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16

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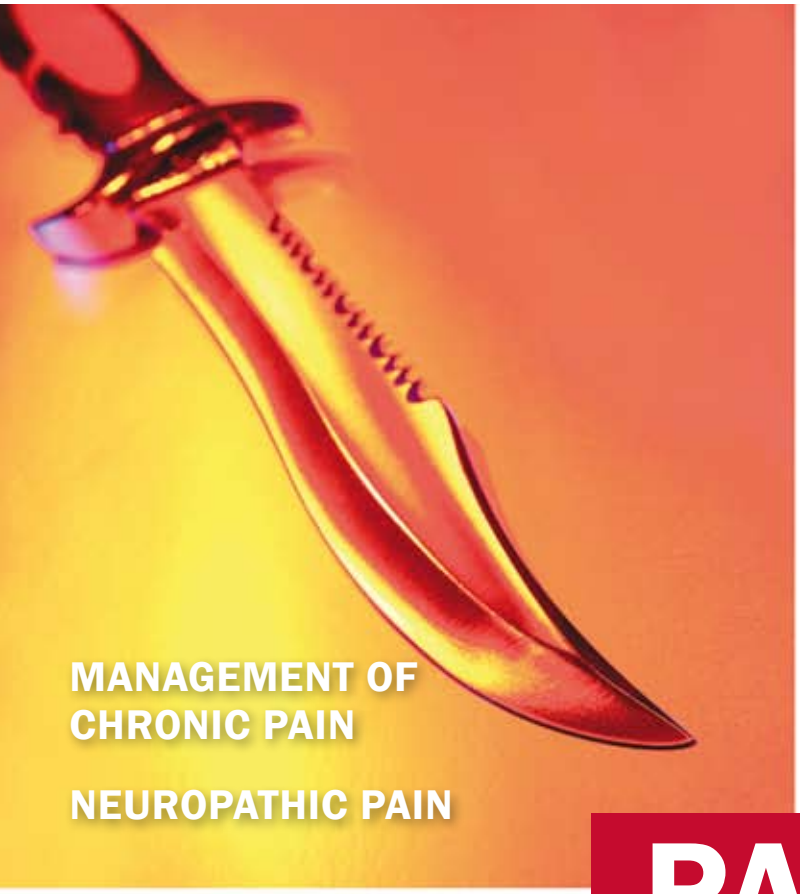
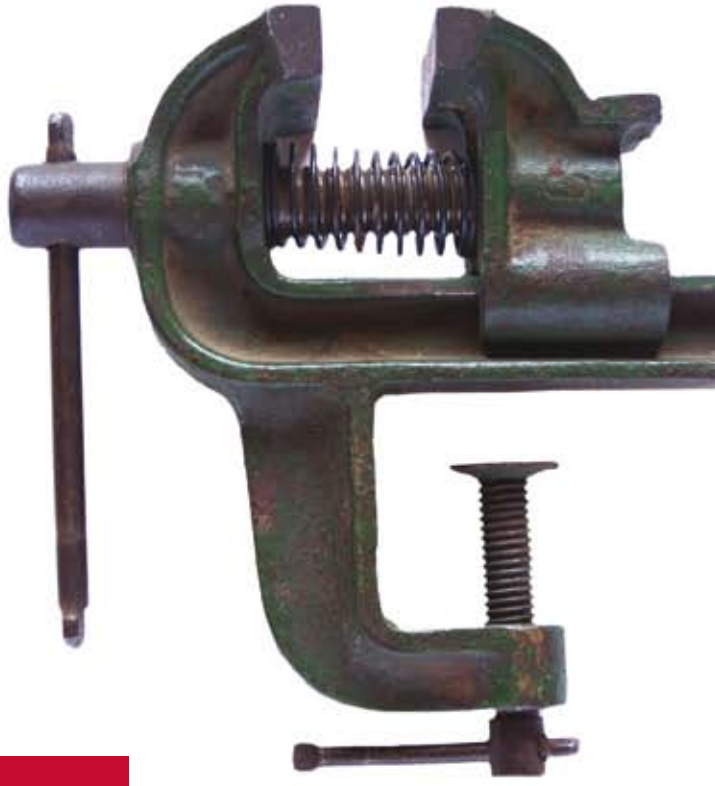


MANAGEMENT OF CHRONIC PAIN

NEUROPATHIC PAIN



PAIN

THE PROBLEM OF PAIN MEMORY

DRUG MISUSE

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INTRODUCTION

IN THIS EDITION OF BPJ we concentrate on the topic of chronic pain. This is one area of medicine that is rarely taught formally and many of us remain unsure about how to manage pain without causing possible harm to our patients through adverse effects such as addiction or respiratory depression.

Chronic pain is often a hidden problem. Many patients do not talk about this spontaneously and therefore pain is generally under diagnosed and under treated. Management of chronic pain includes asking if patients have pain, an assessment of severity and detailed diagnosis of where the pain is originating from. Pharmacological management of pain depends on the type of pain.

Most pain will have some response to paracetamol. The next steps depend on the type of pain diagnosed, either nociceptive (from damage to the tissues) or neuropathic (from damage to the nerves). The WHO analgesic ladder is the worldwide standard for treatment of nociceptive pain and provides a step wise approach to analgesia. There are similar step-wise approaches to the management of neuropathic pain.

Management of chronic pain may include swapping from one opioid to another. Several different opioids are available in New Zealand. A newer formulation becoming available for general practitioner prescribing is fentanyl patches. In all cases a simple approach can be used to move between these medications.

These step-wise approaches to prescribing do not cover all the issues in chronic pain management. Psychological and supportive strategies are a significant part of chronic pain care. They are particularly important in the management of pain memory (persistent central sensitisation pain), chronic pain in drug seekers and medication overuse headache.

Finally we look at Crohn's disease and ulcerative colitis, two types of inflammatory bowel disease, covering the general practitioner's role in initial suspicion, when to refer and ongoing management.

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The **nature** of our **nurture**

genes x environment = human behaviour

Key contributor: **Professor Richie Poulton**, Director, Dunedin Multidisciplinary Health and Development Research Unit.

WHY IS IT THAT TWO PEOPLE who experience the same adversity can differ so markedly in their response? The answer to this question is a complex interplay between nature and nurture, or more technically a gene-environment interaction. To understand why people turn out the way they do (in terms of physical disease or behavioural outcomes) information about their genetic makeup needs to be carefully considered alongside information about what has happened to them during their lives.

Professor Richie Poulton and his team of researchers from the Dunedin Multidisciplinary Health and Development Study have made several key findings that reveal the way that genes and the environment work together. Their research confirms the importance of considering and managing factors within a patient's lifestyle and background that may contribute to their medical problem. Conversely, a negative environment or a risk identified in family history, does not necessarily mean that a negative outcome is certain. This is an area in which GPs can make a significant difference.

Life stress and depression

The Dunedin Study researchers have discovered that a variation in the serotonin transporter gene interacts with life stress to predict depression.[1] What this means is that people who have the short version of this gene are more likely to develop depression if they are exposed to stressful life events, than those who have the long version and who are more resilient. Ultimately this may lead to the development of new and hopefully more effective treatments for depression.

Childhood maltreatment and violence

The researchers have also discovered that adult violence and antisocial behaviour in males can be predicted by an interaction between childhood maltreatment and a variation in the gene that produces the enzyme monoamine oxidase.[2] What this means is that badly treated boys with this gene variation, are more likely to become violent adults than boys who are also badly treated, but do not have this gene variation.

Adolescent cannabis use and psychosis

The third finding by the team was that the development of psychosis following use of cannabis during adolescence is linked to a variation in the catechol-O-methyltransferase (COMT) gene, which helps control the action of dopamine.[3] What this means is that teenagers who use cannabis

and who also carry this gene variation, are more likely to develop illnesses such as schizophrenia as adults. This finding was unique in that it involved an additional factor – age of exposure. Cannabis use in adulthood did not elevate the risk for developing psychosis, even in the presence of the COMT gene variation.

Breast feeding and IQ

More recently, the Dunedin Study team reported that the association between breastfeeding and children's IQ depends, in part, on the baby's genotype in a gene called FADS2.[4] This gene influences how the body processes fatty acids consumed through diet. For over 100 years IQ has been at the heart of scientific and public debates about nature versus nurture. This finding clearly shows that genes may work via the environment to shape IQ.

Evidence that nature and nurture work together drives several nails into the coffin of the often bitter and largely obsolete nature-versus-nurture debate. Clearly, genes are not a blueprint or deterministic; rather they help to shape how our bodies and brains respond to our environment.

It is perhaps ironic then that this cutting-edge genetic research goes full circle to emphasise the importance of the environment. "In all the studies described above, the genes by themselves told us nothing. It was only when we looked at the genes working in association with environmental influences that we were able to predict outcomes. This justifies attempts to manipulate the environment to create better outcomes."

Modifying the environment in a positive way remains the key for influencing how people's lives turn out. This is particularly important when we cannot rely on pharmaceuticals for treating behaviours such as violence and aggression. Effectively tinkering with genes to achieve desired outcomes remains a long way off. Right now, however, that is not necessary. The environment is where the action is.

Acknowledgement

Thank you to Professor Richie Poulton, Director, Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive & Social Medicine, Dunedin School of Medicine, University of Otago, for significant contribution to this article.

"The Dunedin study"

The Dunedin Multidisciplinary Health and Development study is a longitudinal study of over 1000 infants that have been followed for the past thirty-six years. Three new generational studies now exist, involving the parents and children of original study members. More than 1000 publications have been produced from the study since it started. The work of the Dunedin Study has influenced family, child and public health policies in New Zealand and around the world and continues to do so. Their research about depression was rated as the second most important worldwide scientific breakthrough in 2003. Many of the findings are relevant for clinicians, parents, families and others who are making decisions about health and well-being of their patients and family.

References

1. Caspi A, Sugden K, Moffitt TE, et al. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.
2. Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. Science 2002;297:851-854.
3. Caspi A, Moffitt TE, Cannon M, et al. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the COMT gene: Longitudinal evidence of a gene x environment interaction. Biol Psych 2005; 57:1117-27.
4. Caspi A, Williams B, Kim-Cohen J, et al. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. Proc Natl Acad Sci U S A. 2007;104(47):18860-5.

Pharmacological **management** of chronic **pain**

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Key concepts

- Ask about pain
- Diagnose the type of pain (nociceptive or neuropathic) and the source of pain
- Use individualised pain scales to assess the severity of pain and its affect on function
- Manage pain using the WHO analgesic ladder – moving from simple non-opioid analgesia up to potent opioids
- Remember "ABC" when prescribing opioids – consider prescribing an **antiemetic** for nausea, prescribe **breakthrough** pain doses and prescribe laxatives for **constipation**

Further reading: Chronic Pain: A Primary Care Condition. Available from **www.arc.org.uk**

Understanding pain

Pain is a common problem. Patients tell us if they have acute pain they are often vocal, upset and asking for help. In contrast, chronic pain is often hidden and unless we ask patients we may not find out they are in pain. The burden of chronic pain is in its impact on daily life.

"Think of pain as the fifth vital sign"

Managing pain includes helping the patient understand why they have pain, creating realistic expectations for relief and treating the pain.

Although not covered in this article, the psychological aspects of care are paramount. Factors such as anxiety and depression, which may reduce tolerance to pain or be exacerbated by pain, must also be assessed and treated.

There are two types of pain

From a practical point of view, pain is either generated by damage to the nerves (neuropathic pain), or by damage to other tissues (nociceptive pain). The anatomical source of the pain should be identified and this will then guide treatment. It is important to be aware that people can have more than one source or type of pain at one time.

The relationship between a painful stimulus and the experience of pain is extremely complex. Modification of the stimulus occurs in the peripheral and central nervous systems. The final perception of pain is strongly influenced by emotion and cognition.

Recognition of pain

Ask.

Diagnosis of pain

Ask more.

- How bad is the pain?
- Where is it? Does it go anywhere?
- What makes the pain worse? What makes it better?
- How is the pain described? e.g. dull, sharp
- How does it impact on daily life?

Signs of pain in people with communication difficulties[1]

For people with communication difficulties (e.g. dementia, confusion, coma, learning difficulty) diagnosing pain may not be as simple as asking them. Pain can cause a variety of behaviours and signs. Change in behaviour is a key indicator.

Examples of pain behaviours and signs:

Expressive: grimacing, clenched teeth, frowning, eyes open wide or shut, crying, sighing, moaning.

Adaptive: rubbing or holding area, keeping area still.

Distractive: rocking, pacing, biting, clenching fists.

Postural: flinching, head in hands, limping.

There are separate pain scales for children and for patients in intensive care and long term care facilities.

Pain scales can help to determine severity

Pain is what the patient says it is. It cannot be measured directly but pain scales may be used to assess severity. The most clinically useful pain scales include an assessment of impact on daily life.

An example of this is the Support Team Assessment Schedule (STAS) pain module[2]

Measurement of effect of pain on patient:

4 = Severe and continuous overwhelming pain. Unable to think of other matters.

3 = Severe pain often present. Activities and concentration markedly affected by pain.

2 = Moderate distress, occasional bad days, pain limits some activities.

1 = Occasional grumbling, single pain. Patient not bothered to be rid of symptom.

0 = None.

Scales can be made even more useful if they are personalised. For example, in the case of a patient with severe arthritis in their hip, level four could be continuous pain day and night with the patient being unable to sleep, level three could be the patient is able to sleep but is still troubled with pain while they are awake and so on. These scales can be used to set individual goals.

Other commonly used pain assessment tools include:[3]

- Numerical rating scale: pain is rated on a scale from 0 (no pain) to 10 (worst pain imaginable).
- Verbal rating scale: a four-point scale in which pain is rated as none, mild, moderate or severe.
- Visual analogue scale: an unmarked line with “no pain” at one end and “worst pain imaginable” at the other end.
- Faces pain scale: There are several versions available showing smiling or neutral faces for no pain and sad or crying faces indicative of severe pain.

So what is causing the pain?

In order to manage pain, work out which tissue the pain is coming from. At its simplest, this divides neuropathic pain from nociceptive pain. Nociceptive pain then needs to be diagnosed further using the same process as with any differential diagnosis.

For example, chest pain could be:

- Sharp and burning with associated allodynia (sensation of pain due to light touch). Diagnosis: neuropathic pain, query shingles.
- Pain worse on movement, tender to touch, associated with bruising. Diagnosis: nociceptive pain, soft tissue injury.
- Sharp pain worse on breathing, associated crackles on auscultation and fever. Diagnosis: nociceptive pain, pleurisy.
- Central, crushing pain, worse on exercise, associated dyspnoea. Diagnosis: nociceptive pain, ischaemia.
- Central, burning pain, worse after eating. Diagnosis: nociceptive pain, oesophageal irritation.
- Tight, hot, burning sensation localised around wound. Diagnosis: nociceptive pain, skin infection.

Pharmacological treatment of pain

Medications that may be considered for treating pain include drugs that treat specific conditions (adjuvants) and drugs in the analgesic ladder. There is one ladder for nociceptive pain (opposite page) and one for neuropathic pain (see page 13).

