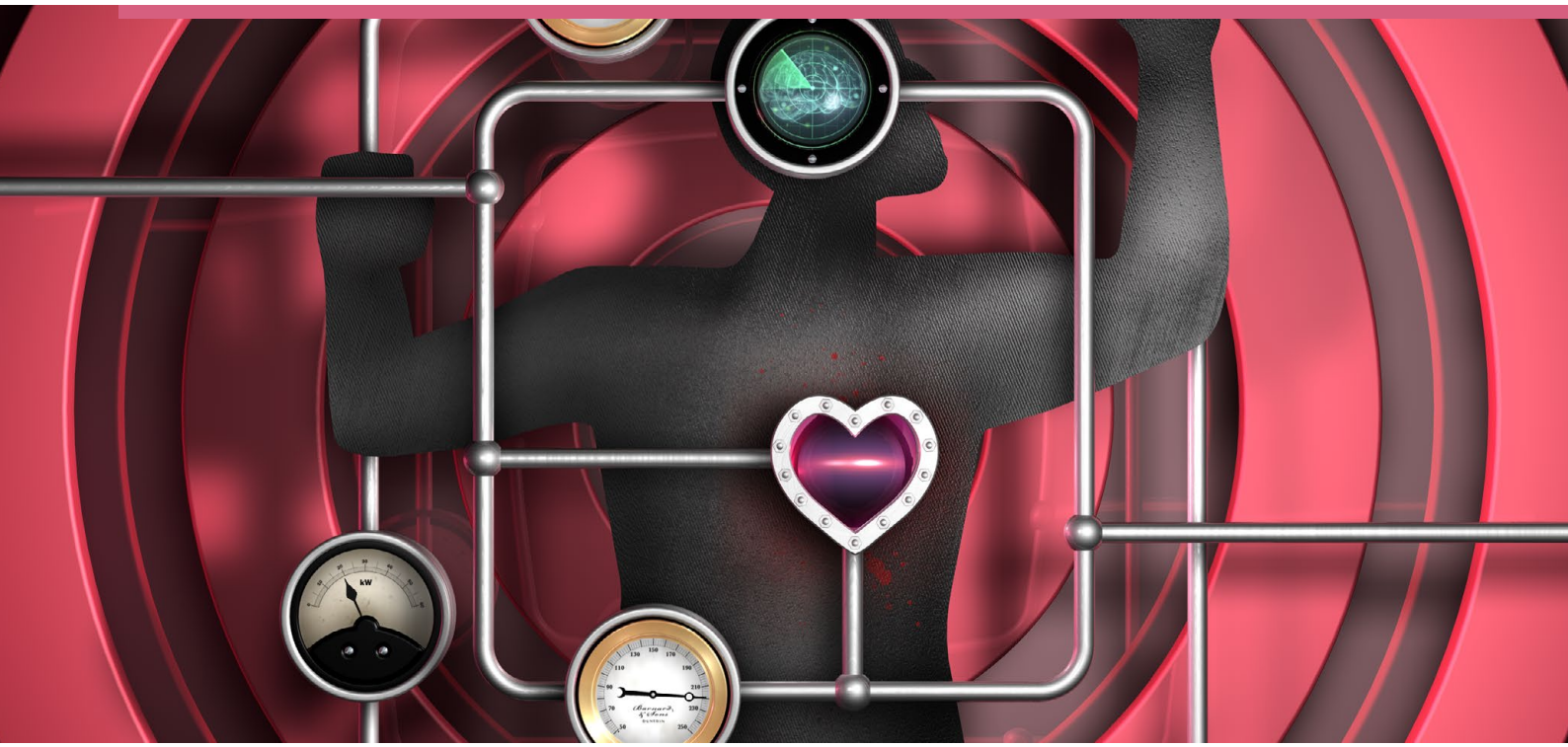

Hypertension in adults: the silent killer

Hypertension is associated with a wide range of cardiovascular and end-organ damage and is one of the most frequent reasons for patient attendance in primary care. The ideal treatment of hypertension continues to be debated. However, management often requires multiple medicines to achieve blood pressure targets and reduce overall cardiovascular risk, alongside lifestyle changes.

KEY PRACTICE POINTS:

- Five-year cardiovascular disease (CVD) risk should be calculated using NZ primary prevention equations in all patients with a blood pressure (BP) consistently ≥130/80 mmHg to guide decisions regarding antihypertensive treatment
- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), calcium channel blockers and thiazide(-like) diuretics are all first-line antihypertensives
  - Beta-blockers are no longer first-line unless indicated
- Guidelines recommend low-dose dual antihypertensive treatment (as opposed to monotherapy) initially unless a patient is within 20/10 mmHg of their BP target, aged ≥ 80 years, frail, or committing to major lifestyle changes
- BP targets should be individualised according to the patient's CVD risk, co-morbidities and treatment objectives
- For patients not achieving targets despite dual antihypertensive treatment, adherence should be assessed, and a third antihypertensive considered, or doses can be increased if the patient is close to their BP target; spironolactone or other medicines (e.g. beta- or alpha-blockers) should then be added if triple antihypertensive treatment has not reduced BP to target levels

Hypertension is a continuum requiring regular review

Hypertension is a risk factor for many conditions including stroke, myocardial infarction, heart failure, atrial fibrillation, kidney disease and cognitive decline.[1] It is described as a silent killer because it is insidious, chronic and progressive.[2]

International guidelines vary in the thresholds used to define hypertension. Although it has previously been common practice in New Zealand to consider any clinic BP ≥140/90 mmHg as being "hypertensive", BP measurements alone are insufficient to define and guide the management of hypertension in primary care.[3] BP has a normal distribution across the general population and the cardiovascular disease (CVD) risk associated with increasing measurements is continuous.[4] If additional factors are present that elevate CVD risk further, a patient is more likely to experience a cardiovascular event, even if their BP is within the "high normal" range, i.e. 130–139/85–89 mmHg:[1,4]

- **Risk factors include:** being aged ≥65 years, male sex, increased heart rate (>80 beats/min), excess body weight, diabetes, high LDL-C/triglycerides, a personal or family history of CVD or hypertension, early onset menopause, smoking, and psychosocial or socioeconomic factors

The line between normotension and hypertension is therefore arbitrary, and patients should be encouraged to make lifestyle adjustments to control or reduce their BP before they are diagnosed with hypertension.

Hypertension in New Zealand

In New Zealand, the mean systolic BP of many people is increasing due to the rise in obesity, sedentary lifestyles and the increasingly high fat, sugar and salt content of food.[5] Hypertension is often under-treated; Māori, Pacific and Asian peoples with hypertension have lower rates of antihypertensive use compared with Europeans (Figure 1).[6] Even though not all patients with hypertension require antihypertensive medicines – and lifestyle modifications may be sufficient for some patients – these disparities need to be recognised and addressed across primary care.

Diagnosing hypertension

Most cases of hypertension are asymptomatic, and treatment often involves lifelong exposure to multiple medicines and their potential adverse effects.[1] Therefore, it is essential that hypertension is accurately diagnosed in primary care.

If the clinic BP is ≥130/90 mmHg a clinical evaluation should be conducted in order to:

1. Confirm the elevated BP
2. Assess the CVD risk of the patient
3. Determine if any end organ damage has occurred
4. Detect any causes of secondary hypertension

1. Confirming elevated BP

To achieve a more accurate assessment it is recommended that at least two BP measurements be taken, at least two minutes apart. Ideally, an additional measurement should also be taken in the patient's other arm in case there is a significant difference.[1] Consistent systolic BP differences >10 mmHg are associated with an increased risk of CVD.[1] If BP measurements are elevated at a single appointment, another reading should be taken at a separate appointment on a different day to confirm a diagnosis of hypertension.[1]

Clinic readings do not always reflect the true BP despite the use of appropriate measurement procedures, due to patient-specific psychological, physiological and behavioural factors.[1] On average, measurements are 5–10 mmHg higher in this setting compared with at-home or ambulatory monitoring.[1] Therefore, 24-hour ambulatory monitoring (the "gold standard") or at-home monitoring may be required to confirm a diagnosis of hypertension and to rule out:

- **White-coat hypertension** if measurements are consistently elevated despite the absence of obvious risk factors
- **Masked hypertension** if office BP is consistently normal but there are clinical features consistent with hypertension, e.g. signs of end-organ damage

For further information on 24-hour ambulatory or at-home monitoring, see: "Out-of-clinic BP testing in primary care", **https://bpac.org.nz/BPJ/2016/May/blood-pressure.aspx**

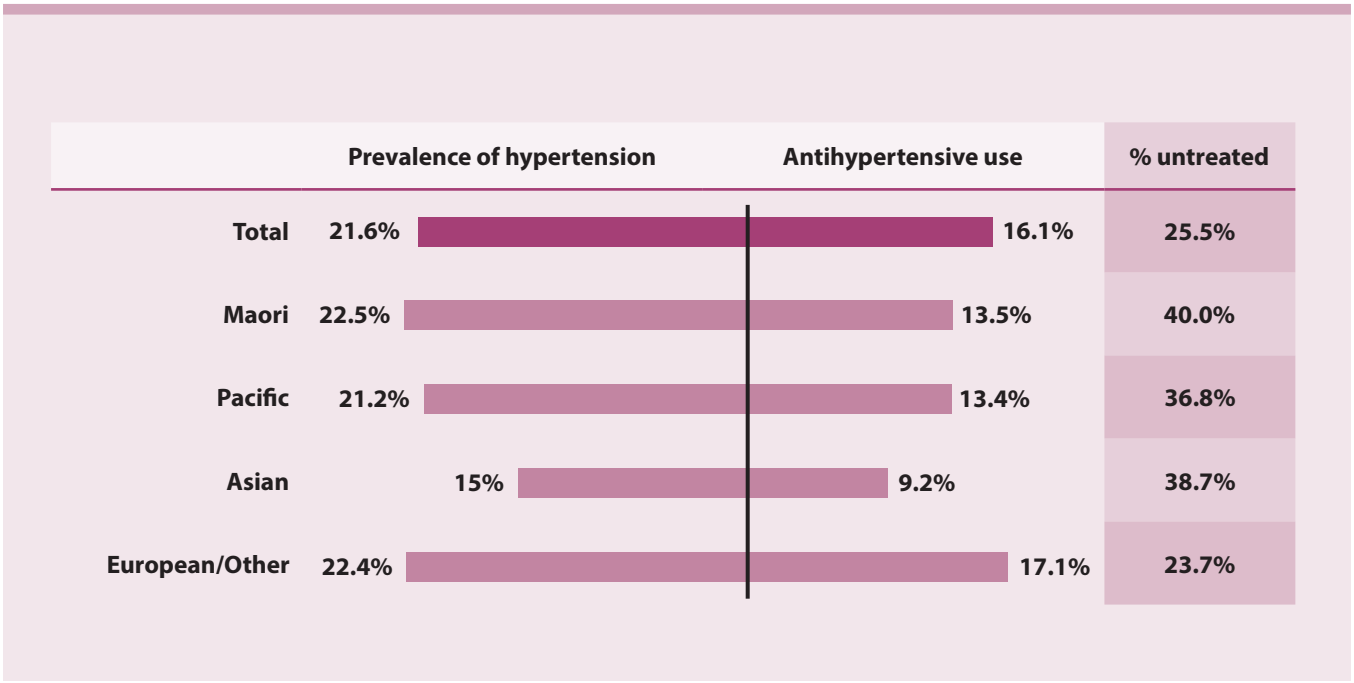

Figure 1. Prevalence of hypertension versus rates of antihypertensive use in New Zealand by ethnicity, 2018.[6]

2. Perform a CVD risk assessment

Risk assessment forms the basis for discussions about prognosis and treatment options with the patient and provides information about other factors affecting CVD management, e.g. diabetes, and the prevention of myocardial infarction and stroke.

A CVD risk assessment should be performed in all patients with a BP consistently ≥130/90 mmHg (see: "When to initiate antihypertensive medicines"). In addition, CVD risk assessment is recommended from age 45 years in males and 55 years in females. However, it is recommended that assessments should be:[3]

- 10 years earlier for people with personal or family risk factors for CVD
- 15 years earlier for people of Māori, Pacific or South Asian ethnicity
- 20 years earlier for people with severe mental illness
- Performed immediately following diagnosis of diabetes

Framingham equations were previously used to calculate a patient's ten-year CVD risk, however, new five-year thresholds have been established based on the NZ primary prevention equations (derived from the PREDICT study), which incorporate a wider range of variables.[3]

Access the CVD risk tool via *bestpractice* Decision Support on your patient management system. If your practice does not have access to this, contact BPAC Clinical Solutions: **https://bpacsolutions.co.nz/contact/.** Alternatively, an online CVD calculator, with the option of using PREDICT data, is available from: **http://chd.bestsciencemedicine.com/calc2.html**

3. Investigate for end organ damage and co-morbidities

Investigations at a minimum should include:[1]

- Dipstick urine test for haematuria and proteinuria
- Quantification of urinary protein with either an albumin:creatinine ratio (ACR) or protein:creatinine ratio
- Blood sample to measure creatinine (eGFR), electrolytes, HbA_{1c}, lipids, urate
- Ophthalmoscopic examination of the fundus
- An ECG to assess for signs of left ventricular hypertrophy (consider referring for an echocardiogram if indicated)

4. Consider secondary causes of hypertension

While the vast majority of people with hypertension have essential (or primary) hypertension – where there is no clinically identifiable cause – consider secondary causes, particularly in patients aged <30 years.[1] Common secondary causes of hypertension include high alcohol intake, obstructive sleep apnoea, renovascular disease or medicines such oral contraceptives, corticosteroids, NSAIDs.[1] If these factors can be managed, then it may prevent unnecessary pharmacological intervention.

