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Proton pump inhibitors: When is enough, enough?

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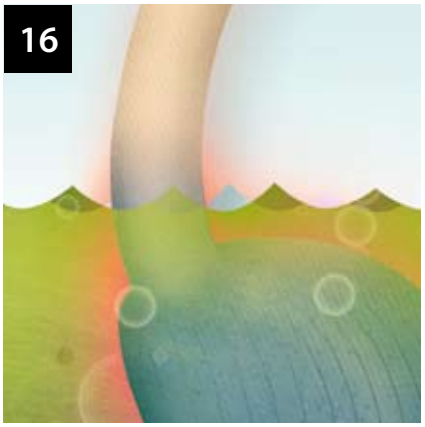

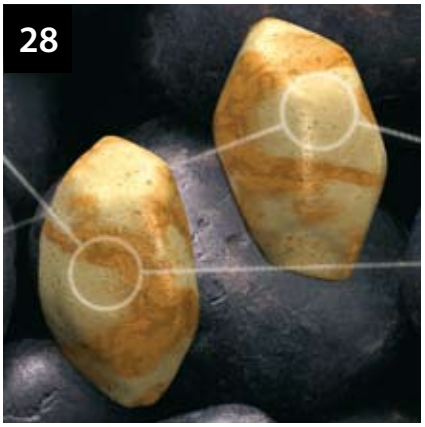

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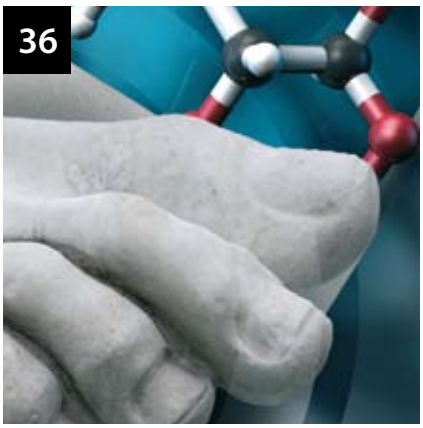

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"A disaster in the making": it's time to take action against misuse of oxycodone

Dr Jeremy McMinn is a consultant psychiatrist and addiction specialist at Capital & Coast DHB. He is also the Co-Chair of the National Association of Opioid Treatment Providers and the New Zealand Branch Chair of the Australasian Chapter of Addiction Medicine. We invited Dr McMinn to answer a series of questions about the role of oxycodone, both as a legitimate option for pain control, and a medicine with a serious potential for misuse. The time for debating who to blame has passed. Oxycodone, and opioid prescribing in general, is already out of hand and we need to collectively take action before it is too late.

How would you describe the current situation in New Zealand in terms of misuse of oxycodone?

With due heed to hyperbole, we are looking at a disaster in the making. We have been complacent about the warnings from the rest of the western world, with harms arising from pharmaceutical opioids overtaking those from heroin. This has reached epic proportions in the United States, with oxycodone particularly over-represented. Pharmaceutical opioids in the United States now kill more people than firearms or road traffic accidents, and more than the combined death rates from heroin and cocaine overdoses. This is shocking and shameful – how can it be possible?

In New Zealand, we have had the good fortune to be last off the starting line, with oxycodone coming to us later. Even so, it is clear from [national dispensing] data that our prescribing of oxycodone has followed comparable trajectories to that seen in Australia and the United Kingdom. There is no good reason for this – oxycodone is more expensive than morphine and more addictive, and is no safer in renal [impairment] or other conditions. And it is not as if we are even prescribing it for the right reasons – the literature on chronic pain increasingly indicates that opioids are harmful long term, not beneficial. Chronic pain is not acute pain – the "benefits" of opioids in chronic pain may be limited to a brief reduction in subjective pain, before tolerance and hyperalgesia negate this, leaving the patient neuro-adapted to a higher dose.

> ***"New Zealand's problem prescribing pharmaceutical opioids, with the predictable onslaught of oxycodone, is a national scandal that should be stimulating profound professional soul-searching."***
>
> *— Dr Jeremy McMinn*

How does oxycodone compare to other prescription drugs of misuse, e.g. morphine?

The appalling aspect of this is that New Zealand has had three decades already of seeing pharmaceutical opioid abuse and dependence rather than heroin addiction – we, as prescribers, have significant responsibility for these harms.

In New Zealand, patients that end up on opioid substitution treatment [i.e. the methadone programme] mainly initiate and maintain their pre-treatment addiction with morphine and methadone. The morphine mainly comes from pain specialists, general practitioners and palliative care physicians, and the methadone comes from opioid substitution treatment (OST). In recent years, OST services have recognised this, and increasingly adopted greater treatment supervision, more restrictive dispensing, and more explicit adherence to evidence-based dose ceilings. Other prescribers need to catch up.

What advice can you give to general practitioners for identifying patients who are drug-seeking? i.e. no legitimate reason for requiring oxycodone

General practitioners need to take control, and use their knowledge of health conditions, prescribing risks and clinical concern appropriately. Patient choice is not the primary reason to prescribe a drug (although it may be a factor in which drug is chosen). But if the condition presented is not sensibly treated with the drug requested, do not prescribe it. Opioids are very likely not to provide a true benefit in pain conditions lasting over a month – just as benzodiazepines are not justified in cases of anxiety lasting more than two weeks.

Worry about a complaint to the Health and Disability Commissioner should not influence the decision – drug-seeking patients know that implying they will complain makes doctors fold. If the patient is likely to move on to a different, "softer touch" doctor, general practitioners can protect their colleagues by making an application for a Restriction Notice and making sure any documentation reflects the doubts about the legitimacy of the drug request.

General practitioners may know the background history and social/family environment better than any other doctor involved. It is likely that most people abusing oxycodone, benzodiazepines, etc, are using medications that were prescribed originally for someone else. *Primum non nocere* (first do no harm) extends to society, not just the patient in the room.

Any patient that insists on an abusable drug by name, without sufficient diagnostic justification, without supporting documentation, with stories of lost prescriptions or stolen medications should not receive a prescription. Medical Council guidance allows for a three day prescription to ease a threatening patient out of an office, but then preparations for the next consultation must be made. This may include talking with colleagues, arranging a chaperone, and applying for a Restriction Notice. Overt threats of violence should be reported to the police. Threats of suicide can be discussed with local emergency psychiatric services.

Chronic pain, current or past addiction to any substance, current or past mental illness, childhood sexual abuse and family history of addiction are all important risk factors for addiction.

"Many GPs already know that we are fighting to retract an opioid tsunami" *— Dr Jeremy McMinn*

What advice can you give to general practitioners for identifying patients who may be addicted to oxycodone? i.e. a legitimate need for pain relief which has turned into a dependency

Oxycodone is highly addictive – between 25–33% of regular users will experience features of dependence. With this risk, all patients with courses lasting longer than one month should be examined for signs of addiction. Requests for increasing doses and early (or replacement) prescriptions are obvious warning signs. It is essential to consider appropriate urine drug testing and examining for injections sites. The perceived stigma of these can be reduced by making this a standard condition of Controlled Drug prescribing.

General practitioners will be alert to treatment that does not achieve a net improvement. Emerging addiction is a powerful, but sometimes opaque, reason that treatment is not as effective as originally predicted.

Are there any safeguard practices for prescribing oxycodone which can help to avoid inadvertently contributing to drug misuse or addiction?

Prescriptions of any abusable medications that may last longer than a month should be subject to the 10 Universal Precautions*[to be discussed in the next edition of Best Practice Journal]. The gist of these precautions is an explicit contract covering treatment duration, dose parameters, outcome measures, side effect safeguards and defined review dates.

Patients (and doctors) should be aware of the relative lack of good evidence that oxycodone is genuinely effective after one month, contrasted with the wealth of evidence of harm. Oxycodone dose ceilings in primary care should be no more than 60 mg per day (broadly the equivalent of morphine 100 mg per day). After this, specialist review or re-thinking is required. Outcome measures should be measurable change in function, not subjective pain score – the pain always eases with a dose increase, but temporarily, just as it always flares with a dose decrease, temporarily. Safeguards for oxycodone prescribing include universal use of urine screens, examination for injection sites and regular discussion with the dispensing pharmacist.

A key advantage of some degree of treatment contract is that it allows the prescriber to back out of prescribing that is getting out of hand. The subsequent re-think can include seeking specialist advice for pain and addiction.

* Gourlay D, Heit H, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Med 2005;6(2):107-12.

What issues are you seeing among patients as a result of oxycodone addiction?

I am seeing patients who tell me how easy it is to get oxycodone – and it is cheap. My impression is that most people find it straightforward to convince a doctor to prescribe for them, although clearly some doctors (and some regions) are easier than others. For the ones that do not go directly to a doctor, they can buy from other individuals or from doctor-shopping rings. These rings can include older women, who may not trigger the same suspicions. I have been surprised how much oxycodone seems to travel by New Zealand Post between regions. It is just a matter of time before the street oxycodone "market share" becomes evident.

People presenting voluntarily for treatment are still mainly presenting with morphine addiction, with methadone a close second. Virtually everyone has added some oxycodone into the mix of what keeps them going, but addictions driven only by street oxycodone are infrequent so far. However, I am not reassured by this – presentations for OST are usually very late: most people struggle with their own attempts to manage before they resign themselves to the restrictive rigours of OST.

I am also seeing a new cohort of patients, who are coming semi-voluntarily. These are the people who have received a long term prescription for pain which has tipped over into problematic use. Most have to see me because the original prescriber has become aware of problems and has wisely, if often belatedly, made further opioid prescription contingent on addiction assessment. Frequently, the problems arise from the short acting nature of the "pain", opioid-on/off effects, tolerance, aberrant use, etc. A transition to a longer acting opioid, i.e. methadone or buprenorphine (in the form of Suboxone) is usually required. Frequently these patients do not wish to characterise themselves as "addicts", but do nonetheless have features of opioid dependence. There may be some good prognostic factors present in this cohort, but a prolonged period of opioid substitution and related counselling still seem to be required.

It surprises me how often general practitioners seem to feel committed to continue a course of opioids started in hospital or recommended by a pain specialist – even though the use of opioids is clearly starting to go wrong. General practitioners usually have the best overall knowledge of the patient – in my opinion, this may trump the often more narrow and frequently time-limited recommendations of specialist care.

"General practitioners should not hesitate to bring their own knowledge to bear, even if this can be challenging initially to align with the specialist recommendations."

— Dr Jeremy McMinn

What advice can you give to a general practitioner managing a patient with an oxycodone addiction who wishes to withdraw?

The best advice is unhelpfully retrospective – do not get there in the first place. In opioid dependence, prevention is absolutely better than cure, as the opioid withdrawal failure rate without a period of substitution is nearly 100% - even if we had the best addiction resources, which we patently do not. Opioid substitution is the mainstay of managing opioid dependence, but funding exists for only around 5400 patients (with an expected need of at least 10 000 New Zealanders).

What is the recommended withdrawal regimen?

Withdrawal requires realism, compassion and determination on both the patient and doctor's part. Most people will require a stabilisation phase of two to four weeks to clarify the daily amount, which may include swapping to a longer acting opioid of the same equivalence. Given the Misuse of Drugs Act, general practitioners will have limited scope to use methadone or buprenorphine, but consolidating an Oxynorm and Oxycontin regimen into a set twice daily regimen of oxycodone as sensible pain management will be required.

After this stabilisation, a steady reduction should be agreed within a reasonable timescale. Factors such as prior treatment duration, size of total daily dose and important upcoming events, come into play when considering the rate of reduction. However, a reduction contained within one to three months should be agreed, with the reduction increments calculated back from this date setting.

Larger dose drops may be easier at the start of the reduction, with smaller drops later reflecting a larger proportion of the total daily dose. Neuro-adaptation plateaux, where the reduction is held for one to two weeks, may be sensible periodically, especially if the patient is struggling. Putting the dose back up is rarely sensible – a hold in reduction to allow the easing that comes with neuro-adaptation is more realistic than an oscillating rising and dropping dose.

What supportive treatments may be required?

The main support is one of compassion whilst maintaining a focus on the prize. Delaying a reduction restart, or providing unwise courses of other abusable drugs (benzodiazepines, zopiclone) will promote a sickness role and treatment failure. Patients need reminding that the discomfort is temporary and will abate. Levels of underlying distress need monitoring, and involving the educated support of family members may be useful. Excessive use of other substances from other sources (e.g. alcohol, cannabis, Nurofen Plus [containing codeine], a family member's opioids) should be addressed.

Loperamide for diarrhoea and non-opioid analgesics for withdrawal aching may be useful. Off-label use of clonidine may be considered for the hot/cold feelings and aching, but will require blood pressure monitoring: courses should be limited to two weeks. Quinine is no longer recommended.

What issues are there in terms of prescribing legitimate pain relief in the future?

Opioids are only part of the treatment of pain, and probably a much smaller part of chronic pain treatment than previously thought. Earlier problems with opioids mean that all potentially abusable future prescriptions may present risks, such that they should be avoided altogether or only provided within closely monitored parameters.

Patients who have experienced problems with opioids need more care, although commonly feel they receive less. A pain condition for which opioids were problematic could be framed as a "treatment resistant" condition and it may be legitimate to seek other less available treatments. In particular, access to non-pharmacological pain strategies may need to be emphasised.

Patients and prescribers should be explicitly discouraged from equating the removal of opioids with the removal of all pain management.

What other support systems are available for patients who have a prescription drug addiction?

Prescription drug addiction is a double act – both the patient and the doctor have, to some extent, entered into drug dyscontrol, drug salience (exclusive importance) and dysfunction. These need to be addressed, and prescription monitoring, dispensing restrictions, and use of the 10 Universal Precautions are good ways to achieve this. In particular, solid external controls on abusable medication availability are the keystones to preventing and managing prescription drug addiction.

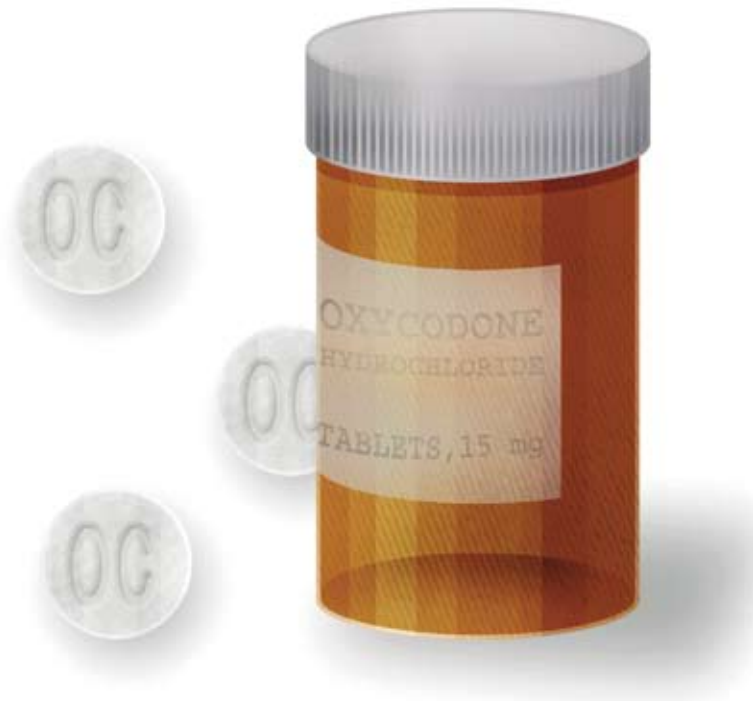
For those who have ongoing opioid problems, the mainstay of opioid management will involve the local specialist Opioid Treatment Service, often with some degree of shared care with the general practitioner. Input from specialist Chronic Pain Services may also be required: in many regions there is regular liaison between Addiction and Pain services already in place.

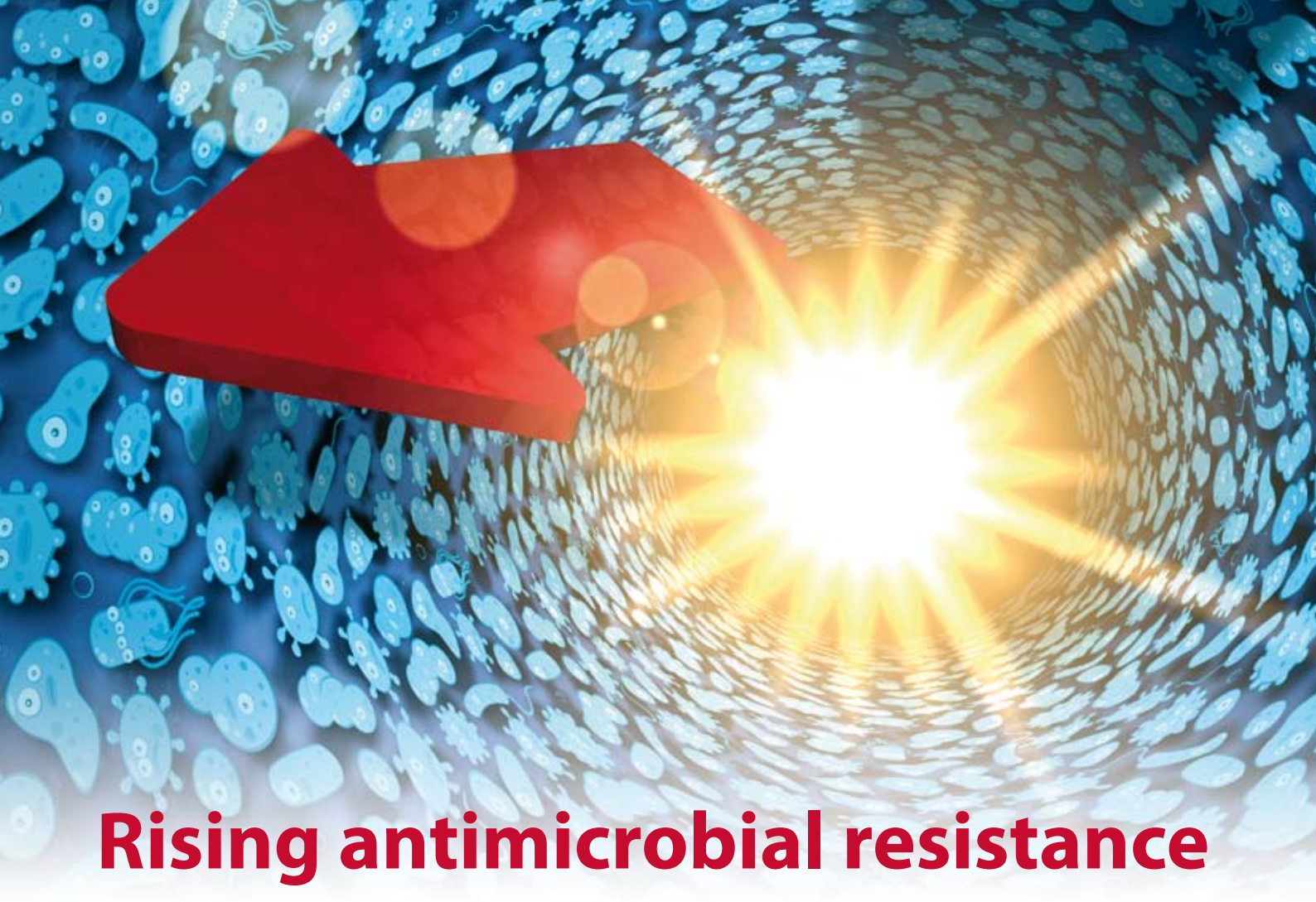
Addiction support can also be available through non-government organisations, including the Alcohol & Drug Helpline, Salvation Army, CareNZ, 12-Step Programmes (e.g. Narcotics Anonymous, Alcohol Anonymous & Al-Anon) and Tranx.

The Alcohol & Drug Helpline (0800 787 797) and local DHB Addiction Services will usually be able to advise on local availability of addiction supports.

We would like to thank Dr McMinn for his willingness to speak out on these issues. We hope that this interview has challenged your thinking in terms of your own prescribing of oxycodone. We plan to publish a follow-up series of articles, expanding on some of the issues Dr McMinn has touched on, including examining the role of oxycodone in acute, short-term and long-term pain management and strategies for safe and rational prescribing of strong opioids.

Rapid response: comment on this article online at:
www.bpac.org.nz/BPJ/2014/June/upfront.aspx





Rising antimicrobial resistance

Associate Professor Mark Thomas from the University of Auckland, in conjunction with Dr Alesha Smith and Professor Murray Tilyard from bpac^{nz} recently published an article in the New Zealand Medical Journal, entitled: "Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand".

The volume of antibiotic medicines used in New Zealand was compared to other countries. The research indicates that in recent years, the amount of antibiotic medicines prescribed for people living in the community in New Zealand has been much greater than the amount prescribed for people in Scandinavian countries and the Netherlands. The amount prescribed in New Zealand is more comparable to the amounts prescribed in Spain and Italy, countries where antibiotic use is considered profligate, and where antibiotic resistance has reached worrying levels. We need to strengthen our efforts to reduce antimicrobial consumption and slow the spread of antibiotic resistant bacteria in New Zealand.