Pain control is not always easy. It can be complicated by psychological and addiction problems. Adverse effects of medications may be problematic. Don’t hesitate to seek advice from a specialist.

The WHO analgesic ladder for nociceptive pain

The WHO analgesic ladder[4] follows a simple step approach to pain management, starting with a non-opioid and moving up to potent opioids. It is important to be guided by the following rules:

By the mouth – oral medication
By the clock – regular medication
By the ladder – use the analgesic ladder
Individual dose titration – find the right dose for the patient
Use adjuvant drugs – treat specific conditions
Attention to detail – keep reviewing the diagnosis and check for adverse effects

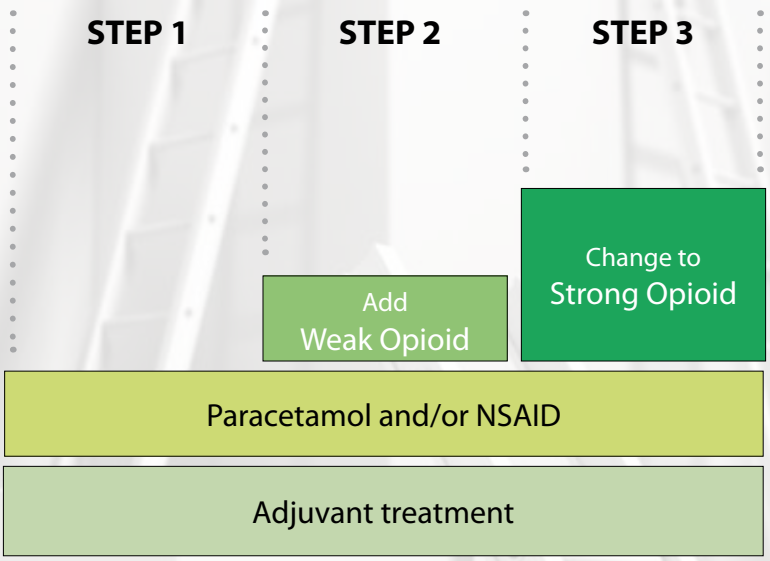
Adjuvants are used at every step of the ladder

Adjuvants are included at every level of the analgesic ladder and may be the only analgesia needed for some conditions.

Some examples of adjuvants:

- Radiotherapy, bisphosphonates – pain from bone metastases
- Antimuscarinics (hyoscine) – bowel colic
- Antibiotics – cellulitis
- Glyceryl trinitrate spray – ischaemia
- Steroids – liver capsular pain

Nociceptive pain ladder



ABC for prescribing opioids

A – consider an **antiemetic**. Opioids may produce nausea at the beginning of treatment. In some cases, it may be ongoing. Opioid related nausea is produced through two effects - the first is reduction in gut motility which can be successfully treated with metoclopramide 10mg, three to four times per day. The second is a central effect which is traditionally treated with haloperidol 1–2mg, once per day. Doses should be modified for individual patients.

B – **Breakthrough**. Analgesics work best with regular dosing, but pain may still break through. When a regular dose of a strong opioid is prescribed, a short-acting formulation should also be prescribed at one sixth of the total 24 hour dose, to cover any breakthrough pain. For example, a 24 hour dose of morphine of 60mg would require a breakthrough dose of 10mg.

C – **Constipation**. "The hand that prescribes opioids should always prescribe a laxative". Unless being used to control diarrhoea, the patient should be prescribed a stimulant plus softener combination laxative such as docusate sodium with sennosides (Laxsol).

Step one: paracetamol and/or NSAIDs

Mild pain of many causes will respond to paracetamol. NSAIDs are also effective in treating mild to moderate pain, particularly if an inflammatory process is involved. If tolerated, it is recommended that these drugs are continued through the analgesic ladder.

Step two: add in a "weak" opioid

One advantage of weak opioids is that they do not require a controlled drug script. However they all act like morphine and have the same range of adverse effects. Consider that giving a patient 60 mg of codeine, four times per day, is the equivalent of 24mg of morphine in 24 hours (Table 1).

The general rules for weak opioid use are:[6]

- A weak opioid should be added to, not substituted for a non-opioid.
- There is no advantage of changing between weak opioids. Do not "kangaroo hop" from weak opioid to weak opioid.
- If a weak opioid is inadequate when given regularly, change to a strong opioid (e.g. morphine).

Step three: change to a "strong" opioid

Morphine is the most familiar strong opioid and therefore is first choice. To move a patient from a weak opioid to morphine, because their pain is not controlled, first work out what their current equivalent morphine dose is. For example 60 mg of codeine, four times per day, is the equivalent of 24mg of morphine in 24 hours (Table 1).

Table 1: Approximate equivalent morphine doses of weak opioids[5]

	Typical dose (oral)	Total 24 hour dose	Equivalent morphine 24 hour dose
Codeine	60 mg, 4 times/day	240mg	24mg
Dihydrocodeine	120 mg, 2 times/day	240mg	24mg
Tramadol	50 mg, 4 times/day	200mg	40mg

Table 2: Adverse effects of opioid analgesics

Common initial	Common ongoing	Occasional	Rare
Nausea and vomiting Drowsiness Unsteadiness Delirium	Nausea and vomiting Constipation	Dry mouth Sweating Pruritis Hallucinations Myoclonus	Respiratory depression Psychological dependence

Therefore, because the pain was not controlled at this dose, a reasonable starting dose of morphine would be 20mg twice per day.

The dose of morphine is titrated until pain control is achieved or adverse effects are intolerable (Table 2). There is no top dose of morphine.

There are two ways of titrating:

Method 1: Add up all the opioids taken in the previous 24 hours including regular and breakthrough doses. Divide this figure by two to make a new regular twice daily dose. Remember to recalculate a breakthrough dose, e.g. a patient on 30 mg twice per day who has taken four 10mg breakthrough doses, has a total 24 hour opioid dose of 100mg. The new regular dose would then be 50mg twice per day, with a breakthrough dose of 10–15mg — one sixth of the total 24 hour dose. Numbers can be rounded to make simple regimens with available strengths.

Method 2: Increase the regular dose by 30 – 50%. For example, if a patient is on a total daily dose of 60mg, an increase of 30% would take this to 80mg and an increase of 50% would take this to 90mg. Choose whatever dose is easiest in terms of available strengths, e.g. 40mg, twice per day. Recalculate breakthrough dose.

Fears of prescribers

Two main fears can inhibit the prescribing of opioids.

The primary concern is regarding addiction. Use of opioids in patients with non-malignant chronic pain is associated with a low risk of addiction (about one in ten thousand patients). Care however should be taken in patients who have a high risk for addiction and those who are suffering from central sensitisation pain (see page 16).

The second concern is the fear of respiratory depression. However pain is a physiological antagonist to the central depressant effects of opioids. Strong opioids do not cause clinically important respiratory depression in patients in pain if titrated according to pain.

If the pain is relieved, such as in a patient who has had successful orthopaedic surgery for low back pain, opioids may be slowly withdrawn to avoid withdrawl symptoms.

Opioid rotation

Ongoing adverse effects may necessitate rotating to another strong opioid. Changing to another opioid requires calculating the equivalent morphine dose that the patient has been using (Table 3). Figures are approximate because individual patients metabolise opioids differently.

Patient apprehension about the use of morphine or the presence of impaired renal or liver function may necessitate selecting an opioid other than morphine.

Pethidine is not recommended for chronic pain control. Its short duration of action and high peak increases the risk of addiction. For the same analgesic effect it has more adverse effects. Be aware that 50mg of pethidine is equivalent to 12.5mg of morphine.

References:

1. Current Learning in Palliative Care. Diagnosing the cause of pain. Available from: http://www.helpthehospices.org.uk/elearning/. Accessed August 2008.
2. Support Team Assessment Schedule (STAS). Available from: http://www.kcl.ac.uk/schools/medicine/depts/palliative/qat/stas.html. Accessed August 2008.
3. Australian Medicines Handbook. Adelaide, July 2006.
4. World Health Organisation Pain relief ladder. Available from: http://www.who.int/cancer/palliative/painladder/en/index.html. Accessed August 2008.
5. NHS. The use of strong opioids in palliative care. MeRec Briefing 2003; 22.

Table 3: Approximate equivalent morphine doses of strong opioids

	Potency Ratio	Notes
Oxycodone (oral)	1.5 – 2	E.g. patient taking oxycodone 5mg four times per day, convert this to oral morphine: total daily dose × potency ratio = 20mg × 1.5 or 2 = 30–40mg morphine.
Fentanyl patch	100 – 150	Refer to manufacturers instructions for dose conversion (see Table 1, page 32 for an example of this).
Methadone (oral)	5 – 20	Dose conversion varies depending on duration of use and dose of opioid. If rotating, specialist advice is needed.

www.bpac.org.nz keyword: neuropathic

Pharmacological management of neuropathic pain

Diagnosing neuropathic pain

Neuropathic pain is often described in the following terms:

- Burning
- Shooting
- Stabbing
- Lancinating

It is classically associated with sensory changes to the skin, either numbness or hypersensitivity (this may include allodynia – sensation of pain from light touch). There may also be visible autonomic changes (e.g. altered colouring or temperature of skin, sweating) or signs of motor damage (e.g. muscle wasting).

Neuropathic pain may be caused by damage to central, peripheral or autonomic nerves.

Pharmacological treatment

A different analgesic ladder is used for neuropathic pain.

Adjuvants

Adjuvants can be continued through the pain ladder. Examples are capsaicin cream and local anaesthetic gels.

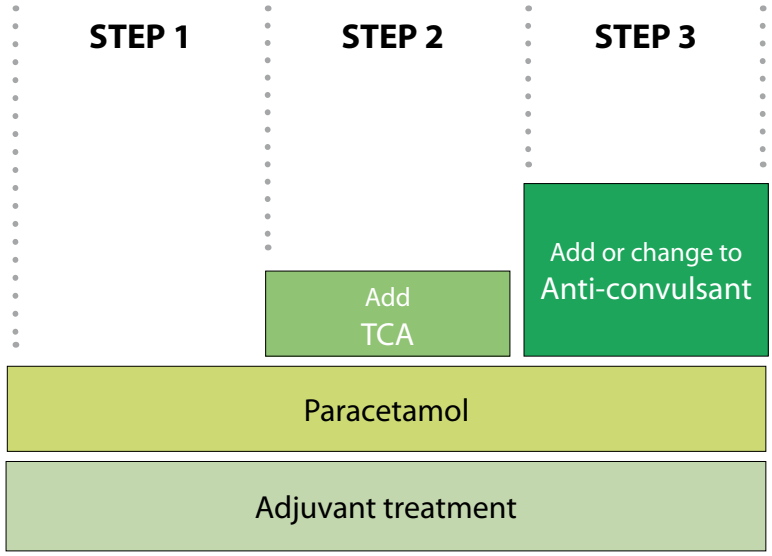
Step one: Paracetamol

Regular use of paracetamol is introduced first and is recommended at every step of the pain ladder.

Step two: Add a TCA

Tricyclic antidepressants (TCAs) are usually prescribed at night as their sedative effects may assist sleep. Nortriptyline may be preferable due to its fewer adverse effects, particularly in elderly people. Initial doses of TCAs are usually low, however doses can be increased to antidepressant level, if tolerated.

Neuropathic pain ladder



TCA dosing e.g. nortriptyline: titrate up from 10mg daily until pain settles.

Prescribe nortriptyline 10mg tablets. Increase the dose as directed. Supply 70 tablets.

Patient information: The dose may be increased as follows until the pain settles – Take one tablet (10mg) at night for seven nights, then take two tablets (20mg) at night for seven nights, then take three tablets (30mg) at night for seven nights etc. You do not have to increase the dose any further once the pain has settled. For example, if the pain is controlled by taking two tablets at night, do not increase the dose any further.

Maintenance doses range from 10mg per night to antidepressant levels (75mg per night).

Step three: Add or change to an anticonvulsant

Carbamazepine, sodium valproate and gabapentin are all effective in treating neuropathic pain.

Traditionally carbamazepine is the first choice but it must be titrated very slowly to avoid side effects such as nausea, vomiting and dizziness. Complete blood count and electrolytes should be monitored when high doses are given.

Carbamazepine dosing: titrate up from 100mg daily until pain settles.

Prescribe carbamazepine 100mg tablets. Increase the dose as directed. Supply 70 tablets.

Patient information: Tell your doctor if you are taking other medications. The dose may be increased as follows until the pain settles - take one tablet at night for seven nights, then take one tablet twice a day for seven days, then take one tablet three times a day for seven days, then take two tablets twice a day for seven days, then take two tablets

three times a day. Do not increase the dose any further once the pain has settled. For example, if the pain is controlled by taking one tablet twice a day stay at this dose.

Maintenance doses range from 100mg to 800mg per day and rarely up to 1.6g per day.

Gabapentin is available funded, on Special Authority for patients who have tried and failed or who have been unable to tolerate treatment with a TCA, and a subsidised anticonvulsant agent. Gabapentin is effective in several types of neuropathic pain. It is generally well tolerated and has few drug interactions. Elderly patients may require titration from 100mg per day.

Gabapentin dosing: initial titration from 300 to 900mg per day.

Prescribe gabapentin 100mg capsules. Increase dose as directed. Supply 36 capsules.

Patient information: Take one capsule three times a day for three days, then take two capsules three times a day for three days, then take three capsules three times a day. Do not increase the dose any further once the pain has settled.

Maximum dose is 3.6g daily.

If pain control is not achieved at this stage, referral to a specialist or a pain clinic is recommended.

Using opioids for neuropathic pain

Opioids can have a place in the control of neuropathic pain but specialist advice is recommended. There is some evidence that oxycodone and methadone may be the most useful.

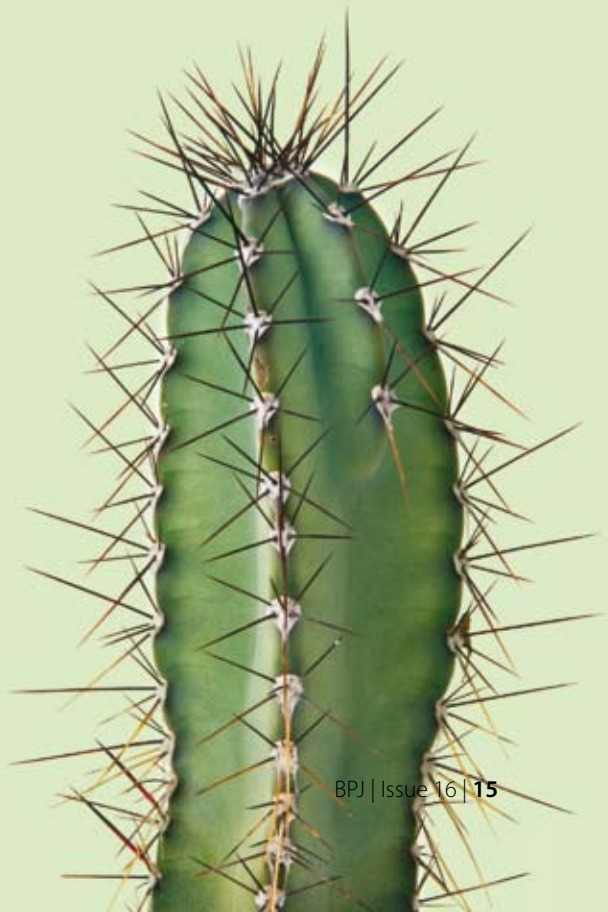
See **www.bpac.org.nz** for downloadable versions of the patient instructions.