The management of hypertension: treatments and targets

Lifestyle modifications are important for all patients

Following a diagnosis of hypertension, the patient's diet (particularly their salt intake), weight, level of exercise, alcohol consumption and smoking status should be assessed, and the patient supported to make positive life changes.[1] If patients can commit to significant enough life-style changes, it may alleviate the need for antihypertensive medicines.

When to initiate antihypertensive medicines

The 2018 Ministry of Health cardiovascular risk consensus statement recommends calculating the patient's five-year CVD risk if their BP is ≥130/80 mmHg to guide antihypertensive medicine decisions:[3]

- **CVD <5%:** antihypertensive treatment is not recommended; proceed with lifestyle changes
- **CVD 5–15%:** consider antihypertensive treatment if BP is ≥140/90 mmHg, alongside lifestyle changes
- **CVD ≥15%:** antihypertensive treatment is recommended, alongside lifestyle changes

For patients with severe hypertension, e.g. ≥160/100 mmHg, antihypertensive treatment should be offered immediately, alongside lifestyle changes, regardless of the patient's CVD risk.

Choosing a suitable antihypertensive

In New Zealand, it is common practice to initiate an angiotensin-converting enzyme (ACE) inhibitor or, if not tolerated, an angiotensin II receptor blocker (ARB). However, calcium channel blockers and thiazide(-like) diuretics have a similar BP lowering effect.[1] Therefore, any of these antihypertensive classes are suitable first-line options in patients with uncomplicated hypertension.[1] An exception is women of child-bearing age, who should not use ACE inhibitors or ARBs as there is an increased risk of foetal abnormalities if they become pregnant.[7] Recommended antihypertensives during pregnancy include labetalol, nifedipine and methyldopa.[7]

For commonly used antihypertensive medicines in New Zealand and their recommended doses, visit the NZ Formulary at: **https://www.nzf.org.nz/nzf_1168**

Consider co-morbidities. Two-thirds of patients with hypertension have a co-morbidity, which in turn influences the

suitability of antihypertensive used. Always consider whether the medicine selected will exacerbate pre-existing conditions or interact with medicines the patient is already taking.[1]

If an ACE inhibitor is selected, consider choosing an alternative to cilazapril. New Zealand has high rates of cilazapril use, however, it is used much less commonly overseas.[8] As such, we are vulnerable to supply issues. PHARMAC has secured stock of cilazapril until 2022 but they cannot guarantee supplies beyond this point.[8] Supply of the fixed-dose combination of cilazapril with hydrochlorothiazide has been discontinued and stocks are expected to run out in September, 2020.[8]

For more information on prescribing ACE inhibitors, see "Prescribing ACE inhibitors: time to reconsider old habits", **https://bpac.org.nz/2018/ace.aspx**

Beta-blockers are not first-line in patients with uncomplicated hypertension. Beta-blockers do not reduce the risk of stroke as much as other antihypertensive medicines and are often poorly tolerated.[1] However, beta-blockers may be preferred early in treatment for patients with some co-morbidities, such as ischaemic heart disease or atrial fibrillation.[1]

Use individualised BP targets

A target BP of <140/90 mmHg within three months is appropriate for many patients in primary care with uncomplicated hypertension.[1] However, BP targets should always be individualised based on the patient's CVD risk, co-morbidities and treatment objectives (Table 1).[1]

Intensive BP management using a systolic BP target of <120 mmHg may benefit some patients, however, its suitability in primary care has not been firmly established.[1] A main concern is that an intensive target may increase the risk of falls in older patients. However, it has been demonstrated this is not the case, and the rate of falls is comparable to what is observed with standard management.[9]

For more information intensive blood pressure management, see "Go low or no? Managing blood pressure in primary care", **https://bpac.org.nz/2017/blood-pressure.aspx**

A pragmatic approach works best with antihypertensive medicines

On average the BP lowering effect of any single antihypertensive at its optimal dose is <10 mmHg.[10] As such, patients with hypertension frequently require multiple medicines to achieve treatment targets.

Monotherapy may be a suitable starting point for patients:

- Aged ≥80 years
- Who are frail
- Within 20/10 mmHg of their BP target
- Who are committing to significant lifestyle changes

International guidelines now recommend initial low-dose dual combination treatment for most patients with hypertension[1]

Half the standard dose of any first-line antihypertensive still provides approximately 80% of the maximal BP lowering effect.[10] In addition, two low-dose antihypertensives used together are approximately five times more effective at lowering BP than increasing the dose of a single antihypertensive; the effect is approximately additive with two.[11] Given that hypertension is almost always caused by a combination of pathophysiological processes, countering it using medicines with different mechanisms of action is therefore thought to

Table 1. BP targets according to patient characteristics.[1]

	Clinic measurement	24-hour ambulatory or at-home measurement
"High" CVD risk, including current atherosclerotic CVD, heart failure, reduced ejection fraction, diabetes, CKD, aged ≥65 years, five-year CVD risk of ≥15%	<130/80 mmHg	<125/80 mmHg
"Lower" CVD risk None of the above risk factors	<140/90 mmHg	<135/90 mmHg
Frailty, dementia, limited life expectancy	Discuss treatment goals to guide decision making; targets can be more lenient and antihypertensives may need to be stopped	

improve treatment efficacy.[12] Safety is sometimes cited as a concern when prescribing multiple antihypertensives, however, the risk of adverse effects has actually been found to be greater with a single high-dose antihypertensive.[12]

An ACE inhibitor or ARB with a dihydropyridine calcium channel blocker such as amlodipine is the most effective antihypertensive combination based on evidence from the ACCOMPLISH trial.[12]

Intensifying treatment

Patients initiating antihypertensive treatment should initially be reviewed at least every four weeks to assess the efficacy of their regimen. At each review, the importance of adherence should be emphasised and addressed if found to be an issue, e.g. electronic alerts, use fixed-dose combinations, or use medicines with once-daily dosing. If a BP target is not achieved, the next step depends on how well the patient tolerates treatment and how close they are to their objective:[1]

- **If the patient is close to their target BP and the antihypertensive medicine(s) are well tolerated:** increase the dose of their existing antihypertensive(s) and re-emphasise lifestyle changes
- **If the patient is not close to their target BP and adherence is not an issue:** add an additional antihypertensive and re-emphasise lifestyle changes, e.g. for patients who started with dual antihypertensive treatment add a thiazide diuretic if the initial combination was an ACE inhibitor (or ARB) and a calcium channel blocker

Resistant hypertension

If a patient's clinic BP remains >140/90 mmHg after treatment with an ACE inhibitor or an ARB, plus a calcium channel blocker and a thiazide diuretic at their optimal (or maximally tolerated) dose, then their hypertension is considered to be resistant.[1] Patient adherence to treatment and possible secondary causes should be re-examined, and an added emphasis placed on lifestyle changes.[1] In addition, if the patient is taking optimal, or maximum tolerated, doses of antihypertensive medicines, an appropriate specialist opinion is recommended, if this has not been sought already.[1]

Ultimately, an additional antihypertensive medicine may be required, including:[1]

- Further diuretic treatment with spironolactone
- Addition of an alpha- or beta-blocker

Follow-up and monitoring

Once a BP target has been achieved, follow-up is important to ensure levels are maintained and to reinforce the importance of adherence to their regimen. In the long-term, depending on the level of risk and control achieved, medicines should be reviewed three to six-monthly with surveillance for end-organ disease and associated conditions.[1] This provides an opportune time to reinforce lifestyle management and to monitor electrolytes and renal function. Home BP measurements are a useful monitoring adjunct.

For the original and extended version of this article see: "Hypertension in adults: the silent killer" (available at: **https://bpac.org.nz/bpj/2013/august/hypertension.aspx**)
Also see: "Cardiovascular disease risk assessment in primary care: managing blood pressure" (available at: **https://bpac.org.nz/2018/bp.aspx**)

A Primary Care Update Series module is available on this topic, see: **https://bpac.org.nz/update-series/order.aspx**

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Melatonin: is it worth losing any sleep over?

Modified-release melatonin is the only approved formulation of melatonin in New Zealand and it has relatively few indications. It is funded for children or adolescents with neurodevelopmental disorders and sleep disturbances. It is moderately effective, but not funded for improving sleep quality in adults with insomnia. Shift-workers or people concerned about jet lag may wish to discuss the "off-label" benefits of melatonin treatment.

KEY MESSAGES

- Melatonin is moderately effective at improving sleep quality in adults with insomnia; non-pharmacological interventions continue to be the first-line treatment and melatonin should only be considered once these have been trialled
- There is only one approved formulation of melatonin in New Zealand, 2 mg modified-release:
  - Indicated, but not funded for adults aged over 55 years with insomnia
  - Fully funded with Special Authority approval for children with insomnia secondary to a neurodevelopmental disorder
- Melatonin may be useful "off-label" for preventing or reducing jet lag and improving sleep in shift-workers or people with vision loss
- Melatonin must be dosed at the correct time in order to be effective
- There is a lack of studies on the potential adverse effects of prolonged melatonin use, particularly in children and adolescents

Melatonin: the hormone and the medicine

Melatonin regulates the circadian rhythm of sleep. It is normally released at night from the pineal gland, typically beginning 14 hours after awakening, i.e. 9 pm in a person waking at 7 am.[1] Ocular light at the retina suppresses melatonin release, thereby providing time-of-day information to organs and tissues throughout the body.

As children enter puberty melatonin release is delayed resulting in later onset of sleepiness and later waking.[2] Melatonin secretion decreases through adulthood and by age 70 years nocturnal melatonin concentrations may be reduced by three-quarters.[3]

As well as regulating circadian rhythms, melatonin has additional physiological functions that are not completely understood.

Melatonin as a medicine for insomnia

Melatonin should only be considered for the treatment of insomnia once non-pharmacological interventions have

been trialled (see "Managing insomnia without medicines"). Most trials that have shown melatonin to be effective in the treatment of insomnia have involved modified-release formulations, which more closely mimic a natural circadian rhythm than immediate release, in people aged over 55 years. The European Sleep Research Society recommends that melatonin should not generally be used for the treatment of insomnia, due to poor evidence of efficacy.[4] This guidance, however, was based on a systematic review mainly comprising studies of immediate-release melatonin.[4]

Melatonin in New Zealand

In New Zealand, melatonin is a prescription only medicine. A 2 mg modified-release formulation is approved, but not funded, for the treatment of primary insomnia in adults aged over 55 years, for up to 13 weeks. The same formulation is fully funded with Special Authority approval for the treatment of persistent and distressing insomnia secondary to a neurodevelopmental disorder in patients aged 18 years or under, where behavioural and environmental approaches have been trialled or are inappropriate. Applications must be made by a psychiatrist, paediatrician, neurologist, respiratory physcian or on their recommendation. All other formulations of melatonin are unapproved and all other uses of melatonin are "off-label".[5]

How effective is melatonin at treating insomnia?

Modified-release melatonin taken one to two hours before sleep onset, with or just after food, is a reasonable dosing regimen for the treatment of general insomnia.[5]

It is reported that melatonin produces meaningful improvements in both quality of sleep and morning alertness in 47% of patients aged over 55 years.[7] There is a significant placebo effect, however, as 27% of patients treated with placebo also experienced improvements.[7] Another study in patients aged over 55 years also reported improvements in sleep quality, and time to sleep was reduced by approximately nine minutes.[8] A review of 14 trials in people of any age (including both immediate and modified-release formulations) found that melatonin was associated with a reduced time to sleep of 12 minutes, compared to placebo, with no significant increase in sleep duration.[9]

The adverse effects of melatonin

Melatonin is considered to have a relatively favourable benefit to risk profile as the adverse effects associated with its use are similarly prevalent in patients taking placebo,[10] however, treatment should be withdrawn if there is no evidence of benefit. Key points to discuss with patients prescribed melatonin include:

- People taking melatonin should not drive or operate machinery for the rest of the evening[10]
- Alcohol should be avoided before bedtime as this may increase the speed of melatonin release, effectively turning the modified-release formulation into immediate-release[10]
- The timing of administration is important, i.e. one to two hours before sleep, as delays in sleep onset can occur if melatonin is taken at another time, e.g. in the morning[11]

It is recommended that patients with hepatic impairment avoid melatonin.[5] The effect of renal impairment on dosing is unknown. There are no safety data on the use of melatonin during breastfeeding or pregnancy.[6]

More studies on the long-term safety of melatonin are needed

The safety of prolonged melatonin use has not been widely studied and there are concerns that the long-term effects of treatment are unknown, particularly in children.[12] The New Zealand Formulary for Children recommends that melatonin should be initiated and supervised by a specialist and reviewed every six months.[13]

Interactions with other medicines

Ciprofloxacin may increase melatonin concentration, and carbamazepine and rifampicin may cause plasma concentrations of melatonin to be reduced.[10] Melatonin may increase the sedative effects of other medicines, e.g. benzodiazepines, zopiclone, antipsychotics and antihistamines.[10]

Further information on potential medicine interactions with melatonin and their clinical significance is available from: **https://nzf.org.nz/nzf_2049**

Off-label uses of melatonin

Evidence suggests melatonin is most useful for adults who have problems sleeping due to changes or difficulties in establishing a circadian rhythm, such as shift-workers, people with jet lag, circadian rhythm disorders or those with visual impairment.[14]

Melatonin should not be prescribed in primary care to children with sleep disturbances who are otherwise healthy. Insufficient sleep and poor sleep hygiene are the most frequent reasons for sleep disturbances in teenagers.[2] Melatonin use in adolescents should be reserved for those diagnosed with a specific circadian disturbance, e.g. delayed sleep phase disorder (see below).

There are no established treatment regimens for off-label melatonin use; dosing is derived from clinical studies.

Melatonin may reduce or prevent jet lag

Jet lag symptoms occur when a person's circadian rhythm becomes desynchronised with the day-night cycle of their travel

Managing insomnia without medicines

Before considering melatonin, it is useful to review the diagnosis of insomnia and first-line methods of management.

