Best Practice

Strong opioids in palliative care

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The week before Christmas

'Twas the week before Christmas
And all through the floor
Not a writer was writing
No words, no more

Diabetes was sorted, HbA_{1c} is the test
Opioids for strong pain, morphine is best
The adults were nestled, all snug in their beds
Fears of night cramps, danced in their heads

The chief with his paper, and I with my pen
Had just settled our brains for final review – again
When out in the hall, there arose such a clatter
We sprang from the room to see what was the matter

The site so beautiful, I reached for my tissues
It was our man from the printers, with eight shiny issues
I knew in a moment, our work must be done
We are off for the holidays, a place in the sun

BPJ, Best Tests and Reports, we call
Now dash away, dash away, dash away all!
So to NZ Post, the journals they flew
With his empty boxes, our printer man too

We wrote and we wrote and got it (almost all!) right
Happy Christmas to all, and to all a good night

Recommended vaccinations for staff working in primary health care

People who work in primary health care facilities are exposed to many vaccine-preventable diseases such as influenza, pertussis and measles. Maintaining a high rate of immunity within health care populations helps to reduce personal disease risk for health care workers and, importantly, reduces health care workers risk of transmission to patients at increased risk of developing complications following infection.

Why should I be up to date with my vaccinations?

1. Unvaccinated health care workers are at increased risk of vaccine-preventable diseases

Health care workers, including both clinical and non-clinical staff, are considered to have a "substantial" risk of acquiring or transmitting vaccine-preventable diseases, such as influenza, measles, mumps, rubella, pertussis, varicella and hepatitis B, depending on the individual setting.[1]

2. Vaccination of health care workers may reduce patient morbidity

Vaccination of health care staff reduces the risk of transmission of illnesses to vulnerable patients, and is also likely to reduce the spread of disease during community outbreaks.[1]

Influenza vaccination rates in health care workers in New Zealand are historically low

All District Health Boards in New Zealand offer free influenza vaccination to staff. In 2012, approximately 48% of all employees received an influenza vaccination. This rate was a slight improvement from 2011 (46%) and 2010 (45%). Rates were highest among doctors (57%) and lowest among midwives (37%). Nurses (46%), allied staff (50%) and other employees (46%) had similar rates of influenza vaccination. Immunisation rates differed among DHBs, with the highest rates achieved in 2012 in Capital & Coast and Canterbury DHBs and the lowest rates in Taranaki and West Coast DHBs.[6]

It has been suggested that annual influenza vaccination should be compulsory for all health care workers in New Zealand, unless medically contraindicated.[7] However, compulsory approaches do not necessarily gain the highest coverage, and at present there is limited evidence to support the clinical justification of this stance.

There is mixed evidence as to whether influenza vaccination among health care staff reduces transmission of influenza to patients. Two studies in long-term care hospitals in the United Kingdom found that overall mortality was reduced amongst residents when vaccinations were offered to staff.[2, 3] A Cochrane systematic review concluded that vaccinating health care workers did not reduce rates of laboratory-confirmed influenza, pneumonia or deaths from pneumonia in older people in long-term care. However, rates of influenza-like illness (which includes other viruses and bacterial infections), hospital admissions and overall mortality amongst older people were reduced.[4]

3. Lead by example

Endorsement of vaccination by health care professionals is a powerful factor in determining community vaccination rates. Numerous studies have shown that discussion with a General Practitioner or Practice Nurse can influence an individual's decision to be vaccinated, even if they did not initially want to be vaccinated.[5] Health care professionals, who have themselves been vaccinated, are better placed to encourage vaccination uptake within practice populations.

Vaccinations recommended for all staff working in primary care

The Immunisation Advisory Centre recently released guidance for vaccinations for both clinical and non-clinical staff working in primary care (Table 1, over page). Testing is also recommended for clinical staff to determine their immunity status against hepatitis B and tuberculosis.

Vaccination is a personal choice and staff should not be pressured into being vaccinated. However, providing education about vaccinations can help to address any barriers or misconceptions.
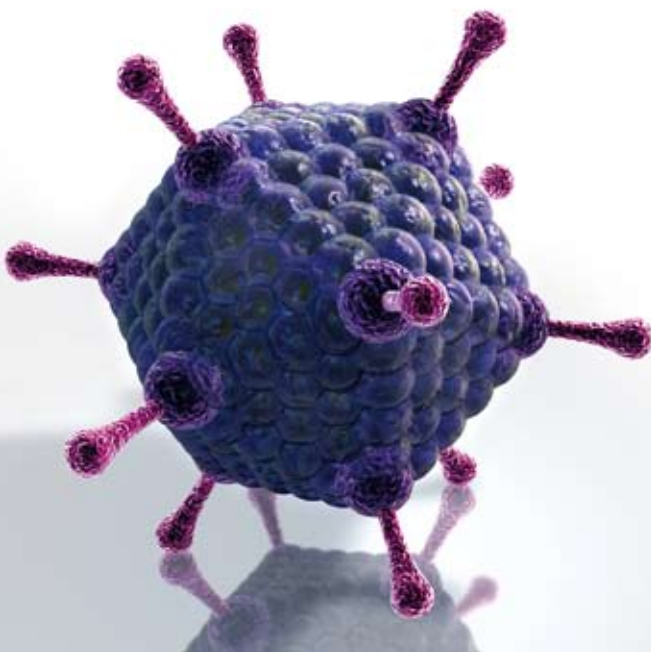
Vaccination among a small group of general practice staff in New Zealand

The Immunisation Advisory Centre vaccination resource was developed in conjunction with Dr Dayna More, based on her General Practice Education Programme project: Vaccination of staff in primary care – Attitudes and recommendations.[8]

Although this study only included 31 primary health care workers in one geographical region, results revealed that:[8]

- All but one person had received their full set of childhood vaccinations
- 71% (22 people) had received an influenza vaccination in the last two years, which was in most cases funded by their workplace
- Of those who did not receive an influenza vaccine, reasons included; no underlying medical conditions/healthy, fear of needles, perception that their risk of contracting influenza was low, belief that the vaccine is ineffective
- 68% (21 people) said that they would be happy to have vaccinations if they were recommended due to their employment in primary health care, although most said they would be less likely to if they were not funded by their workplace
- Of those who would not be happy to receive vaccinations, reasons given included; preferring natural products, perception of low disease risk, wish to become more "holistic" and concerns about adverse effects and the ongoing need for boosters

Table 1: Vaccination recommendations for staff working in primary care (Immunistaion Advisory Centre)

Disease	Vaccine	Who to vaccinate[a]	Testing for immunity	Vaccination required[b]
Hepatitis A	Hepatitis A: Avaxim™ Havrix® Hepatitis A & B:[c] Twinrix®	Clinical and cleaning staff	▪ Serology not routinely recommended.	▪ A course of two doses 6–12 months apart.
Hepatitis B	Hepatitis B: Engerix-B® Hepatitis A & B:[c] Twinrix® HBvaxPro®	Clinical staff	▪ Check anti-HBs serology for clinical staff with a history of hepatitis B vaccination, if no previous laboratory evidence of immunity. ▪ Serology not required when there is no history of hepatitis B vaccination. ▪ An anti-HBs level of ≥10 IU/L at any time is evidence of long-term immunity, even if antibodies have subsequently waned.	▪ If not previously vaccinated: course of three doses at 0, 1 and 6 months. ▪ If previously vaccinated and anti-HBs levels <10 IU/L: give one dose of hepatitis B vaccine and repeat serology a month later. ▪ If repeat serology is <10 IU/L, give two more doses of hepatitis B vaccine one month apart to complete a second course of three hepatitis B vaccine doses and repeat serology one month after the final dose. ▪ If anti-HBs levels <10 IU/L following a second full course of hepatitis B vaccine the person should be considered a vaccine non-responder
Influenza	Fluarix®, Fluvax®, Intanza®, Vaxigrip® Influvac®	Clinical and non-clinical staff	▪ Serology not required.	▪ Annual influenza vaccination recommended.
Measles Mumps Rubella	M-M-R® II	Clinical and non-clinical staff	▪ Serology not required. ▪ Presumptive immunity when two documented doses of MMR vaccine,[d] laboratory evidence of immunity, or born in New Zealand before 1969.	If New Zealand born on/after 1 January, 1969 and does not have two documented doses of MMR vaccine or laboratory evidence of immunity: give a course of two doses of MMR vaccine administered a minimum of one month apart.
Poliomyelitis	IPV: IPOL	Clinical and cleaning staff	▪ Serology not required.	Healthcare workers with a history of a primary course of polio vaccination (three doses) who are at increased risk of exposure or in direct contact with a case of polio should have a single lifetime booster dose of IPV.
Tetanus[e] **Diphtheria**[e] **Pertussis**	Tdap: Adacel® Boostrix®	Clinical and non-clinical staff	▪ Serology not required.	▪ Single booster dose of Tdap every 10 years.