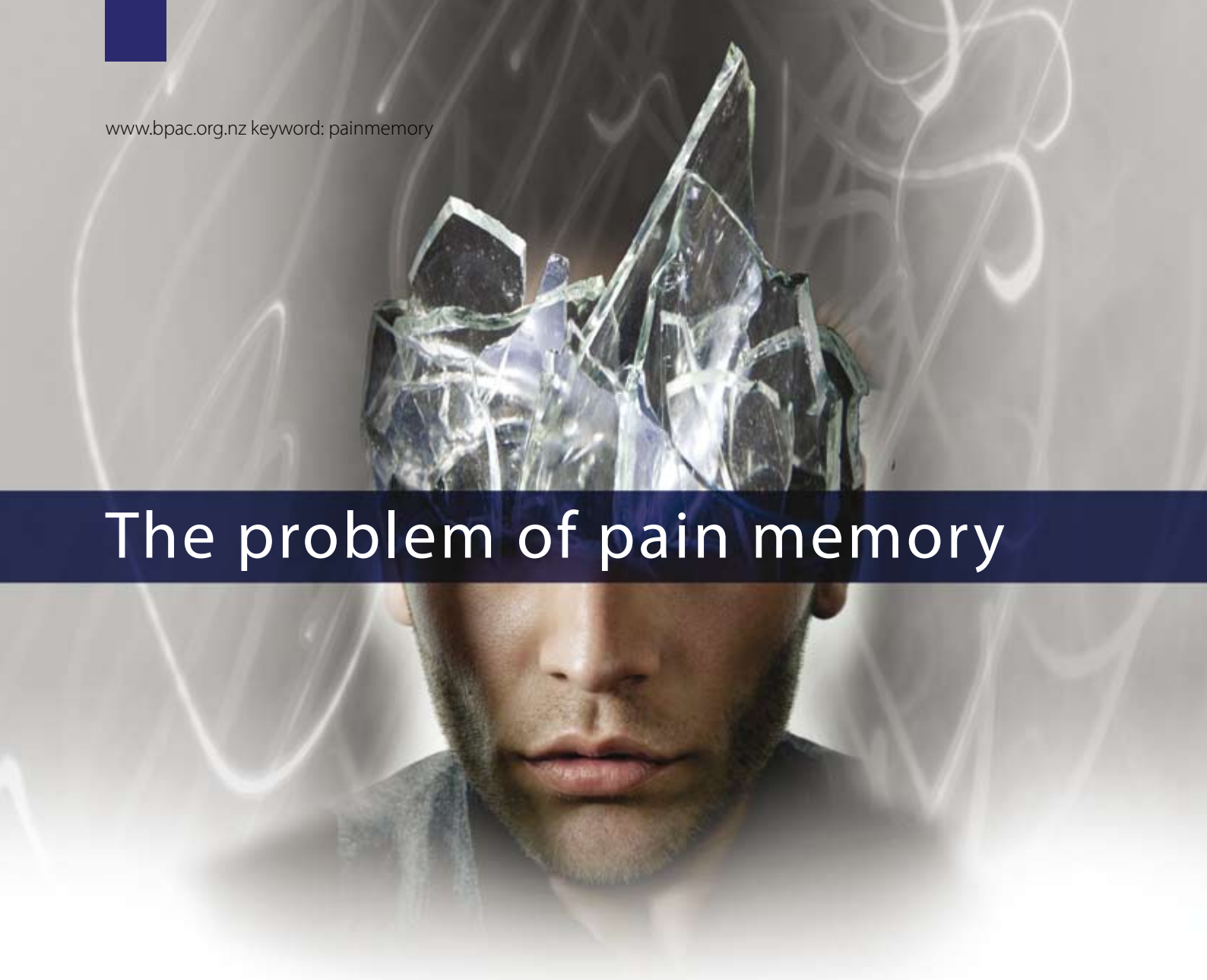
Considerations for prescribing

Both TCAs and anticonvulsants relieve pain in approximately two thirds of patients. Factors to consider when prescribing these medications for neuropathic pain include:

- Elderly people: more sensitive to postural hypotension and antimuscarinic side effects, therefore consider nortriptyline or gabapentin
- Cardiovascular disease: avoid TCAs and carbamazepine if possible. Use nortriptyline or gabapentin with caution
- Prostatism, narrow angle glaucoma, urinary retention, constipation: use gabapentin
- Epilepsy or risk of seizures: avoid TCAs as they lower the seizure threshold
- Bipolar disorder: TCAs may precipitate mania
- Renal impairment: use lower doses of gabapentin

Titrate the dose of TCA or anticonvulsant upwards until pain settles or adverse effects limits further dose increases. After starting treatment for pain always follow up to assess response to treatment and make the necessary adjustments.





The problem of pain memory

Persistent central sensitisation pain

There is one group of patients with chronic pain that is particularly difficult to treat. Despite the best efforts of their doctor, and often the involvement of the chronic pain clinic, they continue to be disabled with pain. Often these patients do not have a discernible disease process, but seem to be suffering from the effects of what may be termed a pain memory.

Pain memory, or persistent central sensitisation pain, arises when the nervous system has become up regulated from previous trauma or severe pain. Despite the removal of the original damage, nerves continue to send pain signals. The situation may be compounded by the coping strategies adopted by the patient.

Central sensitisation pain may be a feature of several chronic pain syndromes such as fibromyalgia, tension-type headache, irritable bowel syndrome and post-traumatic pain.

Simple pain management often does not work. In this situation, it can be wiser to say “we can help you manage and cope with pain even if we can not make you complely pain free”.

Role of primary care in managing persistent central sensitisation pain

Primary care clinicians can make major contributions to improve outcomes for this type of pain. These contributions do not need to take a lot of time and can often be achieved by a simple change in management approach.

Contributions can include:

- Early recognition of the diagnosis
- Pharmacological pain management
- Management of negative mood
- Acknowledging your influence on patients' thought patterns
- Spending as much time discussing reintegration with normal life as discussing pain and disability
- Encouraging adherence to multidisciplinary pain management programmes which are offered through pain clinics or ACC

Characteristics of persistent central sensitisation pain

People experiencing persistent central sensitisation pain often exhibit some of the following features:

- Pain persists significantly longer than expected
- Pain spreads to other areas
- Pain varies for no reason
- Even small movements hurt
- History of harmful physical or emotional events
- Presence of psychosocial risk factors e.g. psychiatric illness, poor coping strategies

Management of negative mood

Depression is common in people with persistent pain. It should be treated like any other depression. This may involve a combination of cognitive and pharmacological interventions. Although TCAs may have some theoretical advantage due to their effect on both pain and mood, their adverse effect profile often means that they may not be tolerated at antidepressant levels.

Cognitive intervention

Clinicians in primary care can have a strong influence on negative thought patterns of people with persistent central sensitisation pain. Examples of harmful thought patterns include:

- Equating hurt with harm
  - It hurts therefore I must be causing damage
- Polarising
  - I am not perfect therefore I am a failure
- Over-generalisation
  - I can't do this therefore I cannot do that
- Catastrophising
  - This has gone wrong, it's a total disaster
- Emotional reasoning
  - This doesn't feel normal there must be something wrong

Recognition of these thought processes, allows clinicians to gently point out to the patient that persistent pain is distorting their thinking, and these thoughts are interfering with their return to normal activities.

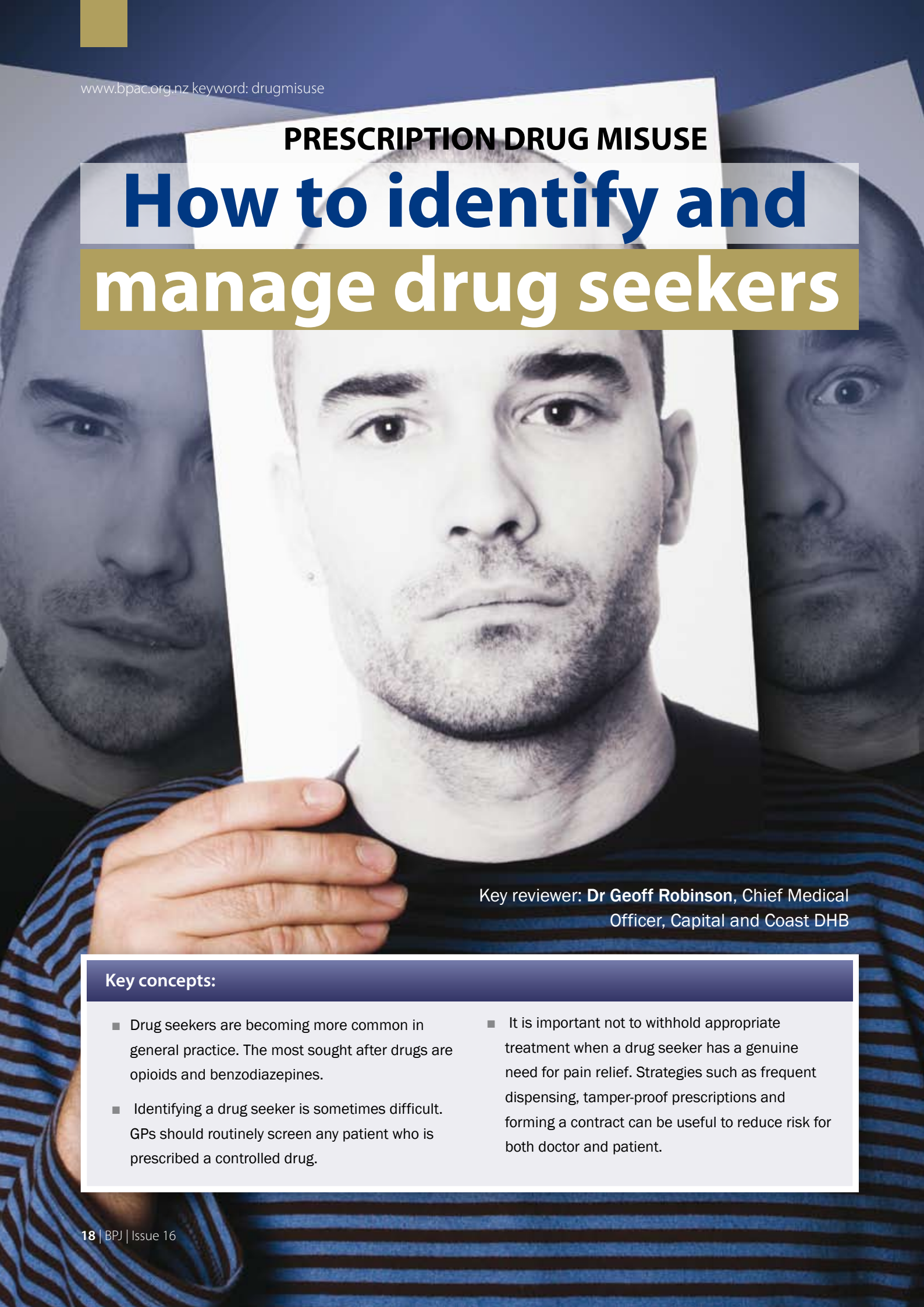
Further reading

Linton SJ. Understanding pain for better clinical practice: a psychological perspective. Chapter 3 The biological-psychological Interface: pain perception. Elsevier. Edinburgh, 2005.

Gatchel R, Peng YB, Peters M, et al. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull 2007;133(4):581-624

PRESCRIPTION DRUG MISUSE

How to identify and manage drug seekers



Key reviewer: **Dr Geoff Robinson**, Chief Medical Officer, Capital and Coast DHB

Key concepts:

- Drug seekers are becoming more common in general practice. The most sought after drugs are opioids and benzodiazepines.
- Identifying a drug seeker is sometimes difficult. GPs should routinely screen any patient who is prescribed a controlled drug.
- It is important not to withhold appropriate treatment when a drug seeker has a genuine need for pain relief. Strategies such as frequent dispensing, tamper-proof prescriptions and forming a contract can be useful to reduce risk for both doctor and patient.

The misuse of prescription drugs is an escalating problem in New Zealand

The fear of being fooled by a drug seeker leaves many doctors feeling uncomfortable about prescribing controlled drugs. As a result, pain is often undertreated and patients who are refused treatment for legitimate illnesses can end up feeling stigmatised.[1, 2]

Which prescription drugs are commonly misused?

Benzodiazepines and opioids are the most commonly misused prescription drugs.

Benzodiazepine misuse frequently occurs when multiple drugs are misused, with the highest correlation between concurrent addiction to opioids and alcohol. Benzodiazepines are used to enhance the euphoriant effects of opioids, enhance cocaine highs and increase the effects of alcohol. They are also used to alleviate withdrawal effects from other drugs.[2]

Stimulants may be taken to prevent fatigue (e.g. shift workers) or for their euphoric effects. Anticholinergics are taken for their hallucinogenic effects.[4]

Prescription drugs most commonly misused in New Zealand:[5, 6]

- Amphetamines e.g. dexamphetamine
- Anticholinergics e.g. procyclidine, benztropine
- Benzodiazepines e.g. clonazepam, diazepam
- Dextropropoxyphene
- Pseudoephedrine (also sourced directly from pharmacies)
- Ketamine
- Methylphenidate
- Opioids e.g. morphine, methadone, codeine, tramadol
- Zopiclone

Drug use in New Zealand

While the exact magnitude of prescription drug misuse in New Zealand is unknown, the Illicit Drug Monitoring System (IDMS) report conducted annually by researchers from Massey University provides some insight into patterns of drug use.[3]

Opioid abuse is common in New Zealand. As the supply of imported heroin is limited, the three main sources are morphine sulphate tablets, "homebake heroin" made from codeine based tablets and opium extracted from opium poppies.[3]

The 2007 IDMS report showed that accessing opioids is very easy. They are mainly sourced from diverted prescriptions for morphine and methadone. The average street price for opioids in New Zealand is $1 per milligram.[3]

Among surveyed injecting drug users, 72% used methadone, 71% used other opioids, 54% used benzodiazepines and 42% used methylphenidate. The misuse of ketamine was also reported. The frequency of use of methadone and methylphenidate is increasing.[3]

Most prescription drugs that are misused trigger dopamine release in the "reward pathway". They are all also habit forming and cause a state of physiological dependence if they are taken in large enough quantities for long enough periods of time.[2]

Identifying drug seekers is not always simple

Recognising signs of drug-seeking and misuse

Many GPs believe they can easily identify drug seekers, but they will not all fit the expected stereotype.

Drug seekers may be known patients or casual attendees to the practice. They may be dependent on the drug or sourcing the drug for black market sale. Drug seekers are not necessarily drug abusers or drug addicts. Anyone regardless of gender, income, ethnicity, health or employment status can be a drug seeker.