Dissatisfaction with sleep quality or distress from not sleeping will be experienced by most people at various times in their lives.[20] Sleep disturbances are reported to affect 10–50% of patients presenting to primary care in New Zealand, depending on the definition that is applied.[21] Duration and quality of sleep also decline with age.

Primary insomnia is diagnosed if a person has a significant sleep disturbance, occurring at least three nights per week, lasting for longer than one month, without other contributing conditions or sleep disorders.[21] Primary insomnia is therefore a diagnosis of exclusion once other potential causes have been ruled-out, e.g. restless leg syndrome, depression, anxiety and stress, sleep apnoea and long-term alcohol use.[20]

Further information on diagnosing insomnia (including differential diagnoses) is available from: "I dream of sleep: managing insomnia in adults – Part 1", **https://bpac.org.nz/2017/insomnia-1.aspx**

Non-pharmacological treatment is first-line for insomnia

The first-line treatment for insomnia should always be the elimination of any underlying causes, e.g. environmental factors, use of medicines or other substances, untreated medical conditions or psychological factors.

Simple changes can make a big difference

Sleep hygiene refers to adopting behaviours and modifying environmental factors to increase the likelihood of sleep. Examples of sleep hygiene include ensuring light and temperature are conducive to sleep, limiting caffeine and alcohol intake, avoiding napping during the day and avoiding heavy meals, smoking or vigorous exercise close to bedtime.[22]

Stimulus control retrains the patient to associate their bedroom as a place of sleep thereby establishing a normal sleep-wake cycle. This involves:[22]

- Only going to bed when sleepy
- Restricting the use of the bedroom to sleep and sexual activity
- Leaving the bedroom if still awake in 20 minutes and returning only when sleepy
- Getting up at the same time every morning

Sleep restriction treatment involves calculating how many hours the patient spends in bed and how many of these hours they are asleep. This is usually done with a sleep diary. The patient restricts their time in bed to their calculated average sleep time, with a minimum time in bed of five hours.[23]

Patients who report severe insomnia or who have insomnia that is not responding to treatment are likely to benefit from referral to a sleep specialist.

Further information on non-pharmacological management of insomnia (including handouts for patients) is available from: "I dream of sleep: managing insomnia in adults – Part 1", **https://bpac.org.nz/2017/insomnia-1.aspx**

destination and it may take four to six days for synchronisation to occur.[15]

There is evidence that immediate-release melatonin is effective in reducing or preventing jet lag.[15] This effect seems to be strongest for people travelling across five or more time zones, particularly in an easterly direction, e.g. New Zealand to New York.[15]

The optimal timing of melatonin dosing for jet lag prevention is important and people should take it in the late afternoon or early evening at their destination.[15] Doses may be repeated for several days after arrival. Exposure to bright light in the morning also assists in adjusting to the new time zone.[16]

Melatonin may increase sleep length for people doing shift-work

People who do shift-work may experience sleep disturbances. In patients with extreme symptoms this is termed shift-work sleep disorder.[17] The use of melatonin may increase the time shift-workers are able to sleep, but there is no evidence that it will reduce the time taken to fall asleep.[17]

Melatonin is beneficial for sleep problems in people with vision loss

People who are blind report an increased prevalence of sleep problems compared to the general population.[18] In people who are totally blind this may result in a lifelong sensation of jet lag which can be improved by melatonin if given at the appropriate time relative to the patient's circadian rhythm.[19]

A daily dose of 0.5 mg of melatonin has been shown to be effective at synchronising abnormal circadian rhythms in people who are either partially sighted or totally blind.[19] As treatment may be lifelong the lowest effective dose of melatonin is preferable.

Melatonin is appropriate for patients with delayed sleep phase disorder

Delayed sleep phase disorder occurs when a person's natural sleep time is mismatched with expectations of what is normal.[20] This disorder is estimated to have a prevalence of 2% in patients attending general practice in New Zealand.[21]

Melatonin is most effective for delayed sleep phase disorder when taken five hours before natural levels of melatonin begin to rise, i.e. in the early to mid-afternoon.[11] The optimal dose is unknown; most studies have used daily doses of melatonin of 5 mg.[11]

For the original and extended version of this article, see: "Melatonin: is it worth losing any sleep over?", **https://bpac.org.nz/bpj/2015/august/melatonin.aspx**

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Managing gout in primary care

For many people, gout is a debilitating condition associated with poor health and reduced life expectancy. However, it can be effectively managed with appropriate and prompt use of urate-lowering treatment. Too often, management is focused on controlling the patient's symptoms in the short-term, while their risk of irreversible joint damage and negative health outcomes continues to grow, particularly among Māori and Pacific peoples. It's time for a re-think.

KEY PRACTICE POINTS:

- Gout flares can be treated with a NSAID, prednisone or low-dose colchicine, depending on individual clinical circumstances; all are considered to be equally effective
- Following the first flare, lifestyle changes are important but alone are generally insufficient for the management of gout; discuss urate-lowering treatment at the first presentation and recommend initiation if indicated
- Allopurinol is the first-line urate-lowering treatment and can be initiated during a flare; the starting dose is based on renal function, followed by gradual up-titration
  - Probenecid can be used second-line either as monotherapy or in combination with allopurinol
  - Febuxostat is a third-line option
- Prophylactic medicines should be routinely prescribed alongside urate-lowering medicines, usually for at least six months or longer if symptoms are ongoing
- Patients should aim for a target serum urate level below 0.36 mmol/L or below 0.30 mmol/L if there are features of severe disease, e.g. tophi; regular review of treatment is required to achieve these levels
- Patients with gout require consistent ongoing management of cardiovascular risk, as well as monitoring for co-morbidities, e.g. chronic kidney disease and diabetes

Gout in New Zealand

New Zealand has among the highest rates of gout in the world, with approximately 3% of the total population affected.[1] Māori and Pacific peoples are disproportionately affected by gout, and rates appear to be increasing over time (Figure 1).[2] In addition, Māori and Pacific peoples have lower rates of use of urate-lowering medicines for the long-term control of gout.[2]

Gout is much more than an intensely painful condition that prevents people from working and performing daily activities. Poorly controlled gout can be a source of long-term disability, and increases the risk of early death due to cardiovascular and renal complications.[3] Despite this, many patients are only using analgesics to reduce the symptoms.[4] This must change to improve health outcomes; primary care, including community pharmacy, has an important role in ensuring patients are aware that gout flares can be prevented.

Managing misconceptions: lifestyle changes alone are generally insufficient for control

Although gout has traditionally been considered a "lifestyle disease", evidence now suggests that dietary intake accounts for <20% of the high urate levels seen in patients with gout, and the remaining >80% is an amalgamation of genetics, excess weight and declining renal function.[5] As a result, while dietary changes are important in gout management – such as reducing purine and fructose/sucrose intake as well as avoiding triggers – these alone are generally insufficient to reduce serum urate levels, and should always be accompanied by weight loss and a review of possible factors that may be influencing renal clearance of urate.[6] Ultimately, urate-lowering treatment is required for the majority of patients with gout to control the risk of flares in the long term (see: "Talk about urate-lowering treatment before the patient leaves").

Once diagnosed, medicine choice for managing flares is patient specific

In primary care, gout is usually diagnosed clinically with supporting evidence provided by elevated serum urate levels.[6] However, scoring tools are also available to help assess the likelihood of patients having gout.[7] The classic presentation of gout involves a sudden onset of severe pain, swelling, warmth and erythema, typically at the first metatarsophalangeal joint; however, other joints may be affected, and flares may be polyarticular in some patients.[8] Caution is required when interpreting serum urate levels during a gout flare as up to 40% of patients have serum urate levels within the normal range.[8] Repeat testing for diagnostic purposes may be required once the flare has subsided.

Best practice tip: Request a renal function test at the same time as the serum urate to allow for the prompt initiation of urate-lowering treatment, should a diagnosis of gout be confirmed.

A NSAID, corticosteroids or low-dose colchicine may be prescribed to treat flares

Patients with gout often initially present due to a flare, which will be their immediate treatment priority. Options for the treatment of gout flares are:[9, 10]

- **Naproxen:** 750 mg initially, 500 mg eight hours later, then 250 mg every eight hours until the flare has settled
- **Prednisone:** 20–40 mg, once daily, for five days; tapering the dose over ten days can reduce the likelihood of a rebound flare, but tapering is not always necessary
- **Low dose colchicine:** 1 mg immediately, followed by 500 micrograms after one hour on day one, and then twice daily dosing of 500 micrograms; in patients with an estimated glomerular filtration rate (eGFR) <50 mL/minute/1.73m^2 the initial dose should not exceed 1 mg in the first 24 hours, with a total maximum of 3 mg over four days

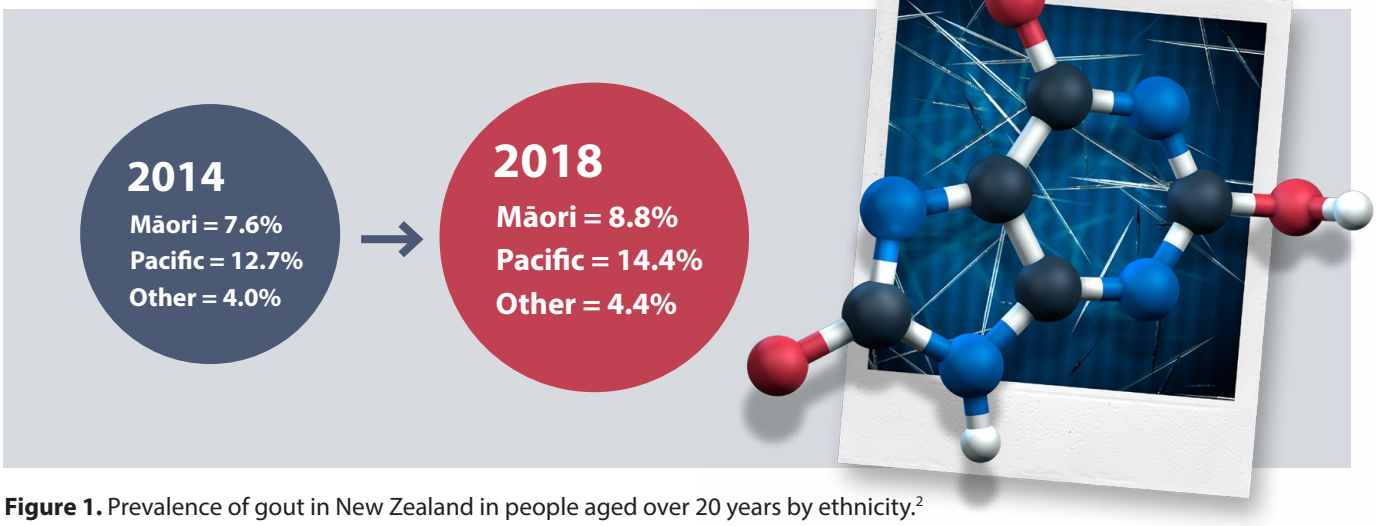

Figure 1. Prevalence of gout in New Zealand in people aged over 20 years by ethnicity.[2]

- **Corticosteroid (triamcinolone acetonide) intra-articular injection:** 2.5–40 mg, determined by the size of the affected joint

There is insufficient evidence to directly compare the efficacy of medicines for the treatment of gout flares. Medicine selection is based on the patient's preference, renal function and the presence of co-morbidities. If a patient is experiencing severe flares of gout, e.g. involving multiple joints, it may be appropriate to prescribe combination treatment.[9]

Urate-lowering treatment improves long-term health outcomes

Talk about urate-lowering treatment before the patient leaves

Discuss urate-lowering treatment with all patients, once a diagnosis of gout has been established; including patients experiencing a flare, as they may not return.[9] Explain that taking urate-lowering medicines life-long can prevent gout flares from returning, and that reducing serum urate levels may also:[11]

- Reduce their risk of cardiovascular events or renal failure by more than half
- Slow renal function decline
- Reduce rates of proteinuria

Long-term control over gout is dependent on strict adherence to urate lowering medicines. If urate-lowering treatment is stopped, even after years of being symptom-free, most patients will experience a return of flares within four years.[12]

Aim to initiate urate-lowering treatment early or immediately

Patients with symptomatic hyperuricaemia and the following characteristics should start urate-lowering treatment immediately:[6]

- Two or more flares per year (this includes flares the patient did not seek treatment for)
- Tophi/tophus or erosions on X-ray
- Renal impairment (eGFR <60 mL/min/1.73 m^2)
- Past urolithiasis
- Serum urate level ≥0.54 mmol/L

Best practice tip: Patients with asymptomatic hyperuricaemia should not be prescribed allopurinol or any other urate-lowering medicine.[6]

Practice changing point: urate-lowering treatment can be initiated during a flare

Traditionally, initiation of urate-lowering treatment has been delayed until the pain of a flare has resolved. The rationale is that dispersion of urate crystals during the initiation phase of treatment may make the patient's pain worse, however, evidence from two randomised controlled trials demonstrated that this is not the case.[6]

Allopurinol is the first-line urate-lowering medicine

Allopurinol is an xanthine oxidase inhibitor that decreases the production of urate by inhibiting the metabolism of purines; it is the first-line urate-lowering medicine for patients with gout.[6]

Table 2. Recommended starting doses and dose titrations for allopurinol determined by renal function.[10]

Estimated glomerular filtration (eGFR) mL/min/1.73m^2	Initial dose of allopurinol	Dose increase
>60	100 mg, daily	100 mg, every four weeks*, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily
30–60	50 mg, daily	50 mg, every four weeks, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily†
<30	50 mg, every second day	

* Some prescribers prefer a more rapid titration, e.g. every two weeks, although this needs to be balanced against the increased risk of adverse effects

† Many people with renal dysfunction will be unable to tolerate the maximum dose of allopurinol; consider referral to or discussion with a rheumatologist if serum urate targets are unable to be achieved and an increase in dose is not tolerated, e.g. over 300 mg allopurinol.