Table 1 (continued): Vaccination recommendations

Disease	Vaccine	Who to vaccinate[a]	Testing for immunity	Vaccination required[b]
Tuberculosis (TB)	BCG Vaccine SSI	Clinical staff	▪ Staff should undergo baseline screening with a risk assessment questionnaire and either two-step Tuberculin Skin Testing (TST/Mantoux test) or an interferon gamma release assay (IGRA, QuantiFERON Gold assay) when starting employment.[f]	▪ Universal BCG vaccination is not indicated for health care workers as most are at comparatively low risk of occupationally acquired TB.
Varicella	Varilrix® Varivax®	Clinical and non-clinical staff	▪ Presumptive immunity when there is a good history of varicella infection, diagnosis or verification of herpes zoster by a health professional, two documented doses of varicella vaccine,[d] or laboratory evidence of immunity or disease. ▪ Check serology if no history of varicella infection and not previously vaccinated.	▪ A course of two doses 4-8 weeks apart if non-immune.

Notes

a. Clinical Staff – General Practitioners (GPs), GP Registrars, Practice Nurses. Non-Clinical Staff – Medical Receptionists, Practice Managers

b. All staff should have received a primary course of vaccines against tetanus, diphtheria, polio, measles, mumps and rubella (funded adult catch-up vaccines) and hepatitis B (non-funded adult catch-up vaccine). If they have not received all of these, they will need to receive catch-up vaccinations (refer to the Immunisation Handbook 2011, pages 20-21 and 384).

c. Twinrix® is an alternative to the monovalent hepatitis A and hepatitis B vaccines when vaccination against both diseases is required. Give a course of three doses at 0, 1 and 6 months.

d. The first vaccine dose must have been administered on or after the first birthday; the second vaccine dose must have been administered no earlier than one month (i.e. a minimum of 28 days) after the first dose.

e. ADT™ Booster (Td) is on the National Immunisation Schedule for adults aged 45 years and 65 years. However, if receiving 10 yearly Tdap vaccination these doses are not required.

f. The QuantiFERON TB-Gold test is appropriate for employment-related screening for latent TB infection, e.g. health care workers. For all other patients, the TST/Mantoux test is the funded test for excluding respiratory TB. Note that a false-positive result is possible with TST/Mantoux in people who have received a BCG vaccination.

References

1. Shefer A, Atkinson Q, Friedman C, et al. Immunization of health-care personnel. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention; 2011. Available from: www.cdc.gov (Accessed Dec, 2012).

2. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet 2000;355(9198):93–7.

3. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis 1997;175(1):1–6.

4. Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev 2010;(2):CD005187.

5. Brunton C, Weir R, Jennings L. Knowledge and attitudes about influenza vaccination amongst general practitioners, practice nurses, and people aged 65 and over. N Z Med J 2005;118(1214):U1434.

6. Ministry of Health (MoH). 2012 workforce immunisation coverage rates by District Health Board (DHB). Wellington: MoH; 2012. Available from: www.health.govt.nz (Accessed Dec, 2012).

7. McLennan S, Celi LA, Roth P. The Health and Safety in Employment Act and the influenza vaccination of healthcare workers. N Z Med J 2007;120(1250):U2442.

8. More D. Vaccination of staff in primary care – Attitudes and recommendations. Unpublished research. Lower Hutt: General Practice Education Programme (GPEP); 2012.

Strong opioids
for pain management in adults
in palliative care

Strong opioids are a safe and effective treatment for moderate to severe pain in adults receiving palliative care, if used appropriately. However, individual patient responses vary making dose titration an important aspect of pain management. Constipation, nausea, falls and other adverse effects are common and should be anticipated in patients who are beginning, or taking increasing doses of, strong opioids. It is important to be alert for opioid toxicity which can be challenging to manage. Switching between opioids should be undertaken with caution as the equivalent dose will vary between patients.

Palliative care, pain and strong opioids

As the New Zealand population ages and increases, the number of people requiring palliative care will grow. It is estimated that by 2026 approximately 20 000 adult New Zealanders will require palliative care.[1] Hospices are traditionally viewed as the institutions that deliver end-of-life care to terminally ill patients, however, most deaths in New Zealand occur in hospitals (34%), residential care facilities (31%) and private residences (22%).[1] Primary care clinicians are therefore frequently and increasingly involved in treating patients with terminal illness in community settings, often alongside palliative care teams.

Pain requiring strong opioids is common in terminally ill patients

Pain is estimated to be the most prevalent symptom preceding all deaths occurring in a palliative care setting in New Zealand.[1] Strong opioids, particularly morphine, are an effective treatment for moderate to severe pain, and as many as two-thirds of adults with terminal cancer will require treatment with a strong opioid.[2] A similar need for opioids is also observed in patients with other advanced and progressive illnesses, e.g. heart failure, kidney and liver disease, and neurodegenerative conditions.[2] Pain is increasingly regarded as the fifth vital sign and all patients in palliative care should be carefully assessed for pain to prevent under-treatment and reduced quality of life.

Opioids are also indicated for the treatment of breathlessness in palliative care. For further information see: "Managing breathlessness in palliative care", BPJ 47 (Oct, 2012).

Which strong opioids are available in New Zealand?

The term strong opioid refers to medicines classified as being on step three of the WHO analgesic ladder.[3] In New Zealand the following strong opioids are available:

- Morphine – oral solutions, immediate-release tablets, modified-release tablets and capsules, injections

- Oxycodone – oral solution, immediate-release capsules, modified-release tablets and injection. Oxycodone + naloxone modified release tablets are also available but are not subsidised.

- Fentanyl – transdermal patches, injection

- Methadone – oral solutions, immediate-release tablet, injection

- Buprenorphine – injection and transdermal patches are available but neither are subsidised

- Pethidine – tablets and injection are available but not appropriate for use in palliative care

The most prevalent diseases causing death in New Zealand adults in palliative care (2005 – 2007) were cancer (43%), circulatory diseases (27%), respiratory diseases (9%), endocrine, nutritional and metabolic disorders (5%) and diseases of the nervous system (4%).[1]

Guidance for pain management

Pain is a complex sensation and symptom control with analgesia is just one treatment approach that should be used in a palliative care setting (see "Total pain and the pain platform"). For people with a terminal illness, maintaining relationships and meaningful activities of living are also important aspects to care. Health care professionals can help terminally ill patients achieve this through knowledge of the patient's interests and by maintaining good communication with the patient's family/whānau.

Pain assessment

Assessing pain is the first step in management. This involves asking the patient about the site, severity and nature of the pain, as well as asking how it interferes with daily activity and what (if anything) provides relief. If the patient has more than one source or site of pain, each should be treated as an individual symptom and the process repeated. Open-ended questions are recommended. Table 1 provides some suggested questions.

The Support Team Assessment Schedule (STAS) is an adapted pain scale that allows the effect of pain on day–to-day life to be assessed. The STAS has been validated in a palliative care setting and may be useful for establishing a baseline against which analgesic effectiveness can be assessed when titrating doses.[4]

The patient is asked to assign a number to their pain based on how it affects them:

- **4** = Overwhelming and continuous pain, unable to concentrate on other matters
- **3** = Severe pain that is frequently present, activities and concentration markedly affected
- **2** = Moderate distress with occasional bad days, pain limits some activities
- **1** = Occasional grumbling, single pain where the patient is not bothered by the symptom

The STAS can be individualised to patient circumstances by providing specific examples of activities that might be affected by pain, e.g. gardening or making a cup of tea.

Pain assessment can also reveal the pathophysiology of a patient's pain. In some circumstances this can guide analgesic treatment, including the introduction or maintenance of adjuvant analgesics (see "Adjuvant analgesics", Page 13).

Table 1: Examples of open-ended questions to use when assessing pain in a palliative care setting

Question	Comment
How bad does the pain feel? (see "Support Team Assessment Schedule")	The effectiveness of interventions for pain control can only be assessed after having measured pain severity. Pain is subjective, so this can only be assessed by the patient.
What do you think this pain means?	Patients may believe that increased pain signals a deterioration in their condition, e.g. cancer metastasising. This is likely to influence their experience of pain.
What is the worst thing about the pain?	Optimising quality of life is the primary focus of palliative care. An important part of this is removing barriers to maintaining/continuing relationships and activities.

If a patient is experiencing cognitive decline or impairment it may be necessary to include behavioural features in the assessment of pain, e.g. breathing patterns, facial expressions or vocalisation. There are many tools available for assessing pain in people with cognitive decline or impaired speech. A New Zealand review found that the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) was easily used by caregivers in specialist dementia care facilities and resulted in increased use of "as needed" analgesic medicines and reduced levels of caregiver stress.[5]

The PACSLAC tool is available from: **www.rgpc.ca/best/PAIN%20Best%20Practices%20-%20ML%20Vanderhorst%20(June%2007)/PACSLAC.pdf**

The WHO analgesic ladder

Pain treatment typically begins at step one of the WHO analgesic ladder with paracetamol and/or non-steroidal anti-inflammatory drugs (NSAIDs). If tolerated, these medicines should be continued throughout treatment. A weak opioid such as codeine can then be introduced at step two, although this step is often bypassed in patients who are terminally ill. If a weak opioid does not provide adequate pain control, this should be replaced by a strong opioid, generally oral morphine.