In addition, not all drug seekers are faking symptoms. They may have a legitimate complaint and over time have become dependent or tolerant and require larger doses to function in their daily life.[1] Patients with chronic pain, anxiety disorders and attention-deficit disorder are at increased risk of addiction co-morbidity.[2]

Some indicators of drug seeking behaviour are:[1, 2]

- Presenting near closing time without an appointment.
- Reporting a recent move into the area, making validation with a previous practitioner difficult.
- Requesting a specific drug and refusing all other suggestions - the patient may claim that other medications don't work, they have an allergy to them, a high tolerance to drugs or report losing prescriptions.
- Inconsistent symptoms that do not match objective evidence or physical examination.
- Manipulating behaviour which may include comparing one doctor's treatment opinions against another's, offering bribes or making threats.
- Use of multiple doctors.
- Assertive personality, often demanding immediate action.
- Unusual knowledge of medications and symptoms or evasive and vague answers to history questions.
- Reluctance to provide personal information such as address or name of regular doctor.
- Signs and symptoms of intoxication or withdrawal (see below).

Many drug seekers will target doctors who are new to a practice or doctors who are sympathetic and dislike confrontation. A usual patient/doctor relationship is based on mutual respect, however a drug seeker has a stronger relationship with the prescription than with the doctor. Some doctors who are pressured for time would rather "write than fight".[2]

Indicators of drug misuse

	Signs and symptoms of intoxication	Signs and symptoms of withdrawal
Benzodiazepines	Sedation, poor co-ordination and balance, impaired memory and general impairment of cognitive function.	Anxiety, irritability, palpitations, tremor.
Opioids	Constricted pupils, itching nose and skin, difficulty concentrating and dry mouth. Injection site marks may be evident.	Dilated pupils, increased heart rate and blood pressure, diarrhoea, muscle cramps, aches and pains, frequent yawning, rhinorrhoea and lacrimation.

N.B. people experiencing opioid withdrawal may seek benzodiazepines

A consistent approach to managing drug seekers is best practice

As anyone can be a drug seeker, and drug seekers are difficult to identify, a recommended strategy is to screen all patients who are prescribed controlled drugs. Ask about previous drug use, alcohol use and family history of addiction.

Managing drug-seeking behaviour

In New Zealand it is illegal to prescribe a controlled drug solely to maintain someone's dependence, unless the prescriber is licensed to do so (e.g. drug clinics).

Practices should develop a plan for dealing with drug seekers, which is consistently adopted by all staff in the practice, at all times. This discourages drug seekers from preying on sympathetic or new staff members.

Planned responses to situations in which a doctor feels pressured to prescribe may include: [2, 4]

- Outright refusal to prescribe
- Prescribing for a limited time (e.g. two to three days)
- Supervised daily dosing
- Prescribing a drug appropriate for the reported symptoms but different from the one requested by the patient
- Seeking a second opinion from a colleague

It is important not to deny appropriate treatment

The prescription of controlled substances should be avoided in patients with current or past addictions, however they should not be withheld if warranted for acute pain.

If these medicines are prescribed, this should be done on a strict regimen rather than on an as needed basis.[2] Frequent dispensing should occur (prescribe as "close control"). A larger than usual dose may be required due to tolerance to effects and the duration of treatment needs to be clearly established.[4] Some doctors may consider forming a written contract with the patient.

Alternatives to controlled substances for pain relief in people with addiction to prescription drugs may include: [2]

- NSAIDs
- Paracetamol
- Antidepressants
- Anticonvulsants (but not clonazepam)
- Steroids
- Muscle relaxants

Definitions

Tolerance is when the dose or frequency of a drug needs to be continually increased to achieve the same level of pain control.[1]

Dependence is a physiological adaptation to a drug. It is dose, time and potency-related. Abrupt cessation, rapid dose reduction, decreased blood level of the drug or administration of an antagonist results in withdrawal syndrome.[1, 2]

Addiction involves the loss of control and an obsessive-compulsive pattern that becomes a primary illness. It may result from genetic, psychosocial and environmental factors. Physiological changes leading to tolerance or withdrawal may occur along with cognitive or psychological complications.[1, 2]

Drug seeking behaviour is defined as the false reporting of symptoms to obtain a prescription or requesting a drug in order to maintain dependence.[4]

Misuse includes using the medication in larger amounts, at a greater frequency, for different indications or by different routes than prescribed, usually resulting in adverse consequences.[2]

Alternatives to medications should also be discussed including relaxation techniques, physiotherapy or psychological therapy.[2]

Prescribing controlled drugs for any patient requires caution

As a routine aspect of taking a new patient history or performing a general health check, ask patients about their substance-use history, including alcohol, illicit drugs and prescription drugs.[2]

Before prescribing a controlled drug consider whether the use is appropriate.

Managing the risk of prescribing controlled drugs[5]

Knowledge – review the pharmacology of controlled substances, drug interactions and signs of intoxication or withdrawal. Become familiar with alcohol and drug addiction screening assessments.

Documentation – this is essential, note the diagnosis, indications, expected symptom end points and the treatment time course. A medication flow chart may be useful to monitor refills, symptoms and prescribing.

Tamper proof prescriptions – prescribe the exact amount to carry through to the next appointment, write out the number dispensed in words not numerals, consider implementing a one doctor/one pharmacy treatment plan with the patient where only one doctor in the practice prescribes to them and prescriptions are only phoned through to one pharmacy.

Don't be hesitant to refer to peers, supervisors or those with specialised expertise such as addiction specialists, pain management clinics or psychiatrists.[2]

Misuse of Drugs Act 1975 and Medicines Act 1981

These Acts allow the Medical Officer of Health to publish statements relating to a person who is, or is likely to become dependent, on any prescription medicine or restricted medicine. The statements are made available to health professionals. The purpose of the statement is to prevent or restrict the supply of medicines to that person, require its supply from only a named source or to assist in the cure, mitigation or avoidance of dependence.

The Misuse of Drugs Act also classifies drugs according to the level of harm they pose. Class A is very high risk e.g. cocaine, heroin and methamphetamine. Class B is high risk e.g. methadone, morphine and pethidine. Class C is moderate risk e.g. codeine and diazepam.

Doctors may not treat a drug dependent person with controlled drugs unless they have ministerial authority to do so. That means that doctors are unable to prescribe drugs such as opioids and benzodiazepines to a person they know, or have reason to suspect, is dependent on prescription or illicit drugs, for the purpose of maintaining or managing their addiction. The exception to this is doctors who are authorised to prescribe methadone.

For practices that keep Class B drugs on site, they must be kept in a safe and it is good medical practice to keep a drug register.[7]

How to seek help in dealing with prescription drug misuse

Early consultation with a Medicines Control Advisor is recommended if a doctor is in any doubt about the legitimacy for a request from a drug seeker. The activities of a Medicines Control Advisor include:

- Liaising with alcohol and drug treatment centres and with doctors and pharmacists in relation to drug misuse issues
- Advising health professionals of current drug misuse issues
- Monitoring controlled drug prescribing
- Working with national Medical Officers of Health in the preparation of restriction notices for drug seekers
- Providing advice on the requirements of the Misuse of Drugs Act and Medicines Act
- Issuing controlled drug prescription pads to prescribers.

Contact: Central Medicines Control Office, Wellington:
Tel: 04 4962437 or 0800 163 060

"One strategy I use for suspected drug seekers is to ask them to show me some identification. Most bona fide patients will have a driving licence, or some kind of card with their name written on it. Almost never will the drug seeker have identification they are prepared to show you, in which case it is easy to say you're sorry you can't prescribe for them. Should they produce some positive identification, then that is useful if they need to be reported to the police or medicines control office."

Christchurch GP

References

1. Friese G, Wojciehoski R, Friese A. Drug seekers: do you recognise the signs? Emerg Med Serv 2005;34(10):64-7.
2. Longo L, Parran T, Johnson B, Kinsey W. Addiction: Part II. Identification and management of the drug-seeking patient. Am Fam Physician 2000;61(8):2401-8.
3. Wilkins C, Gurling M, Sweetsur P. Recent trends in illegal drug use in New Zealand, 2005 - 2007. Auckland: Centre for Social and Health Outcomes Research and Evaluation, Massey University, 2008. Available from http://www.shore.ac.nz/projects/IDMS_2007_MAIN_REPORT.pdf (Accessed August 2008).
4. White J, Taverner D. Drug-seeking behaviour. Aust Prescr 1997;20:68-70.
5. McCormick R. Treating drug addiction in general practice. NZ Fam Pract 2000;27(4).
6. Ministry of Health. National drug policy 2007 - 2012. Wellington, 2007.
7. Chapman M. Cole's Medical Practice in New Zealand. Chapter 3: How medical practice standards are set by legislation: Other legislation: Medical Council of New Zealand, 2008.

Medication-overuse headache

When the **cure** becomes the **cause**

www.bpac.org.nz keyword: headache

Key concepts

- Recognition of the problem is the key
- Over the counter medications are often overused
- All medications used for immediate relief of headache have the potential to cause medication-overuse headache
- Withdrawal of the overused medication is essential

Key reviewer: **Dr William Wallis**, Neurologist, Auckland

Further reading

BPJ 7 (August 2007) – Avoidance, recognition and management of medication overuse headache

A recent comprehensive clinical summary "Medication overuse headache" is available at Medlink neurology:

www.medlink.com (subscription required)

What is it?

Medication-overuse headache is a complex disorder that is best thought of as an "interaction between a therapeutic agent used excessively and a susceptible patient".[1]

Medication-overuse headache develops in people who have a pre-existing primary headache disorder, usually migraine or tension-type headache. The type, location and severity of the headache may vary, but the headaches characteristically occur on a daily or near daily basis. Medication-overuse headache remains one of the most important, frequent, but under-diagnosed cause of chronic headache.[3,4]

Medication-overuse headache can be defined as:

"A headache that is present on 15 or more days of the month and has developed or worsened whilst the patient has been regularly using analgesic or anti-migraine medicines for more than three months." [5]

Diagnostic criteria are available (see Box 1).

Box 1: The latest revised diagnostic criteria for medication-overuse headache are: [6]

A. Headache present on ≥ 15 days/month

B. Regular overuse for ≥ 3 months of one or more acute/symptomatic treatment drugs as defined:

   1. Ergotamine, triptans, opioids or combination analgesics on ≥ 10 days/month on a regular basis for ≥ 3 months.

   2. Simple analgesics or any combination of ergotamine, triptans, analgesics, opioids on ≥ 15 days/month on a regular basis for ≥ 3 months without overuse of any single class alone

C. Headache has developed or markedly worsened during medication-overuse

How big is the problem?

Medication-overuse headache is an increasingly common worldwide health problem. It is estimated that up to 2% of the population have medication-overuse headache.[7,8,9]

Characteristics of people with medication-overuse headache

Studies have identified a higher prevalence of medication-overuse headache in people with the following characteristics or comorbidities:

- Female gender [4,9,10,11]
- Age 40 to 50 years [10,11]
- Migraine [4,11]
- Obesity [12,13]
- Low socioeconomic status[14]
- A tendency to exhibit a low threshold for head pain[7]

What medications are involved?

Almost all drugs used to provide immediate treatment of headache have the potential to cause medication-overuse headache, those used for the prophylaxis of headache do not. [3,18]

The crucial factor in the development of medication-overuse headache is the chronic use of medication on both a frequent and regular basis.[1] Individual doses of medication are generally not higher than recommended. Medication-overuse headache can develop in three months but it may take longer.

What makes some people overuse medications?

Psychological issues that can contribute to the overuse of medications include:[2]

- Belief that medication is the only solution for a headache
- Fear of pain
- Low tolerance to discomfort
- Belief that medication will help with sleep
- Need to continue to function
- Personality disorder
- Clinical diagnosis of anxiety, depression, panic disorder or substance use disorder
- Dependence on other psychoactive substances including alcohol and nicotine[11]
- A family history of substance disorders.[11,15]
- A family history of mood disorders[16]
- Psychiatric comorbidity[15]

Not all people with chronic daily headache overuse medications and not all go on to develop medication-overuse headache. Some people predisposed to headache, may develop medication-overuse headache after frequent use of analgesics for conditions other than headache, particularly chronic neck and low back pain.[7,8,17]

Medications known to lead to medication-overuse headache include simple analgesics (e.g. aspirin, paracetamol), caffeine, ergotamine, combination agents (e.g. paracetamol/codeine, dextropropoxyphene), triptans (sumatriptan, rizatriptan*), NSAIDs and all opioids including codeine, tramadol, oxycodone and morphine.

People who have headache most commonly use over the counter medications. Sumatriptan has been available over the counter for the last few months (see BPJ 9). Triptan use is increasing and these drugs are now regarded as one of the most commonly implicated types of drugs in the development of medication-overuse headache.[9] Triptans cause this type of headache more quickly and with lower doses than other analgesics.[10]

How to recognise medication-overuse headache

Consider this diagnosis in all patients with frequent headache. Direct questions should be asked about patterns of medication use, including those purchased over the counter. Some patients may be vague or evasive and refuse to disclose an accurate level of their medication use. Explaining to them the concept of medication-overuse headache and the way in which it develops may help them understand the importance of your questions. In some cases you may need to check medication use with a partner or family member, the pharmacist or verify the patient's medical record. A daily headache diary can be useful when collecting information on the level of medication use and identifying the extent of overuse.[16]

In addition, a general medical and neurological history is required to make a correct diagnosis.

Do not assume that:[15]

- Medication overuse occurs daily – although this is often true, for some people medication use may be much less frequent.

*Rizatriptan (maxalt 10mg wafers) has been fully funded since 1/6/08

- The medication must be taken in large quantities.
- Medication-overuse headache can be avoided by mixing and matching medications – combinations of medication can frequently be implicated.
- Medications taken for pain conditions other than headache "don't count".

Clinical characteristics of medication-overuse headache

There may be clinical characteristics that can be useful in assisting diagnosis (refer Box 2). It is important that other forms of headaches, both primary and secondary, are considered when making the diagnosis.

How should medication-overuse headache be managed?

For most people with medication-overuse headache, there is no relief until all medication used for acute relief is withdrawn.[19] Patient education is a crucial element and advice must be non judgemental. Information and support from family members may be required.[16]

An approach to management may be:

1. Explain to the patient that medication overuse is causing their headache and that they need to stop using the medication in order for the headache to get better. This may not be accomplished in a single consultation.

Box 2. Clinical characteristics of medication-overuse headache [3,16]

General observations and symptoms:

- Headaches are refractory to treatments and are usually daily, or nearly daily
- Headaches vary in severity, type and location from time to time, but often manifest as morning headache upon awakening
- Physical or intellectual effort ('normal' levels) may bring on headache i.e. the threshold for head pain seems to be low
- Symptomatic headache medications tend to provide only short-term relief
- Spontaneous improvement of headache occurs after a few days off medication
- Prophylactic drugs are often ineffective while the patient is taking excess amounts of drugs for immediate relief

Associated symptoms:

- Nausea
- Weakness
- Restlessness
- Anxiety, irritability or depression
- Forgetfulness, concentration and memory difficulties
- Gastrointestinal symptoms

Symptoms associated with overuse of ergotamine and to a lesser extent with triptans:

- Cold extremities
- Tachycardia
- Paraesthesias
- Hypertension
- Irritable bowel syndrome
- Weakness of the legs and muscle pain in the extremities
- Occasionally bradycardia and lightheadedness

2. Explain to the patient that it may take up to six weeks before there is any benefit from withdrawal of the overused medication.
3. Abrupt withdrawal is usually more successful than gradual withdrawal. If this is not tolerated, gradually withdraw the overused medication over 4 to 6 weeks. Alternatively, start migraine prophylaxis, usually with a TCA, and increase to the maximum tolerated dose, then withdraw the overused medication gradually. If a TCA is not tolerated consider sodium valproate or topiramate.*
4. Follow up is essential to guard against relapse and to make sure that there is improvement. If there is not, and the overused medication is withdrawn entirely for at least six weeks, then the diagnosis is wrong. At this stage refer to a specialist.