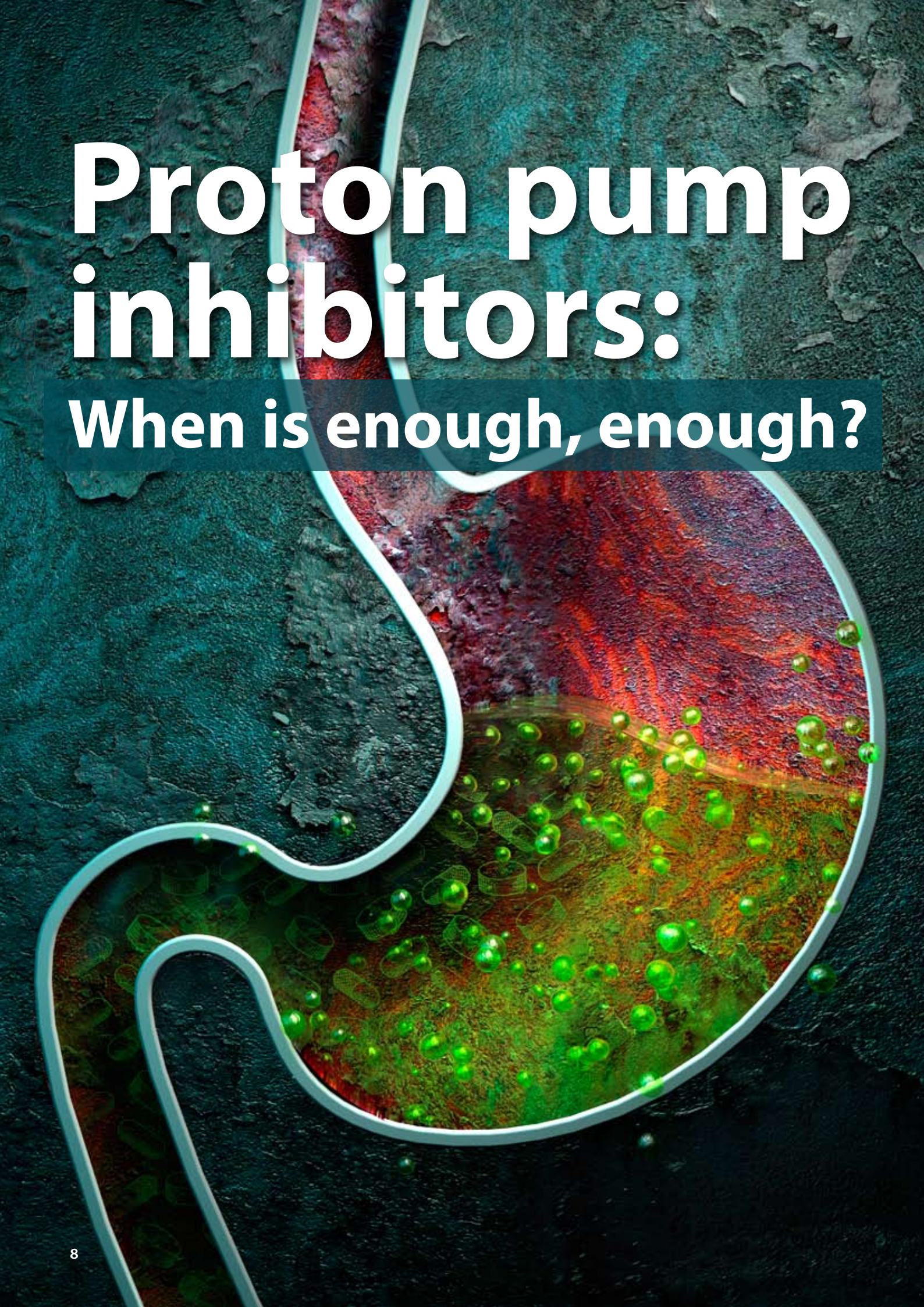
Five key points from this article are:

1. The per capita level of antibiotic consumption within a country is a powerful driver of the emergence and proliferation of antibiotic resistant bacteria within that country.
2. Countries vary greatly in the level of antibiotic consumption and countries with high per capita levels of consumption have high levels of antibiotic resistance.
3. The per capita level of antibiotic consumption in New Zealand in recent years has been higher than that in most European countries. During 2010, only Greece, Belgium, France and Italy (countries widely considered to have profligate levels of antibiotic consumption) had higher levels of consumption than New Zealand.
4. Between 2005 and 2012 the average annual increase in total per capita antibiotic consumption in New Zealand has been greater than 6%.
5. Increased efforts to reduce antimicrobial consumption in New Zealand are required to slow the spread of antibiotic resistant microbes, and preserve the utility of antibiotics for future generations.

For further information, see:
http://journal.nzma.org.nz/journal/127-1394/

Proton pump inhibitors:

When is enough, enough?



Proton pump inhibitors (PPIs) are one of the most widely used medicines in New Zealand; in 2013 omeprazole was the third most commonly dispensed medicine in the community. PPIs are highly effective at reducing symptoms caused by gastric acid, and are generally well tolerated. However, they should not be prescribed indefinitely, without review. PPIs should be used at the lowest effective dose for the shortest possible time. "As needed" use, rather than a regular daily dose, may be appropriate for some patients. Patients should be warned that rebound acid secretion often occurs following withdrawal of treatment, even after periods as short as four weeks. Many patients will be able to manage symptoms during this withdrawal period with alternative medicines, such as antacids.

Use of PPIs in New Zealand

The treatment of symptoms caused by gastric acid dates backs to the ancient Greeks, who used coral powder (calcium carbonate) to alleviate dyspepsia.[1] During the 1970s and '80s H_2-receptor antagonists, e.g. ranitidine, were introduced. This was followed by the introduction of proton pump inhibitors (PPIs), which were even more effective in reducing gastric acid production. PPIs have now largely superseded H_2-receptor antagonists, resulting in an improved quality of life for many patients. Their effectiveness, however, has also led to PPIs being used more widely in primary care than almost any other medicine.

In 2013, there were 428 dispensed prescriptions for omeprazole for every 1000 registered patients, making it the third most widely prescribed medicine in New Zealand.[2] The number of patients prescribed PPIs in New Zealand has increased steadily over the past five years (Figure 1). In 2013, $4.28 million was spent in the New Zealand health sector on omeprazole capsules alone; over one-quarter of this was for omeprazole 40 mg capsules, the highest dose formulation available.[3]

Which PPIs are available in New Zealand?

In New Zealand there are three fully subsidised PPIs available on the Pharmaceutical Schedule: omeprazole, lansoprazole and pantoprazole. These three medicines are also available for purchase in limited quantities, without prescription, as a "Pharmacy only" medicine. Rabeprazole is available unsubsidised, with a prescription. Patients should be asked about any use of non-prescription medicines before acid suppressive medicines are prescribed.

Refer to the New Zealand Formulary for further details on these medicines: **www.nzf.org.nz**

Omeprazole, lansoprazole and pantoprazole are indicated for:[4]

- Treatment of gastro-oesophageal reflux disease (GORD), including Barrett's oesophagus
- Prevention of NSAID-associated duodenal or gastric ulcers (omeprazole and pantoprazole only)
- Treatment of benign duodenal and gastric ulcers
- Eradication of *Helicobacter pylori* (as part of a combination regimen with antibiotics)
- Treatment of Zollinger-Ellison syndrome (omeprazole and pantoprazole only)

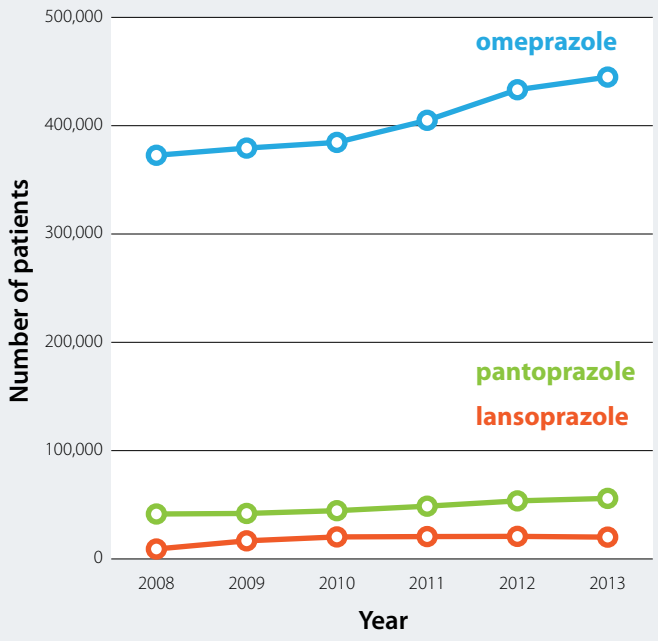
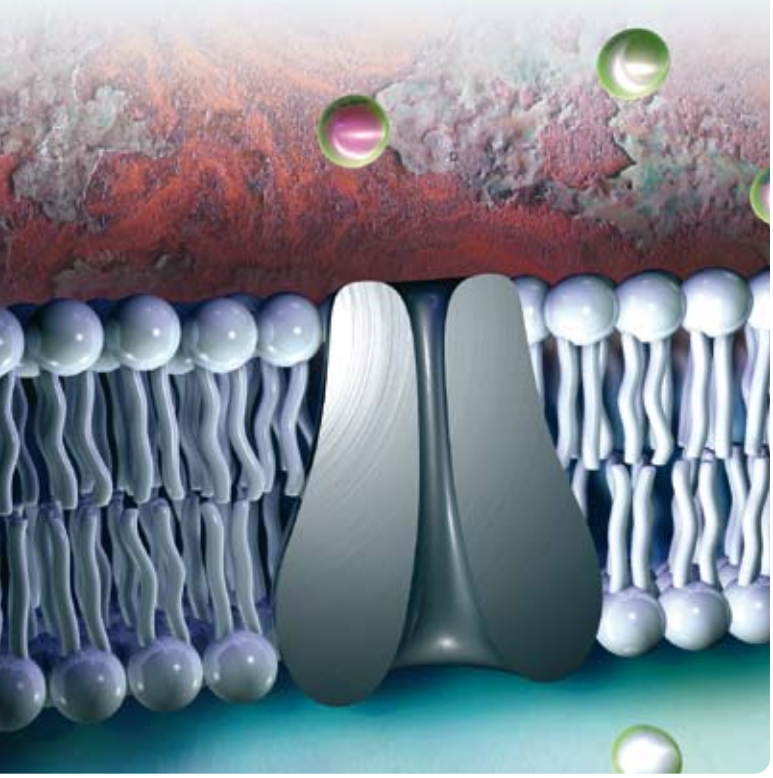


Figure 1: The number of patients who were dispensed omeprazole, pantoprazole or lansoprazole from a community pharmacy in New Zealand (2008 – 2013).[3]

The pharmacology of proton pump inhibitors

PPIs are prodrugs, i.e. they are inactive when administered and undergo conversion to an active form *in vivo*.[6] PPIs are acid labile and are therefore formulated with an enteric coating to protect them from degradation in the acidic environment of the stomach. Once they have passed through the stomach and the enteric coating has dissolved in the small intestine, PPIs are absorbed into the blood where they have a relatively short plasma half-life of 1 – 1.5 hours.[1] The effect of PPIs extends well beyond this half-life, because the active metabolite binds irreversibly to the H^+/K^+-ATPase proton pump of parietal cells. This prevents the transport of acidic hydrogen ions into the gut lumen for 10 – 14 hours.[6] The acid-suppressing effect of PPIs takes at least five days to reach a maximal effect.[1] However, this effect is not absolute; even at high doses approximately one-quarter of proton pumps in each parietal cell will remain active.[6]

Gastrin is the hormone that stimulates parietal cells to release gastric acid. When PPI inhibition of gastric acid production occurs, gastrin release is increased to compensate for the decreased acidity of the stomach. Recently, several studies have suggested that when PPIs are withdrawn the body will continue to produce gastrin at above pre-treatment levels, causing an effect referred to as rebound acid secretion (Page 12).[6]



The PPIs available in New Zealand have a similar efficacy when given at recommended doses; e.g. a meta-analysis found there was no difference in the comparative effectiveness of PPIs in healing oesophagitis.[5] The availability of three subsidised PPIs means that if a patient experiences adverse effects with one PPI, another can be trialled. It also allows for choices in formulation, e.g. pantoprazole is available in small tablets that may be preferable for patients who have difficulty swallowing.

When, and how, is it appropriate to prescribe a proton pump inhibitor?

When initiating PPI treatment it is helpful to discuss with patients what the expected duration of treatment is likely to be. This reinforces the message that treatment will not continue indefinitely, unless the indication remains, and is likely to make later discussions about dose adjustment and treatment withdrawal easier.

For most patients an appropriate starting regimen is omeprazole 20 mg, once daily (depending on the indication).[4] In some patients, treatment may need to be increased to 40 mg, daily, if symptoms are not able to be controlled, but starting treatment initially with omeprazole 40 mg, once daily, is rarely indicated in a primary care setting. Over time, and again depending on the indication for treatment, the dose of PPI may be able to be reduced, e.g. from 20 mg to 10 mg omeprazole, daily, or changed to "as needed" dosing, if adequate control of symptoms is achieved.

N.B. Before prescribing a PPI it is important to consider a patient's risk factors for gastric cancer, as PPI use can mask the symptoms of this malignancy. The incidence of gastric cancer increases substantially after age 55 years, and a decade earlier in people of Māori, Pacific or Asian descent.[7]

Gastro-oesophageal reflux disease

Proton pump inhibitors are indicated in the treatment of suspected or confirmed GORD. The treatment regimen depends on the severity of symptoms and the likelihood of the patient developing complications. PPIs can be used to:[1, 8]

1. Establish a diagnosis of GORD via empiric treatment over several weeks
2. Provide "as needed" relief of symptoms in patients with milder forms of GORD
3. Provide daily symptom relief for patients with more severe symptoms

When managing patients with mild GORD, it is important that the patient and clinician both agree that the regimen will be regularly reviewed, with the goal of treatment being lifestyle

control of symptoms with minimal reliance on medicines. The lowest effective dose of PPI should be used for the shortest possible time.

For further information, see: "Update on the management of gastro-oesophageal reflux disease" (Page 16).

Non-steroidal anti-inflammatory drug (NSAID)-associated ulcers

PPIs are indicated for the prevention and treatment of NSAID-induced erosions and ulcers in at risk patients (see below), and are often prescribed to treat NSAID-induced dyspepsia.[4] PPIs should be taken daily, rather than "as needed", to prevent NSAID-related adverse effects because ulceration or bleeding of the gastrointestinal tract can occur in the absence of dyspepsia.[9]

Risk factors for gastrointestinal adverse effects, e.g. perforations, ulcers and bleeding, associated with NSAID use include:[9, 10]

- Age over 65 years
- Previous adverse reaction to NSAIDs
- The use of other medicines that may exacerbate any gastrointestinal adverse effects, e.g. anticoagulants, antiplatelets and corticosteroids
- A history of cardiovascular disease
- Liver disease
- Chronic kidney disease
- Smoking
- Excessive alcohol consumption

Many of these risk factors are also contraindications to the use of NSAIDs.

A PPI is appropriate for patients with any of the above risk factors, who are taking NSAIDs long-term. Patients should be advised to report any gastrointestinal symptoms (e.g. heartburn, black stools) which may indicate that an erosion or ulcer has occurred.[9] Also consider checking the patient's haemoglobin level after one month of NSAID treatment.[9]

For ulcer prevention, the recommended regimen is omeprazole 20 mg, once daily, for the duration of NSAID treatment.[4] To treat NSAID-associated duodenal or gastric ulcers the recommended regimen is omeprazole 20 mg, once daily, for four weeks, which may be continued for a further four weeks if required.[4] Pantoprazole is an alternative in both regimens if omeprazole is not tolerated.[4] Lansoprazole is not indicated for ulcer prevention in patients taking NSAIDs, but can be used for treatment of ulcers.[4]

For further information see: "Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices", BPJ 55 (Oct, 2013).

Eradication treatment for *H. pylori*

Proton pump inhibitors are recommended for the eradication of *H. pylori* as part of a triple treatment regimen. For example, a seven day course of:[4]

- Omeprazole 20 mg, twice daily; and
- Clarithromycin 500 mg, twice daily; and
- Amoxicillin 1 g, twice daily (or metronidazole 400 mg, twice daily, if allergic to penicillin)

Other regimens using different dosing intervals or other PPIs, e.g. lansoprazole, can also be used (see NZF for further information).

Confirmation of eradication of *H. pylori* after a triple treatment regimen is not required for the majority of patients. A test of cure may be considered in patients with a recurrence of symptoms, a peptic ulcer complication or those with important co-morbidities.[11]

For further information, see: "The changing face of *Helicobacter pylori* testing", BT (May, 2014).

When can you consider stopping treatment with a PPI?

Many patients taking PPIs require long-term treatment and withdrawal of the PPI will be inappropriate, e.g. patients with Barrett's oesophagus. In other patients, e.g. with a history of severe erosive oesophagitis, withdrawal of PPIs should only be considered after discussion with an appropriate specialist. However, in each practice population there will be some patients for whom it is appropriate to reduce the dose of the PPI they are prescribed, e.g. from 20 mg omeprazole, once daily, to 10 mg omeprazole, once daily, or switching to "as needed" dosing. For patients taking PPIs long-term the need for ongoing treatment should be reassessed at every consultation.

The patient's expectations when the PPI was first prescribed will play a large part in their acceptance of the suggestion to reduce their PPI exposure. There is no clear evidence as to what the best regimen for withdrawing PPI treatment is, but in general, downward dose titration should be considered when symptoms are under control.[6] For example, a patient is prescribed 20 mg omeprazole, daily, for four to six weeks to manage symptoms of GORD. The patient responds to treatment

and their symptoms resolve. The dose is then reduced to 10 mg, daily, for two weeks, and then treatment is stopped. The patient is given a prescription for 20 mg omeprazole to use "as needed" if symptoms return.

Advise patients about the possibility of rebound acid secretion

Rebound acid secretion can occur when PPIs are withdrawn; one study found that more than 40% of asymptomatic patients experienced dyspepsia one week after completing a four week treatment course of pantoprazole.[12] Serum markers suggest that acid secretion one week following cessation of PPI treatment can be significantly increased above pre-treatment levels. This should return to normal within two weeks.[12]

The symptoms caused by rebound acid secretion, e.g. gastro-oesophageal reflux, are the same as those that would be an indication for PPI treatment, therefore a reinforcing loop can be formed where initial treatment creates the need for further treatment. The possibility of rebound acid secretion should be discussed with patients so they can be prepared for this when withdrawing from PPI treatment.

Medicines that contain both an antacid and an anti-foaming agent, e.g. Mylanta P oral liquid, Acidex oral liquid, Gaviscon Double Strength tablets are likely to be the most effective treatment for rebound acid secretion. Aluminium hydroxide tablets can also be effective. Any of these products can be prescribed as "rescue" medication and provide reassurance to patients if symptoms return.

For further information see: "Managing gastro-oesophageal reflux disease (GORD): an update", (Page, 16).

How safe are proton pump inhibitors?

The rate of adverse effects associated with PPI treatment is relatively low. However, given that each practice is likely to have many patients taking PPIs, clinicians need to be aware of the potential risks. These risks should be discussed with patients, and the need for periodic monitoring considered in those at increased risk.

All three subsidised PPIs available in New Zealand can cause headache and gastrointestinal adverse effects, e.g. nausea, vomiting abdominal pain, flatulence, diarrhoea or constipation.[4] The gastrointestinal adverse effects of PPIs can be mistaken for symptoms of GORD, sometimes resulting in increased doses of PPI being prescribed. Less frequently, PPI use is associated with dry mouth, peripheral oedema, dizziness, sleep disturbances, fatigue, paraesthesia, arthalgia, myalgia, rash, pruritus and interstitial nephritis.[4]

PPIs are not known to be associated with an increased risk of foetal malformations in humans (Pregnancy Risk Category B3).[4] PPIs are therefore considered safe to use during pregnancy, however, other medicines should be used where possible. A reasonable approach for pregnant women who require acid suppressive medication is to trial antacids (e.g. calcium carbonate, alginate formulations) or ranitidine (Pregnancy Risk Category B1) first and if these medicines are not effective, consider prescribing a PPI.

Higher doses of PPIs should be avoided in patients with moderate to severe liver disease because decreased metabolism may cause the medicine to accumulate (see NZF for details).[4]

The risk of infection is increased

Gastric acid suppression with PPIs increases the risk of infection with gastrointestinal or respiratory pathogens, although the absolute risk to most patients remains low. The higher risk is thought to be due to a reduction in the effectiveness of the "acid wall" stomach barrier. This allows viable pathogens to travel up or down the gastrointestinal tract and also colonise the lower airways.

Where possible, consider delaying the initiation of PPIs in patients with an increased risk of infection, e.g. an older patient with a family member who has influenza, patients who are taking antibiotics or travelling to countries where there is a high risk of enteric infection.[6] It is not known if there is any benefit to temporarily stopping treatment in patients who are already taking PPIs, during periods when they are at an increased risk of infection.