Discussing opioid treatment with patients

Before prescribing strong opioids, discuss any concerns or expectations that a patient or their family/whānau may have concerning treatment. Some patients associate strong opioids with end-of-life and may be reluctant to begin treatment, or they may be worried about overdose or addiction. Pain control through the night, or when family/whānau are absent may also be a concern. Reassurance can be provided that opioids are the most widely used medicine for the treatment of pain in palliative care and that appropriate doses of opioids do not cause respiratory depression. Addiction to opioids is also uncommon in patients with chronic pain or cancer.[8, 9] The use of opioids in palliative care is for symptom control alone and opioid use is not associated with decreased time to death in patients with advanced illness.[8]

Breakthrough pain, incident pain (pain as a consequence of activity) and the management of adverse effects should also be discussed. The ABC acronym (Antiemetic, Breakthrough analgesia and Constipation) is a useful tool for guiding this conversation. Laxatives should be routinely prescribed when commencing opioids (including codeine), either regularly or "as needed". Analgesia "as needed" should always be prescribed for breakthrough pain or to be taken pre-emptively for

"Total pain" and the pain platform

The concept of "total pain" recognises that pain is a subjective experience that is influenced by physical, psychological, social and spiritual elements. A patient's pain threshold can be raised through positive influences, e.g. improved sleep, receiving companionship and sympathy and reducing fear and anxiety.[6] Equally, allowing patients to express negative emotions can alleviate distress causing pain.[6] Patients with a terminal illness, and their families or whānau may be angry or frustrated about bureaucracy, diagnostic delays, the unavailability of resources, or treatment failure. Recognising that such feelings are valid and providing an outlet for expression can be a valuable part of pain management.

Recently, a new model for the treatment of pain called the Pain Platform has been proposed that incorporates the wide ranging inputs which contribute to pain. This model encourages clinicians to think and act broadly when treating pain as well as acknowledging non-pharmacological approaches to pain management that are already employed by many clinicians.[7] This may include adjuvant therapies such as physiotherapy, counselling, support groups, relaxation, acupuncture and complementary and alternative medicines.

The pain platform has yet to be validated in clinical trials in a palliative care setting.

Further information on the pain platform is available from: Leung L. From ladder to platform: a new concept for pain management. J Prim Health Care 2012;4(3):254–8.

incident pain that occurs predictably with certain activities, e.g. showering. Medicines for anticipated adverse effects such as nausea should be prescribed "as needed" and may be useful should problems occur after hours.

Following this discussion the patient and their family/whānau should feel that they understand the expected trajectory of the patient's condition and that they know who to contact if the patient's condition changes suddenly. This may involve hospice or palliative care input or contacting after hours services. An Advance Care Plan (ACP) containing the patient's preferred contacts, plus their wishes and preferences for end-of-life care can be implemented where appropriate. The conversations that occur when discussing a future deterioration in health status are beneficial even if a formal ACP is not completed.

Selecting the appropriate opioid

Oral strong opioids are generally the recommended treatment for moderate to severe pain in people receiving palliative care, in the absence of significant renal or hepatic dysfunction.[2] Alternative routes of administration, e.g. subcutaneous infusions via a syringe driver, may be considered for patients unable to tolerate oral opioids or where pain is poorly controlled.

See "When and how to use a syringe driver in palliative care", BPJ 48 (Nov, 2012).

Oral morphine is generally the first-line strong opioid for pain in palliative care.[2] Morphine is the most extensively studied, widely available and commonly used opioid in palliative care. A recommended starting dose for patients not currently taking opioids is oral morphine 2.5 – 5 mg, every four hours.[10] When a stable regimen has been achieved, generally after two to three days, the patient can be converted to long-acting morphine, usually dosed twice daily, approximately every 12 hours.[10] If the patient is regularly requiring breakthrough analgesia, all doses taken over the previous 24 hours can be added together to calculate a new 24 hour regimen and a new breakthrough dose calculated at one-sixth of the total 24 hour requirement.[10]

There is no maximum dose for morphine in a palliative care setting, although typically doses do not exceed 200 mg in a 24 hour period.[10] If the patient is requiring rapidly increasing doses of opioid, there may either be a neuropathic component to the pain (Table 2), or a degree of opioid tolerance or toxicity, and a careful reassessment is needed. It is recommended that if the dose is greater than 400 mg in a 24 hour period then a palliative care team should be consulted and adjuvant

analgesics may be considered if they are not already being used (see "Adjuvant analgesics").[10] If a patient has poorly controlled pain, despite high opioid doses, the possibility of impaired medicine absorption should be investigated, e.g. a gastrointestinal blockage.

Active opioid metabolites can accumulate in patients who are frail, debilitated or who have significant renal impairment.[10] This can lead to opioid toxicity, characterised by myoclonic jerks, excessive sedation or confusion, restlessness and hallucinations. Hyperalgesia (increased sensitivity to pain) can also be a feature of opioids toxicity. Patients should be reviewed for features of toxicity of doses are being increased rapidly or to high levels. Switching to another opioid should be considered if opioid toxicity is unable to be managed with appropriate dose adjustment.

The central nervous system effects of morphine may also be amplified when it is taken in combination with other centrally acting depressants, e.g. benzodiazepines, phenothiazines, tricyclic antidepressants or alcohol.[10] Long-acting morphine may have a faster onset of action when taken with metoclopramide.[10] If adverse effects are unable to be managed, consultation or review by a palliative care physician is recommended.[2]

Oral oxycodone is a second-line treatment option for patients unable to tolerate oral morphine. An appropriate initial starting dose for patients not currently taking opioids is oxycodone 1 – 3 mg oral solution four to six-hourly, or when a stable regimen has been achieved, slow release oxycodone 5 mg capsules every 12 hours.[10] See oxycodone conversion (Page 15) for dose calculations for patients already taking an opioid.

If a patient has significant renal impairment, oxycodone may not be a suitable treatment as the active metabolite may accumulate.[10] There is also the possibility of increased blood concentrations of oxycodone causing an increased clinical effect and risk of toxicity if oxycodone is taken in conjunction with some CYP metabolising enzyme inhibitors, e.g. fluoxetine, bupropion, paroxetine, quinine and valproate.[10] The central nervous system effects of oxycodone may also be amplified when it is taken in combination with other centrally acting depressants.[10]

Fentanyl is a safer option for pain in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2.[11] Fentanyl may also be considered for patients with problems such as recurrent bowel obstruction, difficulty swallowing, e.g. head or neck cancer, or resistant constipation.

The use of subcutaneous fentanyl in a community setting can be problematic, as it is short-acting. If appropriate, 25 micrograms subcutaneously can be administered "as required", or 10 – 12.5 micrograms if the patient's eGFR is closer to 10 mL/min/1.73 m^2. A syringe driver may need to be considered early in treatment if frequent injections are needed.

Transdermal fentanyl patches deliver a constant amount of drug over 72 hours. Transdermal fentanyl is only recommended in patients with stable pain, and usually only in patients who are currently taking opioids.[10] However, in individual cases, a palliative care physician may recommend that an opioid-naive patient is treated with the lowest strength patch (12.5 micrograms/hour), titrated to achieve pain control. A long-acting morphine or oxycodone preparation can be used to provide analgesia during the first 24 hours, if renal function is satisfactory, until the serum fentanyl concentration reaches a steady state. When a patient's renal function is significantly impaired, occasional doses of immediate release opioids can be used "as needed" until the fentanyl is providing analgesia, as well as being available for breakthrough pain during this time.

A 12.5 microgram/hour fentanyl patch is approximately equivalent to 10 mg oral morphine 4-hourly, however, the rate of fentanyl delivery may be increased if the patient's temperature is elevated or the "patched" area of skin is exposed to heat.[12] Cutting a fentanyl patch is not usually recommended, however, it may occasionally be necessary, and if so, a diagonal cut is the best method to achieve an accurate dose. Fentanyl patches should be removed after 72 hours, and not changed more frequently than this. Once fentanyl patches are discontinued residual medicine in the dermis will continue to have an effect for up to 24 hours, and the patient should be monitored for up to 48 hours for residual effects.

Breakthrough pain can be managed with a different opioid or subcutaneous fentanyl at an appropriate dose and titrated to effect. The same dose of fentanyl can be administered by the sublingual or intranasal (unapproved) route using the injectable formulation (100 micrograms in 2 mL), but these methods of administration may be impractical.[10]

Oral methadone is an alternative, following consultation with a palliative care physician, for patients unable to tolerate oral morphine or oral oxycodone, e.g. due to individual reactions, renal failure, or for patients with poorly controlled neuropathic pain.[10] However, methadone is a difficult opioid to titrate because there is a wide variation in individual patient response, it has a long half-life (approximately 30 hours) and a variable analgesic effect (six - eight hours initially then

Adjuvant analgesics should be continued or introduced for specific indications

The type of pain experienced by a patient is used as a guide for selecting an appropriate adjuvant analgesic, as shown in Table 2.