Note: For patients over the age of 55 years, a CRP and an ESR test should be requested to help exclude temporal arteritis, which can mimic medication-overuse headache.

Avoiding medication-overuse headache

The main way to prevent medication-overuse headache is to prevent medication overuse. When a patient presents with headache, but is not in the category of chronic headache syndrome, it is essential to warn them about the risks posed by excessive analgesic and triptan treatments. Consider avoiding the use of codeine, dextropropoxyphene or opioids for any headache. Patients whose headache is severe enough to require these medications, should be considered for headache prophylaxis.

Continuing to prescribe more and more analgesics, particularly those with addictive potential, without educating patients about the correct use of medications may promote medication-overuse headache.

Withdrawal symptoms

Withdrawal symptoms which may be physical and psychological may last between two to ten days and include withdrawal headache (which initially may be worse than the medication-overuse headache), nausea, vomiting, hypotension, tachycardia, sleep disturbances and anxiety.

Management of withdrawal symptoms

Many people with medication-overuse headache are able to manage withdrawal without additional assistance. However treatments to ease withdrawal may include fluid replacement, TCAs and steroids. For patients with severe withdrawal headache, analgesics may be required, but firm limits on use must be set, e.g. regular naproxen 500mg twice per day for two to three weeks only.

Study results have differed, however a short course of 60–100mg prednisone for five days may be effective in reducing the duration of withdrawal headache.[20,21] Even though this is a short course of prednisone, at this dose tapering is recommended, e.g. decreasing by 20mg per day until finished. If withdrawal symptoms are intolerable, consider referral for hospital treatment.

Patient education is important

The greatest risk of relapse is within the first 12 months after withdrawal.[3,16]

Patient education is important to initiate withdrawal and to reduce the risk of relapse. Encouraging and supporting the patient towards their goals and appropriate follow up is necessary. Behavioural techniques such as relaxation therapies and stress management have been shown to enhance outcome over drug treatment alone.[16]

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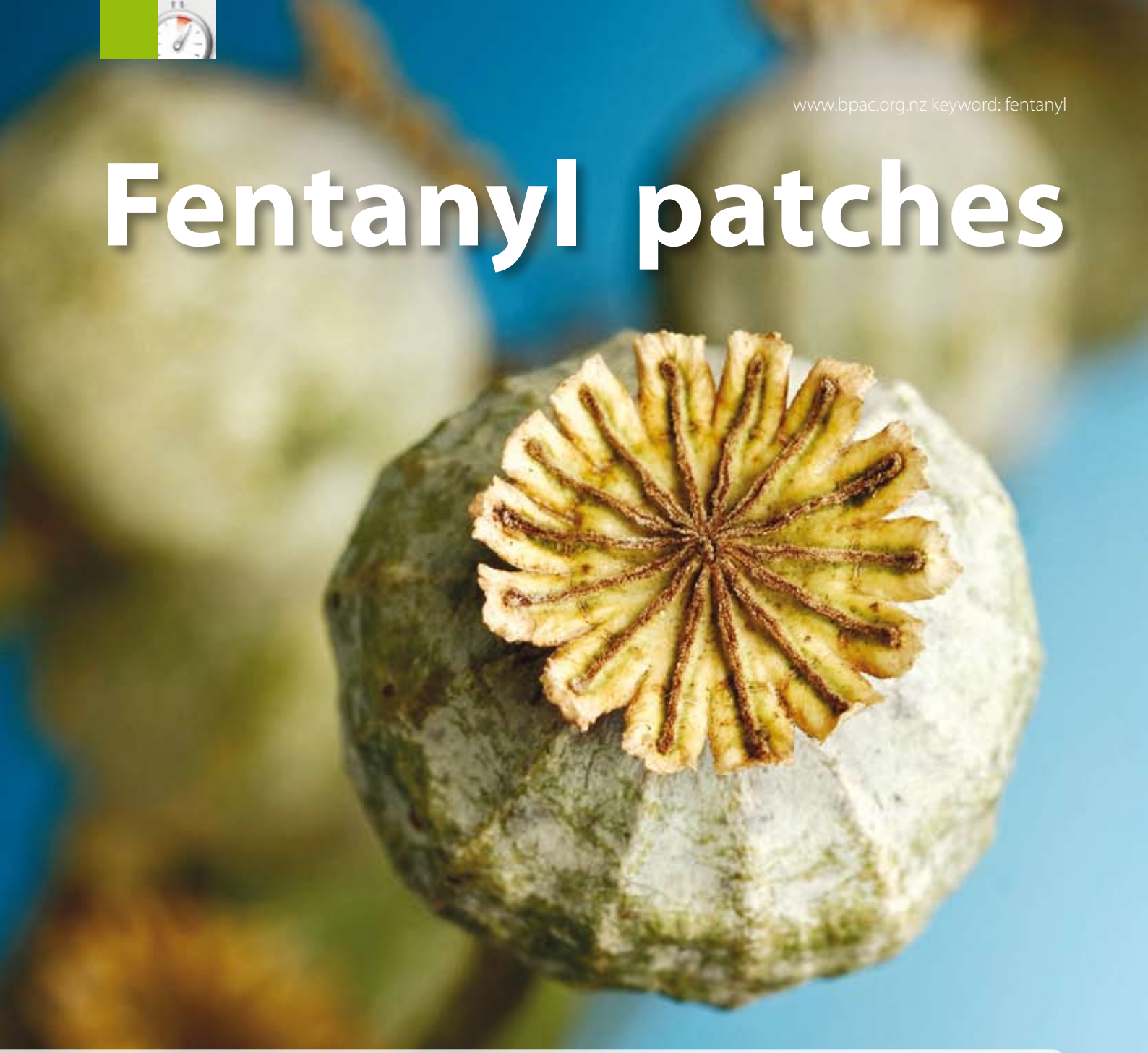
* Topiramate is fully funded without special authority for prophylaxis of migraine from 1 September 2008.

References

1. Silberstein SD, Olesen J, Bousser M-G, Diener H-C et al. The International classification of Headache Disorders, 2nd Edition (ICHD-II) – revision of criteria for 8.2 Medication-overuse headache Cephalalgia 2005;25(6):460-465.
2. Lake AE. Medication Overuse Headache: Biobehavioural Issues and solutions. Headache 2006;46(Suppl 3):S88-S97.
3. Diener H-C, Limmroth V. Medication-overuse headache: a worldwide problem. Lancet Neurol 2004;3(8):475-483.
4. Zidverc-Trajkovic J, Pekmezovic T, Jovanovic Z, et al. Medication-overuse headache: clinical features predicting treatment outcome at 1-year follow-up. Cephalalgia 2007;27(11):1219-1225.
5. McEntee J. UK Medicines Information. Medication-overuse headache: What is it and how do you treat it? Available from www.nelm.nhs.uk Accessed August 2008-08-19.
6. Olesen J, Bousser M-G, Diener H-C, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia 2006;26(6):742-746.
7. Dodick D, Freitag F. Evidence-Based Understanding of Medication-Overuse Headache:Clinical Implications. Headache 2006;46(Suppl 4):S202-S211.
8. Silberstein SD, Welch KMA. Painkiller headache. Neurology 2002;59(7):972-974.
9. Diener H-C, Katsarava Z. Medication overuse headache. Clinical Summary. Available from MedLink Neurology www.medlink.com (Accessed September 2008).
10. Limmroth V, Katsarava Z, Fritsche G. Features of medication overuse headache following overuse of different acute headache drugs. Neurology 2002;59(7):1011-1014.
11. Radat F, Creac'h C, Guegan-Massardier E, et al. Behavioural Dependence in Patients with Medication Overuse Headache: A Cross-Sectional Study in Consulting Patients Using the DSM-IV Criteria. Headache 2007;48(7):1026-1036.
12. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. Pain 2003;106(1-2):81-9.
13. Bigal ME, Liberman JN, Lipton RB. Obesity and migraine. A population study. Neurology 2006;66(4):545-50.
14. Hagen K, Vatten L, Stovner LJ et al. Low socio-economic status is associated with increased risk of frequent headache: a prospective study of 22718 adults in Norway. Cephalalgia 2002;22(8):672-679.
15. Lake AE. Screening and Behavioural Management: Medication Overuse Headache – the Complex Case. Headache 2008;48(1):26-31.
16. Grazzi L, Andrasik F, Usai S, Bussone G. Headache with medication overuse: treatment strategies and proposals of relapse prevention. Neurol Sci 2008;29(2):93-98.
17. Zwart JA, Dyb G, Hagen K, et al. Analgesic use: a predictor of chronic pain and medication overuse headache: the Head-HUNT study. Neurology 2003;61(2):160-164.
18. Ferrari A, Coccia C, Sternieri E. Past, Present and Future Prospects of Medication-Overuse Headache Classification. Headache 2008;48(7):1096-1102.
19. Williams L, O'Connell K, Tubridy N. Headaches in a rheumatology clinic: when one pain leads to another. Eur J Neurol 2008;15(3):274-277.
20. Pageler L, Katsarava Z, Diener H-C, Limmroth V. Prednisone vs. placebo in withdrawal therapy following medication overuse headache. Cephalalgia 2008;28(2):152-156.
21. Krymchantowski AV, Barbosa JS. Prednisone as initial treatment of analgesic-induced daily headache. Cephalgia 2000;2(2):107-113.

Fentanyl patches



FENTANYL IS A SYNTHETIC OPIOID which is available as a transdermal patch. This allows controlled delivery of the drug for up to 72 hours. Transdermal fentanyl is potentially useful if the patient has experienced intolerable adverse effects to morphine or is unable to take oral analgesia. The fentanyl patch is a less flexible dose form than oral morphine and is best reserved for patients with stable opioid requirements.

PHARMAC is to widen access to subsidised fentanyl patches in 2009, via listing a new brand of patches without the requirement for Special Authority (subject to Medsafe registration of the new brand of patch). This will mean that GPs will be able to prescribe funded fentanyl patches for their patients. Fentanyl will be available as 25, 50, 75 and 100mcg/hour transdermal patches.

As GPs may be unfamiliar with using fentanyl patches the following information is provided to ensure patient safety.

Who are fentanyl patches suitable for?

Fentanyl patches are best reserved for people with chronic pain and stable opioid requirements who are unable to take morphine orally.[1,2]

They may also be suitable for people who have intolerable side effects to morphine (e.g. intractable constipation) or who are in renal failure.

Who are fentanyl patches not suitable for?

Fentanyl patches are not suitable for opioid naïve patients with non-cancer pain. [1, 2] These patients are vulnerable to potentially fatal opioid effects such as respiratory depression.

Fentanyl patches should not be used for rapid titration in pain control. Fentanyl patches have a 6–17 hour half life and take at least 24 hours to reach a steady plasma level. If a patient is suffering from serious adverse effects e.g. respiratory depression, on removal of the patch it will take at least 24 hours for levels to drop significantly.

Cautions when using fentanyl patches

- Prescribe with care to elderly and debilitated patients – the elimination half-life may be prolonged. Elderly patients may also have increased sensitivity to the effects of fentanyl. Reduced doses should be used in elderly or debilitated people and they should be observed carefully for signs of toxicity and the dose reduced if necessary.[3]
- Fentanyl patches cannot be cut in half, therefore there is no recommended way to modify the doses available.
- Increased blood flow to the skin will increase blood fentanyl levels. Avoid placing localised sources of heat such as hot-water bottles directly over the patch. Care needs to be taken with electric blankets. To avoid problems with hot baths the patches should be placed on the upper body only. Showers do not usually cause a problem but in all cases extra care is needed with vulnerable patients such as elderly people.
- Potential interactions. Concomitant use of CYP3A4 inhibitors such as itraconazole or erythromycin may lead to potentially dangerous increases in fentanyl levels. Adverse effects of fentanyl may be potentiated by other CNS depressants.
- Patches can lose adherence in which case they can be covered by a waterproof dressing.
- Fentanyl patches need to be disposed of carefully because a significant amount of fentanyl is left in the patch after three days. Discarded patches have the potential to be misused.

Dosing for fentanyl patches

The initial dose of fentanyl should be the lowest possible dose based on the patient's opioid history and current medical status. The dose can be titrated upwards as required.

Ideally patients are initially titrated with other opioids and then converted to fentanyl patches. For some cancer pain, it may be suitable to initiate treatment with a fentanyl patch. In this case, start with the lowest strength patch and titrate upwards. It can take 24–48 hours to reach an effective plasma concentration so previous medication should be phased out gradually.

The dose of the initial fentanyl patch is based on the morphine equivalent daily dose currently used by the patient.

1. Assess current 24-hour opioid use.
2. If not using morphine, convert this to a 24 hour oral morphine equivalent dose.
3. Based on this estimated 24-hour equivalent oral morphine dose, work out the recommended fentanyl patch dose.

Two examples are:

Patient on stable dose of morphine

E.g. Stable daily morphine dose is 90mg. Referring to the manufacturers data (Table 1) shows that the recommended

fentanyl dose for this level of morphine is 25mcg per hour. The 25mcg fentanyl patch should be applied with the final dose of long-acting morphine. As with all opioid use, remember the rules of "ABC":

A consider prescribing an **antiemetic** for nausea

B calculate a **breakthrough** dose based on one sixth of the morphine equivalent daily dose. In this example, this would be 10–15mg taken as required.

C **Constipation.** Fentanyl may be less constipating in individual patients, consider reducing laxative dose.

Patient on stable dose of other opioid

E.g. stable daily oxycodone dose is 160mg. Referring to the conversion (Table 2) shows that this is equivalent to 240-320mg morphine/day. Table 1 shows that the recommended fentanyl dose is either 75 or 100 mcg per hour. Consider using the lowest dose fentanyl patch recommended and then increasing if required.

Again, remember ABC. The breakthrough dose is 40 to 50 mg morphine or oxycodone equivalent.

Review the patient the following day. If they are very drowsy and opioid overdose is suspected remove the patch immediately and consider admission to hospital. If the dose is tolerated, but pain is not controlled, encourage use of breakthrough medication and review over the next two days. Continue to monitor gastrointestinal effects. Once a stable state is reached it is possible to titrate with the fentanyl patch. Remember to increase the breakthrough dose.

Very rarely patients metabolise fentanyl more quickly than normal and develop pain on day three. If this is a regular pattern, it is reasonable to swap from 72 hour dosing to 48 hour dosing.