In a meta-analysis of 12 studies involving almost 3 000 patients, it was found that acid-suppressing treatment increased the risk of *C. difficile* infection. This risk was increased 1.7 times with once-daily PPI use and 2.4 times with more than once daily use.[13] Six studies found a greater than three-fold increased risk of *Salmonella*, *Campylobacter* and *Shigella* infection in patients taking PPIs.[13]

In another study of over 360 000 people, it was found that PPI use was associated with an increased risk of pneumonia, and the risk increased with increasing dose of PPI.[14] The incidence rate of pneumonia in people taking a PPI was 2.45 per 100 person-years, compared to 0.6 per 100 person-years in people not taking a PPI.[14] Another study found that the likelihood of patients developing pneumonia was increased five-fold during the first week of PPI treatment, but decreased after this, falling to 1.3-fold increased risk after patients had been treated

for three months or more.[15] This effect may be explained by patients presenting with the early symptoms of pneumonia being prescribed a PPI.[6]

Malabsorption of nutrients may occur

Acid in the gut increases the solubility of elements, e.g. calcium and iron, from insoluble salts and makes protein-bound vitamins, e.g. vitamin B12, available for absorption. It has therefore been suggested that gastric acid suppression may decrease absorption of some nutrients and lead to an increased prevalence of conditions related to malabsorption. However, this association is controversial. In most cases, patients can be reassured that a balanced diet, including essential elements and minerals (e.g. calcium, iron, folate, magnesium) is adequate to address this risk.

Long-term PPI use has been associated with a small increase in fracture risk. However, the New Zealand Medicines Adverse Reactions Committee (MARC) noted that the association between PPI use and fracture risk in the majority of studies was modest and does not warrant any regulatory action at this time.[16] A study of more than 15 000 instances of osteoporosis-related fractures found that after five years of PPI use patients had an increased risk of hip fracture (adjusted odds ratio = 1.62), and the risk increased further when treatment was continued for seven years (adjusted odds ratio = 4.55).[17] Patients taking PPIs for more than seven years also had an increased risk of non-hip fractures (adjusted odds ratio = 1.92).[17]

An increased risk of osteoporosis should be considered in post-menopausal females who are taking PPIs long-term, especially if they have other risk factors, e.g. a family history of osteoporosis or long-term corticosteroid use. Stepping down PPI treatment to the lowest effective dose, or prescribing "as needed" treatment, if appropriate, may reduce this risk.

Severe hypomagnesaemia has been associated with the use of PPIs, in a limited number of patients, which resolved when PPI treatment was withdrawn.[18] In 2012, Medsafe advised that hypomagnesaemia, and possibly hypocalcaemia, were rare adverse effects of PPI use. Omeprazole, 20 – 40 mg per day, was the dosage most frequently associated with these deficiencies.[19] Magnesium is known to affect calcium homeostasis by deceasing parathyroid hormone secretion and decreasing the response of the kidney and the skeleton to parathyroid hormone.[19]

Patients with a history of excessive alcohol use, who are taking a PPI, have an increased risk of developing hypomagnesaemia due to the additive effects of chronic ethanol exposure on metabolic function. The use of diuretics, ciclosporin or aminoglycosides with PPIs increases the risk of hypomagnesaemia occurring. Symptoms of hypomagnesaemia are non-specific and may include muscle cramps, weakness, irritability or confusion.

Routine testing of magnesium levels in patients taking PPIs is generally not recommended. However, if a patient has been taking a PPI long-term and they present with unexplained symptoms that are consistent with hypomagnesaemia, consider requesting a serum magnesium level. Increased dietary intake of magnesium rich foods, e.g. nuts, spinach or wheat, or magnesium supplementation may be sufficient to improve serum magnesium levels while continuing the PPI. For some patients the PPI will need to be stopped; if the indication for using the PPI is strong, a re-challenge while monitoring magnesium can be undertaken.

For further information see: "Hypomagnesaemia with proton pump inhibitors" BPJ 52 (Apr, 2013).

Vitamin B12 deficiency has been associated with the use of PPIs in older patients.[18] Several short-term studies have shown that PPIs decreased the absorption of vitamin B12 from food.[18] In older patients with poor nutrition, who are taking PPIs long-term, consider testing vitamin B12 levels periodically.[18]

Hyponatraemia has been associated with the use of PPIs in a very small number of patients.[20] Hyponatraemia, however, is a relatively common occurrence in older people, many of whom are likely to be taking PPIs.

Acute interstitial nephritis has been associated with PPIs

Prior to June 2011, the Centre for Adverse Reactions Monitoring (CARM) had received 65 notifications of interstitial nephritis linked to PPI use.[21] Interstitial nephritis can result in permanent kidney damage.[6] Symptoms and signs suggestive of interstitial nephritis include: fever, rash, eosinophilia, malaise, myalgia, arthralgia, weight loss, altered urine output, haematuria or pyuria and/or high blood pressure.[21] NSAIDs are well known for their nephrotoxic potential and their use should increase suspicion of interstitial nephritis in patients with these symptoms. Other risk factors that would increase the suspicion of interstitial nephritis include the use of β-lactams, e.g. penicillins or cephalosporins, sulphonamides and diuretics, or the presence of infection or immune and neoplastic disorders.[21] If interstitial nephritis is suspected, request urine microscopy and renal function tests. The patient should be referred to a Nephrologist for assessment. To confirm a diagnosis of interstitial nephritis a renal biopsy is required.

Interactions with other medicines

Concerns of a possible interaction between omeprazole and clopidogrel are unlikely to be clinically significant. MARC assessed the evidence of an interaction between PPIs and clopidogrel and concluded that while there was evidence that PPIs may affect clopidogrel activity *ex vivo*, the available evidence suggested that this would not translate to clinically significant adverse outcomes.[22] There is no need to switch treatment for patients who are already taking a PPI and clopidogrel. However, if considering prescribing a PPI at the same time as clopidogrel then pantoprazole is the recommended choice. Pantoprazole is known to have less of an inhibitory effect on the CYP2C19 enzyme compared with omeprazole or lansoprazole.[23]

PPIs can cause a minor increase in the anticoagulant effect of warfarin or a decrease when the PPI is stopped. Patients taking warfarin should have their INR measured more frequently following the initiation, or discontinuation of PPIs to ensure they do not experience a clinically significant interaction.[8]

"Take-home" points about PPIs

- Review all existing patients taking PPIs long-term and assess whether the indication for treatment remains and whether the dose of PPI can be reduced
- When new patients are started on PPIs, discuss the expected duration of treatment and have a plan for stepping down or stopping treatment
- In most situations, patients do not need to be started on PPI treatment in primary care with 40 mg omeprazole, daily (or equivalent)
- There are few patients who should be taking 40 mg, omeprazole, daily long-term
- Consider whether "as needed" use would be more appropriate for patients than taking PPIs daily
- Ensure patients are prepared for rebound acid secretion which may occur when PPI treatment is withdrawn; antacids can be used as a "rescue medicine"

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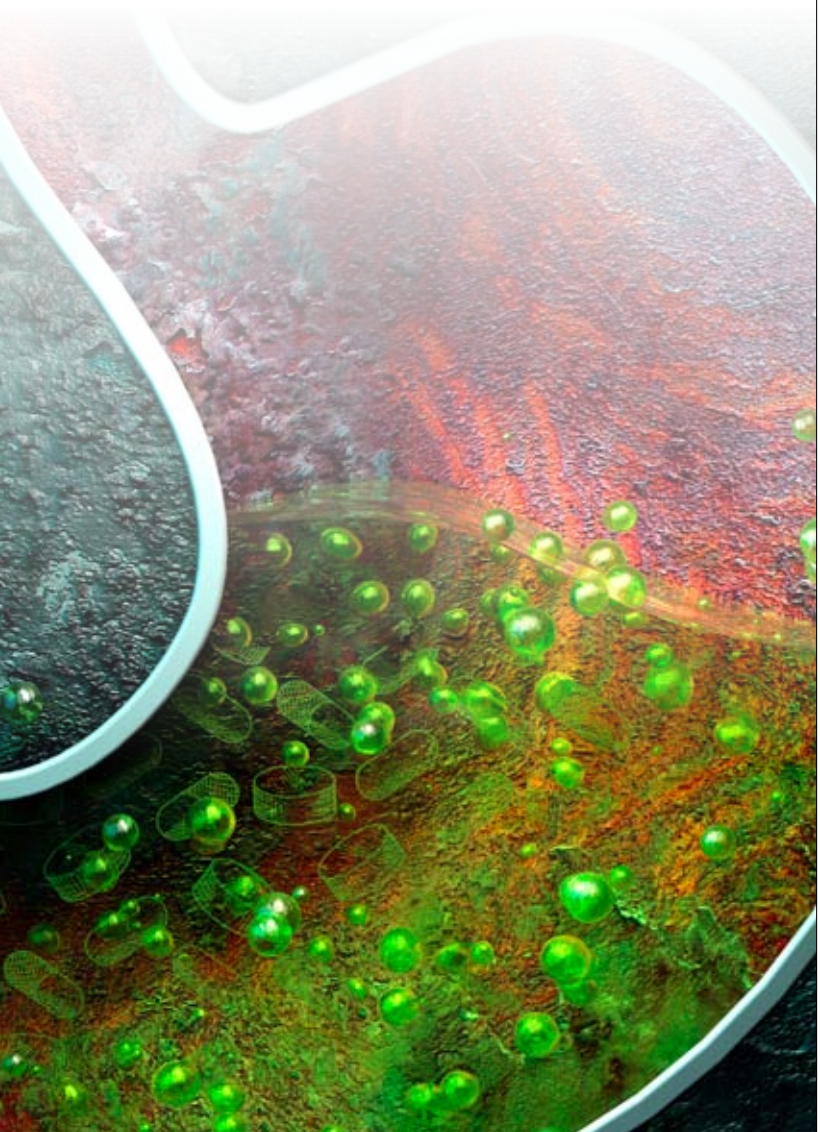

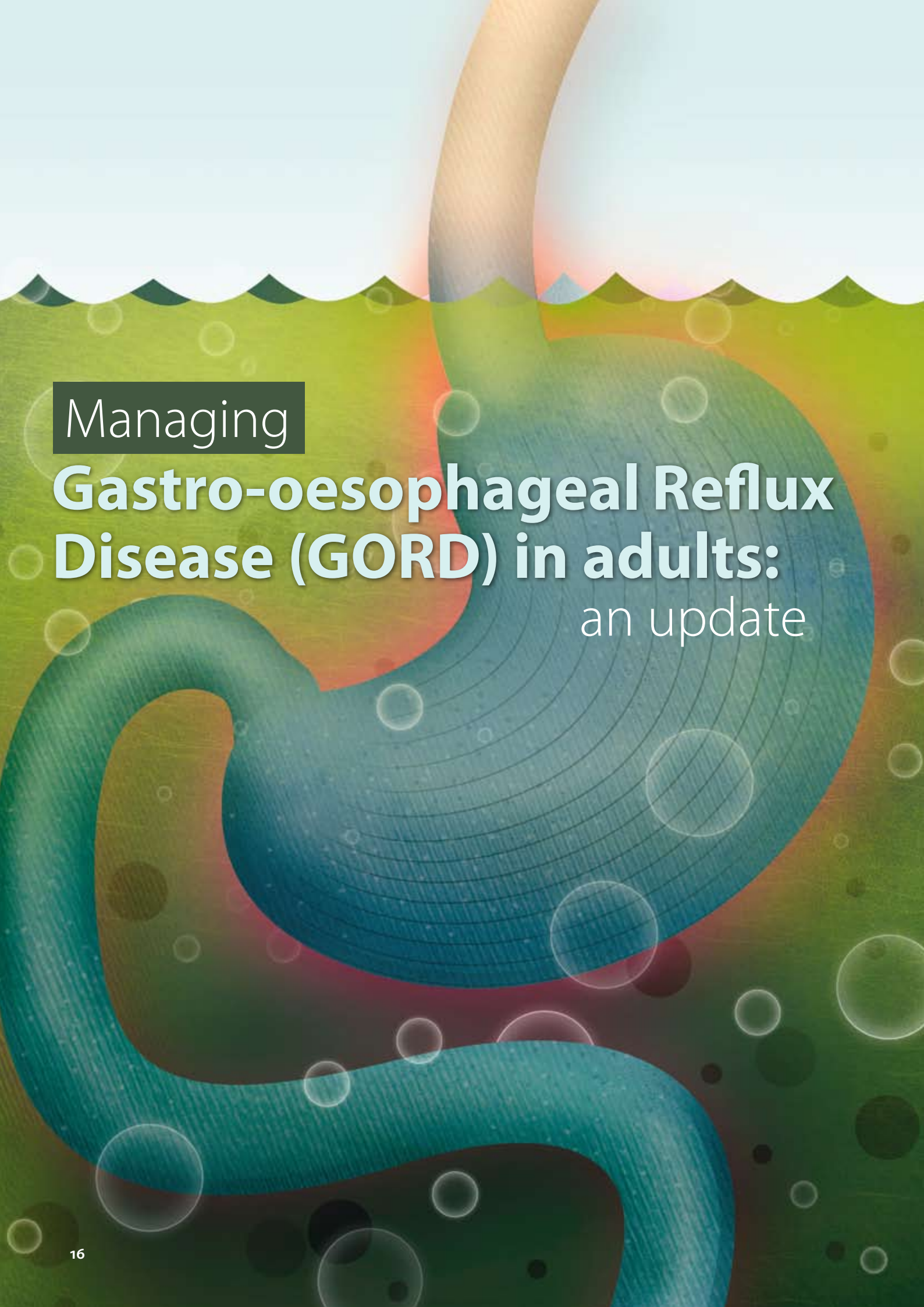

Managing Gastro-oesophageal Reflux Disease (GORD) in adults: an update

Heartburn, the cardinal symptom of gastro-oesophageal reflux disease, is experienced by 15 – 20% of adults at least once a week.[1] The patient's history and their response to an empiric trial with a proton pump inhibitor (PPI) are used to diagnose GORD in primary care. Endoscopy often provides limited diagnostic information as the majority of patients with GORD will not have visible lesions. The role of endoscopy is therefore limited to investigating patients with possible complications of GORD, e.g. erosive oesophagitis or Barrett's oesophagus. PPIs are the mainstay of treatment for GORD, but should be prescribed at the lowest effective dose or "as needed" for patients with mild to moderate forms of GORD. Fundoplication is currently the most effective treatment for patients with severe or complicated GORD.

Gastro-oesophageal reflux disease (GORD) and its complications

Reflux of the contents of the stomach into the oesophagus is a normal physiological event that occurs in many people after eating. When gastric reflux causes a person to have symptoms and/or complications, they are said to have gastro-oesophageal reflux disease (GORD); the Montreal definition.[2] This is a patient-centred definition that frames GORD as a range of disorders, including non-erosive reflux disease, erosive oesophagitis, Barrett's oesophagus and, most seriously, oesophageal adenocarcinoma.

Between 15 – 20% of adults experience heartburn, the cardinal symptom of GORD, at least once a week.[1] GORD is considered to be clinically significant when symptoms are present on two or more days a week.[1] Proton pump inhibitors (PPIs) are used in the short-term to help diagnose GORD and to allow healing of erosive lesions, as well as providing long-term symptom control on an "as needed" or daily basis. If a patient has an uncertain diagnosis or symptoms that do not respond to treatment, they may need to be referred for further investigation (Page 19).

The pathophysiology of GORD

The most common cause of gastric reflux is periodic relaxation of the lower oesophageal sphincter.[1] This exposes the easily damaged squamous mucosa of the oesophagus to acid, proteolytic enzymes (e.g. pepsin and trypsin) and bile salts.[3]

Repeated exposure to gastric reflux can cause oesophagitis that is visible on endoscopy in some people, although approximately two-thirds of people with GORD will not have visible signs of this.[1] For many people the symptoms of GORD result from the presence of abnormal spaces in the epithelium of the mucosa, causing excessive stimulation of nerve endings and peripheral sensitisation.[4] Gas reflux, without any reflux of gastric fluid, can also be experienced as heartburn.[5] In people with GORD symptoms that do not respond to PPI treatment it is possible that gas reflux may be causing distension of mechanoceptors in the oesophageal wall.[5]

Acid production by the stomach is highest when it is empty, but patients often experience GORD after a meal, when acid production is lowest. This is because after eating an unbuffered volume of acid is formed in the proximal region of the stomach, referred to as the acid pocket.[3]

GORD can be caused or exacerbated by:[3, 5]

- Hiatus hernia; which occurs when the oesophageal junction is displaced. Nearly all patients with severe GORD have a hiatus hernia which can be diagnosed on endoscopy.
- Central obesity; which increases the pressure gradient between the abdomen and thorax, increasing the number of reflux episodes and the likelihood of hiatus hernia occurring
- Impaired oesophageal or gastric clearance; which slows the movement of material down the digestive tract

Stress is reported to be a causative factor for symptoms by 60% of people with GORD.[5] Symptoms of GORD may be aggravated by diet and lifestyle, e.g. high-fat foods, spicy foods, caffeine, alcohol and smoking.[1]

Risk factors for GORD

The risk of GORD is increased in people who consume more than seven standard alcoholic drinks per week. The risk is also increased in people who have a first-degree relative with a history of heartburn.[1] The genetics of GORD are poorly understood and multiple genes are likely to be involved.[5] Up to half of pregnant women will experience symptoms related to GORD (see: "GORD during pregnancy", Page 22).[6] GORD is also more prevalent in people who are confined to bed for extended periods of time.[1]

Non-steroidal anti-inflammatory drugs (NSAIDs), some antibiotics (e.g. tetracyclines), iron supplements and potassium supplements can irritate the oesophagus and cause heartburn. The likelihood of GORD and its complications (see below) is increased in people who are obese, have chronic respiratory disease (e.g. asthma), or connective tissue disease (e.g. scleroderma).[1] In people with systemic sclerosis, atrophy of the muscularis mucosa and submucosal fibrosis result in oesophageal and gastrointestinal dysfunction.[7] The relationship between GORD and asthma is less clear and a review on the subject was unable to conclude whether GORD precedes asthma, or asthma triggers GORD.[8]

The complications of GORD

Chronic exposure of the oesophagus to gastric reflux can result in a number of complications requiring long-term management.

Erosive oesophagitis occurs when excessive gastric reflux causes necrosis of the oesophageal mucosa, resulting in erosions and ulcers. This is diagnosed with endoscopy and graded A to D (least to most severe) according to the Los Angeles classification.[9] People with erosive oesophagitis are reported to have a greater than five-fold risk of progressing to Barrett's oesophagus.[9]

Barrett's oesophagus is a complication of chronic GORD involving metaplasia of the lining of the lower oesophagus following exposure to gastric reflux.[9] This results in the squamous epithelium being replaced by a specialised columnar-lined epithelium.[9] The risk of Barrett's oesophagus increases with age and it is more likely in males and in people who are obese, have a poor diet or who smoke.[9] The prevalence of Barrett's oesophagus in the general population has been estimated at 1.6%.[9] The lifetime risk of a person with Barrett's oesophagus developing oesophageal adenocarcinoma is less than 2%.[1]

A peptic stricture is a narrowing of the oesophagus that results from healing and fibrosis of inflammatory lesions following long-term exposure to gastric reflux.[9] There has been a substantial decline in the prevalence of peptic strictures due to the use of PPIs.[9] The likelihood of a peptic stricture is higher in older people with chronic GORD or in people with dysphagia. Peptic strictures are classified as simple or complex, depending on their length and degree of contraction.[9] They are generally treated using invasive techniques that physically dilate the oesophagus.

The risk of oesophageal adenocarcinoma is correlated with the frequency, severity and duration of symptoms. People with frequent symptoms of GORD, i.e. more than three times per week, are approximately 17 times more likely to develop oesophageal adenocarcinoma compared with people without GORD.[10] People with severe symptoms occurring for more than 20 years are over 40 times more likely to develop adenocarcinoma compared with people without GORD.[10]

People with Barrett's oesophagus have a significantly increased risk of developing adenocarcinoma, but very few people with Barrett's oesophagus die from this form of cancer.[1]

Diagnosing GORD

The characteristic features of GORD are heartburn and regurgitation. The meaning of heartburn may not be clear to all patients and providing a description is known to increase GORD detection rates.[1] Heartburn is a burning feeling that rises from the stomach or lower chest towards the neck and frequently occurs after eating.[1] It may also be associated with bending, lying down or straining. Upper abdominal pain or discomfort are reported by approximately two-thirds of people with GORD.[1] Regurgitated food is generally swallowed, but can sometimes be of sufficient quantity to be mistaken as vomit. Patients may also experience water brash. This is a sudden and rapid production of saliva that fills the mouth and may be associated with nausea.[1] The patient's history may reveal triggers for GORD symptoms, which can then be avoided.