Allopurinol is started at a low dose and slowly titrated upwards, to minimise adverse effects, until the patient reaches the target serum urate level (Table 2).[13] In patients without renal dysfunction, 30–50% will require a dose of allopurinol in excess of 300 mg per day to achieve the serum urate target.[9] Treatment with up to 600–800 mg per day of allopurinol can be expected to achieve a serum urate target in 75–80% of patients with gout.[9] Allopurinol can still be safely used in patients who have reduced renal function, with a lower starting dose and slower titration.

Allopurinol is generally well-tolerated, although some patients will experience gastrointestinal symptoms.[3, 10] Hypersensitivity reactions can occur in very rare cases, but the risk is substantially reduced by initiating allopurinol at a low dose and slowly titrating upwards.[13] Patients should stop taking allopurinol and seek medical advice if they develop a rash or itch; an alternative urate-lowering medicine can be trialled if this occurs.

Serum urate levels are treated to target

The goal of urate-lowering treatment is to reduce serum urate levels to below the saturation point in order to prevent urate crystal formation and dissolve existing crystals.[6] The recommended serum urate levels are:[6]

- <0.36 mmol/L for most patients
- <0.30 mmol/L for patients with severe gout,* e.g. those with tophi, chronic gouty arthritis or frequent flares

* After several years of symptom-free treatment and resolution of tophi, patients treated to <0.30 mmol/L can be switched to the less stringent target of <0.36 mmol/L.[3]

Testing of serum urate levels is recommended prior to dose adjustment. This should initially occur every four weeks, while urate-lowering treatment is being titrated, and then every 6–12 months for monitoring.[8] However, serum urate levels should not be tested during a flare for the purposes of monitoring the patient's response to treatment as their serum urate levels may be lower than normal.[8]

Flare prophylaxis is recommended for subsequent flares when initiating urate-lowering treatment

During the first months of urate-lowering treatment there is an increased risk of subsequent acute gout flares. Prophylaxis is therefore generally recommended for the first six months of urate-lowering treatment, or longer if there are ongoing symptoms.[9] For a small number of patients, prophylaxis for three to six months may be suitable, e.g. those who are symptom-free at their three-month review after initiating urate lowering treatment and have had a substantial drop in serum urate levels.[6]

Treatment options for flare prophylaxis include:[3, 10]

- **Naproxen:** 250 mg twice daily for up to six months; consider concurrent use of a proton pump inhibitor
- **Very low dose colchicine** (unapproved indication): 500 micrograms, twice daily for up to six months; reduce dose to 500 micrograms, once daily, or on alternate days, if not tolerated, e.g. diarrhoea develops, chronic kidney disease or concurrent use of CYP3A4/p-glycoprotein inhibitors (e.g. erythromycin, verapamil)
- If contraindications to NSAIDs or colchicine – **Prednisone:** 5 mg, once daily, for up to six months, tapered slowly on withdrawal

Best practice tip: If the patient is receiving treatment for a gout flare with a NSAID or colchicine, continue the same medicine at a lower dose for prophylaxis once the flare has resolved.

Add probenecid if serum urate targets are not achieved with allopurinol alone

Probenecid can be added to allopurinol if the patient is unable to achieve the serum urate target despite taking a relatively high dose of allopurinol, e.g. 600 mg daily; assess adherence to allopurinol first.[9] It can also be prescribed as monotherapy to patients who are intolerant or resistant to allopurinol.[3]

Probenecid dosing is titrated according to the patient's serum urate concentration:[10]

- Initially, 250 mg, twice daily, for one week, then 500 mg, twice daily, with the dose increased by 500 mg every four weeks, to a total of 1 g, twice daily, if required

Probenecid should be avoided in patients with an eGFR < 30 mL/minute/1.73m^2 and is contraindicated in patients with kidney stones.[10] Patients should be advised to drink at least two litres of water per day, to prevent the formation of uric acid stones and to take the medicine with, or just after, a meal to limit nausea.[10]

Febuxostat is a further option for urate-lowering

If treatment with allopurinol and/or probenecid is ineffective, contraindicated or intolerable, febuxostat is another option, which can be used alone or alongside probenecid.[3] Febuxostat is subsidised with Special Authority approval in New Zealand.

The recommended dose of febuxostat for patients with gout is:[10]

- 80 mg, once daily, increased to 120 mg, once daily, after two to four weeks if the serum urate is > 0.36 mmol/L; the maximum daily dose of febuxostat for patients with mild hepatic impairment is 80 mg

Febuxostat and CVD risk. In 2019, the FDA updated their prescribing information with a boxed warning regarding an increased risk of all-cause and cardiovascular mortality with febuxostat. However, the 2020 American College of Rheumatology gout guidelines now prioritise febuxostat as the second-line urate lowering treatment over probenecid in patients without a history of CVD, or if they have significant renal impairment or urolithiasis. This is based on new data from a large observational study that did not show an increased risk of CVD or all-cause mortality with febuxostat.[6] However, given that these recommendations are so recent they are not yet incorporated into guidance in New Zealand, and in addition, Special Authority criteria for funded access to febuxostat still requires that probenecid is trialled first unless contraindicated.

Benzbromarone should no longer be used

Benzbromarone is a uricosuric medicine that has previously been prescribed with Special Authority approval to a small number of patients with gout when other urate-lowering options were ineffective, not tolerated or contraindicated. However, as of May 2020, benzbromarone is out of stock at a wholesaler level in New Zealand, and PHARMAC has advised that it will likely delist it from the Pharmaceutical schedule, although no date is currently set.[14] Therefore, it is now advised that no newly diagnosed patients should be started on this medicine, and those currently taking it should change to another urate-lowering treatment.

Monitoring patients taking urate-lowering medicines

Once gout is well-controlled with urate-lowering medicines, reviews should take place regularly every 6–12 months.[8] Patients need to be consistently monitored to:[3]

- Ensure serum urate levels are achieved and remain below saturation point
- Ensure their renal function has not deteriorated
- Encourage ongoing treatment adherence and lifestyle changes
- Manage CVD risk factors, e.g. $HbA_{1C,}$ blood pressure
- Treat any co-morbidities that may emerge

For the original and extended version of this article (published as a two-part series) see: "Part 1 – Talking about gout: time for a re-think" (available at **https://bpac.org.nz/2018/gout-part1.aspx**) and "Controlling gout with long-term urate-lowering medicines" (available at **https://bpac.org.nz/2018/gout-part2.aspx**)

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Suicide prevention: what can primary care do to make a difference?

"The most critical elements in helping those with suicidal ideation are achieving some engagement with the suicidal person and providing hope that their life can improve. Sometimes, that relies on you carrying the hope for them, until things change enough for them to share it."— PROFESSOR PETE ELLIS

In 12 months through to August 2019, 685 people in New Zealand died by suicide; an increase for the fifth consecutive year and almost double the road toll.[1] N.B. Provisional statistics have now been released for 2020; 654 people died by suicide in the 12 months to June, 2020. Age-standardised rates reveal that Māori die by suicide at approximately twice the rate of non-Māori.[2] New Zealand has the highest rate of youth suicide among 19 developed nations, with approximately 16 adolescents per 100,000 aged 15 to 19 years dying by suicide in 2016, compared to 5 in the United Kingdom, 8 in Australia and 9 in the United States.[3]

Clearly, we have a problem. The reasons for suicide are multifactorial, as are the reasons why it is so challenging to address on a population level. What we can do, however, is to focus on an intervention, one person at a time. We asked several experts around New Zealand for their guidance on consulting with patients in primary care who are experiencing suicidal thoughts or behaviour. This is not a comprehensive guide, but it is the start of a conversation about suicide.

Raising the issue

Only a portion of those who die by suicide are seen in general practice, therefore it is crucial that any opportunity for intervention is acted on. If a patient expresses verbally or non-verbally that their mood is low, they should be assessed for suicide risk. This can be done formally, but it is often best approached as a conversation. There is no right way to ask about suicide; the only wrong way is not to ask at all. The manner and tone of asking is more important than the words. Be empathic, sensitive and non-judgemental, in a way that invites the patient to share their concern and despair. Be direct and specific, leaving no ambiguity about what you are asking. For example:

"How bad has it got?"

"Has it ever been so bad that you have thought about harming yourself in any way?"

"Have you thought about ending your life?"

Questions about the patient's lifestyle, home, relationships, family/whānau, culture, religion/spirituality, education, employment, activities and friends adds to an understanding of their mental wellbeing. Consider other vulnerability factors, such as previous suicidal behaviour or knowing someone who has attempted suicide, mental illness, long-term illness, adverse childhood experiences, abuse, alcohol or drug misuse.

Assessment tools

"Suicide risk assessment has poor predictive accuracy. The better aim is to manage risk, not arrive at a position of certainty about it". — PROFESSOR SUNNY COLLINGS

Stopping a conversation for a formal assessment can be disruptive, but it is useful to be familiar with such tools so they can be incorporated into the clinical interview as appropriate. For example, the SAD PERSONS acronym highlights risk factors for suicide and self-harm (see below). The Beck Hopelessness Scale* is a validated tool for assessing risk severity and is recommended in some guidelines. The HEeADSSS tool is a semi-structured interview framework for assessing the wellbeing of adolescents, including questions about depression and suicide.

* Tool must be purchased, available from: **www.pearsonclinical.com.au/products/view/42**

Further information is available from: "Addressing mental health and wellbeing in young people", **https://bpac.org.nz/BPJ/2015/October/wellbeing.aspx**

The HEeADSSS assessment is available from: **https://www.starship.org.nz/guidelines/adolescent-consultation/**

SAD PERSONS acronym: risk factors for self-harm and suicide

S: Sex – male

A: Age – <19 or >45 years

D: Depression

P: Previous attempt

E: Excess alcohol or substance use

R: Rational thinking loss

S: Social supports lacking

O: Organised plan

N: No spouse

S: Sickness

Taking immediate action

If a patient reveals suicidal thoughts, firstly, make it clear that you would like to help. The next questions should be directed to ascertain their level of:[4]

- **Desire** – psychological pain, hopelessness, feeling trapped, alone or like a burden
- **Capability** – previous attempts, availability of means, acute symptoms of mental illness (see below), impulsivity
- **Intent** – preparatory behaviours (e.g. writing a note, making a will), specific plan and expressed intent to die
- **Buffers/connectedness** – family/whānau and social supports, plans for the future, engagement with people (including what affect their actions would have on others), ambivalence about suicide, sense of purpose

The following points may also be useful:

- Ask the same question in various ways to ensure you elicit a complete response; sometimes a patient may only reveal the thoughts they regard as acceptable, while having other thoughts that are more difficult to share
- Explore the reasons that these thoughts have occurred now; consider psychosis and delusions/hallucinations if their reasons are unclear, or their mood is not congruent with suicidal ideation or if they are severely depressed with elements of psychosis (which may be accompanied by marked psychomotor retardation or agitation)
- If the suicidal thoughts are not current, discuss what has changed since they had these thoughts and whether this change is likely to last.

If the patient's suicidal ideation and degree of planning is marked, a more detailed mental health assessment is indicated, followed by referral to mental health services.

"De-escalating suicide risk can be done by simply asking what is happening for the [patient] that got them to this point and listening non-judgementally. During the course of the conversation there is almost always reference made to things in the [patient's] story that connects them to life. This could be valued relationships, being needed (even by pets), future plans, etc...This can be an opportunity to highlight strengths and help them to realise that while it is very painful to have these feelings, they do pass." — RENEE MATHEWS

Formulating a safety and management plan

After managing any immediate crisis, the next step is to work with the patient to create a safety plan. The plan should include professional and social supports who are always available if the suicidal thoughts are current, or daily if the thoughts were in the recent past. Include phone numbers for seeking help after

hours (e.g. local acute mental health services, help lines such as Lifeline), and identify family or friends that they can rely on (see below).

The plan should also include internal coping strategies that provide a distraction and potential for a sense of pleasure or mastery, e.g. going for a walk, listening to music, playing with a pet. Identify any distressing triggers that can be avoided. Discuss things to look forward to, e.g. a holiday. Recovery involves building strength and resilience so include aspects in the plan that develop these attributes, e.g. joining a group, reconnecting with a cultural or spiritual background, learning a new skill.

"Most people who are suicidal have a degree of ambivalence. Talking it through can help people identify and strengthen the reasons to keep living. Sometimes these conversations may need to be daily."— PROFESSOR SUNNY COLLINGS

Involving partners and family/whānau

The patient should be encouraged to confide in their partner, family/whānau or other support person about their suicidal ideation. Young patients require an adult to support them, not just a friend. N.B. In some cases informing a family member will not be appropriate if they are contributing to the suicide risk, e.g. an abusive relationship.

It can sometimes be difficult to facilitate this discussion as the patient may be ashamed or embarrassed about their thoughts. Ask the patient what they think the risks and benefits are of them (or you) disclosing their situation to their family, and help them to weigh up the decision. Offer to role play the conversation to make the patient more comfortable with what they, or you, will say.

In the interests of the patient's relationship with you (the clinician) and their family, it is preferable to negotiate consent.

Effective engagement with young people

There are many causes of suicidal thoughts, but factors such as social isolation/alienation, violence (physical, sexual, emotional), risk-taking behaviour (especially with alcohol and drugs), sexual identity and breakdown of romantic relationships may be more common in young people. Socioeconomic deprivation increases risk, but an advantaged background does not exclude any of these factors, and it may be accompanied by added risks such as high expectations from family.

Assessment and management of suicidal thoughts in a young person proceeds in much the same way as for other patients. Certain aspects, however, are of greater importance, such as ensuring that they are surrounded by supportive people and engaging with these people to form a clearer picture of the patient's wellbeing and social challenges. As appropriate, and with consent, this may include family, teachers, school counsellors and others involved in caring for the young person.