Table 1: Recommended fentanyl dose based on daily oral morphine dose

Oral 24-hour morphine (mg/day)	Fentanyl dose (micrograms/hour)
60 –134	25
135 – 224	50
225 – 314	75
315 –404	100
405 – 494	125
495 – 584	150
585 – 674	175
675 – 764	200
765 – 854	225
855 – 944	250
945 – 1034	275
1035 – 1124	300

N.B. The dose conversion tables provided by manufacturers are intended as a guide and individual patients may vary in their response to fentanyl. Consider using a lower-dose patch initially and titrating upwards.

Table 2: Morphine equivalent doses[4].

	Equivalent to 10mg morphine (oral)	Ratio
Codeine	100mg	0.1
Dihydrocodeine	100mg	0.1
Tramadol	50mg	0.2
Oxycodone (oral)	5 – 7.5 mg	1.5 – 2
Methadone (oral)	Varies depending on length and dose of opioid use. Specialist advice is needed.	5 – 20

Prescribers should inform patients about the correct use of fentanyl patches:

Stopping fentanyl patches

Levels of fentanyl fall slowly after removal of the patch. Observe patients for adverse effects for up to 24 hours after removal of the patch. Withdrawal symptoms can still occur, if possible taper the dose to minimise these.[1]

- Follow prescribed dose
- Apply the patches at the correct frequency
- Apply to non-hairy skin (but do not shave the area)
- Ensure old patches are removed when the new patch is applied
- Do not cut patches
- Store patches and dispose of used and unused patches safely

Prescribers should also educate patients and carers about the signs and symptoms of fentanyl overdose such as trouble breathing, extreme sleepiness, inability to walk, talk or think properly.

Opioid titration

In some cases it is considered appropriate to initiate fentanyl patches in opioid-naïve patients, i.e. such as with cancer pain. It is recommended that these patients be first titrated with low doses of opioids until an equianalgesic dose equivalent to a 25 mcg/hour fentanyl patch is achieved.

Treatment is usually initiated with a short-acting immediate release opioid given every four to six hours. Usual starting doses are:

- Morphine 5 – 10 mg
- Oxycodone 5 mg

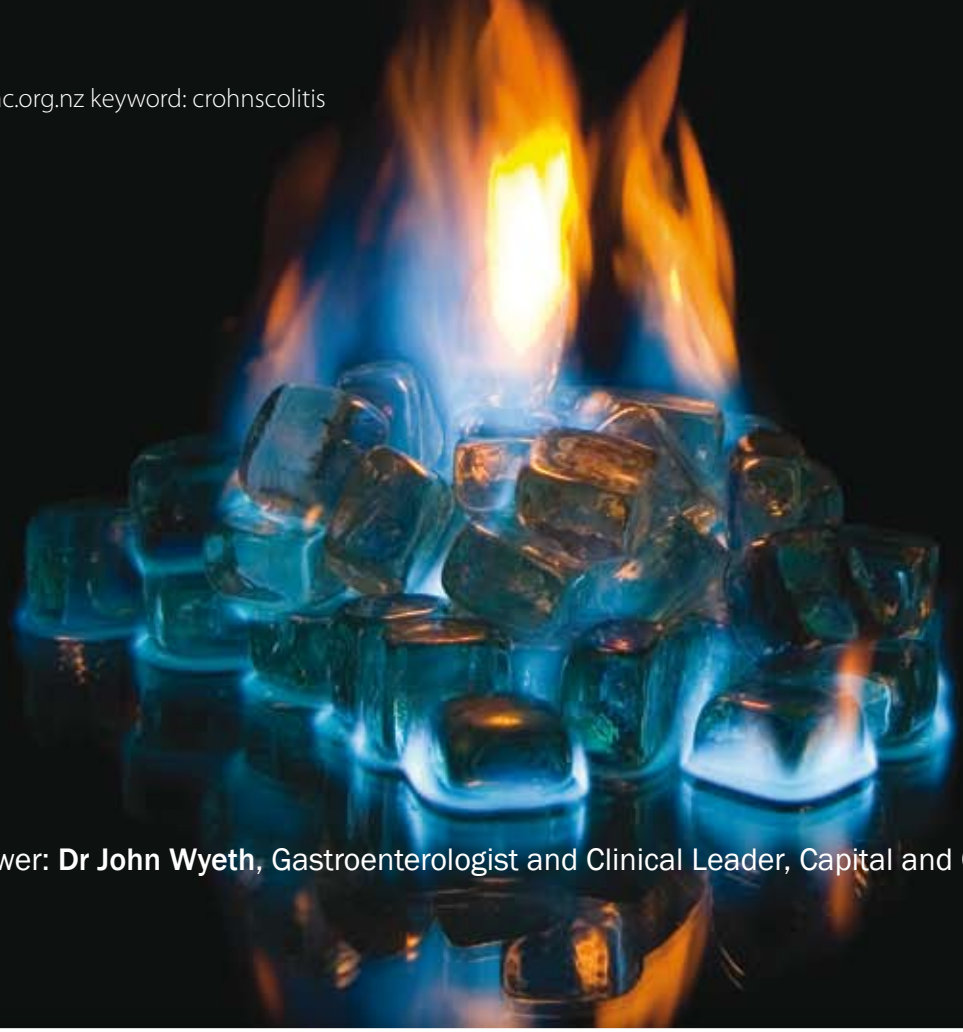
The patient can then be converted to a 25 mcg/hour fentanyl patch.[2]

References:

1. NPS RADAR. Fentanyl patches (Durogesic) for chronic pain. Available from: http://www.nps.org.au/health_professionals/publications/nps_radar (Accessed August 2008).
2. Medsafe. Durogesic datasheet. Available from: www.medsafe.govt.nz. (Accessed August 2008).
3. Sweetman SC (ed), Martindale: The Complete Drug Reference 35. [online] London: Pharmaceutical Press. Available from: http://www.medicinescomplete.com (Accessed August 2008).
4. NHS. The use of strong opioids in palliative care. MeRec Briefing 2003; 22.

CROHN'S DISEASE AND ULCERATIVE COLITIS

www.bpac.org.nz keyword: crohnscolitis



Key reviewer: **Dr John Wyeth**, Gastroenterologist and Clinical Leader, Capital and Coast DHB.

Key concepts

- Crohn's disease and ulcerative colitis are the two most common causes of chronic inflammatory bowel disease
- Initial presentation of the two conditions may be similar. The GPs role is to investigate appropriately, and then refer to secondary care for further diagnostic investigations if inflammatory bowel disease is suspected
- A definitive diagnosis is made histologically and treatment is usually initiated by a specialist
- The GPs ongoing role is in the management of relapse and monitoring for complications and adverse effects of medication

Further Reading:

Rowe WA. Inflammatory Bowel Disease 2008. Available at: www.emedicine.com/med/topic/169.htm
A comprehensive web based review.

Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD).

Although there are significant differences in the gastrointestinal characteristics of the two conditions, (Table 1) there are many similarities in the presentation, ongoing symptoms and management. A definitive diagnosis is made histologically and this will refine management strategies. The long term prognosis varies for each condition.

The incidence and prevalence of ulcerative colitis is approximately twice that of Crohn's disease.

Although the cause is unknown, both diseases are believed to be triggered by environmental factors in genetically susceptible individuals. Possible factors include gut flora, food constituents and infections.

When to suspect

Both Crohn's disease and ulcerative colitis have a peak incidence between 20 and 40 years of age, although the conditions can affect people of any age. Males and females are equally affected. 10–20% of people with IBD have one or more other family members affected with IBD.

Features of IBD include:

Diarrhoea. Most people present with diarrhoea containing blood or mucous (the stool may be solid in ulcerative colitis if there is rectal disease only).

Other bowel symptoms. These may include abdominal pain, faecal urgency or incontinence, tenesmus, and mouth ulcers. Less frequently there may be symptoms of bowel stricture or obstruction, fistulae and abscesses (often perianal). Perforation of the bowel and toxic megacolon are rare but life-threatening complications.

Non bowel manifestations. There is often associated tiredness or malaise, fever and weight loss. Children may present with failure to thrive.

IBD is associated with the following conditions:

- Joint disease – arthritis, sacroiliitis, ankylosing spondylitis
- Eye disease – conjunctivitis, episcleritis, uveitis
- Skin disease - erythema nodosum, pyoderma gangrenosum
- Liver disease – autoimmune hepatitis, gallstones, sclerosing cholangitis

Table 1: Gastrointestinal characteristics of ulcerative colitis and Crohn's disease

	Ulcerative colitis	Crohn's disease
Distribution within the gastro-intestinal tract	Limited to colorectal mucosa	Any part of the GI tract, from mouth to anus, with normal bowel in between affected areas (skip lesions)
Depth of inflammation	Mucosal (affects inner lining of the bowel)	Transmural (affects all layers of the bowel)
Rectal involvement	95% of cases	50% of cases

- Urinary complications – stones, ureteric obstruction and fistulae
- Other – anaemia (both iron deficiency and anaemia of chronic disease), thromboembolism, osteoporosis, amyloidosis

Differential diagnoses include:

- Infectious diarrhoea
- Diverticulitis
- Coeliac disease
- Irritable bowel syndrome
- Colon cancer

Investigations and referral

The GP's role is to perform a physical examination, order appropriate tests, and then refer to secondary care for further diagnostic investigations if IBD is suspected.

Physical examination is required to identify features mentioned above, such as pallor suggestive of anaemia, mouth ulcers, abdominal tenderness or anal fistula.

Appropriate investigations may include:

- CBC – this may show a microcytic anaemia and/or signs of infection.
- CRP – will often be raised in active IBD.
- Electrolytes – can be important especially if diarrhoea is prominent.
- LFTs – liver and bile duct abnormalities may be seen in some patients with IBD.
- Stool culture – to help exclude an infectious cause of diarrhoea (including *C. difficile*).
- IgA TTG – coeliac disease is a differential diagnosis

Urgent referral

Complications of IBD may include infection, malabsorption, strictures, obstruction, abscesses, fistulae, bleeding, perforation, and toxic megacolon.

Consider acute admission to hospital if the patient has any of the following symptoms:

- Severe abdominal pain, especially if associated with tenderness
- Severe diarrhoea (greater than eight times a day), with or without bleeding
- Dramatic weight loss
- Fever or severe systemic illness

The management of IBD

A management plan for IBD will often include a combination of medical and surgical treatments which will be overseen by hospital specialists. However these are chronic conditions and primary care clinicians will be involved in:

- Initial management of relapse
- Recognising complications
- Providing ongoing medication and monitoring for adverse effects
- Providing education and support

Medical management

There are two main goals of medical therapy: to bring active disease into remission and to keep the disease in remission.

Medical management for both conditions usually follows a step-wise approach although it is important to note that often combinations of medications are required, particularly when trying to bring active disease into remission.

Aminosalicylates

Patients receiving aminosalicylates are at risk of blood dyscrasias and should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment.

There are several different aminosalicylates available (sulphasalazine, mesalazine, olsalazine) with different adverse effects and monitoring requirements. GPs are advised to refer to Medsafe data sheets for further information. This will also be addressed in a future article.

Corticosteroids

The long term risks of steroids are well known – osteoporosis, thinning of the skin, hypertension, diabetes, weight gain and fluid retention. These should be discussed with your patient and attention paid to reduction of risks.

When corticosteroids are used to induce remission, review frequently and reduce the dose over eight weeks as rapid withdrawal can increase the risk of relapse. Corticosteroids are not indicated for maintenance treatment in IBD.

Immunosuppressives

Patients receiving treatment with immunosuppressives are at risk of blood dyscrasias or suppression of bone marrow production e.g. leucopenia, thrombocytopenia. There are several different immunosuppressives used (azathioprine, methotrexate, cyclosporin, mercaptopurine) with different adverse effects and monitoring requirements. GPs are advised to refer to Medsafe data sheets for further information. This will also be addressed in a future article.

Anti TNF

There is a range of drugs directed against tumour necrosis factor (TNF), a key component of the inflammatory pathway. These drugs have a significant adverse effect profile. Most importantly, as a result of the generalised effect on the immune system, infection risk is increased. There are also reports of increased risk of lymphoma but this is difficult to ascertain as Crohn's disease is also associated with an increased risk of lymphoma.

Surgical management

For ulcerative colitis there are three main indications for surgery:

- Lack of response or intolerance to medications
- Acute complications e.g. toxic megacolon or haemorrhage
- Precancerous or cancerous changes in the colon, increased risk in people with a seven to ten year history of active disease.[1]

Surveillance colonoscopy to detect cancer may be performed after ulcerative colitis has been present for eight years.[2] In New Zealand this is repeated every two to three years.

Up to 40% of patients with ulcerative colitis will eventually require surgery. After proctocolectomy (removal of large intestine and rectum) an ileostomy is fashioned. For the majority of patients, three to six months later the ileostomy is made into a pouch, to remove the need to have a permanent stoma. However, the pouch still has the potential to become inflamed, known as "pouchitis".

For Crohn's disease the indications for surgery are:

- Lack of response or intolerance to medications
- Complications such as fistulae, abscesses, perforation, excessive bleeding or stricture leading to obstruction.

Up to 70% of patients with Crohn's disease require surgery at some point in the disease.

Other aspects of management

As in any chronic illness, patient education and support are important. GPs have an important role in counselling the patient about the implications of the condition. Patients can be provided with written information and directed to patient support groups.

Smoking cessation has been shown to be effective in reducing the number and severity of flares.[3]

There is conflicting evidence regarding the role of diet in both ulcerative colitis and Crohn's disease. Nutritional deficiencies and weight loss are common and are multifactorial in origin. Patients should be weighed on a regular basis.

Post surgical patients and those with ongoing inflammation require an annual check of B12.

Prognosis

For ulcerative colitis there is usually a relapsing-remitting course. On average there is a 50% chance of a flare in any year but the rate of flares is very variable. Up to 10% of people with ulcerative colitis may remain in remission for as long as 25 years and, less commonly, some will experience almost constant flares . One year after diagnosis, 90% of patients are able to work.

For Crohn's disease, there is also a relapsing-remitting course but it is more variable and less favourable than for ulcerative colitis. Over a four year period approximately one-quarter of people with Crohn's disease will remain in remission, one-quarter will have frequent flares and one-half have a course fluctuating between periods of remissions and periods of flares. One year after diagnosis, 75% of patients are able to work.

References:

1. Eaden J, Abrams K, Mayberry J. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48: 526-35.
2. Winawer S, Fletcher R, Miller L et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997; 112: 594-642.
3. Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease in adults. Gut 2004;53:v1–v16.

www.bpac.org.nz keyword: imiquimod

Imiquimod cream (Aldara) for genital warts and basal cell carcinoma

Imiquimod cream is now funded on special authority for the treatment of genital warts and superficial basal cell carcinoma

The special authority criteria are:

Either:

1. The patient has external anogenital warts and podophyllotoxin has been tried and failed (or is contraindicated); or
2. The patient has external anogenital warts and podophyllotoxin is unable to be applied accurately to the site; or
3. The patient has confirmed superficial basal cell carcinoma where other standard treatments, including surgical excision, are contraindicated or inappropriate.