Atypical symptoms of GORD include angina-like chest pain, cough, hoarseness or throat changes, wheeze, frequent belching and nausea.[1] Several other conditions can cause gastrointestinal symptoms that may be mistaken for GORD. These include gastric ulcer disease, functional dyspepsia (dyspepsia without an obvious cause), and approximately 40% of patients with irritable bowel syndrome will have regurgitation.[1] *Helicobacter pylori* infection should be considered in patients who present with dyspepsia. The possibility of medicine-induced symptoms should also be considered if the patient is taking medicines that cause

dyspepsia or that have a mechanism of action that is more likely to result in reflux, e.g. theophylline, nitrates, calcium-channel blockers, beta-blockers, alpha-blockers, benzodiazepines, tricyclic antidepressants and anticholinergics, which can all reduce oesophageal sphincter pressure and exacerbate the symptoms of GORD.[11]

Low, or absent, gastric acid production (achlorhydria) impairs protein digestion and can cause symptoms similar to GORD, and is more common in older people.[12]

Red flags of GORD

The complications of GORD are more likely in patients with red flags; these patients should be referred promptly for endoscopy. Empirical treatment with a PPI can be initiated for symptom control but should not delay the timing of referral.

Red flags for patients with GORD requiring endoscopy include:[1]

- Dysphagia (difficulty with swallowing); which may be caused by inflammation, abnormal peristalsis or oesophageal hypersensitivity. If dysphagia and globus pharyngeus (the sensation of a "lump in the throat") are present then peptic stricture should be suspected.
- Odynophagia (pain with swallowing); which is generally associated with severe oesophagitis
- Haematemesis
- Weight loss with no obvious explanation
- Patients aged 55 years or older with unexplained and persistent dyspepsia of recent onset; these patients are at increased risk of gastric and oesophageal cancer.[13]

A therapeutic trial can be used to diagnose GORD

A therapeutic trial of PPIs (Page 20) in a patient with symptoms suggestive of GORD has a comparable sensitivity and specificity for diagnosing GORD as measuring the presence of oesophageal acid directly with a pH monitor in a secondary care setting.[1] This approach is suitable for younger patients with no red flags and mild, long-term symptoms.[1] It is unlikely that prescribing a higher dose of a PPI will provide any benefit to patients with uncomplicated GORD as in a primary care setting omeprazole 20 mg, daily, is generally considered to be as effective as omeprazole 40 mg, daily.[14]

The role of endoscopy

The role of endoscopy is limited in the diagnosis of GORD as the majority of patients with GORD will not have oesophageal abnormalities on endoscopy.[1] However, endoscopy is the investigation with the highest specificity for oesophagitis caused by GORD as it is able to differentiate between mucosal lesions caused by infective oesophagitis, peptic ulcer disease, malignancy and other abnormalities of the gut.[1] Endoscopy is also the most sensitive technique for diagnosing Barrett's oesophagus and is used to identify peptic strictures.[1]

Endoscopic assessment is indicated:[1, 11]

- Promptly in patients with red flags whether or not empiric treatment is initiated
- Where there is diagnostic uncertainty, e.g. non-specific or atypical symptoms, or when other diagnoses are being considered, e.g. infective or medicine-induced oesophagitis or malignancy
- When the patients symptoms do not respond to PPI treatment, or worsen despite treatment
- Prior to surgical intervention for GORD, e.g. fundoplication

Endoscopy may also be appropriate for patients with GORD who have multiple risk factors for oesophageal adenocarcinoma, e.g. chronic GORD, frequent symptoms, age over 55 years (local guidelines may vary), males, European ethnicity, a history of smoking, hiatus hernia, increased body mass index and intra-abdominal distribution of fat.[9, 10, 13, 15]

Managing patients with GORD

The management of GORD is determined by the severity of the patient's symptoms and the likelihood of complications. If the patient's symptoms are mild, lifestyle changes and antacids may provide benefit before a diagnostic trial with PPIs is tried (see below). However, there is no evidence that changes in lifestyle alone will allowing healing of established oesophagitis.[1]

Lifestyle treatment strategies include:[1, 11]

- Avoiding foods that cause symptoms, e.g. alcohol, coffee and spicy, fatty or acidic foods
- Avoiding eating three to four hours before sleeping
- Weight loss for obese or overweight patients
- Smoking cessation
- Raising the head of the bed, if this can be done safely. Extra pillows should not be used as they may increase abdominal pressure.

Discussing the patient's stress or anxiety levels and suggesting relaxation techniques may improve symptoms or assist the patient in avoiding triggers for GORD, e.g. alcohol.[11]

Review the use of any medicines which may be contributing to symptoms (Page 19).

Over-the-counter antacids can be used for the occasional treatment of patients with mild or intermittent symptoms of GORD, due to their rapid onset. However, these are not appropriate for the long-term management of GORD.[1]

Proton pump inhibitors are the first-line treatment for GORD

Multiple studies have found PPIs to be the most potent class of acid-suppressive medicine and the most effective class of medicine in the treatment of GORD.[1] For example, a meta-analysis found that PPIs were more effective than H_2-receptor antagonists at treating erosive oesophagitis, especially in patients with severe disease.[16]

When initiating PPI treatment it is a good idea to discuss with patients the expected duration of treatment. For patients with mild GORD the regimen should be regularly reviewed with the goal of treatment being lifestyle control of symptoms with minimal reliance on medicines. Patients with severe GORD are likely to require long-term treatment with PPIs and may require surgery.

The age of the patient should be considered when recommending a treatment regimen as younger patients may be exposed to a greater lifetime risk of adverse effects from long-term PPI use. The possibility of the patient developing rebound acid secretion following treatment withdrawal should also be discussed. This occurs due to increased production of gastrin, which is released to compensate for the decreased acidity of the stomach when PPIs are taken.

PPIs can be purchased in limited quantities, without a prescription, as a "Pharmacist only" medicine. Patients should be asked about any use of medicines for their GORD symptoms before PPIs are prescribed. Patients who self-administer PPIs could potentially develop rebound acid secretion which would complicate the clinical picture.[17]

For further information, see: "Proton pump inhibitors: When is enough, enough? Page 8.

Begin treatment with 20 mg omeprazole, once daily, for four to six weeks. Pantoprazole 20 mg, once daily, or lansoprazole 30 mg, once daily, are alternatives if omeprazole is not tolerated. The safety and clinical efficacy of these medicines is similar.[11] A meta-analysis found there was no difference in the comparative effectiveness of PPIs in healing oesophagitis.[16]

To maximise their effect, PPIs should be taken 30 – 60 minutes before food, ideally before the first meal of the day.[1, 4] Check compliance if the patient reports that the PPI is ineffective. It may be difficult for patients to take medicines before breakfast and it is reported that as few as 10% of patients are adherent to this treatment advice.[4]

The majority of patients who have responded to a diagnostic trial with a PPI can be switched from daily to "as needed" treatment without affecting symptom control or quality of life.[11] This involves the patient waiting for symptoms to develop before taking the medicine, e.g. omeprazole 20 mg, daily, until symptoms resolve.[11] This strategy may be explained to the patient as being analogous to the use of paracetamol for headache, i.e. it is being used for short-term symptom relief. Also explain to the patient that the return of symptoms is to be expected and is reported to occur in 70% of people.[1]

Alternatively, step down treatment to the lowest effective daily dose. For example, a patient taking omeprazole 20 mg, once daily, could be prescribed omeprazole 10 mg, once daily. If the patient experiences a return of symptoms they can resume their previous dose. A small Japanese study of 70 patients with heartburn occurring at least twice a week found that after an eight week course of omeprazole 20 mg, once

daily, 80% of patients whose heartburn had decreased to once a week or less were then successfully managed with a maintenance treatment of omeprazole 10 mg, once daily.[18]

For patients who have had an incomplete response to a diagnostic trial with a PPI consider increasing the dose, e.g. from omeprazole 20 mg, once daily, to omeprazole 40 mg, once daily.[11] The patient's adherence to treatment, e.g. dosing 30 – 60 minutes before eating, should be discussed as well as revisiting any lifestyle factors that may be contributing to symptoms.[11] For patients who are experiencing adverse effects it may be appropriate to trial an alternative PPI.[11]

N.B. When increasing the dose of lansoprazole or pantoprazole it is recommended that the dose is divided to twice daily dosing, i.e. before breakfast and before dinner.[11] Omeprazole is usually dosed once daily, but a divided dose could be trialled if symptoms worsen later in the day.

H. pylori infection may need to be reconsidered as a diagnosis in patients who continue to experience gastrointestinal symptoms following a diagnostic trial with a PPI. The incidence of *H. pylori* is generally higher in the north of New Zealand than in the south. Māori, Pacific, Asian and Indian people and people born outside of New Zealand (depending on their country of origin) are more likely to have *H. pylori*.

For further information see: "The changing face of *Helicobacter pylori* testing", BT (May, 2014).

Antacids can be prescribed as "rescue" medication for rebound acid secretion

Many patients will experience reflux symptoms after PPIs are withdrawn, due to rebound acid secretion. This can be indistinguishable from ongoing symptoms of GORD. Patients can be prescribed "rescue" medication to help them manage symptoms that may arise after stopping the PPI. If symptoms are unable to be managed, or continue for longer than one or two weeks, reconsider the decision to withdraw the PPI.

Medicines that contain both an antacid and an anti-foaming agent are likely to be the most effective treatment for rebound acid secretion. Liquid preparations are often more effective, but chewable tablets may be more convenient for some patients. Some products contain significant amounts of sodium, and should be used carefully, or avoided, in patients with heart failure (see below). These medicines should not be used within two hours of taking any regular medicines for other conditions, to avoid interactions.

The following medicines are currently partially subsidised* and may be prescribed for adults:

Mylanta P or Acidex oral liquid, 10–20 mL, as required, up to four times daily, usually after meals and at night.[19] Prescribe Acidex with caution in people with heart failure.

Gaviscon Double Strength tablets, 1–2 tablets chewed as required, up to four times daily, after meals and half an hour before bed.[19] Prescribe Gaviscon Double Strength with caution in people with heart failure.

Aluminium hydroxide tablets are an alternative antacid that are fully subsidised, but do not contain an anti-foaming agent. Prescribe Alu-tab 600 mg tablets, one tablet, up to four times daily, between meals and at bedtime.[19]

H_2-receptor antagonists are second-line for patients with GORD

Patients with mild symptoms who have not responded to a four to six week trial with a PPI may be offered an H_2-receptor antagonist as an alternative, e.g. ranitidine 600 mg, daily, in two to four divided doses, for up to 12 weeks (if moderate to severe symptoms, otherwise a lower dose is more appropriate – see NZF).[19] However, the use of H_2-receptor antagonists is limited in the treatment of GORD due to tachyphylaxis (sudden pharmacologic tolerance, which can occur after a single dose) and interactions with other medicines.[4, 20] A prokinetic, e.g. domperidone 10 – 20 mg, three to four times daily, to a maximum of 80 mg, daily may be considered as an alternative to an H_2-receptor antagonist, but the results of clinical trials assessing prokinetics have failed to demonstrate a clear benefit to patients with GORD.[19]

H_2-receptor antagonists are occasionally used as an adjunctive treatment to PPIs (usually after discussion with a specialist). For example, patients with nocturnal symptoms that have not improved following morning dosing with a PPI and lifestyle interventions may gain benefit from the addition of a H_2-receptor antagonist at bedtime, e.g. ranitidine, 300 mg, at night, for up to eight weeks.[11, 19]

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* N.B. Medicines that are partially subsidised attract a standard prescription fee the first time a prescription is dispensed (but not when a repeat supply is dispensed), and a portion of the cost of the medicine per unit of medicine that is dispensed. It is therefore important to indicate on prescriptions for "as required" medicines, a suitable quantity to supply at each dispensing, or the patient may receive more medicine than is likely to be used, with unnecessary cost. For example, Mylanta Double Strength tablets have a higher part charge for the patient than the liquid preparations above; one way to reduce the cost to patients is to prescribe fewer tablets, e.g. 40 tablets, plus repeat of 40 tablets.

GORD during pregnancy

Between 30 – 50% of pregnant women experience symptoms of GORD and this is considered a normal part of pregnancy.[6] Often symptoms begin late in the first trimester or in the second trimester, with heartburn becoming more severe and frequent as gestation progresses. Heartburn during pregnancy is more likely in women who have had previous episodes or multiple pregnancies, and is inversely correlated with maternal age.[6]

The clinical features of GORD during pregnancy are the same as for the general population. Lying down is reported to aggravate heartburn in over 80% of pregnant women with GORD.[6] Complications of GORD during pregnancy are rare as the reflux is generally of short duration.[6]

The treatment of GORD during pregnancy is conservative and many women with mild or infrequent symptoms can be managed by lifestyle, dietary modifications and the use of antacids or ranitidine (Pregnancy Risk Category B1).[6] However, PPIs should not be withheld from pregnant women with symptoms of GORD that are affecting their quality of life as the overall risk of these medicines to the foetus is minimal (Pregnancy Risk Category B3).[6, 19] There is reported evidence of potential foetal toxicity due to omeprazole in animal studies, but this finding has not been reproduced in human studies.[6] As with all medicines taken during pregnancy, clinicians should assess the risks and benefits before treatment is begun, particularly for women in the first trimester, and prescribe the lowest effective dose for the shortest possible time.

Many women with GORD during pregnancy will find that their symptoms rapidly improve after giving birth and continued treatment is not necessary. Omeprazole and pantoprazole are considered compatible with breast feeding, but caution is recommended with lansoprazole due to insufficient data.[19] Levels of PPIs excreted in breast milk are low, and a large proportion of any PPI that is ingested by the infant is likely to be destroyed by the acid in their stomach.[6]

Managing patients with complications of GORD

Patients with severe oesophagitis (Los Angeles grades C or D) require long-term, daily dosing with a PPI, e.g. omeprazole 20 mg, once daily, to maintain mucosal healing.[1, 19] Severe GORD can be treated via fundoplication, where the stomach is wrapped around the oesophagus to strengthen the lower oesophageal sphincter.

The majority of patients with Barrett's oesophagus are treated with PPIs to control the symptoms of GORD. It is unclear whether PPIs reduce the risk of a patient developing oesophageal adenocarcinoma.[4, 9] Some patients with Barrett's oesophagus and additional risk factors for oesophageal adenocarcinoma may require endoscopic surveillance following the recommendation of a Gastroenterologist.

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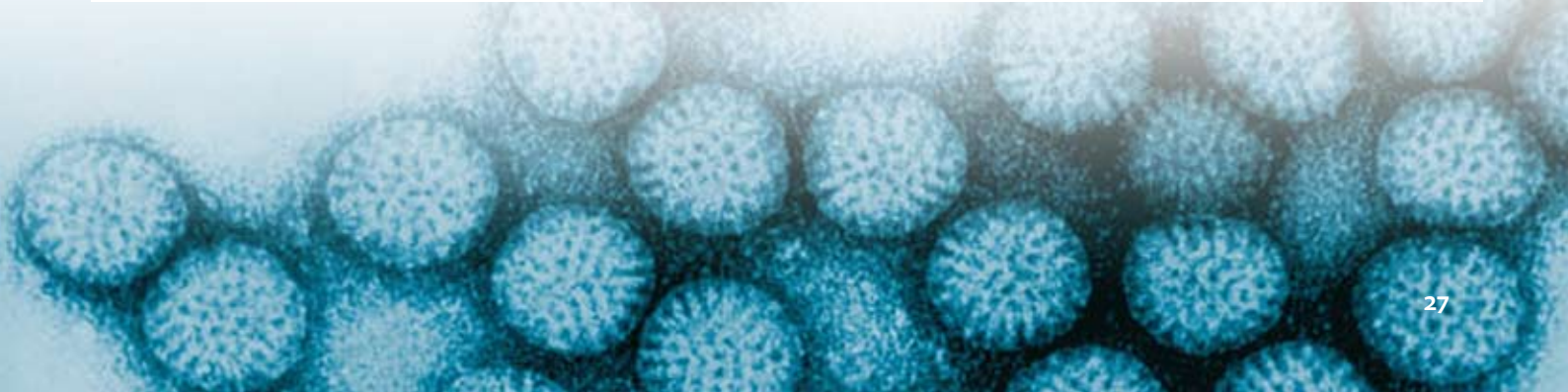
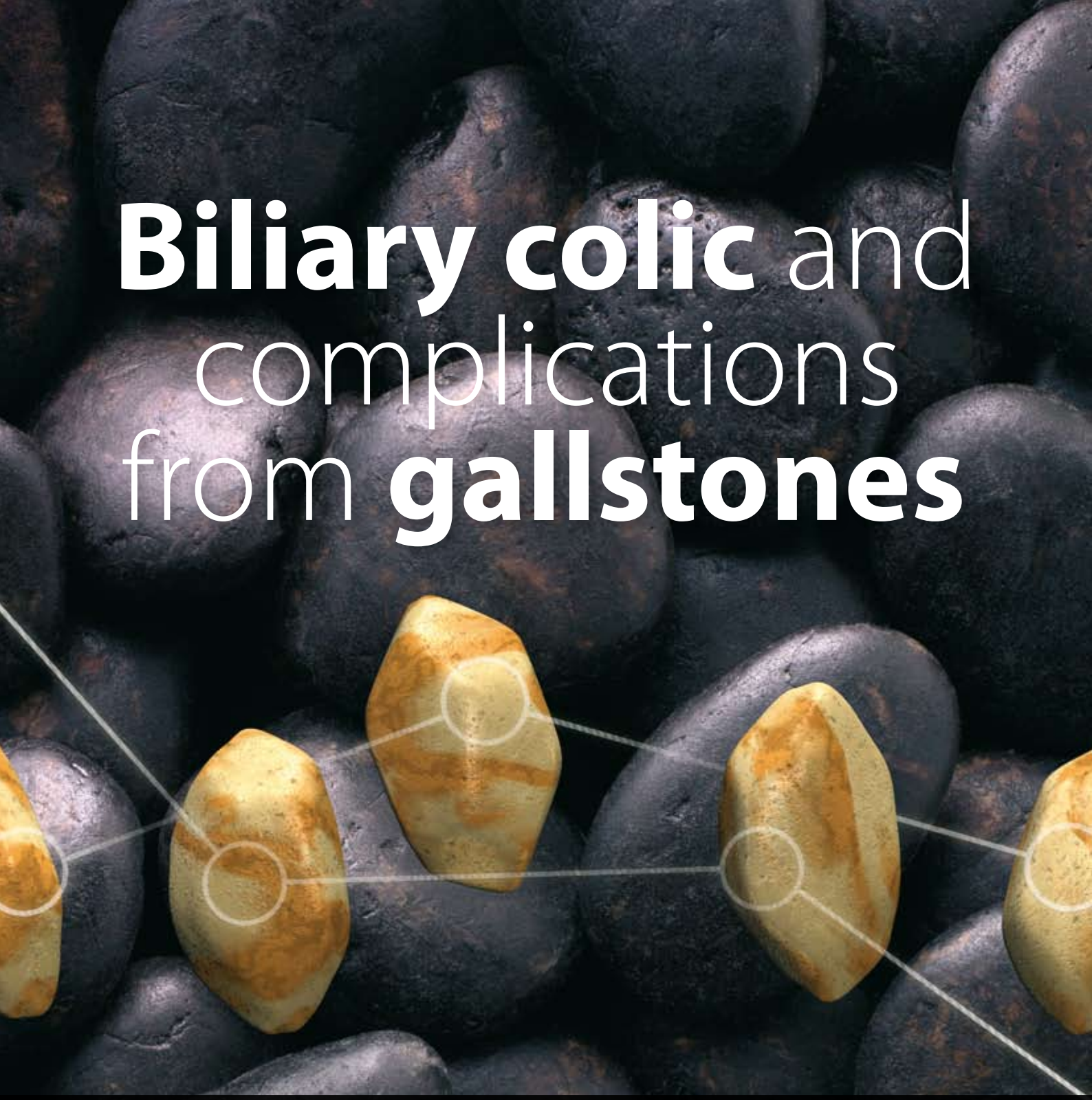
Changes to the National Immunisation Schedule: rotavirus vaccine now added

Contributed by: The Ministry of Health





Biliary colic and complications from **gallstones**

Gallstones are common among the general population, but because they rarely cause symptoms many people are unaware of their presence. Over a ten-year period, approximately one-third of people with gallstones will develop the painful symptoms of biliary colic. This can be a precursor to more serious conditions, such as acute cholecystitis and pancreatitis that require acute advanced endoscopic or surgical assessment. The presence of upper abdominal pain, despite normal physical examination and blood test results, is consistent with uncomplicated biliary colic. An ultrasound should be arranged for all patients with features suggestive of biliary colic to confirm a diagnosis. Patients with biliary colic are generally managed in the community with non-steroidal anti-inflammatory drugs (NSAIDs) and lifestyle advice while awaiting assessment for laproscopic cholecystectomy.