Key points for effective communication with young people include:

- Consider their cognitive development when formulating questions and interpreting responses; e.g. can they think abstractly (think about thinking) or think in the future? A non-committal answer may simply reflect their level of complexity of thought rather than a low mood.
- Consider communicating using emotions rather than logical reasoning
- Build trust before asking questions requiring more private/personal answers
- Explain that the discussion is confidential, unless you think their safety is at risk, but you will involve them in any decisions about this
- Acknowledge their individual identity from their parent/caregiver; if appropriate, ask the parent to leave the consultation
- Listen without judgement and avoid "lecturing"
- Be aware that young people may be more impulsive and have a more romanticised view of death than older people.

Ideally a young person with suicidal thoughts should be referred to a clinician who is skilled in interviewing and working with children and adolescents.

Further information is available from: "Addressing mental health and wellbeing in young people", **https://bpac.org.nz/BPJ/2015/October/wellbeing.aspx**

However, if a patient who is acutely suicidal declines the involvement of others, a clinician may over-ride this in the interests of safety. Note that this authority extends only to the information necessary to keep that person safe.

A statement such as the following can be discussed with patients regarding confidentiality:[5]

"What you say is confidential, unless I believe that you are at serious risk of harm to yourself, or others. In such a case I will take necessary steps to protect your safety, although wherever possible I will discuss these steps with you before I take them".

Supporting the supporters

Family and friends supporting a person who is suicidal require advice and assistance themselves. For further information and tips, see: **https://bpac.org.nz/2017/suicide.aspx**

"Basically just listen without judgement and communicate that you are there for them and that they are valued and cared for. A major contributor to suicidal thoughts is feeling alone and a burden to others." — RENEE MATHEWS

Understanding the warning signs

There are no reliable methods for detecting when a patient is at imminent risk of suicide. There are, however, particular behavioural warning signs, such as if the patient no longer talks about the future, they have made peace with family and friends, they have given away their possessions or they convey a sense of positivity or happiness as they have made the decision to end their pain. Drug or alcohol intoxication and psychosis (e.g. due to mental illness) increases risk, as does knowing someone who has died by suicide.

"I worry particularly about those who have lost any hope of things improving in the future, and people who are so strongly self-centred and committed to their suicidal plans that I feel that I have not been able to engage effectively with them in considering alternatives."— PROFESSOR PETE ELLIS

Providing ongoing support

"Preventing suicide takes long-term support and journeying with it is not a short, sharp fix." — DR SUE BAGSHAW

A patient who has experienced intense suicidal thoughts requires follow-up until they have regained confidence in themselves, and their safety and any contributing factors to their suicidal ideation have been largely resolved. Suicidal ideation is a symptom and the follow-up should focus on identifying and managing underlying causes. Distinguish grief from depression, and post-traumatic stress disorder from them both. Remember that antidepressant medicines are generally only used to treat depression and accompanying anxiety.

Providing culturally appropriate care

Culture is an important determinant of mental health. Understanding a patient's cultural identity may provide insights into causes of suicidal thoughts or how these thoughts are communicated. Do not, however, assume that a someone will assign the same personal meaning to their culture as others, or that their culture has a bearing on their suicidal thoughts. Ask patients about their culture and how this plays a role in their life, do they find strength and resilience from their cultural identity and community or is this contributing to their distress? For Māori, the presentation, explanation and definition of suicidal thoughts may be different from "western views", and it is important to recognise and be respectful of this. If issues related to Māori culture arise in the conversation, it is strongly recommended to seek input from a Māori health provider (e.g. Kaupapa Māori mental health service – ask your local DHB or PHO for contact details) or kaumātua (elder), as guided by the patient and their whānau. This includes issues such as:

- Breaches of cultural protocol, e.g. tapu
- Loss of mana (identity and cultural status) on a personal or collective level
- Experiencing the presence of ancestors

For further information, see: "Recognising and managing mental health problems in Māori", **www.bpac.org.nz/BPJ/2010/June/mentalhealth.aspx**

The frequency and nature of follow-up is dependent on individual circumstances, as well as any barriers to treatment, e.g. financial or location. Daily face-to-face consultations or phone calls are appropriate for most patients after they have disclosed suicidal thoughts. This may be decreased to weekly, then monthly as the patient's symptoms resolve. Knowing that someone will be checking on them can be very comforting to patients who feel alone. Consider longer term follow-up strategies. The "anniversary" of a suicide attempt can be a particularly vulnerable time for some patients, and a phone call or note from the practice at this time may be significant to them.

Additional information is available from: Carter G, Clover K, Whyte I, *et al*. Postcards from the Edge project: randomised controlled trial of an intervention using postcards to reduce repetition of hospital treated deliberate self-poisoning. BMJ 2005;331(7520):805.

Final thoughts

Many people experience suicidal ideation at some point in their life, but only a few will seek help. We need to ensure that these people do not go unnoticed. Primary care practitioners are skilled in looking for clues in the patient's history that reveal an underlying illness – the same principles apply for detecting unspoken thoughts. Always consider if there is more to the story than the reason the patient has presented, e.g. for tiredness, sore back or headache. Always ask; "Is there anything more?"

People who are contemplating suicide think that it is a reasonable option, so our job is to show them that there are other, better options. Death is final and inevitable, so we must make the most of life.

"Really just showing you care enough to ask about suicide and are not afraid of the answer can make a difference for someone who is thinking about suicide."— RENEE MATHEWS

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For the original and extended version of this article see: "Suicide prevention: what can primary care do to make a difference?", available from: **https://bpac.org.nz/2017/suicide.aspx**

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Stopping medicines in older people: the flip side of the prescribing equation

Older people are generally prescribed more medicines than younger people, which contributes to a higher risk of adverse effects. Not all medicines are intended to be used indefinitely and the balance of benefits and harms associated with each medicine and dose can change over time.

KEY PRACTICE POINTS:

- The use of multiple medicines increases with age; Māori and Pacific peoples use multiple medicines at a younger age than Europeans, likely due to the earlier onset of long-term conditions in these groups
- A higher number of medicines is associated with an increased risk of medicines interactions, adverse effects and difficulties with medicines use and adherence
- Regularly review the medicine regimen of all older patients, particularly those prescribed multiple medicines, e.g. five or more, or taking combinations of medicines with a higher risk of adverse effects
- The aim of a medicine review is to ensure that medicines and doses remain appropriate based on a current indication, that the benefits of treatment outweigh the associated harms and the regimen is as simple as possible
- If a medicine is identified that is no longer necessary, develop a plan in consultation with the patient for stopping, stop one medicine at a time and monitor for symptoms of discontinuation or recurrence of the condition being treated

"There are many evidence-based guidelines to help clinicians start drug treatment. There is much less evidence to guide clinicians about withdrawing medicines" [1]

Medicine use increases with age

The use of multiple medicines, known as polypharmacy, is common in older people and increases the risk of adverse outcomes.[2] In New Zealand in 2019, 51% of people aged over 65 years were prescribed five or more medicines; 10% were prescribed 11 or more.[3*] Rates of prescribing increase sharply with age and are highest in people aged 85 years and over.[3]

* Data based on dispensed pharmaceuticals for registered patients. N.B the original version of this article referenced data from the HQSC atlas which utilises different methodology to generate polypharmacy data.

Polypharmacy begins earlier in people of Māori or Pacific ethnicity

People of Māori or Pacific ethnicity are more likely to receive multiple medicines at a younger age than people of European/Other ethnicity. In 2019, 44% of Māori and 53% of Pacific peoples aged 65–74 years were prescribed five or more

medicines, compared to 32% of European/Others of the same age.[4] This likely reflects the earlier onset of long-term conditions, e.g. cardiovascular disease and chronic kidney disease, in Māori and Pacific peoples.

For further statistics on polypharmacy in older people in New Zealand, see: **www.hqsc.govt.nz/our-programmes/health-quality-evaluation/projects/atlas-of-healthcare-variation/polypharmacy/**

More medicine does not necessarily mean better medicine

There are valid clinical reasons why older people may be prescribed large numbers of medicines, including an increasing prevalence of multiple long-term conditions in older age. For some people polypharmacy is necessary and reflects that they are receiving appropriate evidence-based care according to current guidelines, and some people receiving multiple medicines may still have unmet need in terms of pharmacological treatment. However, all medicines are associated with risks, and these risks are increased when multiple medicines are used, including:[5]

- Interactions between medicines
- Additive risk of adverse events, e.g. increased risk of falls with the combination of anticholinergic and sedative medicines[6]
- Interactions between a medicine prescribed for one condition and management of another (medicine-disease interaction), e.g. for a patient with osteoarthritis and chronic kidney disease, initiation of a non-steroidal anti-inflammatory medicine (NSAID) can worsen renal function
- Reduced adherence due to "pill burden", i.e. confusion over the regimen, and the financial cost of multiple prescription items

A pressure to prescribe and unclear evidence can lead to high use of medicines

Guidelines usually focus on the treatment of a single condition, which can lead to the use of multiple medicines in patients who have several co-morbidities.[2] In addition, less attention is often given to when to reduce the dose or stop the treatment, than when to start it. The evidence regarding the benefits and harms associated with a particular medicine can be uncertain for older people, especially those with frailty or co-morbidities, as these groups are often excluded from clinical trials.

Other aspects of medical practice that may contribute to polypharmacy include:[2]

- Time constraints leading to the renewal of prescriptions without review; conversations about stopping preventative medicines may bring up challenging discussions about life expectancy which require time
- Prescribing cascades where a medicine is initiated to treat an adverse reaction to another medicine, e.g. prochlorperazine prescribed for dizziness caused by an ACE inhibitor[7]
- Continuing to a prescribe a prophylactic treatment after the original medicine is stopped, e.g. ongoing use of omeprazole after stopping a NSAID
- Difficulty stopping a medicine due to adverse discontinuation effects, e.g. benzodiazepines or antidepressants
- Reluctance of general practitioners to withdraw medicines initiated in secondary care
- Difficulty accessing services that provide specialist support and advice regarding appropriate prescribing in older people, e.g. geriatric medicine specialists, Long-Term Conditions pharmacy services
- Clinician and patient fears about the condition returning, worsening or an adverse event occurring if a medicine is stopped

Stopping can be just as important as starting

Stopping medicines, often referred to as de-prescribing, is an integral part of the prescribing process.[8] In clinical trials, deprescribing in older patients has been associated with fewer falls and fractures, reduced referral to acute services, improved cognitive function and better quality of life, with fewer medicines errors and improved adherence to the medicines they continue to take.[9–11]

Reviewing medicine use in older patients

General practitioners often have a detailed knowledge of a patient's medical history and life circumstances and are therefore well-placed to take a lead role in reviewing a patient's prescribed medicines. Some practices may have a clinical pharmacist available to carry out a medicines review.
When reviewing a patient's medicine regimen:

- Consider their overall state of health, e.g. co-morbidities or frailty, rather than basing treatment decisions solely on chronological age; it may be appropriate to withdraw medicines at a younger or older age than is recommended in guidelines
- Discuss their goals for treatment, e.g. which symptoms they want to improve the most or what activities they would like to be able to do, and what benefits and harms might be associated with achieving these goals
- Frame the conversation around providing the best balance of benefits and risks at each stage of their life;

emphasise that withdrawing a preventative medicine does not mean you are "giving up" on them. It may be appropriate to discuss Advance Care Planning.

For further information on assessing frailty, see: "Identifying frailty in primary care" in "Frailty in older people: a discussion", **www.bpac.org.nz/2018/frailty.aspx**

Training material and an Advance Care Planning manual for health professionals are available from: **www.hqsc.govt.nz/our-programmes/advance-care-planning/projects/staff-information/**

Conduct a medicines reconciliation or "brown bag review"

A medicines reconciliation aims to ensure that the medicines a patient is actually taking are the same as what has been prescribed to them according to their medical records.[2] Ask patients to bring in all the medicines they are currently taking, including over-the-counter (OTC) medicines and supplementary products. This is also an opportunity to check that the patient understands what each of their prescribed medicines are for and whether there are any issues with adherence.

Clinicians can reflect on whether any changes should be made to a patient's prescribed regimen by asking themselves or the patient/caregiver:[9]

- Is the original condition which the medicine was prescribed for still present?
- Are medicines initiated for symptomatic management providing adequate relief?
- Are there any medicines which do not have a clear indication for use?
- Has there been a change in the patient's health status, e.g. frailty or falls, which alters the balance between the benefits and possible harms of a medicine?
- Are there any duplications, e.g. two medicines from the same class to treat the same condition when one is sufficient?
- Are any simplifications in their regimen possible? e.g., once daily medicines or combination tablets.
- Were any medicines initiated to treat an adverse reaction to another medicine, i.e. a prescribing cascade? If so, could both medicines be stopped?
- Is there a risk of medicine interactions, including OTC or supplements?
- Is the treatment target appropriate, e.g. HbA_{1c} or blood pressure?
- Is the dose appropriate? e.g., declining renal function may mean a lower dose is required in an older adult.
- Could a non-pharmacological treatment be used instead? e.g., exercise or physiotherapy for patients with osteoarthritis, instead of NSAIDs.
- Does the patient have any concerns regarding their prescription regimen?

Best practice tip: Provide patients with a medicines list that includes what each medicine they take is prescribed for and whether it is used for prevention or treatment of an existing condition; pharmacists can also provide this list. An example of a medicines list can be found here: **https://activities.nps.org.au/nps-order-form/Resources/English-Medicines-List-March-2016.pdf**

The balance of benefits and harms associated with a medicine may change in older people

Commonly prescribed medicines that are associated with an increased risk of adverse effects in older adults, particularly those with frailty, are shown in Table 1. Increased attention to combinations of medicines that can lead to adverse effects may be more useful than focusing on individual medicines.

Implementing changes

Act while the patient is engaged. Many people are open to the idea of stopping medicines if their general practitioner considers it beneficial.[16] If a patient or caregiver raises questions or concerns about the number of medicines they are taking, use this as an opportunity to carry out a review.