Table 2: Examples of analgesics given in addition to strong opioids for the treatment of pain in adult palliative care[10]

Type of pain	Treatment examples
Neuropathic pain	Tricyclic antipressants (e.g. amitriptyline, nortriptyline), antiepileptics (e.g. gabapentin, sodium valproate)
Bone pain	NSAIDs (e.g. ibuprofen, diclofenac or naproxen), bisphosphonates (e.g. zoledronic acid)
Pain from skeletal muscle spasm	Muscle relaxant (e.g. diazepam, clonazepam, baclofen)
Pain from smooth muscle spasm	Anticholinergic/antimuscurinic (e.g.hyoscine butylbromide)
Bladder pain	Urethral or suprapubic catheterisation for lower urinary tract obstructions
Increased intracranial pressure, liver capsule stretch pain or tenesmus due to tumour	Steroids (e.g. dexamethasone)

22 – 48 hours on repeated dosing).[10] It takes five to seven days, or longer, to reach steady-state.[10] If titration occurs too quickly, accumulation and toxicity can occur. Patients who have tolerance to other opioids are also at risk of respiratory depression due to incomplete cross-tolerance.[13] Methadone can cause QT prolongation and should be used with caution in patients with a history of cardiac disease, respiratory depression or who are concurrently taking medicines that can also prolong the QT-interval, e.g. citalopram.[12]

For patients not currently taking opioids, methadone 2.5 – 5 mg, twice daily is an appropriate starting dose.[10] See methadone dose conversion (opposite page) for dose calculations for patients currently taking opioids.

Prescribing restrictions with opioids

Under the new dispensing frequency rule, pharmacists can now determine the frequency at which some medicines are dispensed, however, pharmacists are NOT eligible to initiate patients for more frequent dispensing for medicines on the "safety list". Strong opioids are classified as a "safety medicine". Prescribers no longer need to endorse safety medicines, but must specify the maximum quantity or period of supply to be dispensed at any one time.

There is a legal prescribing limit of 30-days total supply on any prescription for strong opioids (Class B controlled drugs). Pharmacies can generally only supply strong opioids at a maximum of ten-day quantities for subsidy purposes, however, a patient with problems of mobility or access to a pharmacy can sign a declaration at the pharmacy to have the 30 day supply dispensed all at once. If the prescriber wishes to limit supply of the controlled drug they can specify the frequency at which the medicine can be dispensed, e.g. seven day supply with three repeats.

Without specific prescriber instructions, pharmacy convention is to supply the maximum "as required" doses allowable on a prescription. This can lead to risks associated with patients storing a surplus of strong opioids at home. Therefore "as required" prescriptions should include the appropriate quantity and the dispensing frequency.

Examples of prescription instructions for morphine

Example 1:

Rx Morphine oral liquid 1 mg/mL

Take 2.5 - 5 mg (2.5 – 5 mL) as required for pain, up to every 4 hours

Mitte one hundred mL

Note: If "one hundred mL"* is not specified on the prescription the patient will be given three hundred mL (10 days at the maximum of 6 doses/24 h = 60 doses).

If a patient runs out early of "as required" morphine oral liquid, the prescriber should take the opportunity to review pain control and change the oral liquid to modified release tablets or capsules.

Example 2:

Rx Morphine LA 30 mg capsules

Take one capsule twice daily

Mitte fourteen capsules with 3 repeats

AND

Rx Morphine immediate release tablets 10 mg

Take one tablet as required for breakthrough pain, up to every 4 hours

Mitte twenty tablets with 2 repeats

If "7 days supply", rather than "20 tablets" is stated, the patient will be given 42 tablets of 'prn' immediate-release tablets (7 days at the maximum of 6 doses/24 h = 42 doses).

* When writing a controlled drug script, it is recommended that the volume of liquid/number of pills supplied is written out in words rather than numerals to prevent the possibility of prescription tampering.

Switching from oral morphine to another opioid

Increased dosing of opioids is often required in patients receiving palliative care. This can be due to a combination of opioid tolerance and disease progression. A change of opioid may be considered if the patient develops opioid toxicity or if severe opioid-induced adverse effects occur that are unresponsive to treatment. Generally, patients who change opioids begin on morphine and then switch to oxycodone, fentanyl or methadone. Depending on knowledge and clinical experience, consultation with a local hospice or palliative care service may be advisable before trialling another opioid if a patient has co-morbidities, e.g. hepatic and renal dysfunction, complicated opioid intolerance, or when switching to methadone.[2]

Oxycodone conversion following morphine treatment is the simplest opioid switch. The oral availability of oxycodone is approximately twice that of morphine, therefore 20 mg oral morphine is approximately equivalent to 10 mg oral oxycodone.[10] In practice the conversion appears to be less than 2:1 for patients in palliative care, and it is important to review efficacy. If the medicines are being delivered subcutaneously then the doses are approximately equivalent, i.e. 10 mg subcutaneous morphine equals 10 mg subcutaneous oxycodone.[10]

Fentanyl delivered via patches or subcutaneous injections is approximately 150 times more potent than oral morphine, e.g. 10 mg oral morphine is equivalent to 66 micrograms subcutaneous fentanyl (Table 3).[10]

Table 3: Conversion dose equivalence estimates for oral morphine and fentanyl patches*[10]

Oral morphine (mg/24 hours)	Fentanyl patch (micrograms/hour)
<60	12.5
60 – 134	25
135 – 224	50
225 – 314	75
315 – 404	100
405 – 494	125
495 – 584	150

* It is important to consult this table when calculating an appropriate opioid dose for breakthrough pain

Fentanyl is less likely to cause constipation than morphine, and diarrhoea may occur if converting from morphine to fentanyl.[10] Doses of laxatives should be reduced when converting from morphine to fentanyl.[10]

Methadone dosing is rarely influenced by renal or hepatic dysfunction.[10] However, the dosing ratio between morphine and methadone varies widely and consultation with a palliative care service is strongly recommended when converting to methadone from another opioid. The Toombs/Ayonide method is one method for calculating the appropriate methadone dose, however, extreme caution is required.[10] Table 4 is used to convert the total daily morphine dose into a predicted daily methadone dose. This is then divided by three and given eight-hourly, e.g. a total daily dose of 300 mg of oral morphine equates to 30 mg of methadone daily given as 10 mg, eight-hourly.[10] However, for patients on stable doses of methadone, 12-hourly dosing is acceptable.[12] In these situations, methadone can also be used for breakthrough pain at a dose of one-tenth of the daily dose, given no more frequently than every three hours and at a maximum of four doses per 24 hours without clinical review or expert advice. Alternatively, short-acting preparations of morphine or oxycodone can be used for breakthrough pain.

Table 4: Approximate conversion ratios for calculating morphine to methadone dose equivalences[10]

Oral morphine (mg/24 hours)	Ratio of morphine to methadone
<100	3 : 1
100 – 300	5 : 1
300 – 600	10 : 1

For further information see: "Methadone – safe and effective use for chronic pain", BPJ 18 (Dec, 2008)

Managing adverse effects

Almost all patients taking strong opioids will experience ongoing constipation.[2] Nausea, vomiting and drowsiness are also common in people taking strong opioids, but are often transitory.[2] Regular follow-up is important to monitor adverse effects, particularly during the titration stage of treatment.

Constipation is an expected adverse effect of strong opioids and regular preventive laxatives should be prescribed prophylactically, e.g. docusate + senna 50 mg tablets (combined stool softener and stimulant), one or two tablets, twice daily. If constipation occurs, and there is no

gastrointestinal obstruction, increase the dose to two or three tablets, twice daily.[14] Bisacodyl is an alternative stimulant laxative, available as tablets and suppository. Docusate 120 mg tablets, one or two tablets, twice daily, can be useful as a stool softener. Consider stopping medicines that exacerbate constipation, e.g. ondansetron, tricyclic antidepressants, and encouraging adequate fluid and fibre intake and mobility if appropriate. If gastrointestinal obstruction or perforation is not suspected, the macrogol 3350 laxative powder (Movicol or Lax-Sachets) may be added (funded under Special Authority). These medicines draw fluid into the bowel to soften the stool and stimulate bowel motions.

If treatment is ineffective after 24 – 48 hours then a digital rectal examination should be performed and treatment adjusted depending on whether the rectum is empty or full. If soft faeces are present, two 10 mg bisacodyl suppositories should be administered against the wall of the rectum.[14] If hard faeces are present, one 10 mg bisacodyl suppository should be placed against the rectum wall and one glycerine suppository placed in the faeces.[14]

Patients with an empty rectum can be treated with dantron (danthron) + poloxamer, 5 – 10 mL, taken before bed. The formulation comes in two strengths – dantron 25 mg/5 mL + poloxamer 200 mg/5 mL and dantron 75 mg/5 mL + poloxamer 1 g/5 mL. Dantron with poloxamer is contraindicated in patients with an intestinal obstruction or an inflamed bowel.[12]

Once constipation is relieved, continue regular treatment with a higher dose of laxatives to prevent further constipation. Naloxone with oxycodone is formulated to minimise opioid-induced constipation, and is a possible alternative strategy for preventing constipation in people using oxycodone, although this is not subsidised and patients will have to meet the cost of treatment.[15]

Nausea with or without vomiting is experienced by approximately 25% of people taking strong opioids and is more common in females than males.[16] For some people taking opioids, nausea is more distressing than pain.[10] However, the nausea is often transitory. Opioid-induced nausea can be produced through direct stimulation of the chemoreceptor trigger zone, reduced gastrointestinal motility or enhanced vestibular sensitivity.[16] In some patients, multiple antiemetics with different mechanisms of action will need to be trialled, or combined, to establish an effective treatment, these include:

Haloperidol, 0.5 – 1 mg orally, once at night, can be given for the treatment of chemoreceptor trigger zone induced nausea.[12] This can be increased to twice daily and also given

subcutaneously by injection or infusion. Doses above 3 mg/day are rarely indicated for the management of nausea.