Gallstones and their associated complications

Cholelithiasis, the presence of gallstones in the gallbladder, is estimated to occur in 10 – 15% of the adult population in the United States.[1] In New Zealand, a small study estimated that 20% of the New Zealand population aged 30 to 75 years had cholelithiasis.[2] Most people with cholelithiasis are asymptomatic, but over a ten year-period approximately one-third will develop symptoms.[3] Symptoms are usually caused by blockage of the cystic duct by a gallstone or by migration of a gallstone into the common bile duct. Blockage of the cystic duct causes pressure within the gallbladder to rise, resulting in symptomatic cholelithiasis that is usually accompanied by a distinctive pattern of abdominal pain, referred to as biliary colic. Blockage of the common bile duct causes a similar pain, but may be accompanied by jaundice, pancreatitis or cholangitis (Page 30).

Approximately 70% of gallstones are cholesterol stones, i.e. more than half the stone is formed from cholesterol.[4] These stones form when bile becomes supersaturated with cholesterol, following increased secretion of cholesterol from the liver or when production of bile salt or lecithin (an emulsifying fatty substance) decreases.[4] Cholesterol microcrystals then precipitate from biliary sludge within the gallbladder.[1] Black pigment stones are the other significant type of gallstone found among people in Western countries.[4] These are made up of calcium bilirubinate and are related to haemolytic disorders with an increased bilirubin load, and occasionally cirrhosis.

Cholelithiasis is formally diagnosed by abdominal ultrasound, and in symptomatic patients, is treated surgically with cholecystectomy.[4] Patients with uncomplicated episodes of biliary colic can generally be managed in the community with analgesics and lifestyle advice while they wait for surgery.

Risk factors for gallstone formation

Factors associated with an increased risk of cholelithiasis include:[4]

- Increasing age
- Increasing body mass
- Female sex
- Pregnancy (see: "Cholelithiasis in women who are pregnant", Page 32)
- Medicines, e.g. oral contraceptives, fibrates
- Family history
- Rapid weight loss, e.g. following bariatric surgery
- Haemolytic disorders, e.g. haemolytic anaemia

Gallstones are more prevalent in people who are obese because increasing body mass is associated with an increased production of cholesterol by the liver.[4] Periods of rapid weight loss are also associated with gallstone formation and people are more likely to become symptomatic during this time. This is possibly due to an increase in the relative amount of cholesterol in the gallbladder and reduced gallbladder contractility.[4] In contrast, people who take statins long-term are less likely to undergo surgery for biliary colic. One study found that statin use for periods of five years or more was associated with a decreased risk of cholecystectomy.[5] Exercise can also reduce a patient's likelihood of developing gallstones and moderate physical activity is reported to prevent gallstone formation independently of body mass.[6]

The higher prevalence of cholelithiasis among females is most likely related to oestrogen increasing biliary secretion of cholesterol and progesterone reducing bile acid secretion by increasing gallbladder stasis.[7] The risk of gallstone formation in females is increased by taking oral contraceptives.[8]

People who have a first-degree relative with cholelithiasis are almost 4.5 times more likely to develop gallstones.[9] Diabetes, hypertriglyceridaemia, Crohn's disease, cirrhosis and conditions that cause the bile duct to become blocked, or procedures that cause bile salt loss, e.g. ileal resection, are also associated with cholelithiasis.[4]

Diagnosing biliary colic

Biliary colic typically refers to a steady pain, rather than a series of "colicky" waves that might be expected from the term.[4] The pain originates in the right upper quadrant or epigastric area and can radiate around to the subscapular region.[8] The pain will typically last for more than 30 minutes with an upper limit of six hours, and is unaffected by movement, body position or defaecation.[4] The patient will often be nauseated and may vomit.[8] Episodes of biliary colic often occur following a meal

or at night, and after an initial episode, recurrence is common and may occur within hours.[4] In some patients, however, recurrence may occur years later.[4]

Atypical symptoms of biliary colic are not unusual and include: chest pain, belching (eructation), rapid satiety, dyspepsia and non-specific abdominal pain.[4]

Choledocholithiasis (see glossary) can cause pain that is indistinguishable from biliary colic but may be accompanied by obstructive jaundice, cholangitis or acute pancreatitis.[11] The risk of bacteraemia is also increased in patients with choledocholithiasis as increased biliary pressure can force bacteria from the bile duct into the blood stream of the liver.[10]

Consider differential diagnoses

As gallstones are prevalent, and most people who have them are asymptomatic, their presence does not necessarily mean that a patient's abdominal pain is due to cholelithiasis.

Gastro-oesophageal reflux disease (GORD), peptic ulcer disease, non-ulcer dyspepsia, hepatitis, right-sided pyelonephritis, nephrolithiasis, appendicitis, pancreatitis, bowel obstruction, bowel ischaemia, right-sided pneumonia, abnormal aortic dissection and an atypical presentation of ischaemic heart disease are among the many conditions that may cause upper abdominal pain. Irritable bowel syndrome should also be considered, particularly in patients with a longer history of symptoms who report pain that is relieved by defaecation and

A glossary of the complications of cholelithiasis

1. **Acute cholecystitis** is the most frequent complication of symptomatic cholelithiasis and is characterised by inflammation of the gallbladder wall.[6] The risk of this is increased in patients with larger gallstones that are more likely to be trapped within the gallbladder. Gangrenous cholecystitis and perforation of the gallbladder are serious complications of acute cholecystitis.[13] In severe cases acute cholecystitis can be fatal.

2. **Chronic cholecystitis** is also common and results from recurrent or relapsing bouts of acute cholecystitis. Rare but serious complications of chronic cholecystitis include:
   a) **Mirizzi syndrome**, which is an unusual cause of obstructive jaundice occurring when a large stone becomes impacted in Hartman's pouch causing extrinsic compression and eventual erosion of the common hepatic duct
   b) **Gallstone ileus**, which occurs when there is mechanical obstruction due to the impaction of a large gallstone at the ileocaecal valve, often after spontaneously eroding into the small bowel via a cholecystoenteric fistula
   c) **Gallbladder cancer**, which in most cases develops from long-term cholelithiasis and chronic cholecystitis. Patients are often asymptomatic until the cancer develops. Most early gallbladder cancers are diagnosed incidentally following cholecystectomy for cholelithiasis.

3. **Choledocholithiasis** is the migration of gallstones from the gallbladder into the common biliary duct. This is more likely to occur in patients with small gallstones because these can pass with greater ease through the cystic duct.[6] There are three main clinical consequences of choledocholithiasis:
   a) **Obstructive jaundice**, which occurs when a bile duct stone obstructs the flow of bile into the duodenum. Patients will typically present with biliary colic accompanied by jaundice, dark urine, pale stools and pruritus.
   b) **Acute pancreatitis**, which is caused by temporary obstruction to the pancreatic duct during passage of a bile duct stone through the ampulla of Vater into the duodenum. It can range in severity from mild and transient to life-threatening.
   c) **Ascending cholangitis**, which occurs when bile in an obstructed bile duct becomes infected, often from bacteria embedded in the matrix of a gallstone within the bile duct.[10]

pain that is more constant over 24 hours.[8] Colorectal cancer should be considered in patients, particularly those aged over 50 years and those with a family history of this malignancy.

For further information, see: "Surveillance of people at increased risk of colorectal cancer", BPJ 44 (May, 2012).

Examining the patient

Patients with uncomplicated biliary colic will typically display pain in the right upper quadrant and epigastrium, and on examination may display voluntary guarding.[4] Severe and ongoing pain and rebound tenderness on examination suggest that the patient has developed acute cholecystitis, the suspicion of which should be increased if the patient displays a positive Murphy's sign.

To assess for a positive Murphy's sign ask the patient to inspire deeply while palpating the right subcostal region. Increased discomfort in patients with a positive sign is due to inflammation of the peritoneum overlying the gallbladder and therefore palpation causes the patient to "catch" their breath. However, a negative sign does not necessarily exclude cholecystitis and should be interpreted with caution, particularly in older patients.[12]

Ascending cholangitis is a dangerous condition identified clinically by Charcot's triad of jaundice, fever and right upper abdominal pain.[10] Mirizzi syndrome is usually diagnosed after imaging a patient with long-term gallstone disease. The presentation of Mirizzi syndrome can vary greatly but usually includes jaundice or abnormal liver function tests (LFTs), associated with dilated intra-hepatic ducts on ultrasound with a large stone in Hartman's pouch.

Investigating biliary colic

Routine testing of patients with suspected biliary colic should include:

- Full blood count (FBC)
- Liver function tests (LFTs)
- Serum creatinine
- CRP
- Serum amylase
- Urine dipstick

In patients with uncomplicated biliary colic, FBC, LFTs and markers of pancreatic injury, i.e. serum amylase, should be within the normal range.[4] Leukocytosis and an elevated CRP are typical in patients with acute cholecystitis, but liver enzymes are either normal or only marginally elevated. Markedly elevated liver enzymes are suggestive of choledocholithiasis, which may be complicated by acute pancreatitis (elevated serum amylase) or cholangitis, indicated by Charcot's triad. Gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) levels will be raised in 94% and 91% respectively of patients with choledocholithiasis.[10] Serum amylase is elevated transiently in the majority of patients with acute pancreatitis. Transient elevation of aspartate aminotransferase (AST) and ALT in combination with acute biliary pain and elevated amylase is strongly suggestive of passage of a bile duct stone. If the patient has atypical chest pain then an ECG should be performed and a troponin test requested to help exclude a cardiac cause for the pain.

Ultrasound is the gold-standard diagnostic test for biliary colic

Abdominal ultrasound is used to confirm a diagnosis of biliary colic in all patients before a laparoscopic cholecystectomy is performed. Local guidelines may vary, but usually recommend a prompt abdominal ultrasound (within five days) for patients with:

- Jaundice and abnormal LFTs
- Significant, persistent or recurrent upper quadrant pain

A routine ultrasound (within four weeks) should be arranged for patients with characteristic abdominal pain and laboratory results that are normal or mildly abnormal, but without jaundice.

Red-flags for acute referral to hospital for surgical assessment include:

- Biliary colic that cannot be effectively controlled with analgesia
- Obstructive jaundice
- Suspected acute cholecystitis
- Cholangitis
- Acute pancreatitis

Abdominal ultrasound can detect approximately 95% of gallstones as well as being able to detect complications of gallstones, e.g. inflammation of the gallbladder wall or obstruction of the common bile duct.[4] Ultrasound can also identify biliary sludge in some patients, which is seen as layering within the gallbladder.

The sensitivity of ultrasound for detecting gallstones decreases as the patient's body mass increases and may also be affected by increased bowel gas, which can occur in patients with acute complications, such as pancreatitis. The sensitivity of ultrasound for bile duct stones is approximately 60% and

patients with dilated bile ducts or other suspicious features on ultrasound will usually require further investigation.

Magnetic resonance imaging (MRI) will detect bile duct stones in approximately 90% of patients with choledocholithiasis.[10]

Endoscopic retrograde cholangiopancreatography (ERCP) may be used to diagnose and treat common bile duct stones and to clear the common bile duct prior to or after laproscopic cholecystectomy in patients with cholelithiasis complicated by choledocholithiasis.[14] ERCP requires the patient to be sedated and involves fluoroscopy and may include biliary sphincterotomy.

Managing biliary colic in primary care

Patients who have had an episode of uncomplicated biliary colic may be managed in the community while they wait for a definitive diagnosis and surgical assessment. During this time recurrent bouts of biliary colic may occur.[17]

Lifestyle management

The patient's dietary history may indicate foods that are triggers for biliary colic which can then be avoided, e.g. fatty food and high-fat dairy products. A high-fibre diet that contains nuts and is low in saturated fat is associated with a reduced risk of gallstone formation and it is possible that making dietary changes will improve the patient's symptoms.[6] Paradoxically, for patients on a low-calorie diet the consumption of 10 g of fat per day has been shown to prevent gallstone formation,

Cholelithiasis in women who are pregnant

During pregnancy, physiological changes increase the likelihood of gallstone formation. These include: increased gallbladder stasis, increased bile production by approximately 50%, elevated levels of cholesterol, and reduced levels of the bile acid chenodexycholic acid.[1] The risk of gallstones forming also increases with the number of pregnancies a woman has had.[1] Biliary colic is estimated to occur in three to five women per 1000 pregnancies.[1] The most important predictors of biliary colic during pregnancy are a personal history of biliary colic, increased body mass index (BMI) and reduced exercise.[1]

The symptoms of biliary colic in women who are pregnant are the same as for other patients, although pregnancy-related causes of abdominal pain must be considered, particularly in later pregnancy, e.g. pre-term labour, placental abruption, acute fatty liver of pregnancy, severe pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome. Acute pancreatitis during pregnancy is a rare but potentially severe complication of choledocholithiasis that is associated with high maternal mortality rates.[1] Pregnant women with suspected biliary colic or acute pancreatitis are best managed by immediate referral to an emergency department.

Initial treatment of biliary colic in pregnant women generally involves temporary fasting and administration of intravenous fluids, analgesia and antibiotics, if signs of infection are present. The goal of management is to defer invasive procedures, if possible.[1]

Although in most circumstances NSAIDs are the recommended choice for managing pain from biliary colic, they should generally be avoided during pregnancy unless the benefit outweighs the risk.[15] NSAIDs are associated with adverse effects on foetal development early in pregnancy and an increased risk of miscarriage or premature closure of the ductus arteriosus later in pregnancy.[15, 16] Oral morphine can be used short-term, if required, for moderate to severe pain during pregnancy.[15]

Occasionally, surgical intervention is needed when a conservative approach is not effective. Where possible, this is performed during the second trimester.[1] During the first trimester there is an increased risk to the foetus due to surgical general anaesthesia and during the third trimester there is an increased risk of uterine damage and the enlarged uterus can make access to the gallbladder difficult.[1] During the post-partum period bile rapidly reverts back to pre-pregnancy composition and some women will have spontaneous resolution of cholelithiasis.[1]

most likely by promoting gallbladder emptying.[6] Coffee and moderate amounts of alcohol have also been suggested by some researchers to have a protective effect against biliary colic.[6] Coffee is known to affect a number of processes involved in gallstone formation, including enhancing gallbladder contractility and decreasing cholesterol crystalisation in bile.[18]

NSAIDs are the first-line analgesic

NSAIDs are generally the preferred class of analgesia for biliary colic in patients with severe pain and those treated in the Emergency Department. However, there are a limited number of studies assessing the comparative effectiveness of analgesics in the treatment of biliary colic. In particular there are no studies assessing the effectiveness of combinations of analgesics, e.g. NSAIDs with opioids or NSAIDs with anti-spasmodics. In practice it may be necessary to provide multiple analgesics to patients who are in severe pain.[3]

Before prescribing NSAIDs for upper abdominal pain consider if the patient's pain may have another cause, e.g. peptic ulcer disease, for which NSAIDs are contraindicated.

Diclofenac injectable preparation is indicated for rapid onset pain relief in patients with biliary colic:[15]

- This can be given as diclofenac 75 mg (3 mL) injection, deep into the upper outer quadrant of the gluteal muscle, repeated once (may be given 30 minutes later if required, in the contralateral muscle)
- It may also be combined with oral diclofenac, 75 mg, to a maximum total dose of 150 mg, daily, for a maximum of two days
- Diclofenac suppositories may be considered as an alternative route of administration for patients unable to tolerate the oral or intramuscular route

Diclofenac is often the first-line NSAID for patients with biliary colic because of its speed of onset, when given intramuscularly, and its availability. Ten diclofenac 50 mg suppositories and five 75 mg injections are available fully subsidised on a PSO for general practices to have available for acute administration.

Oral ibuprofen, 200 – 400 mg, three to four times daily, or naproxen 250 – 500 mg, twice daily, may be considered as an alternative for subsequent bouts of biliary colic in some patients as these NSAIDs are associated with a lower cardiovascular risk than diclofenac.[15, 19] For example, diclofenac is contraindicated in patients who have had a myocardial infarction in the past 12 months.[19]

A review of eleven studies involving over 1000 patients found that NSAIDs (mainly diclofenac 50 – 75 mg) were more effective at controlling the pain of biliary colic than anti-spasmodic medicines, e.g. hyoscine butylbromide, and were equally as effective as opioids (mainly pethidine).[3] NSAIDs may also halt the progression of biliary colic to cholecystitis and other complications by limiting the production of prostaglandins.[6] NSAIDs were found to reduce the overall risk of short-term complications, i.e. jaundice, acute cholangitis, acute cholecystitis and acute pancreatitis, by approximately half compared to placebo.[3] Patients who were potentially at increased risk of the adverse effects of NSAIDs were excluded from this study, e.g. patients aged over 65 years, patients with diabetes or other systemic co-morbidities.[3]

NSAIDS may not be the most appropriate analgesic for some patients with biliary colic, e.g. patients with a history of peptic ulcer. For these patients other analgesics such as codeine and paracetamol or morphine may need to be considered (see below).

For further information see: "Non-steroidal anti-inflammatory drugs (NSAIDs): Making safer treatment choices", BPJ 55 (Oct, 2013).

Codeine and paracetamol may be superior to NSAIDs for moderate pain

Codeine and paracetamol may be an effective alternative to NSAIDs in patients with moderate biliary colic. A combination product of paracetamol 500 mg with codeine 30 mg, was found to provide superior pain relief to tramadol, oral or intramuscular diclofenac, ibuprofen and hyoscine in a survey of patients with biliary colic.[17] However, for the 79% of patients with severe pain it was found that NSAID analgesia was the most effective.[17]

Codeine is available fully subsidised in New Zealand in 15 mg, 30 mg and 60 mg tablets which can be prescribed in addition to paracetamol. Combination medicines containing both paracetamol, 500 mg, and codeine, 8 – 15 mg, are available in New Zealand, but only the 8 mg formulation is fully subsidised.

Opioids are an alternative to NSAIDs for severe pain

Morphine 5 – 10 mg, IM, is an alternative treatment to NSAIDs for acute pain management in patients with severe pain due to biliary colic and for patients when an NSAID is unsafe or fails to provide effective pain relief.[15] Antiemetics can be prescribed "as needed" if nausea occurs with the use of morphine (see over page).

Morphine is generally preferred over pethidine in New Zealand. Historically, morphine has been avoided in the treatment of acute biliary colic and pancreatic pain because it was thought to induce spasm in the sphincter of Oddi to a greater degree than other opioids. Pethidine has therefore traditionally been used in preference. However, a systematic review found that all narcotics increased biliary pressure to a similar degree and that there was no outcome-based evidence to support the use of pethidine over morphine.[20] Furthermore, it was concluded that morphine may be of more benefit to patients with acute pancreatitis than pethidine as it provides longer pain relief and a lower risk of seizures.[20] Pethidine is still suggested by some international guidelines for pain control in patients with acute cholecystitis while waiting for hospital admission, e.g. pethidine intramuscularly, 25 – 100 mg, which may be repeated after four hours.[15, 19]

Antispasmodic medicines may be combined with NSAIDs or opioids

Antispasmodic medicines, e.g. hyoscine butylbromide, are reported to produce effective analgesia in some patients with biliary colic, however, other patients may not gain any benefit.[8] If hyoscine butylbromide is prescribed to patients with biliary colic, it is recommended that it is used in combination with an NSAID or opioid.

Hyoscine butylbromide is available in 10 mg tablets at a recommended dose of 20 mg, four times daily.[15] Hyoscine butylbromide is also available in a 20 mg/mL injectable formulation which can be given by intramuscular or subcutaneous injection, 20 mg, repeated after 30 minutes if necessary, to a maximum of 100 mg, daily.[15]

Antiemetics may be required for some patients

Nausea is a common symptom in patients with biliary colic and may also be experienced by patients taking opioids. For some patients with biliary colic their nausea will be relieved once an analgesic has been administered. For patients that experience ongoing nausea once their pain has been controlled, antiemetics such as metoclopramide, cyclizine and ondansetron (see NZF for dosing details) may be considered. Some patients may need to trial more than one antiemetic before they achieve effective symptom control.

Surgical management of biliary colic

Patients with biliary colic should be referred for consideration of laparoscopic cholecystectomy to prevent future episodes. This surgical procedure takes approximately 60 – 90 minutes and requires an average hospital stay of one to three days.[11] Laparoscopic cholecystectomy is associated with a similar level of risk as open cholecystectomy but with less post-operative pain and faster recovery. Evidence supports early surgical intervention for patients with acute cholecystitis and the majority of these patients can be managed laparoscopically.[21] Patients with severe acute cholecystitis, whose health is too fragile to undergo surgery, can be managed through the acute episode with percutaneous drainage of the gallbladder, plus antibiotics. In all patients the individual risks and benefits of the choice of procedure will need to be balanced. Patients with severe co-morbidities may be unfit to undergo elective cholecystectomy.

Patients will be asked to consent to both laparoscopic and open procedures before surgery is performed. Conversion to open surgery generally occurs in less than 5% of patients, but is higher in patients treated acutely or in those with previous abdominal surgery. Wound complications, e.g. haemorrhage, infection and incisional hernia, bile leaks, diarrhoea and the rare but important complication of bile duct injury can occur after laparoscopic or open cholecystectomy.[11] Incomplete surgical removal of stones, injury or scarring can result in patients experiencing long-term, post-operative symptoms.