Withdraw one medicine at a time. This can help identify which medicine was causing an adverse effect or discontinuation symptoms develop after stopping.[1] Some medicines, e.g. benzodiazepines, antidepressants, proton pump inhibitors (PPIs), should be withdrawn by tapering doses (see: "Stepping down PPI treatment").

Work in collaboration with a pharmacist. This can help to ensure that a patient's regimen is the most appropriate for their circumstances and co-morbidities. Pharmacists also offer services to assist with medicine adherence and simplifying regimens, e.g. Medicines Therapy Assessment, Medicines Use Review, Long-Term Conditions pharmacy service.

Review medicines before and after a stay in hospital. Where possible, simplify a patient's regimen prior to planned hospital admission, ensure that all medicines have a clear indication, and check that they are aware of, and follow, any changes to their usual regimen. Following discharge, ensure that medicines initiated in hospital with the intention of short-term use are not continued long-term and any duplicated or inappropriate medicines are stopped.[5]

Table 1. Commonly prescribed medicines associated with changes in the balance of benefits and risks in older adults.[2, 12]

Medicine class	Potential harms, particularly in older patients
Anticholinergic medicines	Increased risk of falls, delirium, cognitive impairment and urinary retention
Antihypertensive medicines	Increased risk of hypotension and falls
Antipsychotics	Increased risk of mortality in patients with dementia, increased risk of falls and postural hypotension when used as sedatives or hypnotics, e.g. quetiapine
Aspirin*	Increased risk of gastrointestinal bleeding, limited evidence of benefit for CVD prevention[13]
Benzodiazepines or zopiclone	Increased risk of falls, cognitive impairment and possible association with Alzheimer's disease
Bisphosphonates	Increased risk of atypical fractures with prolonged treatment
Diabetes medicines	Intensive glucose lowering is unlikely to benefit older patients; risk of hypoglycaemia with some medicines
Hypnotics	Cognitive effects the following day, increased risk of falls, possible increased risk of Alzheimer's disease
NSAIDs	Greater increase in absolute risk of bleeding than in younger patients, increased risk acute kidney injury, particularly if used in combination with an angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) and diuretic (i.e. the "triple whammy", see: https://bpac.org.nz/2018/triple-whammy.aspx)
Opioids	Constipation, delirium, sedation, increased risk of falls or unintentional overdose[14]
Proton pump inhibitors (PPIs)	Increased risk of fractures, *Clostridium difficile* infection and renal adverse effects such as interstitial nephritis
Statins*	Risk of adverse effects, e.g. myalgia, new onset diabetes mellitus, limited evidence of benefit for cardiovascular disease prevention[15]
Tricyclic antidepressants	Cognitive impairment, urinary retention, postural hypotension, increased risk of falls

* For further discussion, see "Reviewing medicines for cardiovascular disease: aspirin and statins" in: **www.bpac.org.nz/2018/stopping.aspx**

For further information on stopping medicines, including some de-prescribing algorithms for specific medicines, see: **www.deprescribing.org/resources/deprescribing-guidelines-algorithms/**

For the original and extended version of this article see: "Stopping medicines in older people: the flip side of the prescribing equation" (available at **https://bpac.org.nz/2018/stopping.aspx**)

Stepping down PPI treatment

There are several approaches to stepping down PPI treatment and there is no evidence that one protocol is superior to another.[17] The process of withdrawing a PPI should be individualised to the patient and guided by the presence or absence of symptoms at each step.

A protocol for stepping down can be carried out over two to four weeks as follows:[17]

- **Step 1:** Establish the patient's regular PPI requirements
- **Step 2:** Halve the daily dose of the PPI or change the frequency of dosing, e.g. from twice daily to once daily or from daily use to alternate days. Patients who have been on a high dose are likely to require a second or third step-down to reach the lowest dose, e.g. 10 mg on alternate days.
- **Step 3:** Stop the PPI

If at any stage during the step-down process, or after stopping, acid reflux symptoms occur, trial a histamine H_2-receptor antagonist, e.g. famotidine*, an antacid, e.g. aluminium hydroxide tablets, or a medicine that contains an antacid and an alginate.†

* Half the normal dose is recommended for patients with eGFR <50 mL/min/1.73 m^2, refer to the New Zealand Formulary for further details: **www.nzf.org.nz/nzf_745.** N.B Ranitidine is no longer available.

† Acidex contains an antacid and alginate and is available partially subsidised. The high sodium content in some of these medicines may not be suitable for patients with renal or hepatic impairment, refer to the New Zealand Formulary for further details: **www.nzf.org.nz/nzf_9894**

For further information on stopping PPIs, see: "Stopping proton pump inhibitors in older people", available from: **www.bpac.org.nz/2019/ppi.aspx**

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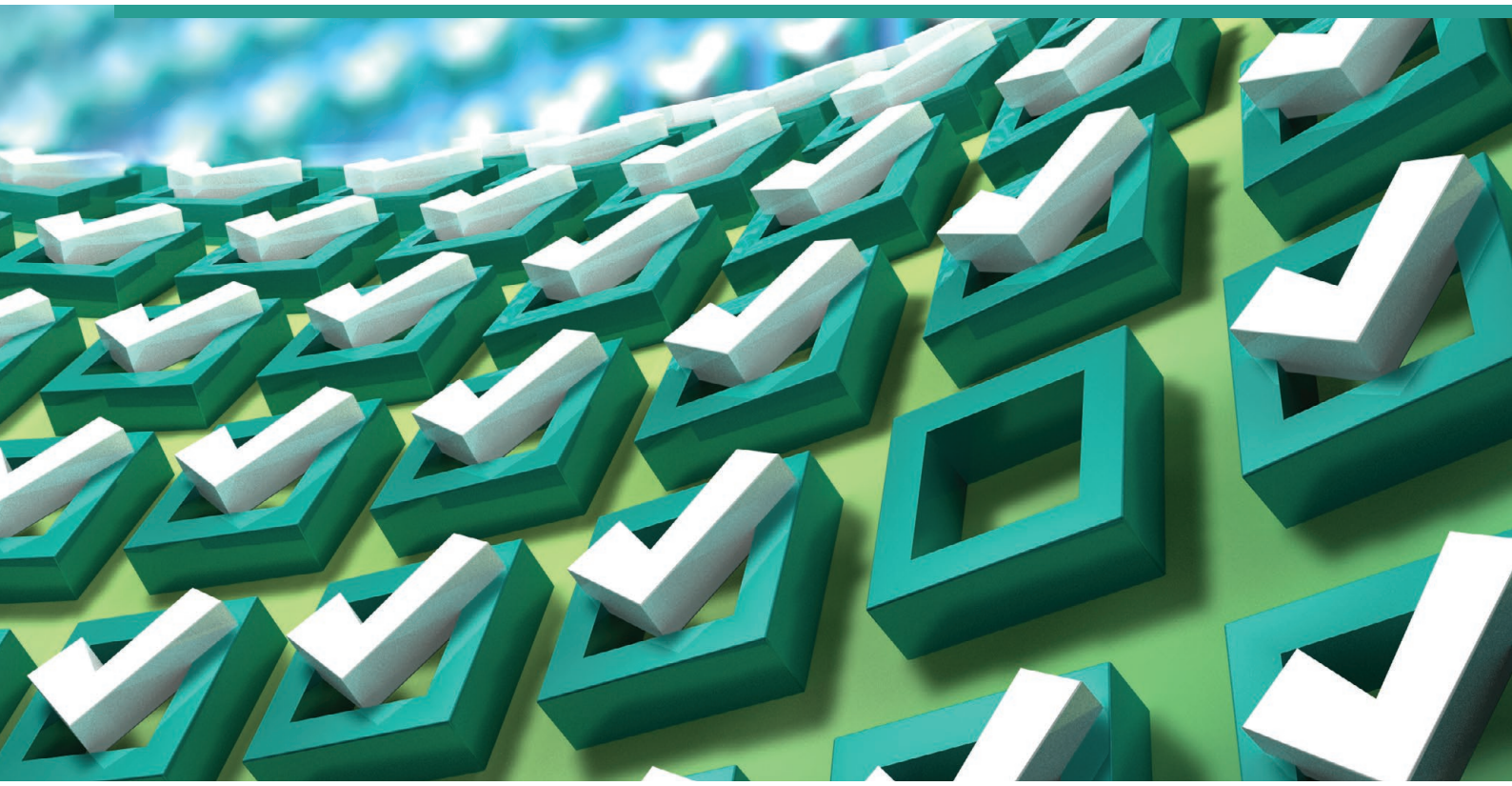

Best tests? The general principles of laboratory investigations in primary care

Laboratory investigations are essential for the diagnosis and management of many conditions, however, they do not provide clinical value in every scenario, and in some cases, may even cause harm. Before requesting a test, consider the aim, how the result will be interpreted and how the patient's management will be affected by the result. Understanding the clinical situations where laboratory testing may be problematic can help to improve the overall approach to testing.

"Testing, testing: one, two, three"

1. Think twice before you test
2. Select the right test, at the right time, for the right patient
3. Ask yourself: can I improve my testing?

Think twice before you test

Laboratory tests are generally requested in primary care for one of the following reasons:

1. **Diagnosis:** to include or exclude a disease, e.g. thyroid stimulating hormone (TSH) levels in a patient with suspected thyroid dysfunction
2. **Establishing a baseline:** e.g. liver function test (LFT) before commencing methotrexate
3. **Monitoring:**
   a. To ensure a medicine is within a therapeutic range, e.g. serum lithium concentration
   b. To detect early signs of an adverse effect to treatment, e.g. full blood count in patients taking clozapine
   c. To monitor or predict the response to treatment, e.g. INR in patients taking warfarin, serum urate monitoring in patients taking allopurinol, or antimicrobial susceptibility of a pathogen
   d. To monitor long-term conditions for disease control and complications, e.g. HbA_{1c}, renal function and albumin:creatinine ratio (ACR) in people with diabetes
4. **Targeted testing**, e.g. antenatal screening, lipid levels as part of a cardiovascular assessment.

In each of these situations the test result will benefit the patient and the clinician by allowing better decisions to be made about future management. However, testing is not always beneficial, and in certain situations the balance may shift from benefit to harm. Understanding the clinical situations that may lead

to a poor outcome can provide insight into when to be more cautious in deciding if laboratory investigation is needed, or if a request for tests should be deferred or delayed.

Considerations before testing

Before requesting a laboratory test consider the following questions:

- What is my reason for requesting this test?
- Will the test improve patient (or in some cases, family/whānau or partner) care?
- Is this the right test or combination of tests for the clinical situation?
- How will the test result be interpreted?
- How will the test result influence patient management?
- Are there potential harms of doing this test?

The following examples demonstrate potentially problematic scenarios when considering laboratory investigations.

Laboratory tests may reveal incidental findings

The early discovery of dormant conditions or incidental findings that have little or no long-term health consequences can be unveiled by laboratory investigations. Once a condition is identified, it can sometimes be difficult for the patient to understand and accept that treatment is not necessary.

Over-diagnosis and over-treatment are the most important adverse effects of screening programmes. It is estimated that 50–60% of cancers detected by prostate specific antigen (PSA) screening are over-diagnosed.[1] The risk of patients receiving a diagnosis and treatment for a cancer that would not have affected their long-term outcome is one of the reasons why PSA screening is controversial, especially in older patients with co-morbidities. A discussion with patients about the potential risks of testing, and consideration of what a positive or negative result will mean for their management, can help when making an informed decision about whether to test or not.

For further information on PSA testing, see: "Testing for prostate cancer: helping patients to decide", **https://bpac.org.nz/2020/prostate.aspx**

Some symptoms are medically unexplained

In some cases, patients with underlying psychosocial distress may present with a complex pattern of medically unexplained symptoms or signs. Diagnostic uncertainty can lead to an increased number of laboratory tests requested. This situation provides the "perfect storm" of clinical uncertainty. Normal laboratory results may not provide reassurance and multiple test requests are also likely to eventually result in a value being identified outside the normal reference range, regardless of whether it is clinically significant (Table 1).

Instead of requesting a battery of tests, it may be more appropriate to identify any psychological or environmental stressors or administer a depression or anxiety screening tool if a mood disorder is suspected. In this scenario, providing an explanation for the patient's symptoms in relation to psychosocial distress is likely to have more benefit than a series of laboratory tests.[2]

For further information, see: "Somatisation: demystifying the "ghost in the machine", **https://bpac.org.nz/2019/somatisation.aspx**

Patients ask for tests themselves

Patients often ask for laboratory tests based on their own research or following discussion with friends or family. A common scenario is for a patient to be concerned about possible dietary deficiencies, e.g. zinc or selenium. However, in most cases, patients will not have a deficiency, and borderline low levels are a non-specific finding, with low predictive value of organic disease (see: "Deciding when a test is useful: how to interpret the jargon" for further discussion of these terms).[3]

Education and evidence-based discussions can be helpful in explaining to patients why testing is not always appropriate. Patients need to be aware that they may need to pay for some tests themselves, if they are not clinically justified.

Selecting the right test, at the right time, for the right patient

Once the decision is made to request laboratory investigation, selecting the right test at the right time for the right patient can sometimes be a challenge. This decision may be influenced by many factors including patient and family/whānau expectations, emerging evidence, changing guidelines, clinical experience and individual patient factors. All of which are combined with the need to identify the problem within the consultation time, and the natural concern of the clinician not to get it wrong and miss a diagnosis.

By having a clear purpose when selecting a test and selecting the right test, in the right circumstances, with a clear understanding of how results will be interpreted, clinicians can improve patient outcomes while making the best use of tests.

Selecting the most appropriate test

Sometimes it is clear that an investigation is required, but there is uncertainty as to what test to use. Consider the resources you have available to assist you in your test selection, e.g. HealthPathways, written guidance such as bpac^{nz} articles, laboratory testing handbooks and online guides and directly contacting your local laboratory.