Metoclopramide (oral, subcutaneous or intravenous) 10 mg, three times daily (half an hour before food) is effective for the treatment of nausea caused by reduced gastrointestinal motility.[12] Reduce this dose by 50% in patients with significant renal dysfunction and avoid if there is a complete intestinal obstruction present. Four times a day dosing (40 mg/day) may be needed for gastric stasis or dysmotility syndromes. Akathisia (motor restlessness) is a known adverse effect of metoclopramide.

Domperidone, (oral) 10 – 20 mg, four times a day (half an hour before food) has a lower incidence of adverse effects than metoclopramide.[10] It is useful as pro-motility medicine, however, no parenteral preparations are available.

Cyclizine, 50 mg (12.5 – 25 mg in older patients), three times a day orally or by intravenous injection is effective for the treatment of nausea caused by vestibular stimulation, however, this should be used with caution where there is clinical evidence of gastrointestinal obstruction as it may cause constipation.[12] Cyclizine can also be given via subcutaneous infusion.

Hyoscine patches, one patch (1 mg per 72 hours) behind the ear is effective for nausea caused by vestibular sensitivity.[10] This medicine should not be used with metoclopramide or domperidone, as their prokinetic effects may be reduced. Hyoscine patches are often poorly tolerated due to anticholinergic adverse effects, such as dry mouth, constipation and confusion.[10]

Ondansetron may cause or exacerbate constipation and is not recommended routinely in a palliative care setting.[10]

If the patient is experiencing persistent nausea then advice from a hospice or local palliative care service should be sought.

Drowsiness often occurs when opioid treatment begins or doses are increased, but it is often transitory, resolving over a period of days.[2] Patients who are mobile are at increased risk of falls during this time. Persistent drowsiness that is accompanied by respiratory depression, constriction of the pupil, ventricular arrhythmias or seizures, suggests opioid toxicity and a reduction in dose should be considered.[2] If a patient taking strong opioids is persistently drowsy then, depending on the stage of the illness, consider switching opioids.[2]

References

1. Palliative Care Council of New Zealand. National health needs assessment for palliative care. Phase 1 report: Assessment of palliative care need. Cancer Control New Zealand: Wellington; 2011.

2. National Institute for Health and Clinical Excellence (NICE). Opioids in palliative care: safe and effective prescribing of strong opioids for pain in palliative care of adults: NICE clinical guideline 140. NICE: Manchester; 2012. Available from: www.nice.org.uk (Accessed Dec, 2012).

3. World Health Organisation. WHO's pain ladder. 2012. Available from: www.who.int/cancer/palliative/painladder/en/ (Accessed Dec, 2012).

4. Higginson IJ, McCarthy M. Validity of the support team assessment schedule: do staffs' ratings reflect those made by patients or their families? Pal Med 1993;7(3):219–28.

5. Cheung G, Choi P. The use of the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) by caregivers in dementia care facilities. N Z Med J 2008;121(1286):21–9.

6. MacLeod R. Total pain - physical, psychological and spiritual. Goodfellow Symposium; 2007. Available from: www.fmhs.auckland.ac.nz (Accessed Dec, 2012).

7. Leung L. From ladder to platform: a new concept for pain management. J Prim Health Care 2012;4(3):254–8.

8. Gallagher R. Killing the symptom without killing the patient. Can Fam Physician 2010;56(6):544–6.

9. Dalal S, Bruera E. Assessment and management of pain in the terminally ill. Prim Care 2011;38(2):195–223.

10. Macleod A, MacLeod R, Vella-Brincat J. The palliative care handbook. 6th ed. Hospice New Zealand; 2012.

11. National Health Service (NHS) Lothian. Palliative care guidelines: Renal palliative care - Last days of life. Version 2. NHS, 2010. Available from: www.palliativecareguidelines.scot.nhs.uk/documents/RenalLastDays.pdf (Accessed Dec, 2012).

12. New Zealand Formulary (NZF). NZF v6. NZF; 2012. Available from: www.nzf.org.nz (Accessed Dec, 2012).

13. U.S. Food and Drug Administration (FDA). Information for healthcare professionals methadone hydrochloride text version. FDA, USA; 2010. Available from: www.fda.gov (Accessed Dec, 2012).

14. Canterbury District Health Board (CDHB). Management of constipation associated with opioid use. CDHB; 2011. Available from: http://palcare.streamliners.co.nz/Constipation%20flow%20chart.pdf (Accessed Dec, 2012).

15. Kapoor S. Opioid/naloxone prolonged release combinations for opioid induced constipation. World J Gastroenterol 2012;18(29):3921.

16. Swegle JM, Logemann C. Management of common opioid-induced adverse effects. Am Fam Physician 2006;74(8):1347–54.

The night time hustle:
managing **restless legs syndrome** in adults

Restless legs syndrome is a common condition that can significantly affect a patient's quality of life. It is a neurological disorder, which can be diagnosed on the basis of the patient's description of their symptoms. Lifestyle modification is the mainstay of treatment for patients with mild or infrequent symptoms. Pharmacological treatments, starting with dopamine agonists, should be reserved for people with more severe symptoms.

What is restless legs syndrome?

Restless legs syndrome is a neurological disorder characterised by throbbing, pulling, creeping or other unpleasant sensations in the legs and an uncontrollable, usually overwhelming, urge to move them. Symptoms occur primarily in the evening when a person is relaxing, and can increase in severity throughout the night. Both legs may be affected or one may be worse than the other. In more severe cases, the arms and lower trunk may also be affected.

Restless legs syndrome can be a primary condition or secondary to another disorder. It is known to have a genetic basis and a positive family history is a strong risk factor. Despite this, the pathophysiology of restless legs syndrome remains unclear; what is known about the function of the implicated genes does not yet explain the syndrome. Dopaminergic dysfunction and iron deficiency are both thought to have a role in restless legs syndrome.[1] The syndrome is also strongly associated with depression and anxiety disorders, although whether these conditions are caused by restless legs syndrome or are the result of lower sleep quality is not known.[2]

Restless legs syndrome is thought to affect between 7 – 15% of the population.[3, 4] It is twice as common in females as in males and prevalence increases with age in most populations.[2] Most people with restless legs syndrome first report symptoms after middle-age, however, early onset is thought to be associated with increased severity later in life.[3]

Approximately four in five people with restless legs syndrome also experience periodic limb movement of sleep (PLMS). This is characterised by involuntary leg movement while the person is asleep. The condition can cause repeated waking and poor sleep quality. The presence of PLMS in a person with restless legs syndrome is likely to increase the severity of impact on the person's quality of life through the combination of delayed sleep onset from restless legs syndrome and poor quality sleep from PLMS.

A diagnosis is made based on description of symptoms

There is no specific examination or test that will confirm a diagnosis of restless legs syndrome. The patient's description of their symptoms, combined with a brief history, is sufficient to make a diagnosis.

The diagnostic criteria for restless legs syndrome is a history of:[5]

- A strong and often overwhelming urge to move the affected limbs, often associated with an uncomfortable or tingling sensation (paraesthesia or dysaesthesia)
- Sensory symptoms that are triggered by rest, relaxation or sleep and relieved with movement
- Symptoms that are worse at night and are absent or negligible in the morning
- Symptoms that are partially or totally relieved by leg movement

The presence of sleep disruption or sleep onset problems, a positive family history and a history of response to dopaminergic medicines (if previously taken), provide supportive evidence for the diagnosis.

The limb movements associated with restless legs syndrome are characteristic and repetitive – usually repeated dorsiflexing of the big toe or flexion of the ankle, knee or hip, lasting between 5 – 90 seconds and occurring periodically.

Assess whether the cause is secondary to another condition

Restless legs syndrome can occur secondary to one of the following factors or conditions:[6, 7]

- Iron deficiency
- Pregnancy, especially in the last trimester (prevalence of 11 – 26%), resolving after delivery
- Hypothyroidism or hyperthyroidism (can cause night-time restlessness)
- Rheumatoid arthritis
- Uraemia from chronic kidney disease
- Peripheral neuropathies, due to conditions such as diabetes and Charcot-Marie-Tooth disease
- Medicines, including anti-emetics (e.g. prochlorperazine), most antipsychotics (e.g. haloperidol, quetiapine and olanzapine), anti-depressants (TCAs, SSRIs and SNRIs) and some over-the-counter cold and allergy remedies that contain sedating antihistamines (e.g. diphenhydramine)

Further investigation is guided by the suspected secondary cause. Management of the cause, if identified, is likely to eliminate or reduce the severity of restless legs syndrome in most people.