Bile duct exploration to remove common bile duct stones can be performed during laparoscopic or open cholecystectomy and is necessary if ERCP is unavailable or has failed. A Cochrane review found both surgical and endoscopic approaches to bile duct stone removal to be equally safe and effective.[22] The choice of approaches will be influenced by local availability and expertise.

The long-term consequences of gallstones and cholecystectomy

Gallstones are a risk factor for gallbladder cancer. Although 85% of people with gallbladder cancer have gallstones, only 3% of people with gallstones have gallbladder cancer.[23] The age-adjusted incidence rates of gallbladder cancer in New Zealand are reported to be 1 case per 245 000 people in males and 1 case per 135 000 people in females, which compares to an approximate incidence rate of 1 case per 2 500 people for colorectal cancer.[24, 25]

Following cholecystectomy, patients who make positive dietary changes will improve their general health, but there are no specific dietary recommendations for patients who undergo this procedure.

Gallstones and subsequent cholecystectomy are associated with a small increased risk of cancer throughout the digestive tract. In a large study of over 236 000 patients with primary cancer in the United States, gallstones were associated with

an increased risk (odds ratio) of: liver cancer (OR 2.35), small intestine carcinoid (OR 1.27), pancreatic cancer (OR 1.24) and non-cardia gastric cancer (OR 1.21).[26] In the same study cholecystectomy was associated with an increased risk of: small intestine carcinoid (OR 1.78), non-cardia gastric cancer (OR 1.26), liver cancer (OR 1.26) and pancreatic cancer (OR 1.23).[26] It has been suggested that this increased risk of malignancy is due to enhanced exposure of the stomach and small intestine to bile following cholecystectomy. This suggestion was supported by a reduced risk of colorectal cancer occurring in the colon with increasing distance from the common bile duct.[26]

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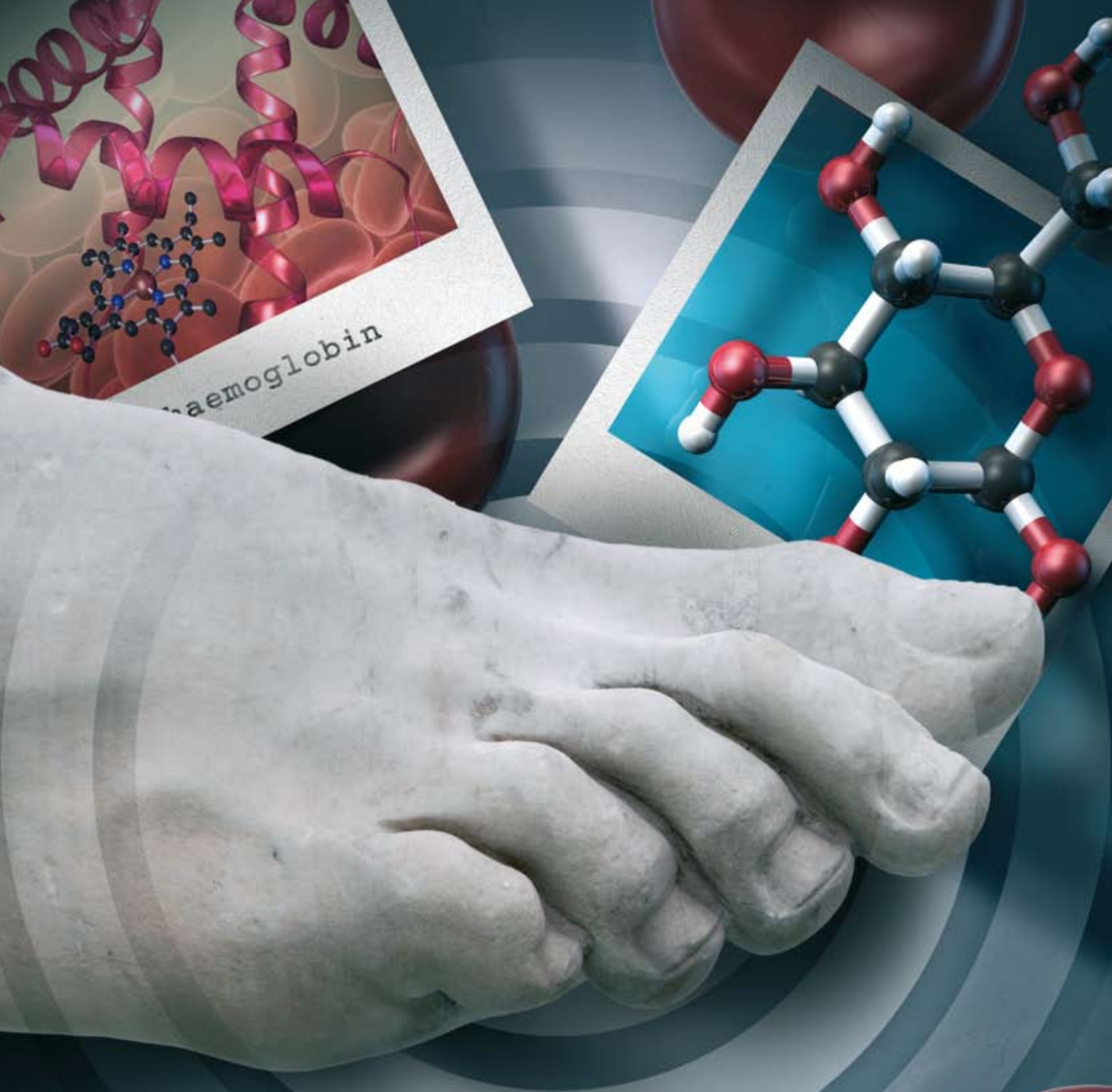


Assessing **diabetic peripheral neuropathy** in primary care

Diabetic peripheral neuropathy is one of the most common long-term complications of diabetes. It develops in up to half of all people with diabetes, and is one of the main risk factors contributing to foot ulceration and eventual amputation. In developed nations the main cause of non-traumatic lower limb amputation is "diabetic foot", which is a result of a combination of decreased sensation and reduced arterial supply. Assessing for peripheral neuropathy is a routine part of ongoing care for patients with diabetes. Treatment of diabetic neuropathy includes optimal control of hyperglycaemia, appropriate foot care (often involving input from a podiatrist), and symptomatic management of any neuropathic pain.

Losing touch: diabetic peripheral neuropathy

Diabetes is one of the most common causes of neuropathy, with up to 50% of people with type 2 diabetes eventually developing some degree of peripheral neuropathy.[1] Diabetes can affect many different elements of the peripheral nervous system and result in neuropathies of several types, characterised by a variety of symptoms, including sensory disturbance, autonomic dysfunction and weakness (see "Classification of neuropathies in people with diabetes", Page 38). It is estimated that 90% of people with diabetic peripheral neuropathy have symmetric distal polyneuropathy, where multiple nerve groups are affected.[1] This often occurs in combination with autonomic neuropathy.[1, 2] Focal and multifocal neuropathies, affecting one nerve or nerve group (mononeuropathies), e.g. cranial nerve palsies or radiculoneuropathies, occur less often. It is important to note that a person with diabetes may have more than one form of neuropathy, e.g. both symmetric distal polyneuropathy and carpal tunnel syndrome (which occurs in up to one-third of people with diabetes).[2, 3, 4]

Many mechanisms are thought to be involved in producing the damage to nerves in people with diabetes, and this is an ongoing area of research.[5] In diabetic neuropathy, a number of metabolic and vascular changes interconnect to cause damage to nerve cells in a similar way to that seen in diabetic retinopathy and nephropathy, with the primary underlying factor being hyperglycaemia.[5, 6] Changes include increased oxidative stress, a build-up of glycation end-products, increased activity of the polyol pathway, activation of pro-inflammatory mechanisms and ischaemia.[5, 6] These processes have direct and indirect adverse effects, not only on neurons and Schwann cells, but also on the vascular tissue of the blood vessels that supply the nerves.[5] All types of nerve fibres, e.g. sensory, autonomic, motor, both myelinated and unmyelinated, are adversely affected in people with diabetes.[5]

As with the other microvascular complications associated with diabetes, the risk of developing neuropathy is proportional to both the magnitude and duration of hyperglycaemia.[7] The development of diabetic neuropathy is therefore less likely in people with optimal long-term control of HbA_{1c} levels (< 55 mmol/mol).

Additional modifiable risk factors for the development of diabetic peripheral neuropathy include smoking, hypertension, obesity and dyslipidaemia.[7] Increasing age, a family history of neuropathy and the duration of diabetes are non-modifiable risk factors.[7]

Although in a person with diabetes it is most likely that this condition will be responsible for the neuropathy, other diagnostic possibilities should be considered, including medicines, systemic conditions, infections, autoimmune disorders, toxins, trauma and inherited conditions.[8] Neuropathy due to vitamin B12 deficiency, uraemia or hypothyroidism are known to occur more often in people with diabetes.[9] Chronic inflammatory demyelinating polyneuropathy (CIDP) may also be more common in people with diabetes. Diabetic peripheral neuropathy, therefore, is often regarded as a diagnosis of exclusion.[9]

See: "Alternative causes for peripheral neuropathy in a person with diabetes", Page 45.

For most people with diabetic peripheral neuropathy, the outcome that is most feared is "diabetic foot", where the loss of protective sensation, often accompanied by reduced perfusion from arterial disease, increases the risk of ulceration, infection and, ultimately amputation. In addition, diabetic peripheral neuropathy can have a significant impact on a patient's quality of life due to its negative impact on sleep, daily activities, independence and mood, and also due to an increased risk of falls and fractures.[4,10]

The risk of amputation in a patient with neuropathy increases 1.7-fold, further increasing to 12-fold if there is also deformity of the foot (which may be a consequence of the neuropathy) and up to 36-fold if the patient has a previous history of ulceration.[4] It is estimated that at least half the foot ulcers that occur in people with diabetic neuropathy could be prevented

Classification of neuropathies in people with diabetes*[2]

Generalised neuropathies:

- **Symmetric distal polyneuropathy** with or without autonomic neuropathy – also referred to as chronic sensorimotor neuropathy or diabetic sensorimotor polyneuropathy. This is the most commonly encountered type of neuropathy in people with diabetes.
- **Hyperglycaemic neuropathy** – also referred to as acute sensory neuropathy. This is characterised by a symmetrical polyneuropathy of acute or sub-acute onset, with severe sensory symptoms, which may involve pain (of various types), paraesthesia or numbness. It is rare, but usually occurs following an episode of glycaemic instability, such as the initiation of insulin or rapid correction of long-term hyperglycaemia.[9] Symptoms are often most prominent in bed at night.[9] This form of neuropathy usually resolves within twelve months.[9]
- **Acute painful sensory neuropathy** variants, e.g. insulin neuritis

Focal and multifocal neuropathies:

- **Cranial neuropathies**, e.g. sixth nerve palsy and less often a third nerve palsy, with full recovery usually within three to six months
- **Focal limb neuropathies** – secondary to compression or entrapment, e g. carpal tunnel syndrome or ulnar neuropathy
- **Thoracolumbar radiculoneuropathy** – generally unilateral pain and hyperaesthesiae involving a focal area on the chest or abdomen with an abrupt onset and spontaneous recovery over a few months (seen in people with both type 1 and type 2 diabetes)
- **Lumbosacral radiculoplexus neuropathy** – also referred to as diabetic amyotrophy, femoral neuropathy or Bruns-Garland syndrome. This form of neuropathy primarily affects the motor nerves of the proximal muscles of the legs.[7] Usually seen in patients who have type 2 diabetes, are older and are male. Characterised by severe aching or burning pain that affects the lower back, buttocks and thighs, that is often worse at night.

* both type 1 and type 2 diabetes

by appropriate management and increasing the patient's understanding of their condition.[3] This involves considering the principles of cultural competency, with health literacy being an important component of this.

"I never noticed that, Doc!" – Recognising and diagnosing diabetic neuropathy in a primary care setting

Of the estimated 50% of people with diabetes who develop peripheral neuropathy, up to half will be asymptomatic or have numbness as their only symptom;[3] they literally cannot feel it coming. Diabetic peripheral neuropathy is usually insidious in onset and therefore assessment for neuropathy must be an active part of the routine follow-up of all people with diabetes. Patients need to be asked about the presence of symptoms, such as numbness, tingling or pain, and examined for signs of neuropathy, including specific sensory testing (e.g. monofilament testing, tuning fork tests), which may detect patients with diabetic peripheral neuropathy who are asymptomatic. An absence of symptoms, however, does not mean an absence of neuropathy.[9]

There is no readily-available clinical gold-standard test for diagnosing peripheral neuropathy. The diagnosis is based on clinical suspicion, generated by a combination of findings from the history and examination, followed by the exclusion of other potential causes (Page 45).[4] If a patient with diabetes has retinopathy or nephropathy it is likely that they will also have neuropathy.[2]

What are the symptoms of peripheral neuropathy?

Symmetric distal polyneuropathy, the most common form of diabetic peripheral neuropathy, usually has a mild, insidious onset, with a predominance of sensory symptoms over motor symptoms.[4] It is present at the time of diagnosis of diabetes in up to 10% of patients with type 2 diabetes.[3]

The symptoms vary widely, depending on the specific pattern of damage to nerve fibres of different size and function. A loss of pain sensation and the ability to perceive changes in temperature tend to be the result of damage to small sensory fibres (Type-C). The loss of sensation to touch, vibration, proprioception and motor innervation of the intrinsic muscles of the foot from damage to large fibres (Type-A).[2, 4, 11] Neuropathic symptoms are defined as positive ("painful") or negative ("non-painful").[3, 12]

Positive symptoms include a sensation of burning or knife-like pain, electrical sensations, squeezing, constricting, freezing or

throbbing and allodynia – pain provoked by a stimulus that is not normally painful, e.g. stroking the skin.[3, 12] Pain may be highly variable in presentation, but patients are usually more prone to nocturnal exacerbations.[3] Positive symptoms appear to stem from increased uninhibited sensory firing from the damaged nerve fibres.

Negative symptoms include sensations of tingling, swelling, prickling, numbness, a feeling of "walking on cotton wool" or that the limb is "asleep" or "dead".[3, 12] Negative symptoms are thought to be generally due to reduced signalling from damaged nerves. Patients with negative symptoms are at higher risk of foot ulceration due to the lack of protective sensation.

The sensory symptoms usually first appear in the toes and gradually progress proximally in a "stocking distribution" to involve the feet and legs.[6] This is because the sensory nerves with the longest axons are affected first and the neuropathy is often termed "length-dependent".[6, 7] Patients may also develop symptoms in the fingers which gradually involve the hand, however, this is uncommon unless the symptoms in the legs have progressed to mid-thigh level, typically in people with later-stage diabetic neuropathy.[2] Generally, the symptoms have a symmetrical distribution and typically there are nocturnal exacerbations of painful sensory symptoms.[6]

Motor symptoms such as atrophy, weakness and unsteadiness are also potential manifestations of diabetic peripheral neuropathy, although traditionally these were not considered symptoms of the condition and they are more common later in the disease course.[3, 13] The development of unsteadiness and ataxia generally occur due to abnormalities of proprioception and muscle sensory function.[4] Severe sensory ataxia is not a feature of diabetic peripheral neuropathy and if present should prompt consideration of alternative causes.

Best Practice Tip: If a patient with diabetes has peripheral symptoms that are more prominent in the upper limbs than the lower limbs then an alternative explanation for the sensory changes in the upper limb should be considered.[2]

Autonomic neuropathic dysfunction affecting both sympathetic and parasympathetic functions can also occur in people with diabetes, with or without sensorimotor neuropathy. Typically dysfunction can involve the cardiovascular, gastrointestinal, genitourinary, sudomotor (control of the sweat glands) and ocular systems.[14] Some problems, e.g. erectile dysfunction, are often not reported, so should be enquired about at least once per year.[15]

Autonomic symptoms therefore vary widely but may include:[14]

- Cardiovascular – resting tachycardia, orthostatic hypotension, exercise intolerance, silent myocardial ischaemia
- Gastrointestinal – symptoms of gastroparesis (early satiety, bloating, vomiting, digestive problems, erratic glucose control following meals),[15] diarrhoea, constipation, faecal incontinence
- Genitourinary – bladder-voiding problems (e.g. neurogenic bladder), erectile dysfunction, retrograde ejaculation, female sexual dysfunction (e.g. loss of vaginal lubrication)
- Metabolic – hypoglycaemia unawareness, hypoglycaemic-associated autonomic failure
- Sudomotor – excessive sweating in the upper body and reduced sweating in the legs and feet, heat intolerance, localised sweating over the face and neck after meals (gustatory sweating), dry, flaky, cracked skin on the feet and increased formation of callus (caused by reduced sweating in the feet)[7, 16]
- Ocular – pupillomotor function impairment (e.g. decreased diameter of dark-adapted pupil), Argyll-Robertson pupil (small pupil that constricts poorly to light, but rapidly to a close object)

Best Practice Tip: If a patient with diabetes has a peripheral neuropathy that is mild, but prominent or severe autonomic symptoms, other causes for the autonomic neuropathy should be considered, e.g. amyloid neuropathy.[2]

Hyperglycaemic neuropathy (acute sensory neuropathy); in contrast to many patients with symmetric distal neuropathy, patients with hyperglycaemic neuropathy will typically have a relatively normal physical examination.[3] There may be loss of light touch sensation, allodynia may be present on sensory testing and, occasionally, ankle reflexes will be reduced. Motor function will usually be normal.[3]

"The sole issue": examining for diabetic peripheral neuropathy

Many patients with diabetes have asymptomatic peripheral neuropathy and those that are symptomatic tend to have variable symptoms which are reported to have a relatively poor diagnostic accuracy. Therefore, a diagnosis may rely heavily on the clinical signs detected on examination.[13] The most common causes of foot ulceration in a patient with diabetes are peripheral neuropathy, deformity of the foot and external trauma, with peripheral arterial disease and peripheral oedema also having a significant contribution.[17]

Examination of a patient with suspected diabetic neuropathy should include:[4, 18]

- A general inspection of the feet and the patient's footwear
- Musculoskeletal assessment for deformity (including Charcot arthropathy – Page 41)
- Neurological assessment
- Vascular assessment of the feet, and assessment of the heart rate and blood pressure (lying/sitting and standing)

General inspection of the feet

Examine both feet and check the condition of the skin, particularly looking for erythematous areas, dryness, flakiness, thickness, cracking, callus formation, infection and ulceration.[18] Dermatological changes, such as dry or scaly skin, may be secondary to a degree of autonomic dysfunction which can begin distally. There may also be abnormalities of sweating or circulatory instability in the feet, e.g. a hot or cold foot.[13] Heavy callus formation over the pressure points of the foot and signs of localised rubbing or friction, blisters or erythema can also be an indication of inappropriate footwear.[18] Foot ulcers are not caused by neuropathy alone but can occur without injury once hard callus is present over pressure points. If a patient has a loss of sensation in the foot there will be prolonged and increased forces on the callused areas which then increases the risk of tissue breakdown and ulceration.[11]

Musculoskeletal assessment

Foot deformity has a significant role in the development of pressure points in the foot which predispose it to ulceration. There may be prominence of the metatarsal heads and other bony prominences that increase the risk of skin breakdown. Callus formation frequently results in a deformity sufficient to lead to ulceration. Callus is most commonly formed on the plantar surface beneath the first metatarsal head due to focal pressure during walking.[11] Hyperextension of the metatarsal phalangeal joints with flexion of the interphalangeal joints can result in claw toes, while extension at the distal phalangeal joints causes hammer toes.[18] Extreme deformity can develop very acutely in a neuropathic foot, usually in the midfoot, and cause a "Charcot foot" (see: "Charcot arthropathy", over page).[11] Signs of motor involvement may include muscle atrophy, particularly "guttering" between the metatarsals, and muscle weakness beginning with weakness of toe dorsiflexion followed by weakness of foot dorsiflexion.[13, 18]

Neurological assessment

The classic pattern of sensory loss in a patient with symmetric distal polyneuropathy is a length dependent, non-dermatomal distal loss affecting all modalities, e.g. light touch, pin prick and temperature.[2, 9] This is referred to as a "sock or stocking" distribution that may extend to the mid-calf.[2] In severe cases it may extend further up the leg and even rarely on to the trunk, or involve the upper limbs, beginning in the fingers (a "glove" distribution).[1, 2]

In a patient with diabetes, sensory loss is most often determined with the use of monofilament testing (Page 42). An ability to detect pain and light touch can be assessed with the use of a sharp examination pin or sterile needle and a wisp of cotton wool. An impairment of the perception of vibration, assessed with a 128 Hz tuning fork, is often regarded as the first objective evidence of symmetric distal polyneuropathy.[4]

The deep tendon reflexes may be reduced or absent, particularly those at the ankle. Some experts regard the loss of ankle reflexes as a cardinal sign of symmetric distal polyneuropathy, however, other possible causes such as an S1 radiculopathy, other focal neuropathies and a tendency for an age-related decrease in the reflexes must also be considered.[2, 13]

Best Practice Tip: The presence of asymmetrical neurological symptoms or findings on examination (e.g. loss of the ankle jerk in one leg only) is likely to suggest an alternative cause for the symptoms (Page 45).[1] More marked symmetrical proximal weakness can suggest an alternative type of neuropathy, e.g. CIDP.[4]

Vascular assessment

Peripheral arterial disease is an important risk factor for the development of ulceration in the lower limbs. It is estimated to be a significant underlying cause in approximately one-third of patients with foot ulcers.[18] The patient's foot should be palpated to determine the presence and character of the posterior tibial and dorsalis pedis pulses. Further investigation using the ankle-brachial pressure index (ABPI) can provide additional information and help determine the patient's risk of ulceration and the need for referral.[18] N.B. ABPI can be falsely elevated in some patients with diabetes, due to medial artery calcification.[21]

On examination, patients who have autonomic neuropathy affecting the cardiovascular system may be found to have a resting tachycardia and orthostatic hypotension, and may report reduced exercise tolerance. Orthostatic hypotension in particular can increase the risk of falls and cardiovascular autonomic neuropathy is associated with an increased risk of cardiovascular morbidity and mortality.[14]

For further information, see: "The ankle-brachial pressure index", BPJ 60 (Apr, 2014).