The usefulness of some tests depends on the clinical setting. For example, tumour markers are useful for patients receiving cancer treatments, but as a first-line rule in/rule out

test for cancer they have a limited diagnostic value in most circumstances. A UK study found that 84% of tumour marker tests requested by general practitioners were inappropriate.[4]

The timing of laboratory tests is an important consideration

Even if a test is appropriate, it needs to be requested at the right time for the patient, and with the right preparation, where necessary.

Some tests require certain factors to be present (or not present) in order to produce a meaningful result. For example, the measurement of antibodies to tissue transglutaminase (TTG) in a patient with suspected coeliac disease may be falsely-negative if the patient has already removed gluten from their diet.

Other tests must be undertaken at specific times. For example, therapeutic drug monitoring must occur at a certain time/interval to measure the drug concentration relative to dosing. Similarly, a test for serum cortisol levels should be collected in the morning, as diurnal variation leads to a fall in levels later in the day. Some tests must be timed to coincide with a certain stage of the disease cycle, e.g. if an HIV serology test is requested too early, seroconversion may not have occurred, and therefore a false-negative result is possible.

Can I improve my testing?

There are several examples of ways in which clinicians can use laboratory investigations in a more effective way.

Use serial testing rather than parallel testing

Serial testing is when subsequent tests are requested, based on the results of initial tests, rather than testing all at once (i.e. parallel testing). For example, if a patient presents with feeling "tired all the time" a full blood count, ferritin and TSH may be considered as first-line tests. Based on these results, the clinician can then instruct the laboratory to further analyse the sample for other tests*, such as B12/folate and electrophoresis, if there is unexplained anaemia.

* Provided the laboratory has sufficient sample remaining and in the correct collection tube

Manage test ordering forms

Online laboratory test ordering systems tend to be arranged with the most frequently requested tests appearing on the first screen, with tests that are often ticked, but that may not be indicated, such as antinuclear antibody (ANA) and serum magnesium, sited on other tabs. This can help to reduce the temptation for "tickboxitis", i.e. routinely selecting certain tests with every laboratory request. Both online test ordering systems and older PMS generated laboratory request forms can be customised, e.g. tests that are routinely requested together can be grouped and selected with one click, e.g. full blood count, C-reactive protein, renal function and liver function in people taking methotrexate.

Be aware of standing orders for tests

Unnecessary tests can occur when regular tests are automatically repeated, without checking that the clinical justification for testing is still present. For example, continuing to test INR levels in patients who are no longer receiving warfarin or testing lipids in patients no longer receiving statins.

Consider if treatment can commence without testing

Vitamin D testing is an example of a laboratory test that is frequently unjustified in New Zealand. Due to seasonal variation in sunlight, most people's vitamin D levels fluctuate through the year, making interpretation of vitamin D test results difficult. Testing vitamin D levels is rarely beneficial for patients, is expensive and often unreliable. Clinicians should focus on treating individuals who have a high likelihood of vitamin D deficiency, e.g. frail older people in residential care or people with very dark skin pigmentation.[5]

Consult with the laboratory

When in doubt about what test to order, or how to interpret the results, phone the laboratory. Laboratory staff, including pathologists, are available to provide expert assistance, and this resource should be utilised.

Deciding when a test is useful: how to interpret the jargon

The usefulness of any laboratory test is determined by the clinical context. For example, a study of diagnostic tests ordered by 87 General Practitioners for over 1200 patients found that when a test was ordered purely for patient reassurance, approximately 66% of results outside the reference range were interpreted as normal, however, when a test was ordered to confirm a suspected diagnosis, only 28% of results outside the reference range were interpreted as normal.[6]

To determine the likelihood that a patient has a specific condition, based on a test result, the clinician must first consider:

1. How likely is it that the patient has this condition? This is termed the pre-test probability and is based on the clinical characteristics of the patient, the local prevalence of the condition being considered, and the clinician's personal experience.
2. How accurate is this diagnostic test? This is determined by the sensitivity and specificity of the test.

Pre-test probability is the likelihood that the condition being tested for is the cause of the symptoms, before a diagnostic test result is known. This helps clinicians to decide whether it

is worthwhile requesting a diagnostic test. The probability may change during the consultation as symptoms and signs are weighted as being "somewhat more suggestive" or "somewhat less suggestive" of the suspected medical condition.

The sensitivity of a test is the proportion of people with the condition who have a "positive" result (above or below the diagnostic threshold used), i.e. the ability of the test to correctly identify patients with the condition. Because the number of false-negatives decreases as the sensitivity of the test increases, a highly sensitive test is useful for "ruling out" a condition if the patient tests negative. Highly sensitive tests are used when the consequences of missing a condition are potentially very serious, such as for an acute myocardial infarction.

The specificity of a test is the proportion of people without the condition who have a "negative" result, i.e. the ability of the test to correctly identify patients without the condition. Because the number of false-positives decreases as the specificity of the test increases, a test with a high specificity is useful in "ruling in" a condition if a person tests positive. As with sensitivity, the specificity of a test will vary somewhat depending on the diagnostic threshold chosen.

There are very few tests, if any, that have 100% sensitivity and specificity. The choice of what threshold is used depends on the parameters of the test and what the purpose is when using it. Deliberately setting the threshold for optimum sensitivity can result in increased numbers of false positives (above or below the threshold) as well, resulting in reduced specificity. Conversely, in other circumstances optimising specificity may be more relevant, at the cost of reduced sensitivity.

Performing several tests serially increases the overall specificity for detecting a condition, with each test being sequentially more specific than the previous one.

Positive predictive value is the probability that a patient with a positive test result really does have the condition for which the test was requested. Unlike sensitivity and specificity which are independent of the population being tested, the positive predictive value of a test changes depending on the prevalence of the disease in the population being tested.

The negative predictive value is the probability that a patient with a negative test result really is free of the condition for which the test was conducted.

The probability of an abnormal result increases when the number of tests increases

The risk of a healthy individual having a result outside the reference interval increases as the number of tests selected increases. This is because the normal reference interval for most biochemical tests is defined as being two standard deviations from the mean of a healthy population. Therefore, an average of 5% of all test results from healthy patients will fall outside the normal range and be recorded as abnormal (Table 1).[7, 8]

False-positive results are more likely when people with a low probability of a condition undergo testing. Although false positive results can cause significant anxiety to the patient, false-negative results can often have more serious health consequences. Test results should always be interpreted in the context of other information gained from the clinical history and physical examination. Results which are borderline need to be interpreted with caution as the inter-test variability could mean the result is either normal or abnormal, so may need to be repeated after a period of time. If there is doubt, consultation with a pathologist about the test results can be helpful.

Table 1: Probability of a healthy person returning an abnormal biochemical test result, adapted from Deyo (2002)[8]

Number of tests	Probability of at least one abnormal test (%)*
1	5
6	26
12	46
20	64
100	99.4

* Assuming each test outcome is independent

For the original and extended version of this article, see: "Best Tests?" (available from: **https://bpac.org.nz/BT/2013/February/02_principles.aspx**)

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Interpreting urine dipstick tests in adults: a reference guide for primary care

A urine dipstick positive for haematuria or proteinuria is relatively common in primary care. For many patients there may be a transient, e.g. urinary tract infection, or benign explanation for the result, however, persistent positive results require further investigation. Management is determined by the presence of associated symptoms, risk factors for malignancy and additional investigations to identify a urological or nephrological cause.

Haematuria on dipstick

Haematuria can be visible i.e. macroscopic or gross haematuria, or non-visible i.e. microscopic.[1] Haematuria can originate from the kidney, ureter, bladder, prostate, urethra or other structures within the urogenital tract.

Urine dipsticks are a rapid and relatively sensitive (>80%) method for detecting red blood cells (RBC) in a freshly voided urine sample.[2] As well as intact RBC, urine dipstick may also detect haemoglobin caused by haemolytic conditions, or myoglobin from crush injuries, rhabdomyolysis or myositis.[2] The specificity of urine dipstick for haematuria therefore ranges from 65 – 99%.[3] Significant haematuria occurs at readings of 1+ or above, and trace levels should be considered negative.[1]

Urine microscopy is not routinely required to confirm a diagnosis of haematuria.[1] In some situations, however, microscopy may help to distinguish haematuria from haemoglobinuria and myoglobinuria and to detect dysmorphic RBC and urinary casts that indicate a renal cause.[3]

Visible haematuria (macroscopic)

Visible haematuria is primarily associated with urological conditions, e.g. urinary tract infections (UTI), stones, trauma or strictures.[4] Rarely, changes in urine colouration may be due to other causes, e.g. haemoglobinuria, myoglobinuria (usually associated with rhabdomyolysis), beeturia (after eating beetroot), porphyria or medicines, e.g. rifampicin and chlorpromazine.[1] Haemoglobinuria can occur with haemolytic anaemia, which may be accompanied by rapidly developing pallor, splenomegaly and jaundice.

Non-visible haematuria (microscopic)

Transient, non-visible haematuria is common and depending on the population, may be reported in as many as 39% of people.[3] It is associated with a mixture of urological and glomerular causes. Persistent, non-visible haematuria is defined as urine positive on two out of three consecutive dipsticks,[1] e.g. over a one to two-week period. It is estimated to occur in 2.5 – 4.3% of adults seen in primary care.[3]

Assessing haematuria

Haematuria can be asymptomatic or symptomatic, e.g. dysuria, frequency, urgency and hesitancy. Table 1 provides guidance when considering causes of haematuria. Risk factors for significant urological disease include:[5, 6]

- History of recurrent visible haematuria
- Age over 45 years
- Current or recent history of smoking
- History of UTI or other urological disorders
- Occupational exposure to chemicals or dyes
- Previous pelvic irradiation
- History of high analgesic use
- Treatment with cyclophosphamide

Risk factors specific for bladder cancer include family history, smoking, male gender and occupational exposure to carcinogens.[7]

Investigating visible haematuria

If a UTI or other obvious causes has been excluded, imaging of the urinary tract is indicated (see: "Urinary tract imaging"). Assessment by a urologist and subsequent cystoscopy will be required in most cases, although cancer is unlikely in people aged under 40 years without risk factors. If investigations do not suggest a urological cause, discuss with a nephrologist, with urgency determined by the level of persistent haematuria. Investigation and referral guidance for patients with visible and non-visible haematuria is provided in Figure 1.

Investigating symptomatic non-visible haematuria

Non-visible haematuria is significant once transient causes, e.g. UTI or exercise, or benign causes, e.g. menstruation, have been excluded. Urinary tract imaging is indicated for all patients with recurrent, symptomatic, non-visible haematuria regardless of age or for patients with risk factors for malignancy.[1, 9, 10] Urological assessment and cystoscopy to detect possible cancer is also required for patients aged 60 years and over with unexplained non-visible haematuria and either dysuria or an elevated white blood cell count.[6] When lower urinary tract symptoms are present in males aged over 50 years the possibility of prostate cancer should be investigated. Incidental, non-visible haematuria may be present when prostatic cancer is diagnosed, usually as a result of associated benign prostatic hypertrophy. Visible haematuria in a patient with a PSA level ≥ 10 micrograms/L requires urgent referral to a urologist due to the risk of advanced prostate cancer.[11]

Baseline assessment of blood pressure and renal function with estimated glomerular filtration rate (eGFR) and albumin:creatinine ratio (ACR) or protein:creatinine ratio (PCR), and urine microscopy for urinary casts and dysmorphic red cells are also recommended to identify non-visible haematuria potentially due to glomerulonephritis.[1]

Investigating asymptomatic non-visible haematuria

Age determines the likelihood of a urological or renal explanation for asymptomatic non-visible haematuria.[1] For patients aged over 40 years or younger patients with risk factors for urothelial malignancy, urinary tract imaging is indicated. Patients aged under 40 years have a low risk of a urological cause therefore investigation of a potential renal cause with ultrasound is recommended.