Imiquimod is an immune response modifier

Imiquimod enhances the immune response to viral infections and tumours by stimulating the immune system to release interferon and other cytokines.[1]

Therapeutic uses of imiquimod

Imiquimod is registered for use in the following conditions[2]:

- Superficial basal cell carcinoma
- External genital warts
- Actinic keratosis (also known as solar keratosis)*

*** Although registered for use imiquimod is not funded for this indication.**

Superficial basal cell carcinoma

Surgical excision remains the first line therapy for superficial basal cell carcinoma. It has a higher cure rate than imiquimod and allows histological assessment of tumour clearance.[3]

Imiquimod may be useful when surgery is contraindicated. Patients must be willing to follow the six week course

Table 1. Dosing for imiquimod cream[2]

- Imiquimod cream should be applied with the fingertip and rubbed into the affected area until the cream vanishes
- Wash hands before and after application
- The treatment should be washed off with mild soap and water after six to ten hours
- Local inflammatory reactions may occur. If severe, stop treatment for a few days and then resume once the reaction subsides. Rest periods are considered part of the treatment and the treatment period does not need to be extended to make up for missed doses
- Each condition has a different dosing frequency:

Condition	Dose	Comment
Superficial basal cell carcinoma	The patient should apply imiquimod cream once daily at bedtime for five consecutive days per week (e.g. Monday to Friday) for six weeks.	Sufficient cream should be applied to cover the area and 1cm of skin surrounding the lesion
Genital warts	The patient should apply imiquimod cream once daily at bedtime, three times a week (e.g. Monday, Wednesday, Friday) until the warts have resolved or up to a maximum of 16 weeks.	Imiquimod cream can weaken latex condoms and reduce their barrier function. Avoid use prior to sexual activity.
Actinic keratosis	Imiquimod cream should be applied once daily, two times per week.	Imiquimod is not funded for this indication

Tip: While the manufacturer states that the sachet is for single use only, sachets are commonly used for more than one application. The sachet can be sealed using a paper clip or tape and stored in a closed container to prevent the cream drying out.[5, 6]

of therapy and tolerate the possible adverse skin reactions.[3]

Imiquimod is not suitable for use within 1cm of the hairline, eyes, nose, mouth or ears, because tumours in these areas are less likely to be superficial and there is a greater risk of hard-to-manage recurrence.[3]

Imiquimod is not indicated for recurrent, invasive, infiltrating, or nodular basal cell carcinoma.

Dosing instructions are explained in Table 1.

External genital warts

Treatment choice for genital warts needs to be considered on an individual basis. There is no definitive evidence that one treatment is better than others and no single treatment is suitable for all patients or all warts.[4] The method of treatment may be largely decided based on patient preference. Other factors include the size, number and site of the warts.

Commonly used patient-applied treatments in primary care are podophyllotoxin and imiquimod. Cryotherapy is also commonly used in general practice.

Podophyllotoxin is suitable for external warts that can be visualised by the patient. It is more difficult to use safely on genital warts in females and perianal warts as inadvertent application to other areas may cause significant skin irritation.[4]

While imiquimod requires careful application, it causes minimal irritation, so inadvertent application to surrounding skin should not cause significant problems.[5]

Neither podophyllotoxin nor imiquimod are suitable for use in pregnancy.

Dosing instructions are explained in Table 1.

Actinic keratosis

Imiquimod cream is one treatment option for actinic keratosis, but is not funded for this indication. Other treatments include cryotherapy, curettage and cautery, excision, and 5-fluorouracil cream.

Dosing instructions are explained in Table 1.

Adverse effects

Many adverse effects associated with imiquimod cream are the result of its therapeutic action.[2]

Local skin reactions are common

Inflammation in areas treated with imiquimod cream is expected as part of the treatment process. Effects may include itching, burning, redness, scabbing, flaking, pain and ulceration. Increasing severity of these reactions may be associated with higher clearance rates of skin lesions.

Systemic adverse effects and skin pigmentation changes have been reported

Topical imiquimod can cause intense local inflammatory reactions. These rare reactions are often accompanied or preceded by flu-like systemic symptoms such as malaise, pyrexia and nausea. Treatment may need to be interrupted.[7, 8] Mild symptoms can be treated with paracetamol.[3, 6]

Permanent localised hypo- or hyper- pigmentation has been reported.[8]

References:

1. Tyring S, Conant M, Marini M, et al. Imiquimod; an international update on therapeutic uses in dermatology. Int J Dermatol 2002; 41:810-816
2. iNova Pharmaceuticals Limited. Aldara (imiquimod) cream datasheet. Available from: www.medsafe.govt.nz (Accessed September 2008).
3. NPS. Imiquimod cream (Aldara) for superficial basal cell carcinoma. NPS Radar December 2006. Available from: http://www.nps.org.au/ (Accessed September 2008).
4. Australia and New Zealand HPV project. Guidelines for the management of genital HPV in Australia and New Zealand 2007. Available from: http://www.nzgg.org.nz/ (Accessed September 2008).
5. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. Arch Dermatol 1998; 134: 25-30.
6. DermNet NZ. Imiquimod. Available from: http://www.dermnet.org.nz/ (Accessed September 2008)
7. Hanger C, Dalrymple J, Hepburn D. Systemic side effects from topical imiquimod. NZMJ 2005; 118(1223).
8. Medsafe. Imiquimod cream – skin pigmentation changes and flu-like symptoms. Prescriber Update 2008; 29(1): 3.

Evidence That Counts

No Need to Select Specific Antihypertensive Drugs According to Age

Journal Watch, Vol. 28, No.13, July 1, 2008

Some authorities recommend selective use of antihypertensive drugs based on patient age. For example, some recommend angiotensin converting enzyme inhibitors and β-blockers as initial blood-pressure-lowering drugs for younger patients, and diuretics for older patients, because younger patients tend to have higher renin levels than do older patients. However, little evidence supports this recommendation. In this meta-analysis of 31 prospective randomised trials that involved more than 190,000 patients, investigators compared relative risk reductions for cardiovascular events (stroke, coronary heart disease and heart failure) associated with various antihypertensive drug regimens in younger (age, <65) versus older (age, ≥65) adults.

In trials that compared antihypertensive regimens with placebo, or more intensive antihypertensive regimens with less-intensive regimens, relative risk reductions did not differ significantly between the two age groups. Similar results were found for trials in which antihypertensive regimens based on different drug classes were compared. Finally, risk reduction achieved per unit of reduction in blood pressure reduction, did not differ between the two age groups.

Comment:
Both younger and older adults with hypertension benefit from blood pressure control. However, this study provides no evidence for selective use of specific antihypertensive drug regimens according to age.

— **Paul S. Mueller**, MD, MPH, FACP

Reference

Turnball F et al. for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: Meta-analysis of randomised trials. BMJ 2008 May 17; 336:1121.

Metabolic Syndrome Adds Little to Prediction of Diabetes and Cardiovascular disease

Journal Watch, Vol. 28, No.16, August 15, 2008

To evaluate the usefulness of the metabolic syndrome in predicting onset of diabetes and cardiovascular disease (CVD), researchers reviewed two large prospective studies in which baseline data were collected from older men on all five metabolic-syndrome components (body-mass index, triglyceride level, HDL cholesterol level, fasting glucose level, blood pressure). These studies provided outcome data on incident CVD and type 2 diabetes. In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER; JW Feb 1 2003, and Lancet 2002; 360:1623), 4218 older patients (age range, 70–82) with vascular disease or high risk for vascular disease received pravastatin or placebo and were followed for a mean of 3.2 years. In the observational population-based British Regional Heart Study (BRHS; BMJ 1981; 283:179), 2737 older men (age range, 60–79) were followed for a mean of seven years. Data on participants with baseline diabetes were excluded.

Baseline prevalence of metabolic syndrome was 28% in PROSPER and 27% in BRHS. In both PROSPER and BRHS, metabolic syndrome was associated strongly with risk for new-onset diabetes (relative risks, 4.41 and 7.47, respectively). However, high fasting glucose levels (≥110 mg/dL), with or without other components, also predicted diabetes onset (RRs, 18.42 and 5.97, respectively). Metabolic syndrome was associated only weakly with incident CVD in BRHS (RR, 1.27) and was not associated at all in PROSPER. In BRHS, adjustment for Framingham risk scores eliminated the association between metabolic syndrome and CVD.

Comment:
An editorialist calls this study "another nail in the coffin of the metabolic syndrome." Fasting hyperglycaemia alone was a much stronger predictor of incident diabetes than were the combined metabolic-syndrome components.

Similarly, the Framingham risk score, which includes important non-metabolic factors such as smoking, was a strong independent predictor of cardiovascular disease, whereas the metabolic syndrome was not. The concept of the metabolic syndrome has been useful in suggesting common pathophysiological pathways, but little evidence shows that diagnosing the syndrome adds value in clinical decision making.

— **Bruce Soloway**, MD

References

Sattar N et al. Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies. Lancet 2008 Jun 7; 371:1927.

Kahn R. Metabolic syndrome — What is the clinical usefulness? Lancet 2008 Jun 7; 371:1892.

SSRIs and Gastrointestinal Bleeding

Journal Watch, Vol. 28, No.16, August 15, 2008

Several observational studies have demonstrated an association between use of selective serotonin reuptake inhibitors (SSRIs) and upper gastrointestinal bleeding (JW Dec 15 1999, and BMJ 1999; 319:1106). The presumed mechanism is depletion of serotonin from platelets, resulting in impaired platelet function.

In this case-control study, researchers analysed data from a U.K. general practice database; they compared 1321 patients with upper GI bleeding and 10,000 age- and sex-matched controls. Case patients were more likely than controls to be current users of SSRIs (5.3% vs. 3.0%); excess risk for GI bleeding after SSRI exposure was significant after adjustment for potential confounding variables (adjusted odds ratio, 1.6). An interaction between SSRIs and nonsteroidal anti-inflammatory drugs was noted (adjusted OR for GI bleeding, 4.8, comparing use of both drugs vs. use of neither drug); this interaction was attenuated in patients who used acid-suppressive drugs. Tricyclic antidepressant use was not associated with GI bleeding.

Comment:

This study adds to a body of literature — comprising cohort and case-control studies — suggesting that SSRI use raises risk for GI bleeding. Clinicians should be aware of this possible association and should consider prescribing acid suppressive therapy for patients who require long-term treatment with both SSRIs and NSAIDs.

— **Allan S. Brett**, MD

Reference

de Abajo FJ and García-Rodríguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: Interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Arch Gen Psychiatry 2008 Jul; 65:795.

Does flu vaccination lower risk for pneumonia in elderly people?

Journal watch, Vol. 28, No. 17, September 1, 2008

Previous observational studies have shown that influenza vaccination lowers risk for pneumonia in older patients. In a population-based case controlled study, conducted during the pre-influenza and influenza seasons of 2000, 2001 and 2002, Seattle investigators studied managed-care records for 1173 older patients (age range, 65–94) with community-acquired pneumonia (CAP) and for 2346 age- and sex-matched controls without CAP. Both groups were equally likely to have been vaccinated (roughly 60% before the CAP index date and 77% by the end of each influenza season).

In unadjusted analyses, vaccinated patients had a 40% lower risk for CAP than did unvaccinated patients in the pre-influenza period — when no biologically plausible explanation exists for vaccine benefit — but the difference

Evidence That Counts

disappeared when analyses were adjusted for a wide range of chronic diseases and functional impairment. No difference in risk for CAP was observed between vaccinated and unvaccinated groups during the influenza season, whether analyses were adjusted or not, and no difference was observed in risk for CAP that required hospital admission during peak influenza season.

Comment:
According to this provocative study, influenza vaccination offered no benefit in broad measures of risk for community acquired pneumonia. Editorialists noted that this study has several strengths that have been missing in many other studies: It was conducted during seasons when the antigenic match between influenza strains and vaccine was good; CAP was ascertained with chart audit rather than by evaluating administrative data; the analysis was controlled for a wide range of chronic disease and functional status measures; and both inpatient and outpatient cases were identified.

— Thomas L. Schwenk, MD

Jackson ML et al. Influenza vaccination and risk of community-acquired pneumonia in immunocompetent elderly people: A population-based, nested case-control study. Lancet 2008 Aug 2; 372:398.

Belongia EA, Shay DK. Influenza vaccine for community-acquired pneumonia. Lancet 2008 Aug 2; 372:352.

What is the best treatment for an adult whose asthma exacerbation has not completely responded to 5 days of oral corticosteroids?

Evidence-Based Practice, Vol. 11, No. 8, August 2008

Current guidelines recommend that patients with acute asthma exacerbations be treated with systemic corticosteroids for five to ten days, so continued steroid therapy is an option. However, limited evidence suggests that a two week course of oral steroids may be no more effective than a 1 week course.

A small (n = 20) prospective trial enrolled adult patients (aged 44 - 58 years) being discharged from the hospital after three days of intravenous methyl prednisolone for an acute asthma exacerbation. Patients were randomised to either one or two weeks of oral prednislone (0.5 mg/kg). The average discharge peak expiratory flow (PEF) was 51% of best for those randomised to one week of therapy, and 58% of best for those randomised to two weeks.

At the end of the first week, both groups improved to 68% of best PEF. After two weeks, the one week group improved to 71% of best and the two week group improved to 73% of best (P=.08). The authors concluded that more than ten days (three days IV + seven days oral) of systemic steroids does not offer additional benefit.[1]

The National Asthma Education and Prevention Program Expert Panel guidelines were composed after a structured literature review and standardised assessment of the quality of the evidence. The guidelines were then developed by panel members, outside experts and the public through the National Heart, Lung and Blood Institute website. They recommend that adults who have undergone a mild, moderate, or severe asthma exacerbation should be started on oral systemic steroids, and should be treated until the patient's PEF is 70% of predicted or personal best. They also recommend that the outpatient treatment last for five to ten days, at a dose of 1 or 2 mg/kg (maximum 60 mg daily) until the patient reaches a PEF of 70% of predicted or personal best. Patients do not require a taper after ten days, especially if the patient is taking concurrent inhaled steroids.[2]

Earlier recommendations from the Canadian Medical Association state that a 14 day course of oral corticosteroids may be required for patients with a history of multiple or recent exacerbations.[3] Experts state that patients should not be considered steroid resistant until they have failed three weeks of oral steroid treatment.[4]

— **Mikel Hofmann**, BS, **Jose E. Rodriguez**, MD, and **Carolyn Klatt**, MLIS

Florida State University College of Medicine

References

1. Hasegawa T, Ishihara K, Takakura S, et al. Duration of systemic corticosteroids in the treatment of asthma exacerbation; a randomized study. Intern Med 2000; 39:794-797.
2. Busse W. Section 5, managing exacerbations of asthma. In: National Asthma Education and Prevention Program (NAEPP). Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: NHLBI; August 2007:373-417. NIH publication no. 07-4051. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. (Accessed July 17, 2008).
3. Beveridge RC, Grunfeld AF, Hodder RV, Verbeek PR. Guidelines for the emergency management of asthma in adults. CAEP/CTS Asthma Advisory Committee. Canadian Association of Emergency Physicians and the Canadian Thoracic Society. CMAJ 1996; 155:25-37.
4. Leung DY, Spahn JD, Szefler SJ. Steroid-unresponsive asthma. Semin Respir Crit Care Med 2002; 23:387-398.