Laboratory investigations may help confirm the underlying cause

Laboratory investigations are not generally required for the diagnosis of diabetic peripheral neuropathy, however, they are usually requested to help exclude other causes of neuropathy. Initial investigations would usually include a full blood count, CRP, HbA_{1c}, liver function tests, creatinine clearance, vitamin B12, folate and thyroid-stimulating hormone tests.[8] Additional tests, may be considered if there is clinical suspicion of a specific potential cause. Generally these tests would only be requested in consultation with a relevant specialist, such as an Endocrinologist or Neurologist, e.g. cerebrospinal fluid (CSF) analysis to evaluate for CIDP or genetic testing if hereditary peripheral neuropathy is suspected.[8] Investigation for a paraprotein may also be recommended.

Referral for electrodiagnostic testing is rarely required, but may be considered for patients with atypical features of neuropathy, e.g. onset of symptoms in the hands, proximal rather than distal weakness or marked sensory ataxia.

Charcot arthropathy

Charot arthropathy is a neuropathic arthropathy resulting in degeneration of the stress bearing part of a joint, usually affecting the foot and ankle. The pattern of bone destruction was first described in 1868 by Jean-Marie Charcot, although it was not until 1936 that this neuroarthopathy was associated with diabetes.[7] It is more characteristically found in people with long-standing, often poorly controlled diabetes and is estimated to affect up to 10% of people with neuropathy.[7]

There are two theories proposed for the development of Charcot arthropathy: neurotraumatic involving impaired proprioception, with overuse injuries of insensate joints; and neurovascular, focusing on autonomic dysfunction, with increased blood flow (through arterial-venous shunting) and an imbalance of bone destruction and synthesis.[7]

The classic deformity ("Charcot foot") in a patient with neuropathy is collapse of the midfoot (the tarsometatarsal joint), giving a flat appearance termed a "rocker bottom" foot.[19] The loss of normal architecture in the foot (loss of the medial arch, abnormal foot abduction) results in deformities that cause new pressure points which may lead to ulceration, infections and amputation.[7, 19] This, however, represents a late stage of the condition and patients may present acutely much earlier before any deformity develops, with a hot, swollen, red foot with little or no pain.[7, 19] The foot pulses are usually easily palpable (often bounding), the foot veins may be distended and swelling may extend up to the calf. The differential diagnosis at this stage includes infection (e.g. cellulitis or osteomyelitis), deep venous thrombosis and acute gout.[7, 19] Suspected acute presentation of Charcot arthropathy is considered an emergency, and patients should be promptly referred to a specialist service.

Plain x-rays may be normal in the early stages of the condition, but with time may resemble "osteoarthritis with a vengeance". MRI can be helpful when plain x-rays are normal and can also assist with differentiating between a Charcot joint and osteomyelitis, although making this distinction can be challenging.[19]

Management of a patient with Charcot arthropathy will depend on the stage and severity of the condition and if ulceration or infection is present. Prevention is the optimal treatment, so early identification of patients who may be at risk (e.g. older, diabetes for > 10 years, loss of protective sensation in the foot) is important.[7] Treatment initially includes rest and restrictions on weight-bearing, with immobilisation required in a total contact cast or "moon boot" for some patients. The foot may need to be kept non-weightbearing for up to six months to minimise the development of deformity. Surgery may be required to stabilise the foot, once the acute phase of the arthropathy has settled, with the aim of reducing the prominence of pressure points and to allow ulceration, if present, to heal.[7, 19] Arthrodesis of the affected joints or amputation can be required in patients with severe deformity. Once the acute symptoms have been stabilised, ongoing protective footwear will be required, often for life, which can range from custom inserts in the shoes to various types of braces or walking boots.[19]

Sensory testing in primary care

There are a range of defined clinical tests that are used to assess sensory loss in a patient with suspected peripheral neuropathy – their degrees of sensitivity, specificity, complexity and practicality vary. The most practical test used in a primary care setting is monofilament testing, often with the addition of an assessment for the presence of vibration sensation.[2] It is widely reported that the loss of sensation, tested with a 10 g monofilament, is strongly associated with the subsequent development of ulceration.[18]

Monofilament sensory testing uses a 10 g monofilament to assess a patient's ability to feel light pressure at a number of separate sites on the foot. The New Zealand Society for the Study of Diabetes guidelines suggest the examination of 12 sites in total – six on each foot (Figure 1), although some clinicians believe that fewer sites are required, e.g. four sites on each foot.[18, 20] If the patient cannot detect the light pressure at more than one of the designated testing sites, then loss of protective sensation is deemed to be present.[20]

To perform the test the patient is placed supine with bare feet (or their feet raised on a stool in front of the clinician). The use of the filament should be demonstrated to the patient on their upper arm. Ask them to close their eyes and say "yes" when they can feel the filament. The filament should then be placed against the foot, avoiding areas of callus if possible, and pressed until the patient indicates they can feel it, or until the filament bows (Figure 1). The filament should be pressed against the foot slowly over three seconds, not tapped. Site selection should be random and not predictable by the patient.

N.B. It is recommended that a monofilament is not used on more than ten patients in 24 hours, as they may buckle. The monofilament should also be replaced on a regular basis to ensure it still has a 10 g pressure. In addition, the monofilament should be cleaned with alcohol after each use.

Figure 1: Recommended sites for cutaneous sensory pressure perception testing using a monofilament. Monofilament bent to form a C shape.

Managing diabetic neuropathy in a primary care setting

The primary goal of treatment of diabetic neuropathy is reduction of the patient's symptoms to a tolerable level and prevention of further nerve damage. There is no specific treatment that can reverse nervous system damage in people with diabetic peripheral neuropathy, but good glycaemic control may stabilise or even improve peripheral neuropathy over the long-term.[6] This reinforces the importance of ensuring people with diabetes have been provided with the tools to understand their condition and their ability to self-manage. Management beyond glycaemic control is aimed at controlling symptoms, particularly pain, and improving the patient's quality of life. Protecting insensate feet from trauma is also an important part of the management to avoid the development of ulcers.

Managing glycaemic levels can prevent further damage and control pain

Research has indicated that neuropathic pain in people with both sensory and sensorimotor diabetic neuropathy is associated with periods of erratic glycaemic control.[3] Stabilising and reducing glycaemic levels will benefit the majority of patients, and will help to prevent further nerve damage.[6] There is some evidence that optimal control of glycaemic levels may improve symptoms over time,[6] but this must be weighed against the increased risk from hypoglycaemia and other serious adverse effects.

In people with **acute sensory neuropathy**, stabilising glycaemic levels is the primary goal of treatment. Once stable glycaemia is achieved, severe symptoms will typically resolve in less than 12 months.[3] Reducing the overall glycaemic level is also important to prevent the development of chronic forms of neuropathy and other sequelae associated with hyperglycaemia.

Foot care is essential

Foot care should be assessed and discussed with patients. This may require the input of a Podiatrist, Orthotist or Orthopaedic Surgeon, depending on the level of dysfunction and deformity of the patient's foot. Referral to community podiatry services is recommended for people with intermediate to high risk of foot complications.[20] People with an active lesion, ulceration or infection require urgent referral to a multidisciplinary foot care team.[20]

Appropriate foot wear with cushioning insoles, custom made orthoses and/or supportive shoes is important in protecting

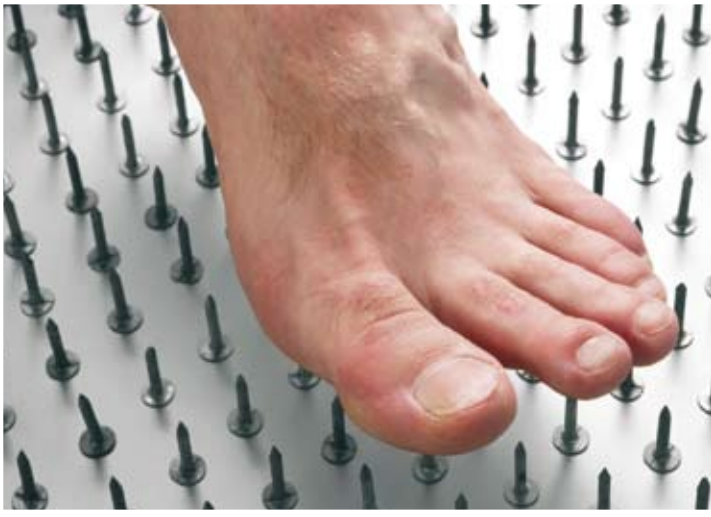
Neuropathy Disability Score

A modified form of the Neuropathy Disability Score (NDS) is a relatively simple, quick clinical assessment tool that aims to combine a number of clinical tests to provide an assessment of the risk of neuropathic ulceration.[3, 17]

The clinical tests used in the modified NDS are:[3]

- **Vibration perception threshold** – Using a 128-Hz tuning fork, can the patient distinguish between vibration/no vibration when the tuning fork is applied to the apex of the big toe? (score 0 if normal, 1 if abnormal)
- **Temperature perception** – Using the tuning fork and a beaker of ice or warm water, can the patient distinguish temperature on the dorsum of the foot? (score 0 if normal, 1 if abnormal)
- **Pin prick testing** – Using a sharp single use neurological examination pin applied proximally to the big toe nail, with just enough pressure to deform the skin, can the patient distinguish between sharp and not sharp? (score 0 if normal, 1 if abnormal)
- **Achilles tendon reflex** – Is the reflex present (score =0), present with reinforcement (score = 1) or absent (score = 2)?

Both feet should be tested and scored independently, and the results added together. The maximum score for the modified NDS is 10, indicating a complete loss of all sensory modalities and absent reflexes. A score of six or more has been found to indicate an increased risk of foot ulceration.[3]



the tissues of an insensate foot from the effects of trauma – which may occur with activities as apparently benign as walking. A simple small pressure area can form a callus which then splits or the skin breaks down to form an ulcer. An unprotected foot can be injured by a small, sharp object or by repetitive rubbing inside an ill-fitted shoe.

Regular foot checks should be performed in all patients with diabetes.

 For further information see: "Screening and management of the diabetic foot", BPJ 31 (Oct, 2010)

Managing neuropathic pain

The pharmacological management of pain secondary to diabetic neuropathy can be challenging due to the multiple potential underlying causes of the pain, and the range and severity of symptoms.[23] Non-pharmacological methods, e.g. exercise, should be trialled alongside medicines for the treatment of neuropathic pain.

Mild neuropathic pain may respond to paracetamol or NSAIDs

Paracetamol or a non-steroidal anti-inflammatory (NSAID) can be considered for patients with mild neuropathic pain.[24] NSAIDs should be used with caution in people with renal impairment, particularly if they are taking an angiotensin converting enzyme inhibitor (ACEI) or angiotension receptor blocker (ARB).

 For further information, see: "NSAIDs: making safer treatment choices", BPJ 55 (Oct, 2014).

Consider the addition of a tricyclic antidepressant or an anticonvulsant

Amitriptyline, nortriptyline, gabapentin, pregabalin or duloxetine are all used in the management of moderate to severe neuropathic pain.[6, 23, 24] However, the treatment of neuropathic pain remains an unapproved indication for tricyclic antidepressants (TCA). Gabapentin requires Special Authority approval for subsidy, following a trial of treatment with a TCA, which has failed due to lack of efficacy or the patient is unable to tolerate the adverse effects.[24] Duloxetine or pregabalin are not currently subsidised in New Zealand.

The choice of treatment should be made after the usual consideration of contraindications, potential adverse effects, interactions with other medicines, co-morbidities, potential benefits for co-morbid conditions (e.g. using an antidepressant as a first choice in a person with diabetes and depression) as well as the patient's preference.[23]

Topical treatment with capsaicin cream, 0.075%, can be considered for people with relatively localised neuropathic pain who do not wish to take, or cannot tolerate, oral treatments.[23] A Cochrane review of capsaicin cream (0.075%), however, suggested that it had little meaningful effect in people with neuropathic pain.[25]

Consider adding an opioid if pain is not controlled

If the pain has not been controlled with a combination of paracetamol, NSAID, a TCA or an anticonvulsant such as gabapentin, consider the addition of a weak opioid, e.g. codeine.[24] Short-term use of tramadol can also be effective for neuropathic pain, as an alternative to codeine.[26] Tramadol can be considered for acute breakthrough pain if required, but should not be used long-term without specialist consultation, or as a first-line monotherapy.[23] Similar restrictions apply to the use of strong opioids, such as morphine.[24]

There is insufficient data to recommend one opioid over another, so the choice should be made based on potency, adverse effects, likelihood of misuse and/or in consultation with a relevant specialist.

 For dosing information for medicines used in neuropathic pain, refer to the New Zealand Formulary: **www.nzf.org**

Exercise may be beneficial for neuropathic pain and peripheral neuropathy in general

There is evidence that exercise combining strength and aerobic activities is beneficial in reducing neuropathic pain, as well as improving function in patients experiencing numbness, weakness and poor balance as a result of diabetic peripheral neuropathy.[27] In addition, exercise is a beneficial lifestyle intervention for patients with diabetes in general and can help to prevent, or delay, diabetic peripheral neuropathy.[27]

It is thought that the most beneficial types of exercise for patients with peripheral neuropathy include strength-stability (e.g. Tai Chi) and aerobic (e.g. walking) activities. Routine exercise has been shown to alleviate neuropathic pain, increase plantar sensation, increase the ability to detect vibrations and improve trunk and ankle proprioception. The exact mechanism by which exercise reduces neuropathic pain requires further investigation, but is thought to involve glial cell activation and the release of noradrenaline and cytokines.[27] Other benefits of exercise include enhanced macro- and micro-vascular health (e.g. improved endothelial function and blood flow, reduced vasoconstriction), reduced risk of hypertension, atherosclerosis and other cardiovascular conditions, increased muscle strength and reduced glycaemic levels.[27]

Managing autonomic neuropathic symptoms

Autonomic neuropathic symptoms are likely to be present in many patients with diabetic peripheral neuropathy. Features of diabetic autonomic neuropathy can relate to one or more organ systems, e.g. cardiovascular, gastrointestinal, genitourinary, sudomotor or ocular (Page 39).[14] Therefore management is individual, depending on which symptoms are present, but always involves maintaining optimal control of diabetes.

When to refer patients with neuropathy

Patients with atypical features or who fail to respond to management strategies should be referred to a Neurologist for further investigation. This includes patients with:[4, 23]

- Pronounced asymmetry of the neurologic deficits
- Predominant motor deficits, mononeuropathy or cranial nerve involvement
- Rapid development or progression of neuropathic impairment
- Progression of the neuropathy despite optimal glycaemic control
- Symptoms arising in the upper limbs
- Proximal weakness
- Significant sensory ataxia
- Family history of non-diabetic neuropathy
- Pain that is difficult to manage, limiting the patient's lifestyle and daily activities or if their underlying health has deteriorated as a result

Alternative causes of peripheral neuropathy in a person with diabetes

Diabetes is the primary cause of peripheral neuropathy in more than 90% of people with diabetes who develop peripheral neuropathy.[3] However, it is important in any patient with suspected diabetic neuropathy to ensure that diabetes, and not an alternative condition, is causing the neuropathy.

There are a wide range of conditions, genetic abnormalities and environmental factors that can cause damage to the peripheral nervous system. Peripheral neuropathy can be broadly classified into two groups: acquired or inherited. Acquired neuropathies are more common and more likely to be encountered in primary care. They generally arise from three sources; physical trauma, systemic disease or infections and autoimmune conditions.

Clinically there are few differentiating symptoms between the various causes of neuropathy. In some situations, there will be a clear cause apparent in the patient's history, e.g. a history of alcohol misuse or recent trauma. Patients who have any mononeuropathy, evidence of a neuropathy with an asymmetrical distribution or an acute onset of symptoms are more likely to have a cause other than diabetes for their neuropathy – although diabetes can cause isolated mononeuropathies, e.g. a third cranial nerve palsy or lumbosacral radiculoplexus neuropathy (diabetic amyotrophy).

Acquired neuropathy

Traumatic neuropathy

Physical injury is a common cause of peripheral nerve damage and, if present in the history, is the most likely cause of a neuropathy. Traumatic neuropathy occurs when the nerve is partially or completely severed, crushed, compressed or stretched during an injury.

Referral will often be required for surgical management or rehabilitation, and symptomatic treatment of pain may also be required.

Autoimmune and infectious neuropathy

Neuropathy can develop as a result of the inflammatory response of the body to many immune triggers, including infection. A classic example of this in an acute illness is Guillain-Barre syndrome.[28] CIDP may be considered a more chronic version of a similar disease process which,

although relatively rare, may be over represented in people with diabetes.[9] CIDP should be suspected if a patient with diabetic neuropathy has proximal or both proximal and distal weakness, early or marked upper limb involvement, severe sensory ataxia or continued rapid progression despite reasonable glycaemic control. The patient should be referred to secondary care and further testing with electrodiagnosis and CSF protein levels undertaken. In some cases of CIDP, immunomodulatory therapy can produce a rapid and substantial improvement so making an accurate and early diagnosis is important.[9]

Viruses and bacteria can damage nerve tissue, usually sensory fibres, leading to a painful neuropathy. The most common example of this is herpes varicella-zoster. Less commonly, Epstein-Barr virus, cytomegalovirus and herpes simplex virus can also cause damage to the peripheral nervous system, mostly in immunocompromised patients.[28]

Most infective neuropathies tend to be asymmetrical in distribution rather than symmetric and have an acute onset corresponding with a history of infection, however, HIV-derived neuropathies may present in a similar way to symmetric distal neuropathy in people with diabetes, e.g. insidious, distal symmetrical with a limited history of infection.[28]

Systemic causes of peripheral neuropathy

In addition to diabetes, many other systemic metabolic, haematological and endocrine disorders, such as chronic liver disease, alcoholism, renal failure, nutrient deficiencies, paraproteinaemic disorders and thyroid dysfunction can cause peripheral neuropathy. Nerve damage in people with systemic disorders usually occurs due to impairment of nutrient transfer, waste product removal or manufacture of necessary tissue products. Clinical and biochemical vitamin B12 deficiency is common in people with diabetes,[29] and metformin can reduce B12 absorption. It is still unclear, however, if metformin treatment results in a clinically significant deficiency, as a peripheral neuropathy caused by vitamin B12 deficiency is clinically indistinguishable from that caused by diabetes.[29] Regardless of the mechanism an assessment of vitamin B12 levels should form part of the work-up in a person with diabetes and peripheral neuropathy.

Other causes

Many medicines can cause or contribute to neuropathies, e.g. anti-infectives such as chloroquine, metronidazole and nitrofurantoin; cardiovascular medicines, such as amiodarone; chemotherapy agents; colchicine; and phenytoin.[12]

In addition, neuropathy may sometimes be idiopathic (estimates are up to 20%, even in specialist centres), i.e. no identifiable cause.

Inherited neuropathy

Hereditary neuropathies range from mild conditions with symptoms which arise in early adulthood to severe conditions, present from birth or infancy, that cause significant disability. The most common inherited peripheral neuropathies are a group of conditions known as Charcot-Marie-Tooth disease which arise from gene mutations that code for neuronal proteins – primarily affecting the myelin sheath but also the axon. A positive family history, with an insidious onset, very gradual progression, a lack of sensory symptoms despite clear sensory signs and the presence of pes cavus (high arched foot) suggest an inherited process.

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Fluoxetine brand change:
Arrow-Fluoxetine sole subsidised brand from 1 July

Reminder: Most broad-spectrum antibiotics do not interact with combined oral contraceptives*

In 2011, United Kingdom guidelines were updated to remove the advice regarding the need for additional contraceptive precautions during courses of antibiotic treatment in women who are taking a combined oral contraceptive. This followed similar changes from the World Health Organisation in 2010. Bpac[nz] reported on this in June, 2011.

See: "New recommendations advise that the majority of broad-spectrum antibiotics do not affect the contraceptive effectiveness of the combined oral contraceptive", News in Brief, BPJ 36 (Jun, 2011).