Table 1: Causes of haematuria that may be considered when assessing a positive dipstick.[8]

Common in primary care	Transient/other	Do not miss	Consider
■ UTI ■ Urinary tract or kidney stones ■ Prostatitis	■ Menstruation ■ Exercise-induced ■ Benign prostatic hyperplasia ■ Mild trauma ■ Pseudohaematuria, e.g. beeturia	■ Urinary tract, kidney or prostate malignancy ■ Cardiovascular: – Kidney infarction – Kidney vein thrombosis – Prostatic varices ■ Acute glomerulonephritis ■ Severe infection: – Infective endocarditis – Kidney tuberculosis ■ Papillary necrosis ■ IgA nephropathy	■ Urethral prolapse ■ Foreign body ■ Radiation cystitis ■ Familial: – Thin basement membrane disease – Adult polycystic kidney disease

N.B. Anticoagulant and anti-platelet medicines are more likely to exacerbate, rather than cause haematuria and haematuria in patients taking these medicines requires investigation.[1]

Haematuria on dipstick

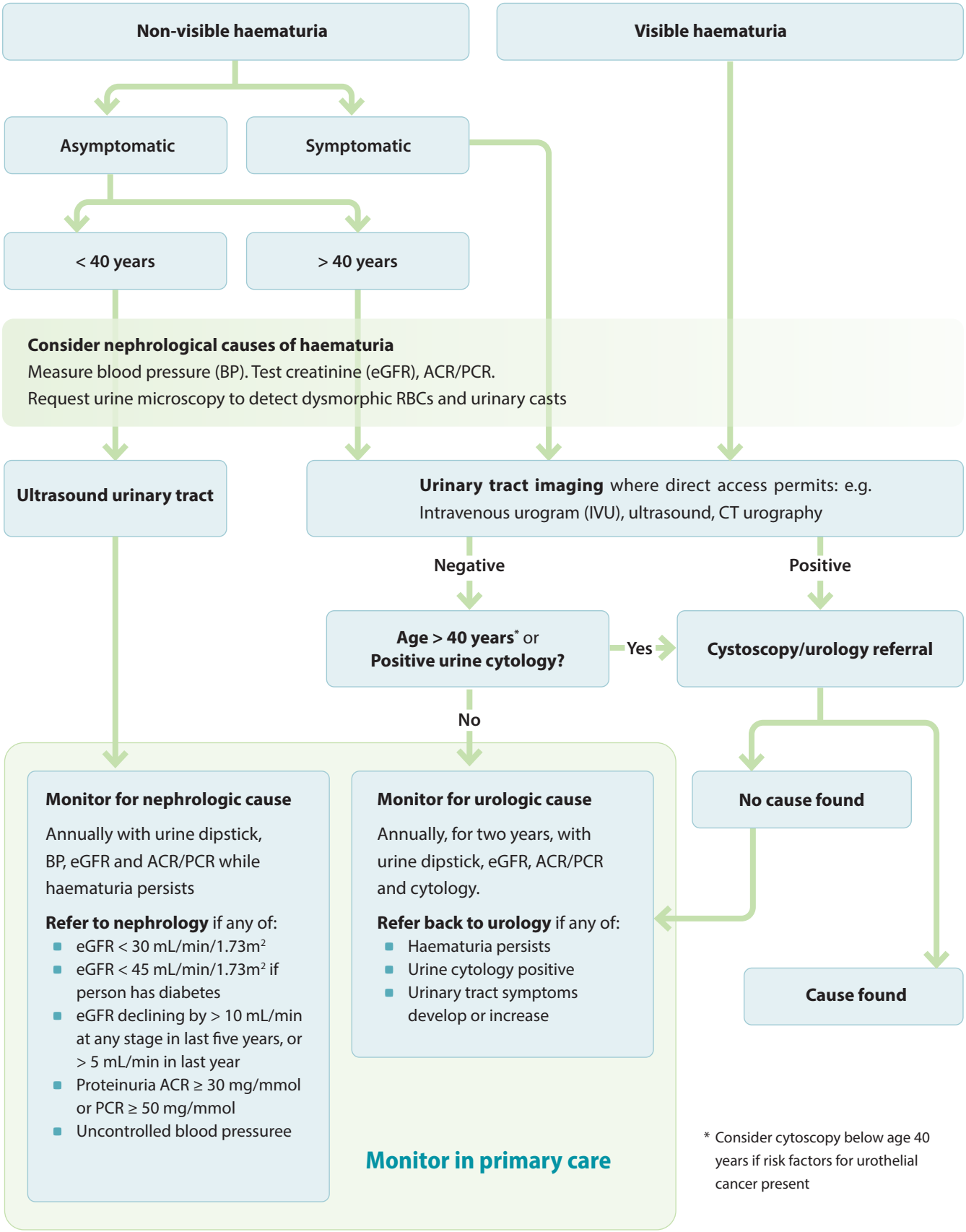

Figure 1: Investigation and referral algorithm for significant haematuria in adults once UTI and benign causes have been excluded[1, 10, 12, 13]

N.B. Local pathways may differ, and clinical judgement is required when assessing cancer risk

Primary care monitoring of unexplained haematuria

Primary care surveillance of unexplained haematuria requires annual assessment of urine dipstick, serum creatinine and urinary ACR, or urinary PCR. This should be conducted until two consecutive negative urinalyses occur.[12] Patients with stable CKD should be monitored according to their stage of disease. Refer patients back to urology if haematuria persists, or urinary tract symptoms develop or increase.

For further information see: "The detection and management of patients with chronic kidney disease in primary care", **https://bpac.org.nz/BPJ/2015/February/ckd.aspx**

Cystoscopy is recommended to exclude bladder cancer

Cystoscopy is the preferred technique for excluding bladder cancer as the cause of haematuria as it has a specificity for malignancy of over 90%, although it is a subjective and invasive tool that may miss flat lesions.*[14, 15] Urine cytology is a non-invasive method, however it is not a "rule-out" test due to modest sensitivity which may be 30% for low-grade tumours.[15]

Urine cytology is not routinely recommended for the investigation of asymptomatic microscopic haematuria but is recommended for the investigation of macroscopic haematuria or symptomatic microscopic haematuria.[15] Urine cytology results are dependent on operator skill and it is important to have an experienced pathologist interpret the results.[16]

* Fluorescent, or blue light, cystoscopy is associated with a higher rate of lesion detection than standard white light cystoscopy

Proteinuria on dipstick

Persistent proteinuria is a marker for kidney disease and kidney disease progression, and of increased cardiovascular risk.[17] Urine dipstick mainly detects albumin and is relatively insensitive to non-albumin proteins, e.g. free light chains, haemoglobin and tubular proteins, although, the level of protein can be estimated from the result:[18]

- Trace = 150–300 mg/L
- 1+ = 300–1000 mg/L
- 2+ = 1-3 g/L
- 3+ = >3g/L

A urine dipstick reading of +1 has a 94–96% specificity for detecting significant proteinuria.[19] The sensitivity of the test for detecting significant proteinuria ranges from 46–81%.[19] In people diagnosed with, or suspected of having diabetes the more sensitive ACR is recommended to quantify proteinuria.[17]

Proteinuria on dipstick is frequently an incidental finding and is often benign and transient, e.g. due to stress, illness or vigorous exercise.[18] However, the presence of proteinuria may also suggest endothelial/glomerular injury. The first step in assessment should be to consider the possibility of a false positive result, which can be caused by alkaline urine (pH >7), gross haematuria, leukocytes or the use of iodinated contrast agents.[18, 20]

Confirm persistent proteinuria

Proteinuria may be transient or persistent. Transient, mild proteinuria can be caused by exercise, standing for long periods (orthostatic proteinuria), pregnancy, UTI and acute febrile illness.[18] Orthostatic proteinuria is typically absent in the morning, occurs in the afternoon and is seen mainly in young adults and usually resolves in 10–20 years.[18] Congestive heart failure is a more serious cause of proteinuria that can also be transient.

Persistent proteinuria can be confirmed by multiple positive results over one to two weeks.[20] If persistent proteinuria is present on dipstick, an ACR or PCR should precisely quantify the level (Figure 2). ACR is the preferred method as it has greater sensitivity than PCR for low concentrations of protein, and albumin is the predominant protein excreted in the majority of proteinuric kidney diseases.[21] Spot (random) urine samples are generally sufficient, although early morning collection is preferable as the sample will be more concentrated.[18]

Follow-up investigations of confirmed proteinuria

If proteinuria and non-visible haematuria is present, a sample should be sent for urine microscopy.[3] Red blood cell casts and dysmorphic red blood cells are likely to be caused by glomerular disease.[3]

Renal function should be assessed and serum electrolytes requested.[23] Patients should be referred to nephrology regardless of the level of proteinuria if they have progressive CKD and an eGFR < 45 mL/min/1.73 m^2 or there is evidence of intrinsic kidney disease, e.g. glomerulonephritis, polycystic kidney disease or interstitial nephritis.[17] Patients with proteinuria who are not referred to nephrology should have blood pressure, urinalysis and renal function assessed every six to 12 months.[24]

Further information on diagnosing and managing CKD is available from: "The detection and management of patients with chronic kidney disease in primary care", **https://bpac.org.nz/BPJ/2015/February/ckd.aspx**

Request further testing if multiple myeloma is suspected

Suspicion of multiple myeloma should be increased in patients aged over 60 years with bone pain or fractures, and fatigue and recurrent infections, with or without hypercalcaemia.[25] There may also be laboratory evidence of anaemia and renal impairment.[25] Protein dipstick is inappropriate to exclude multiple myeloma due to its inability to detect light-chain

Proteinuria on dipstick

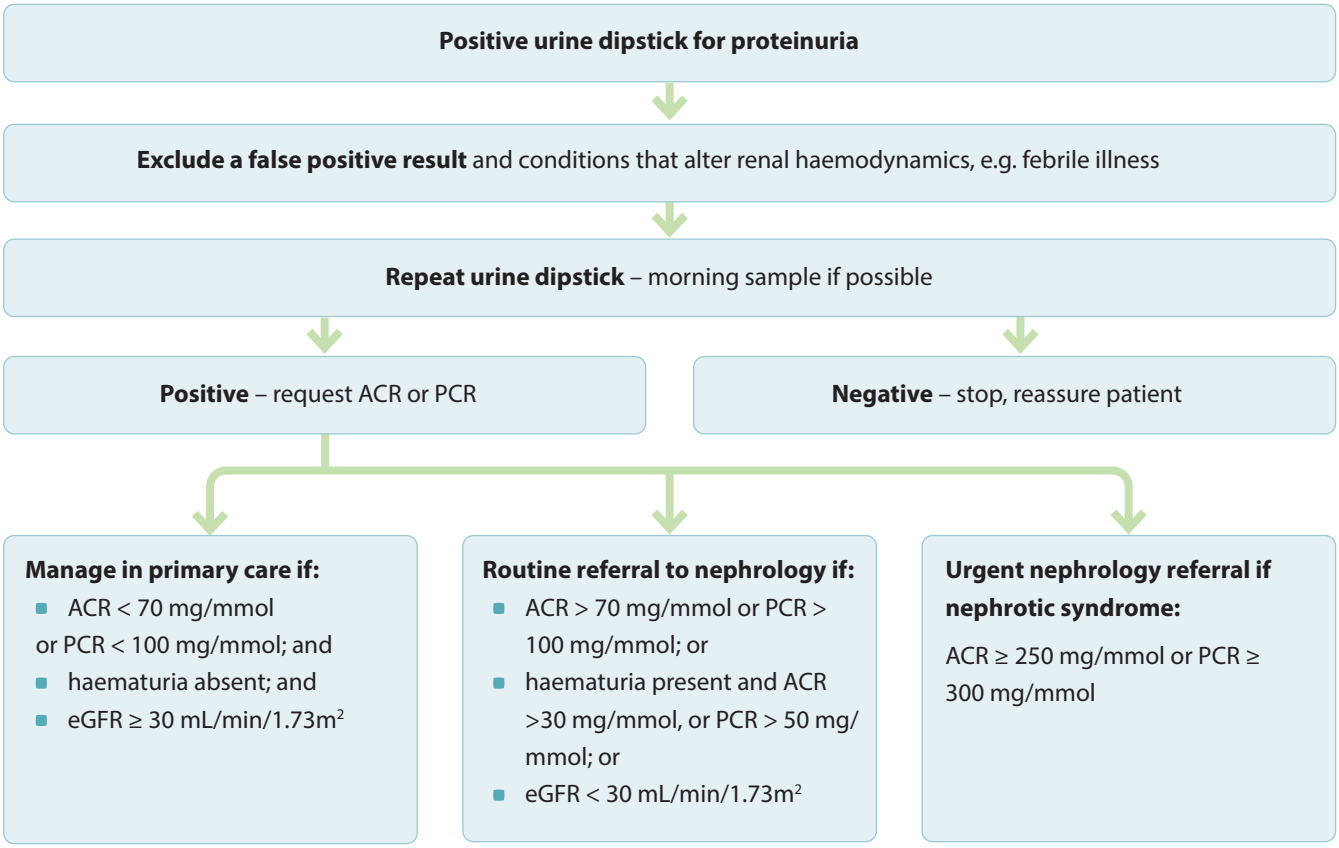

Figure 2: Investigating urine dipstick positive for proteinuria in primary care.[22]
N.B. Local pathways may differ.

immunoglobulins.[25] Electrophoresis may be automatically performed if the laboratory finds immunoglobulins are raised; if it is not performed, the potential need for further testing can be discussed with a haematologist as required.

For the original and extended version of this article, see: "Interpreting urine dipstick tests in adults: a reference guide for primary care" (available from: **https://bpac.org.nz/bt/2013/june/urine-tests.aspx)**

Urinary tract imaging

A computed tomography urogram (CTU) is the imaging gold standard when investigating visible and non-visible haematuria. Some regions, however, have reduced access to CTU and funding constraints mean that intravenous urogram (IVU/IVP) and ultrasonography still have a role when investigating patients at the lowest risk of renal tract malignancy. Cystoscopy is still required to exclude a cause for haematuria located in the bladder.

How to collect and store urine samples

Clean-catch, midstream collection is recommended when collecting a urine sample for a dipstick test in both males and females. This method generally results in an uncontaminated sample, and there is no evidence that prior cleansing of the external genitalia reduces contamination.[3] If further analysis of the sample is required, it should be stored in a fridge. Delays greater than two hours between collection and analysis are reported to produce unreliable results.[27] N.B. The nitrite dipstick reagent is sensitive to air exposure and containers of strips should be sealed after use.[27]

Interpretation of leukocyte esterase and nitrites on dipstick in females

Urine dipstick testing is not necessary to diagnose a textbook UTI, but in practice it is often performed as the presence or absence of leukocyte esterase and nitrites can provide useful information, e.g. ruling out a UTI in a patient with non-specific symptoms.

Leukocyte esterase is an enzyme released by neutrophils and macrophages. A urine dipstick positive for this enzyme indicates pyuria (an increased number of leukocytes). UTIs are a common cause of pyuria and haematuria, but also consider sexually transmitted infections such as chlamydia.[26] The presence of leukocyte esterase on dipstick may also be due to non-infectious renal diseases such as glomerulonephritis. Contamination of samples by vaginal secretions may cause a false-positive result.

Nitrites are generally found in urine due to the reduction of nitrates to nitrites by Gram-negative bacteria such as *Escherichia coli*. The detection of bacteria in urine by nitrite positive dipstick is also dependent on nitrates from the patient's diet (vegetables) and incubation time in the bladder. Gram positive uropathogens such as *Staphylococcus saprophyticus* and *Enterococcus* do not produce nitrate reductase and the dipstick will be negative for nitrites if the infection is due to these bacteria.

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