Steroids Ineffective in Patients with Medication-Overuse Headache

Journal Watch Vol. 27, No. 15, August 1, 2007

Overuse of headache medications (e.g. analgesics, triptans) is thought to cause or exacerbate chronic daily headaches in some patients. Results from uncontrolled studies have suggested that corticosteroids might ease the process of withdrawal from overused headache medications.

This study from Norway included 100 patients with medication-overuse headache; in 87, the underlying headache disorder was migraine (with or without tension headache). Patients were hospitalised, headache medications were stopped, and patients were randomised to receive oral prednisolone (60 mg daily for 2 days, 40 mg daily for 2 days, and 20 mg daily for 2 days) or placebo. After 3 days, they were discharged from the hospital and told to refrain from headache medication for 4 weeks.

The primary endpoint — the mean score on a headache pain scale during the first 6 days of withdrawal — did not differ between the groups. At 28 days, mean scores had decreased modestly in both groups, with no between-groups difference. Nearly all patients said that they did not use headache medication throughout the follow-up period.

Comment:

This randomised trial failed to confirm reports from uncontrolled trials that oral steroids reduce the severity of withdrawal headache in patients who chronically overuse headache medication. Remarkably, most patients stated that they remained drug free 1 month after the intervention, but it is unclear whether these reports were verified in any way.

— **Allan S. Brett**, MD

Reference

Bøe MG et al. Prednisolone does not reduce withdrawal headache: A randomized, double-blind study. Neurology 2007 Jul 3; 69:26-31.

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Level 8, 10 George Street, PO Box 6032, **Dunedin**
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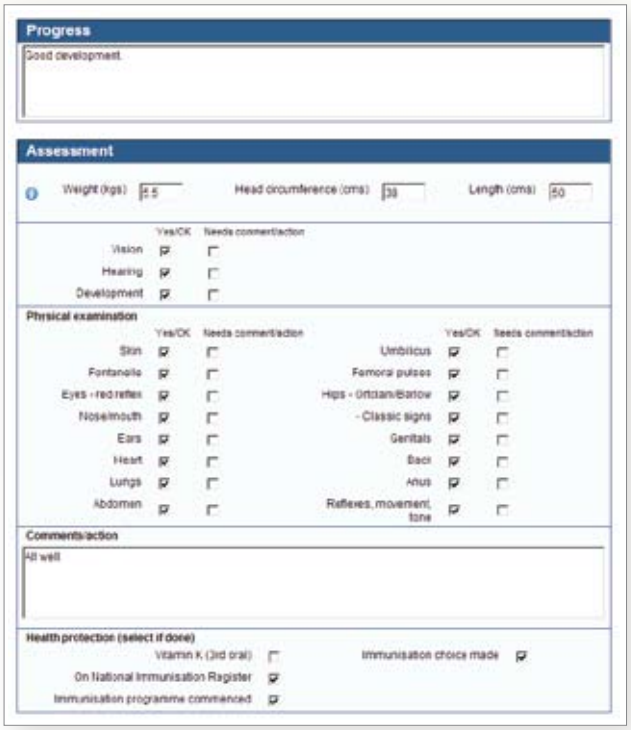
Well Child - Tamariki Ora



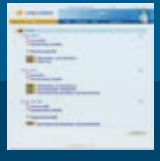
The ***Six Week Check*** module is designed to assist health professionals in completing a ***Six Week Well Child Assessment***. It does this by providing:

- A checklist of data required and physical examinations to perform.
- A facility for the storage of relevant information in the Practice Management System as an Outbox document for recording purposes and later reference.
- Plots of the recorded weight, height and head circumference measurements against the relevant growth percentile charts.
- Health promotion resources for babies and families.

*The screenshot to the left shows the form presented by the **Well Child - Six Week Check** module to gather the required information. This form doubles as a checklist for measurements and physical examinations required.*

These screenshots show some of the most popular of the currently available modules.


Diabetes

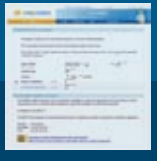

Nursing Management Guides


CVD


Chronic Kidney Disease

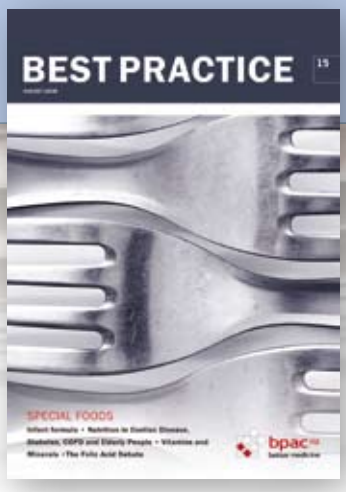

Atrial Fibrillation


Forms


Clinical Toolkit


Interactive Education


Healthy Children



Cultural Competence

Dear bpac,

You have featured two articles on "Cultural Competence" in the last two Best Practice Journals. BPJ13 had several articles on Maori issues and BPJ14 had the byline "Cultural Competence Series" above the article on Maori Mental Health.

I have been concerned that "Cultural Competence" is seen by many to be about Maori issues. The RNZCGP fuelled this concern by delegating its material on "Cultural Competence" to the Maori faculty and produced a document about "Cultural Competence" that made no mention of the use of interpreters. Of all the issues surrounding the care of people from other cultures, inability to communicate due to lack of shared language, surely has to go at the top of the list.

I have no problem at all with focussing on Maori health and really appreciated the focus on this. My problem is two-fold. The first is the invisibility of other cultural groups in this discourse; in fact many Maori view the issue as being about "Biculturalism": Maori and the rest as if all of us who are not Maori are in some way the same.

The second, which is more subtle, is that I am a supporter of Irihapeti Ramsden's thesis around Cultural Safety that argues that the best way to learn about the culture of a patient is to ask them....and that attempts to learn about "Maori" from sources other than the patient in front of you, risks stereotyping and compounding the problem of cross cultural care.

Language Line is now able to be used by GPs needing interpreting services at a cost of $22 per consultation. An article about the dangers of using "Ad hoc" interpreters and how to use professional ones might be a useful addition to this series.

Regards

Dr Ben Gray,
Senior Lecturer
Department of Primary Health Care and General Practice, Wellington School of Medicine and Health Sciences

When discussing cultural competence we have deliberately focused on Māori given that this is where the greatest health inequalities exist and therefore where the greatest gains can be made. This focus is relevant given the New Zealand context and provides examples to which all clinicians can relate.

This is not to imply that all non-Māori are the same. We have emphasised that even within one ethnic group there may be different world views and beliefs and agree that clinicians must not generalise and stereotype patients. As New Zealand becomes more culturally diverse, clinicians need to develop increased sensitivity to the influence of different cultures on health care beliefs and practices.

The evidence of disparities in health care is significant and the responsibility for achieving better outcomes is clearly shared broadly across society. Bpac will continue to contribute through education, analysis and advice.

Metformin and folate

Dear bpac

We are in a tutorial discussing the latest bpac publication and we note that metformin is listed as inhibiting folate absorption. As metformin is very commonly prescribed it is important to know how much of a clinical issue this effect could be. Should all type 2 diabetics on metformin have a folate check and at what age and how often? Any clues about this?

Regards

Dr Logan McLennan

GP, Wellington

Chronic therapy with metformin is associated with decreased absorption of vitamin B12. As certain processes in the body are dependent on the presence of both vitamin B12 and folate, folate levels are also subsequently decreased.

People using metformin are therefore at an increased risk of vitamin B12 and folate deficiency. The extent to which vitamin B12 and folate levels are decreased during treatment varies between patients and length of therapy.

There are no clear guidelines on who should be checked and at what age, however it would be reasonable to monitor vitamin B12 status once a year in people taking continuous metformin, especially older people and those who have taken metformin for several years. Unexplained anaemia-like symptoms would also indicate that testing is required. It is not necessary to monitor folate status as well, as vitamin B12 will be indicative of a metformin-related deficiency.

People taking metformin could also be encouraged to include foods in their diet that are rich in folate and B12 such as leafy green vegetables, red meat or fortified foods.

Gargling with aspirin

Dear bpac

Is there any evidence that gargling with aspirin relieves the pain of a sore throat?

GP, Dunedin

Although a common remedy for sore throat, there is no evidence that aspirin gargles are clinically effective for this indication.

There are no relevant systematic reviews of the effectiveness of aspirin gargles for sore throat. One small study found that a preoperative aspirin gargle was better than placebo in reducing the incidence of postoperative sore throat. However aspirin gargle was not as effective as benzydamine hydrocholoride (e.g. Difflam) gargle.[1]

Despite the lack of evidence, most medical references advise that aspirin gargles can be tried for sore throat. Aspirin gargles should not be swallowed if other methods of pain relief are being used. In some cases, gargling with aspirin may cause irritation to an already inflamed throat. Aspirin should not be used in children under 16 years.

Other methods for relieving the pain of a sore throat include paracetamol, lozenges (or anything that acts as a demulcent e.g. honey) and warm drinks.

1. Agarwal A, Nath S, Goswami D et al. An evaluation of the efficacy of aspirin and benzydamine hydrochloride gargle for attenuating postoperative sore throat: A prospective, randomised, single-blind study. Anaesth Analg 2006; 103(4):1001-3.

Do you prescribe Amizide?

Dear bpac,
I am writing as Chair of the Medicines Adverse Reactions committee (MARC) to seek BPAC's assistance in ensuring wider recognition of an important safe and quality use of medicines issue related to Amizide.

Amizide is a combination of hydrochlorothiazide 50 mg and amiloride HCl 5 mg. This is a very old formulation which is not used often now, but there are a number of patients who have been on it for long periods. The inappropriately high dose of hydrochlorothiazide, compared with 12.5 - 25 mg in all other modern thiazide combinations, represents a potential risk for patients. There are case reports of hyponatraemia and hypokalaemia with this combination, particularly in the elderly and it is not an effective potassium sparing combination. The only other hydrochlorothiazide combination containing a dose of greater than 12.5 mg is Triamizide (25 mg + 50 mg triamterene) - both are marketed generics and still fully subsidised by PHARMAC.

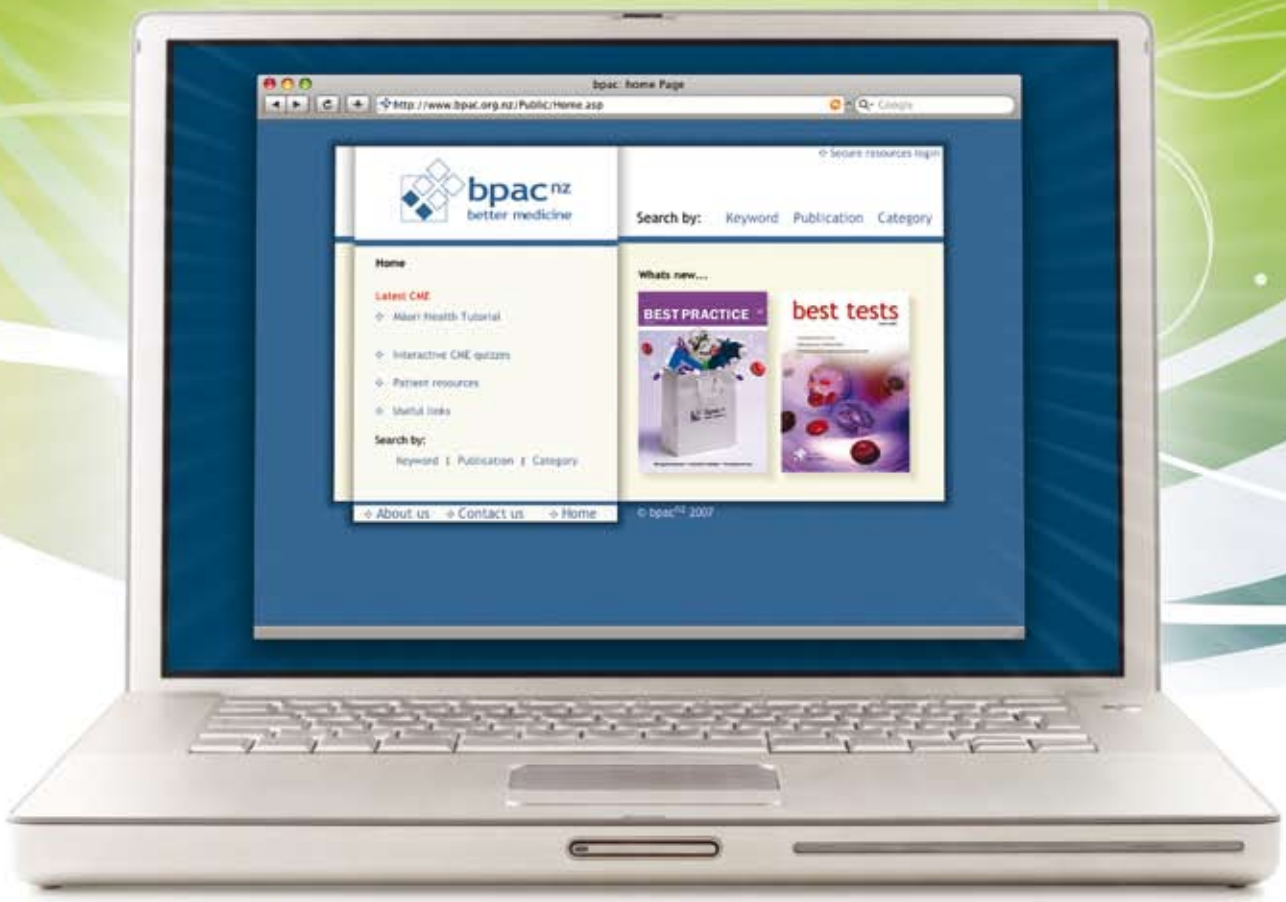
Review of the CARM data base does not suggest a disproportionate number of reported adverse reactions compared to other thiazides, partly because new use of Amizide is low. Nonetheless, patients are still being admitted to hospital with hyponatraemia or hypokalaemia on this combination. It is likely that most of these cases are so well recognised that they are not reported to CARM. Although the real incidence of these adverse effects remains uncertain, there is an important practice principle when using thiazides long term – use the lowest possible dose to minimise risks such as gout, new onset diabetes and hypokalaemia. Hydrochlorothiazide should not be used in doses exceeding 12.5 mg daily. Bendrofluazide doses should not exceed 2.5 mg daily and lower doses such 1.25 mg daily are often adequate.

The risk of metabolic adverse effects associated with thiazides is dose related. Furthermore, any additional antihypertensive benefit from the use of hydrochlorothiazide doses of greater than 12.5 mg daily is outweighed by the increase in metabolic adverse effects. The MARC considers the Amizide formulation to be inappropriate, given current knowledge, and that its risks may out-weigh benefits because of the inappropriately high dose of hydrochlorothiazide, particularly in the elderly.

Sincerely,
Timothy Maling
Chair, MARC.

We value your feedback. Write to us at:
Correspondence, PO Box 6032, Dunedin
or email: editor@bpac.org.nz

bestpractice online



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