A serum ferritin test should be considered for patients with restless legs syndrome without an obvious secondary cause, as iron deficiency is a common underlying cause.[6] Although iron deficiency alone is not sufficient to cause restless legs syndrome, serum ferritin correlates inversely with symptom severity.[5] MRI, cerebrospinal fluid and autopsy studies have shown that brain iron stores are reduced in patients with restless legs syndrome.[5] Testing is therefore a low cost, low harm way of potentially identifying a commonly implicated factor.

Symptomatic treatment of restless legs

Recommend lifestyle changes

Advice includes improving sleep hygiene (behaviours to enhance sleep), brief exercise, e.g. walking, before bedtime, performing gentle leg stretches for five minutes prior to sleep and eating a healthy diet. Distracting activities, e.g. reading a book, may also reduce the awareness of the discomfort.

Reassurance and support is also important, as many people believe that restless legs syndrome is a precursor condition to Parkinson's disease. There is a large body of evidence showing no link between the two conditions.[5, 8]

Best Practice Tip: Find out if there are any support groups within the community that patients can be referred to for advice and education.

Medicines for severe symptoms

Pharmacological treatment should be limited to people with severe symptoms who are distressed by their condition and whose daytime function is affected by poor sleep quality, despite lifestyle intervention and exclusion of secondary causes. It is estimated that approximately 20% of people with restless legs syndrome have severe symptoms.[5, 9]

Medicines are usually taken one to three hours prior to going to bed, as guided by symptom onset.[8] Because restless legs syndrome fluctuates over time, patients may require only intermittent medicine use.

The choice of medicine should be based on the patient's symptoms and requirements:

- Low-dose dopamine agonists, e.g. ropinirole, are first-line treatment for daily symptoms of restless leg syndrome[8]
- Dopamine precursors, e.g. levodopa, can be trialled if dopamine agonists are not tolerated or if medicine is only required intermittently
- Anticonvulsants (particularly gabapentin) may be considered if treatment with dopaminergic medicines has failed or is contraindicated, or where symptoms are painful

Dopaminergic medicines such as ropinirole and levodopa should never be abruptly stopped, as this can precipitate neuroleptic malignant syndrome, particularly if the medicine has been used for a long time. If cessation is necessary, the dose should be tapered gradually over at least one month. In addition, significant adverse effects, such as sleep attacks and impulse control issues, are possible with dopaminergic medicines. These potential adverse effects should be discussed with patients, and those with a history of addictive or compulsive behaviours should be monitored more closely while taking dopaminergic medicines.

Dopamine agonists

Ropinirole has the most evidence of efficacy for restless legs syndrome (among dopamine agonists).[8, 9] In New Zealand it is fully subsidised, but unapproved for this indication. Ropinirole can be started at 250 micrograms, daily, taken two to three hours before bed, gradually titrated up to a maintenance dose of 0.5 – 3 mg /day.[8]

Pramipexole is subsidised and approved for use in restless legs syndrome.[10] Pramipexole can be started at 125 micrograms, once daily, two to three hours before bed, doubled weekly as needed, to a maximum of 750 micrograms daily.[8, 11]

Bromocriptine is often suggested as a treatment for restless leg syndrome, but there is limited evidence for its use.[12]

Dopamine precursors

Levodopa was traditionally used first-line for the treatment of restless legs syndrome, however, adverse effects and the high occurrence of augmentation with levodopa (see "Augmentation") mean that it is now considered second-line to dopamine agonists. Levodopa is a short-acting medicine, therefore it is recommended in patients with intermittent symptoms or if dopamine agonists are not tolerated.[13] It is fully subsidised, but not approved for this indication.

Levodopa can be started at 50 mg, daily, one to two hours before bed, titrated to a maintenance dose of 100 – 200 mg/day. It is formulated with either carbidopa or benserazide to prolong its actions in the central nervous system and reduce rebound restless legs syndrome that can occur in the early morning.[8] For some patients, symptoms may rebound late at night. If rebound occurs regularly, switch to an alternative long-acting formulation.

Anticonvulsants

There is some evidence that gabapentin is an effective treatment for restless legs syndrome, and is useful where pain is a significant symptom.[5, 8] It can be started at 300 mg, daily, although evidence suggests doses of 1300 – 1800 mg/day are needed for full effect.[8]

Gabapentin is not approved for use in restless legs syndrome and not subsidised for this use, therefore the cost of the medicine should be discussed with the patient.

N.B. Gabapentin is fully subsidised under Special Authority for the treatment of neuropathic pain, where a tricyclic antidepressant has previously been trialled and is not tolerated or not effective.

Iron supplementation

Iron supplementation should be considered for patients with a serum ferritin level below 50 micrograms/L.[5, 15] However, there is a lack of quality evidence for the treatment of restless legs syndrome with iron supplementation in patients without an iron deficiency.[1] The underlying cause of anaemia should always be assessed.

Augmentation is a common adverse effect of dopamine treatment

Augmentation is the worsening of restless leg symptoms over time, with symptoms occurring earlier in the day (than before treatment) and may begin to involve the trunk and arms. It occurs in up to 70% of patients three to four weeks after beginning treatment with a dopamine precursor, e.g. levodopa, but can occur with any dopaminergic medicine.[14] Augmentation may be less likely with intermittent treatment. If augmentation occurs, reduce the dose or stop the medicine for a short time (low-dose opioids may be used as an adjunctive medicine, however, the evidence for their use is weak[15]). Alternatively, switch to a longer acting formulation, or if using levodopa, switch to a dopamine agonist such as ropinirole.[14]
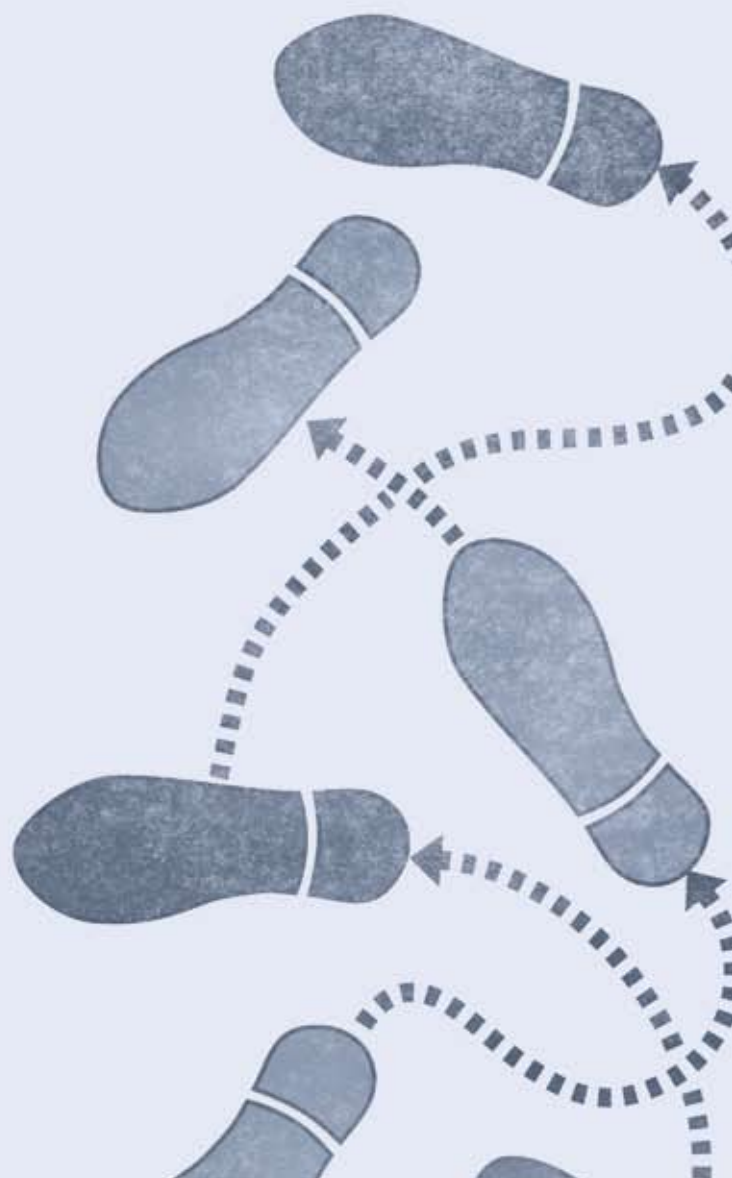
Burning feet syndrome

Burning feet syndrome is a condition resembling restless legs syndrome, caused by the dysfunction of peripheral neurons.[17] It is most commonly seen in people aged over 40 years. Symptoms are described as a burning sensation, heaviness, numbness or dull ache in the feet that is worse at night.[17] The sensation is usually limited to the soles of the feet, but may be more widespread. The condition may be idiopathic or secondary to another condition, such as hyperthyroidism or diabetes.[17] An underlying vitamin B deficiency may be present in some people with burning feet.

Neurologic examination may reveal hypoaesthesia (reduced sense of touch), allodynia (the perception of non-painful stimuli as painful) or hyperalgesia (exaggerated pain perception). Objective signs are typically absent: there should be no muscle atrophy, and knee and ankle reflexes should be normal.

Physical deformities such as muscle loss, high medial arch or toe clawing rule out burning feet and suggest other conditions, such as autonomic neuropathy or Charcot-Marie-Tooth disease. The presence of marked erythema and increased skin temperature is characteristic of erythromelalgia, a neurovascular pain disorder in which blood vessels become periodically blocked, rather than burning feet syndrome. Burning feet may rarely co-exist with these conditions, but would be the less significant diagnosis.