> The majority of broad-spectrum antibiotics do not reduce the effectiveness of combined oral contraceptives and it is no longer necessary to advise women using a combined oral contraceptive and requiring a course of antibiotics to use additional contraceptive precautions.

This advice does not apply to every antibiotic and every situation:

- Women taking enzyme-inducing antibiotics, such as rifampicin and rifabutin, do require additional contraceptive precautions (see "Advice for women taking enzyme-inducing antibiotics")
- If an antibiotic causes vomiting or diarrhoea women should be advised to follow the "seven day rule", which refers to advice to use other methods of contraception (e.g. condoms or abstinence) during the period of illness and until seven active pills have been taken.

* This advice does not apply to enzyme inducing antibiotics such as rifampicin and rifabutin.

As the advice to use additional contraceptive methods with antibiotic treatment has been standard practice for many years, health professionals may find a reminder on the new advice helpful. In addition, many manufacturers have not updated their datasheets to reflect this information, which may be a source of confusion for both patients and health professionals.

Evidence for the change in advice

The ethinyloestradiol component of the combined hormonal contraceptive undergoes enterohepatic recirculation. This means it is metabolised in the liver and conjugated with glucuronide to form inactive conjugates, which are then excreted in the bile. Gastrointestinal bacteria cleave these conjugates and the oestrogen is reabsorbed.

The original theory was that if these bacteria are suppressed by the use of an antibiotic, the conjugates are not cleaved and therefore poorly absorbed, resulting in lower than normal concentrations of ethinyloestradiol and contraceptive failure.[1] However, evidence has accumulated suggesting that enterohepatic metabolism of ethinyloestradiol is not clinically important.[1]

Direct evidence

Several studies looking at combined oral contraceptives administered in conjunction with a range of non-enzyme inducing antibiotics have not shown any decrease in ethinyloestradiol levels.[2, 3] One study found that ciprofloxacin did not affect serum concentrations of gonadotrophins when used in combination with a combined oral contraceptive, and two other studies found no evidence of ovulation following

the combination of hormonal contraception and ciprofloxacin or ofloxacin (not available in New Zealand).[4, 5]

Indirect evidence

Other studies indirectly support the lack of a causal relationship between antibiotic use and contraceptive failure, e.g.:

- Serum contraceptive steroid levels and combined oral contraceptive efficacy do not appear to be affected in women with an ileostomy following lower bowel surgery, in whom enterohepatic circulation of ethinyloestradiol does not occur.[6]
- Most of the reports of contraceptive failure with antibiotic use comes from a time when ethinyloestradiol doses were higher (e.g. 50 micrograms). Currently ethinyloestradiol doses as low as 20 micrograms are considered to be an effective contraceptive so it seems unlikely that the small reduction in ethinyloestradiol levels following antibiotic use when using 30 to 50 microgram preparations would have resulted in contraceptive failure.[1]
- Reports of pregnancies have occurred in women taking erythromycin and fluconazole which actually increase levels of ethinyloestradiol.[1]

Alternative reasons for the anecdotal reports of contraceptive failure following antibiotic use could be:

- Contraceptive failure due to vomiting or diarrhoea induced by the antibiotic, or failure to take the contraceptive properly during a period of illness
- The total number of contraceptive failures is small when compared to the numbers of women worldwide using combined hormonal contraception. Given that there is an expected failure rate for oral contraceptives, the pregnancies that do occur when women are taking antibiotics are likely to be simply coincidental.[1]

While a cautious approach is often recommended in medicine, in this case, it is possible that these sorts of precautions may actually confuse patients, complicate pill taking and could have the opposite effect of increasing the failure rate of hormonal contraceptives.[7]

Advice for women taking enzyme-inducing antibiotics

The effectiveness of combined oral contraceptives (and other hormonal contraceptives) can be considerably reduced by the co-administration of medicines that induce hepatic enzymes, including the antibiotics rifampicin and rifabutin.

For short courses of rifampicin or rifabutin (two months or less), continue with a combined oral contraceptive containing ethinyloestradiol 30 micrograms or more daily and use a "tricycling" regimen, i.e. taking three packets of tablets without a break, followed by a shortened tablet-free interval of four days. Additional contraceptive precautions are required while taking rifampicin or rifabutin and for four weeks after stopping.

For a long-term course (over two months) of rifampicin or rifabutin, an alternative method of contraception (such as an IUD) is recommended and should also be continued for four weeks after stopping the enzyme-inducing medicine.

For more detailed contraceptive advice for women using enzyme inducing drugs, see: **www.nzf.org.nz/nzf_4164.html**

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Oseltamivir (Tamiflu) and Zanamivir (Relenza): Are they actually effective?

Many governments and health authorities throughout the world have stockpiled the neuraminidase inhibitors, oseltamivir and zanamivir in preparation for an influenza pandemic. The decision to stockpile these medicines was based on the belief that they reduced the duration of influenza and prevented hospital admissions and complications, such as pneumonia. The available evidence in 2009, when the decision was made, included only manufacturer-sponsored trials and this evidence was incomplete at that time. New evidence suggests these medicines may not be as effective as previously thought.

New evidence is now available

Oseltamivir

A recent systematic review , published in April, 2014, looked at the available evidence for the efficacy of oseltamivir for influenza illness, including previously unseen complete reports from the original research carried out by the manufacturers Roche and GlaxoSmithKline.[1] The review found that compared to placebo, oseltamivir led to a quicker alleviation of influenza-like symptoms, approximately half a day sooner in adults (from seven days to 6.3 days), but it was unclear if this was the case in children. There was no evidence of a reduction in hospital admissions or serious influenza complications, such as confirmed pneumonia, bronchitis, sinusitis or ear infection in either adults or children. There was also an increased incidence of adverse effects including nausea and vomiting (5% in children and 4% in adults). There was no evidence that oseltamivir prevented person-to-person transmission of influenza.[1]

Zanamivir

The findings for zanamivir were similar.[2] There was a reduction in the time to symptomatic improvement in adults (but not children) by approximately half a day, however, this effect could be attenuated by symptom relief medicines, i.e. symptoms were not better in the treatment arm when compared with symptoms in people in the placebo group taking relief medicines. There was no evidence that zanamavir reduced the risk of complications, particularly pneumonia, or the risk of hospital admission or death. Its use was not associated with a significant risk of harm, but there were occasional reports of bronchospasm.[2]

To sum up: Benefits of oseltamivir and zanamivir appear to be modest

The benefits of both oseltamivir and zanamivir appear to be modest at best, and these benefits must be balanced against the possibility of adverse effects occurring, such as nausea and vomiting.

Treatment for future pandemics?

What this data does not tell us is how well these medicines are likely to perform in a pandemic. The data included in the systematic reviews was for the treatment of seasonal influenza with oseltamivir and zanamivir.[1, 2] More recent observational data collected in 2009 and 2010, during the "swine flu" pandemic suggests that neuraminidase inhibitors are effective for managing people admitted to hospital with severe influenza.[3] These researchers found that neuraminidase inhibitors reduced mortality and that early treatment was associated with a reduction in mortality risk compared with late treatment.[3]

However, others have questioned the robustness of this data, suggesting that the methodology may not have been adequate.[4] It is also suggested that, as influenza is a predictable seasonal threat which poses serious risk to people, particularly those with co-morbidities, adequately designed research is required to fully address whether these medicines are worth the billions of dollars spent on stockpiling them.[4]

Freemantle *et al*[4] concludes: "*Influenza is a predictable threat that occurs every year, and people with co-morbidities face potentially serious consequences as a result. Requiring or facilitating adequately designed research would be in the public interest, and public funding mechanisms have failed in their duty of care towards patients*."

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Emergency contraception: potential problems in overweight women?

Recent evidence suggests that the efficacy of levonorgestrel, a widely used emergency contraceptive pill, is significantly lower in women weighing greater than 70 kg. Medsafe, in conjunction with the Australian Therapeutic Goods Administration (TGA), are continuing to evaluate this efficacy concern and a review is expected soon.[1] There are no specific recommendations from Medsafe or the TGA for action at this time.

The most common form of emergency contraception in New Zealand is levonorgestrel, administered at a single 1.5 g dose. It is estimated that the emergency contraceptive pill (ECP) prevents 85% of pregnancies that may have occurred if taken within the first 48 hours after intercourse.[2] The efficacy drops significantly, to 58%, when used between 48 and 72 hours.[2] The ECP may be used up to 96 hours after unprotected intercourse, but efficacy is uncertain during this time period (between 72 and 96 hours).[3]

There is some evidence that the efficacy of the ECP may be reduced in women who are overweight. Manufacturers of a levonorgestrel-containing ECP available in Europe stated that: "In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more, and levonorgestrel was not effective in women who weighed more than 80 kg".[4] This has prompted the European Medicines Agency to start a review of emergency contraceptives, levonorgestrel and ulipristal (not available in New Zealand) to assess whether increased bodyweight and body mass index (BMI) reduce the efficacy of these medicines.[5]

This finding is supported by earlier evidence that the efficacy of levonorgestrel is affected by BMI. Clinical trials found that the risk of pregnancy was doubled in overweight women (BMI 25 – 29.9 kg/m^2) taking levonorgestrel compared with normal or underweight women.[6] Obese women (BMI ≥30 kg/m^2) were four times more likely to become pregnant following use of levonorgestrel as emergency contraception compared with normal or underweight women. Using computer modelling predictive techniques based on clinical trial data, researchers found that pregnancy rates following use of levonorgestrel would be the same as for a woman with a BMI of 26 kg/m^2 who used no emergency contraception, and the limit of efficacy for levonorgestrel ECP was reached at a body weight of 70 kg.[6]

However, researchers noted that there were several limitations to their study, including that:[6]

- The data came from clinical trials that were not designed to explore the effect of body weight or BMI on the efficacy of levonorgestrel ECPs
- The number of women in the studies with a BMI greater than 35 kg/m^2 was small,
- The number of pregnancies in women in this weight range was extremely small

Current advice still stands

Until further evidence is available, and pending review by Medsafe and the TGA, the overall benefit-risk balance of levonorgestrel remains positive and there is no change in advice for women who have had unprotected intercourse. All women, regardless of weight, should be advised to use emergency contraception as soon as possible following unprotected intercourse.[1] This includes using the ECP in women who are overweight or obese, as this is often the most practical method of emergency contraception; however, it is important to explain the possible increased risk of pregnancy. Insertion of an intrauterine device (IUD) within five days can be recommended to women who are particularly concerned, but access to a clinic offering this service may not be available in all areas within the necessary time period.

Another risk factor for emergency contraception failure is further episodes of unprotected intercourse following use of emergency contraception. One study found that women who had unprotected intercourse after using emergency contraception were more than four times as likely to become pregnant compared with those who did not report further unprotected intercourse after using emergency contraception.[6] Therefore, it is important to advise women about ongoing contraceptive needs and recommend barrier methods of contraception after using emergency contraception.

Women prescribed or supplied emergency contraception should be provided with the following additional advice:[3]

- That their next menstrual period may be early or late
- To seek medical attention promptly if any lower abdominal pain occurs; this may indicate an ectopic pregnancy
- To return in three to four weeks if their subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if there is any doubt as to whether menstruation has occurred. In these cases, a pregnancy test should be performed at least three weeks after unprotected intercourse.

Copper intrauterine device (IUD) for emergency contraception

Insertion of a copper IUD is more effective than oral levonorgestrel for emergency contraception, if inserted within 120 hours (five days) after unprotected intercourse. If intercourse has occurred more than five days previously, the device can still be inserted up to five days after the earliest likely calculated date of ovulation, regardless of the number of episodes of unprotected intercourse earlier in the cycle.[3]

Some women may consider a copper IUD for emergency contraception, especially if they weigh more than 70 kg and had protected intercourse close to ovulation, and would benefit from the ongoing, long-term contraceptive effect.[7]

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Allopurinol dosing in renal impairment

Dear Editor

In the recent article entitled "Managing patients with renal colic in primary care: Know when to hold them", BPJ 60 (Apr, 2014), it states: "Allopurinol is indicated for the prophylaxis and treatment of patients with either urate or calcium oxalate stones...Lower doses of allopurinol are recommended for patients with estimated glomerular filtration rates less than 60 mL/min/1.73m^2."

Dr Linda Bryant, in a December 2011 article in the Journal of Primary Health Care states: "Treat the target serum uric acid concentration rather than according to renal function. This has been shown to be safe and effective"

Your comments please.

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In 1984 a seminal paper on allopurinol toxicity in patients with renal insufficiency was published.[1] For many years this study served as the basis for allopurinol dosing guidelines due to its conclusion that there is a direct relationship between severe allopurinol toxicity and decreased creatinine clearance. Dr Bryant quite rightly points out in the article "Allopurinol – dose according to effect, not renal function" that current guidelines no longer support allopurinol dose adjustments based on the study from 1984.[2] Our renal colic article did not cover allopurinol dosing in any detail, however, this change in practice was highlighted in our article "An update on the management of gout" BPJ 51 (Mar, 2013) by the statement:

"*…recent evidence has shown no increase in serious toxicity with higher doses of allopurinol.*" Nonetheless, renal function should still be carefully considered for safety reasons when initiating allopurinol in patients with gout. A "start low and go slow" method of titrating the patient's allopurinol dose is recommended to avoid adverse reactions; mainly skin, subcutaneous and immune system reactions, as well as reducing the likelihood of precipitating gout attacks.

The majority (70%) of the active metabolite of allopurinol, oxypurinol, is excreted by the kidneys.[3] In patients with renal impairment, oxypurinol accumulates due to inadequate renal clearance.[4] In some patients, accumulated levels of oxypurinol may contribute to delayed hypersensitivity reactions, referred to as the allopurinol hypersensitivity syndrome (AHS). This is a rare but serious adverse effect of allopurinol treatment, characterised by rash, eosinophilia, leukocytosis, fever, hepatitis and renal failure.[5] AHS is reported to occur in 0.1% to 0.4% of patients taking allopurinol and is reported to have a mortality rate of over 25%.[4] In March 2014, Medsafe added allopurinol to the medicines monitoring scheme due to concerns about lichenoid-type (medicine-induced) skin reactions.[6]

Risk factors for AHS include:[4, 5]

- Initiation of allopurinol treatment within the last four to six weeks
- Renal impairment
- A high starting dose of allopurinol relative to renal function
- The HLA-B5801 genotype that is most prevalent in people of Asian descent

The clinical significance of reduced renal function in patients taking allopurinol is emphasised by international estimates that between 40% to 50% of patients with gout also have chronic kidney disease (CKD).[4]

Dr Bryant largely bases the recommendation to focus less on renal function when dosing allopurinol on a study published by Stamp *et al*, 2011, which concluded that "*increasing the dose of allopurinol above the proposed creatinine clearance-based dose led to a significant reduction in the serum urate concentration.*"[7] However, there is one important point to note about the patients in this study: the patients with gout who were recruited had already been receiving a stable dose of allopurinol for at least one month. Therefore, one important risk factor for AHS, i.e. the recent initiation of allopurinol, was excluded from the patient cohort. In 2012, Stamp *et al* published another study showing that a high starting dose of allopurinol relative to renal function was also a risk factor for AHS.[5] This paper suggested starting doses for patients with reduced renal function, and these were published in our 2013, BPJ article "An update on the management of gout".[5]

Stamp *et al*, 2012, concluded: "*In summary, we have shown that the starting dose of allopurinol is an important risk factor for the development of AHS… Progressive up-titration of allopurinol is not associated with an increased risk of AHS, and once allopurinol treatment is established, this strategy should be adopted to achieve the target serum urate level.*"[5]

Renal function is therefore an important factor in determining the starting dose of allopurinol, from which point doses can then be slowly and relatively safely titrated upwards, until the patient achieves the target serum uric acid concentration of less than 0.36 mmol/L. Dr Bryant suggests starting all patients with gout on allopurinol 150 mg, daily, and doubling the dose to 300 mg, daily, after four weeks.[2] However, according to Stamp *et al*, 2012, this starting dose is only appropriate for patients with a estimated glomerular filtration rate (eGFR) of 91 – 130 mL/min/1.73m^2.[5] For example, the appropriate starting dose for a patient with an eGFR of between 46 – 60 mL/min/1.73m^2 is allopurinol 50 mg, alternating with allopurinol 100 mg, every other day.[5]

The challenge for the clinician when prescribing allopurinol to a patient with reduced renal function is to lower the serum urate level in order to prevent either attacks of gout or kidney stone formation, without the occurrence of the hypersensitivity reactions that are more likely to occur within the first six weeks of starting the medicine. A one-size fits all approach to dosing of allopurinol treatment is unlikely to achieve this goal and may put some patients at risk; treatment should be individualised.

In regards to the management of urinary stones – lifestyle measures are first-line in the prevention of urinary stone formation, e.g. increasing water intake, reducing salt intake and avoiding foods rich in oxalate and fructose-containing soft

drinks. The majority of urinary stones contain calcium oxalate, and potassium citrate is subsidised under Special Authority for patients with recurrent calcium oxalate urinary stones. Allopurinol should be reserved for patients with either calcium oxalate or urate stones, and elevated serum urate levels.[8] There is currently no consensus on what the target serum urate level should be when treating patients with a history of urinary stones. Any reduction in serum urate is likely to be beneficial, but a reasonable approach would be to treat to a target serum urate level less than 0.36 mmol/L. Serum urate, creatinine and LFTs should be monitored during allopurinol dose titration.

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Non-pharmacological management of pain

Dear Editor

Reading the March issue of Best Practice Journal, regarding managing pain in children, I was prompted to write about another useful tool - smartphone games. I was recently able to remove some very large splinters from a young boy's foot while he was absorbed in a game. Before we thought of this he would not keep still enough, but while playing he barely felt it.

I have also had an anxious adult patient use similar games to keep her mind off minor surgery, and it would probably also work for immunisations!

Dr Joanna Joseph
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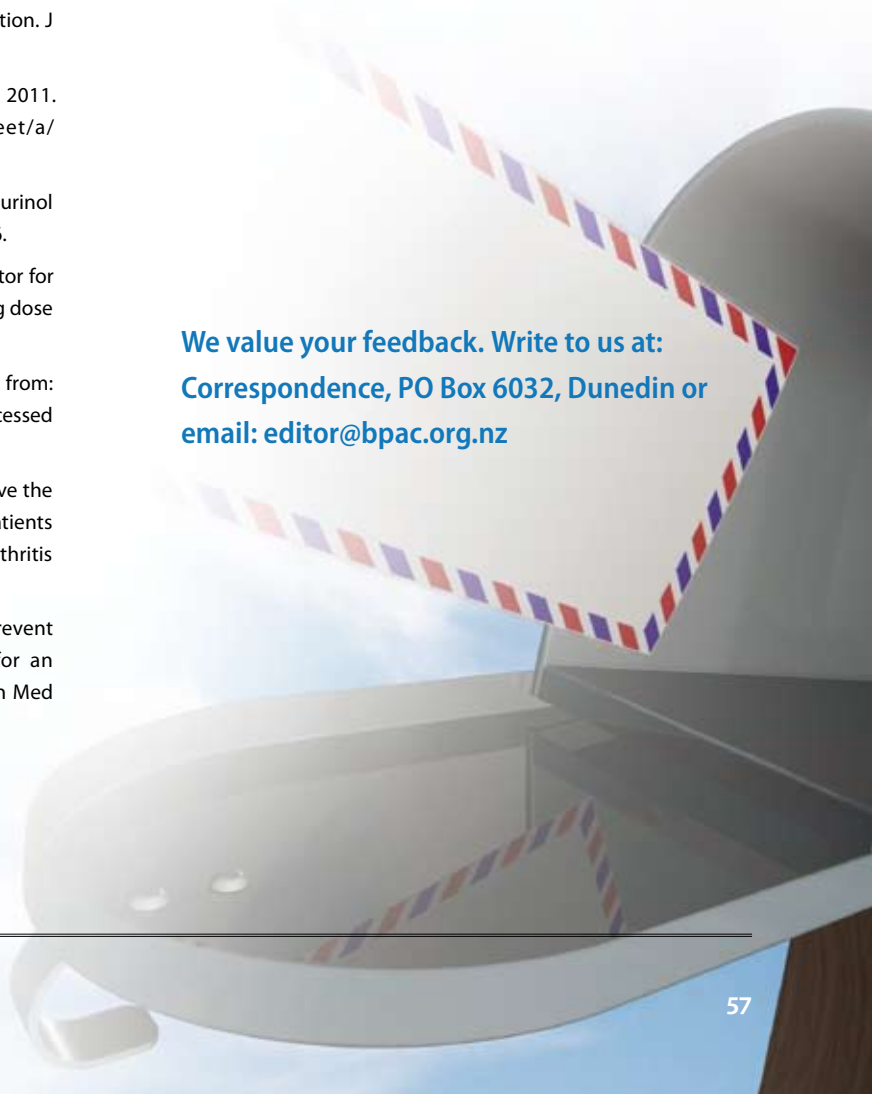
Thank you for your contribution. We would love to hear about "Best Practice Tips", on any subject, from our readers.



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