Investigation for burning feet syndrome is directed by the suspected secondary cause (Table 1).[17]

Treatment should include advice on symptom control and relief: avoid tight shoes/socks and exposure to excessive heat. During an episode, soaking the feet in water for fifteen minutes may relieve symptoms. Where required, pharmacological management is similar to the management of neuropathic pain; begin with paracetamol and an adjuvant treatment such as capsaicin ointment.[17] Tricyclic antidepressants, carbamazepine or gabapentin may be added if symptoms are more severe.[17]

Table 1: Initial investigations for burning feet syndrome[17]

Suspected condition	Appropriate testing may include:
Diabetes	HbA_{1c}
Alcoholism	Liver function test
Multiple myeloma	ESR, serum free light chain testing (Bence Jones protein) in urine and serum protein electrophoresis
Nutritional deficiencies	Ferritin / B12 / folate
Hypothyroidism	TSH
HIV infection	HIV status in at-risk patients

Other medicines

Low-dose strong opioids may be used temporarily to permit a lowering of the dose of dopaminergic medicines when augmentation occurs.[6] However, the evidence base for this group of medicines for the treatment of restless legs syndrome is limited.[15]

Clonazepam may be considered for patients who have significant sleep disturbance as a result of restless legs syndrome, particularly difficulty falling asleep. There is modest evidence for the intermittent use of clonazepam for sleep disturbance at 1 mg, daily, before bedtime.[9]

Pharmacological treatment in pregnancy

Reassurance and advice about lifestyle measures is usually sufficient for most women who are pregnant and experiencing restless legs syndrome. Pharmacological treatment should be a last resort.

Restless legs syndrome in women who are pregnant may be associated with iron or folic acid deficiency. Supplementation with iron and folic acid is a safe treatment option, and these supplements are commonly used by women during pregnancy. Where supplementation is ineffective and symptoms are severe, gabapentin (pregnancy safety category B1) or benzodiazepines (category C) may be used, with careful consideration of the risks to the foetus associated with these medicines during pregnancy, such as cleft palate, and neonatal syndromes, e.g. hypotonia, hypothermia and respiratory depression.[16]

Referral if treatment fails

Refer patients to a neurologist or sleep specialist, if:[5, 8]

- There is an insufficient initial response despite adequate duration and dose of treatment
- Response to treatment becomes insufficient despite maximum dosage
- Adverse effects become intolerable
- Significant augmentation develops

References

1. Trotti L, Bhandriraju S, Becker L. Iron for restless leg syndrome. Cochrane Database Syst Rev 2011. 2012;5:CD007834.

2. Ohayon MM, O'Hara R, Vitiello MV. Epidemiology of restless legs syndrome: A synthesis of the literature. Sleep Med Rev 2012 Aug;16(4):283–95.

3. National Institute of Neurological Disorders and Stroke. Restless legs syndrome. National Institutes of Health, USA; 2011. Available from: www.ninds.nih.gov/disorders/restless_legs/detail_restless_legs.htm (Accessed Dec, 2012).

4. Hamilton-Stubbs P, Walters AS. Restless legs syndrome. In: Katie Kompoliti, Leo Verhagen Metman, Editors. Encyclopedia of Movement Disorders. Oxford: Academic Press; 2010. p. 32–7.

5. Leschziner G, Gringras P. Restless legs syndrome. BMJ 2012;344:e3056.

6. Thyagarajan D. Restless legs syndrome. Aust Prescr 2008;31:90–3.

7. Wilson S, Nutt D, Argyropoulos S, et al. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders. J Psychopharm 2010;24(11):1577–600.

8. Yee B, Killick R. Restless legs syndrome. Aust Fam Phys 2009;38(5):296–300.

9. Vignatelli L, Billiard M, Clarenbach P, et al. EFNS guidelines on the management of restless leg syndrome and periodic limb movement disorder in sleep. Eur J Neurol 2006;13(10):1049–65.

10. U.S. Food and Drug Administration (FDA). Mirapex (pramipexole): drug safety communication -ongoing safety review, possible risk of heart failure. FDA; 2012. Available from: www.fda.gov (Accessed Dec, 2012).

11. New Zealand Formulary (NZF). New Zealand Formulary v6. NZF; Dunedin, NZ; 2012. Available from: www.nzformulary.org (Accessed Dec, 2012).

12. Bandolier. Bromocriptine for RLS. Oxford University, UK; 2007. Available from: www.medicine.ox.ac.uk/bandolier/booth/RLS/bromo.html (Accessed Dec, 2012).

13. Scholtz H, Trenkwalder C, Kohnen R, et al. Levodopa for the treatment of restless legs syndrome. Cochrane Database Syst Rev 2011;(2):CD005504.

14. Hogl B, Garcia-Borreguero D, Kohnen R, et al. Progressive development of augmentation during long-term treatment with levopoda in restless legs syndrome: results of a progressive multi-center study. J Neurol 2010;257(2):230–7.

15. Garcia-Borreguero D, Stillman P, Benes H, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurology 2011;11(28):DIO: 10.1186/1471.

16. Balendran J, Champion D, Jaaniste T, Welsh A. A common sleep disorder in pregnancy: Restless legs syndrome and its predictors. Aust N Z J Obstet Gyn 2011;51(3):262–4.

17. Makkar R, Arora A, Monga A, et al. Burning feet syndrome. Aust Fam Phys 2003;31(12):1006–9.

Nocturnal leg cramps: is there any relief?

Nocturnal leg cramps are common, particularly in older people and in women who are pregnant. The condition is characterised by painful cramps in the legs or feet, that affect sleep quality. Is there an effective treatment? Unfortunately, treatment options are limited, but lifestyle modifications and gentle stretching may have some effect. Pharmacological treatment may be considered for people with frequent, severe leg cramps, however, quinine is no longer recommended.

What are nocturnal leg cramps?

A nocturnal leg cramp is a sudden contraction of muscles in the leg or foot during sleep. This painful tightening of the muscle can last from a few seconds to several minutes. Cramps often cause waking, and although the cramps themselves are benign, the affected muscle may be painful for some hours afterwards and the consequences of sleep impairment can be considerable.

Severe nocturnal cramps are characterised by painful, incapacitating episodes, which last on average for nine minutes, and recur intermittently throughout the night.[1] This can lead to secondary insomnia and impaired day-time functioning. Approximately 20% of people who experience regular nocturnal cramps have symptoms severe enough to affect sleep quality or require medical attention.[1]

Nocturnal cramps are common, with a lifetime prevalence of between 50 – 60% in adults and approximately 7% in children.[1] Nocturnal leg cramps, particularly calf cramps, are common in women who are pregnant, and are considered a normal part of pregnancy.[2]

The cause of nocturnal cramps for many people is unknown; however, dehydration, electrolyte and mineral imbalances, muscle fatigue and reduced peripheral blood flow have been suggested as possible contributing factors.

Factors known to be associated with an increased risk of nocturnal cramping, include:[1]

- Age over 50 years
- Pregnancy
- Exercise, particularly over-exertion
- Leg positioning, e.g. prolonged sitting with legs crossed, tight bed covers which cause the toes to point downwards
- Excessive consumption of alcohol
- Chronic dehydration
- Structural disorders, e.g. flat feet or other foot and ankle malformations
- Medicines, e.g. diuretics (especially thiazide and potassium-sparing diuretics), some anti-inflammatories (e.g. naproxen), long-acting beta-2 agonists, statins, opioids, raloxifene (used in osteoporosis) and lithium
- Co-morbidities, e.g. osteoarthritis, vascular diseases, cirrhosis, diabetes, Parkinson's disease, hypo- and hyperthyroidism

Nocturnal cramps are diagnosed clinically

The patient's description of their symptoms is usually sufficient to diagnose nocturnal leg cramps, e.g. the patient may describe a sudden onset of painful cramping of the leg or foot muscles that wakes them from sleep.

The history (including a review of medicines) and a focussed physical examination can help to identify any underlying conditions that may be causing or contributing to the leg cramps (Table 1). Examination should include blood pressure measurement and neurological and vascular examination of the legs.[1]

Laboratory investigations, such as electrolyte levels, are not routinely required, unless there are relevant findings in the history and examination, e.g. investigation of serum calcium would be considered in a patient with numbness in the feet and tetany (continuous involuntary muscle contractions).[1]

Treatment of nocturnal leg cramps

The aim of treatment of nocturnal cramps is symptom control, unless an underlying cause has been identified and can be managed. Lifestyle modifications to prevent the cramp from occurring can be trialled first. If the patient remains symptomatic and symptoms are severe, pharmacological treatment may be considered. However, there is currently no pharmacological treatment for leg cramps that has been proven to be both safe and significantly effective.[1]

Acute management

Patients should be given advice on what to do when they experience a cramp. Physically stretching the muscle that is cramping, e.g. for cramp in the calf, flexing the ankle by pulling the toes upward in the direction of the shin, is the most effective way of stopping the cramp, but this can be painful.[3] Passive stretching may also be effective and is less painful: this involves relieving the tension on the affected muscle by massage and postural changes.[3] Getting out of bed and briefly walking may also provide relief.

There is no evidence of benefit of other acute management strategies, but patients may have their own methods that, if safe, can be encouraged, e.g. having a hot shower or placing a wheat bag or an ice pack on the affected leg.

Table 1: Important differential diagnoses of nocturnal leg cramps[1]

Signs and symptoms	Diagnosis to consider
Aching, deep pain that may be similar to cramping, often brought on by exercise and relieved by rest	Intermittent claudication
Aching, deep pain unrelated to exercise; general weakness; history of statin use	Myositis, myalgias, Bakers cysts, deep vein thrombosis
Non-painful repetitive leg movements that impede sleep	Restless leg syndrome or periodic limb movement disorder
Numbness, tingling and "electric" pain, with secondary cramps; unrelated to sleep or exercise	Peripheral neuropathy
Cramps accompanied by metabolic signs or symptoms	Kidney failure
Cramps accompanied by jaundice, weight loss, weakness or signs of alcohol misuse	Cirrhosis of the liver

For further information on restless leg syndrome, see "Managing Restless Legs Syndrome in Adults", Page 18

Lifestyle interventions: diet, exercise and stretching

Encourage sufficient fluid intake during the day and avoidance of caffeine and alcohol, particularly later in the day.[1]

There is mixed evidence as to whether brief stretching prior to sleep is beneficial, however it can be trialled. A randomised controlled trial, found that the frequency of nocturnal leg cramps decreased significantly after six weeks in participants who performed brief stretching before bed each night.[4] However, a limitation of this study was that the control group did not receive a placebo intervention. In another study where the control group performed sham exercises, calf-stretching was not shown to be effective in reducing the frequency or severity of night cramps.[5]

Brief light exercise, such as walking or cycling on a stationary bike prior to bed time can be trialled, although evidence of significant benefit is also lacking.[1]

Pharmacological interventions and supplements

Mineral and vitamin supplements are unlikely to be beneficial for most people. Magnesium supplementation has no benefit in the treatment of nocturnal cramps,[6] although there is conflicting evidence that it may reduce nocturnal cramps in women who are pregnant.[2] Supplementation with both vitamin E and calcium has been found to be no more effective than placebo in reducing leg cramps.[7]

Over-the-counter "anti-cramp" formulations, such as Crampeze, contain some variation or combination of calcium, magnesium, high-dose vitamin B6 or B12 and associated supplements. There is no evidence of benefit for these preparations, although there is anecdotal evidence that they may be helpful for some people.

There is limited evidence that nortriptyline, diltiazem, orphenadrine, verapamil or gabapentin (not subsidised) may be effective for night cramps, and can be considered in patients with severe symptoms.[1, 6] Despite good evidence that quinine is effective for the treatment of nocturnal cramps it is no longer recommended due to safety concerns.

If medicines are used, they should be initiated at the lowest possible dose and discontinued if no obvious benefit is observed.

Quinine is not recommended as treatment

Quinine has traditionally been used at a low dose (200 – 300 mg/day) for nocturnal leg cramps, and is effective at reducing the frequency and severity of cramps.[8] However, it is no longer recommended for nocturnal leg cramps due to concerns over its safety. In 2007, Medsafe issued a warning that the risk-benefit ratio of quinine for leg cramps no longer supported its use, and manufacturers were required to remove leg cramps as an indication for quinine.[9, 10]

The main concern with quinine is the risk of potentially fatal thrombocytopenia. Quinine-related thrombocytopenia is thought to be due to an idiosyncratic hypersensitivity reaction, and therefore can occur unpredictably, either immediately or after years of treatment.[8] Other hypersensitivity reactions associated with quinine include haemolytic uraemic syndrome, disseminated intravascular coagulation and acute kidney injury.[8] Quinine is significantly toxic at high doses (causing cardiac arrhythmias, blindness and seizures), and has significant interactions with many other medicines.[8] The frequency of serious adverse effects has been estimated to be 2% – 4%.[11]

Quinine is also contained in tonic water, and some people use this as a remedy for nocturnal leg cramps. However, Medsafe has warned that even low doses of quinine, such as that found in 500 mL of tonic water, have been shown to cause severe thrombocytopenia.[10]

References

1. Allen R, Kirby K. Nocturnal leg cramps. Am Fam Physician 2012;86(4):350–5.

2. Young G, Jewell D. Interventions for leg cramps in pregnancy. Cochrane Database Syst Rev 2002;(1):CD000121.

3. BMJ Best Practice. Muscle cramps. BMJ; 2011. Available from: http://bestpractice.bmj.com/best-practice/monograph/569.html (Accessed Dec, 2012).

4. Hallegraeff JM, van der Schans CP, de Ruiter R, de Greef MHG. Stretching before sleep reduces the frequency and severity of nocturnal leg cramps in older adults: a randomised trial. J Physio 2012;58(1):17–22.

5. Coppin R, Wicke D, Little P. Managing nocturnal leg cramps - calf-stretching exercises and cessation of quinine treatment: a factorial randomised controlled trial. Br J Gen Pract 2005;55(512):186–91.

6. Garrison S, Allen G, Sekhon R, et al. Magnesium for skeletal muscle cramps. Cochrane Database Syst Rev 2011;(9):CD009402.

7. Young G. Leg cramps. Clin Evidence 2009;3:1113.

8. El-Tawil S, Musa T, Valli H, et al. Quinine for muscle cramps. Cochrane Database Syst Rev 2010;(12):CD005044.

9. New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Prescriber update: Quinine - not for leg cramps anymore. Medsafe; 2007. Available from: www.medsafe.govt.nz (Accessed Dec, 2012).

10. Food and Drug Administration (FDA). Quinine: important warning. FDA, USA; 2006. Available from: www.fda.gov/bbs/topics/news/2006/new01521 (Accessed Dec, 2012).

11. Katzberg H, Khan A, So Y. Assessment: Symptomatic treatment for muscle cramps (an evidence-based review). Neurology 2010;74(8):691–6.

> " **Learn from the mistakes of others. You can't live long enough to make them all yourself.**

– ELEANOR ROOSEVELT

The bpac[nz] Patient Safety Incident Reporting system is an online resource for people working in community health care to report and review patient safety incidents.

Reports are submitted anonymously, to identify factors which have contributed to patient safety incidents and to share solutions to prevent these incidents from occurring again.

Incidents can be reported and cases reviewed at:

www.bpac.org.nz/safety

Appropriate use of
sulfonamide antibiotics

What are sulfonamides and how do they work?

Sulfonamides are a group of synthetic medicines that contain the sulfonamide chemical group. As well as antibiotics,* this group includes thiazide diuretics, furosemide, acetazolamide, sulfonylureas and some COX-2 inhibitors.

The only antibiotic medicine containing a sulfonamide routinely available, and subsidised, in New Zealand is sulfamethoxazole with trimethoprim (co-trimoxazole). Sulfadiazine (unsubsidised, Section 29 medicine) is occasionally used in a hospital setting.

Sulfonamide antibiotics work by interfering with folic acid synthesis in susceptible organisms, due to their structural similarity to para-aminobenzoic acid (PABA) in bacterial cells. Folic acid is essential for nucleic acid synthesis. When used alone, sulfonamide antibiotics are bacteriostatic to susceptible organisms. However, sulfamethoxazole in combination with trimethoprim (co-trimoxazole), which acts at a different enzyme in the pathway of folic acid synthesis, is thought to be synergistic and may be bactericidal in certain cellular conditions.

Which infections should sulfonamide antibiotics be used for?

There are limited uses for sulfonamide antibiotics due to increasing bacterial resistance, potential for adverse effects and

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* By definition sulfonamides are antimicrobials rather than antibiotics, i.e. an antibiotic is a substance produced by bacteria or fungi which have antimicrobial activity, whereas sulfonamides are synthetic.

the availability of more active antibiotics.[1] In most cases, they are used in primary care only when first-line recommended antibiotics have been ineffective or are contraindicated.

First-line indications for sulfonamide antibiotics

Co-trimoxazole is commonly used in general practice, but in most circumstances, it is indicated as a first-line antibiotic in hospital settings only, such as for the treatment of pneumocystis pneumonia and nocardiosis (rare bacterial infection affecting lungs, brain or skin) in immunocompromised people. Toxoplasmosis is usually treated with a combination of sulfadiazine and pyrimethamine (both unapproved Section 29 medicines), also in a specialist setting.

A first-line indication where co-trimoxazole may be considered in a primary care setting would be for the treatment of mild, lower urinary tract infection in a child. However, it is the trimethoprim component, rather than sulfamethoxazole, which is important. Trimethoprim is only available in tablets of 300 mg, therefore unsuitable for use in children. As co-trimoxazole is available in a liquid formulation, and contains trimethoprim, this is an appropriate choice.

For further information see: "Managing urinary tract infections in children", BPJ 44 (May, 2012).

Second-line indications for sulfonamide antibiotics

Co-trimoxazole is not recommended first-line for the majority of patients in primary care with infections. However, it can be considered when first-line choices have been ineffective,

Co-trimoxazole for MRSA

The rate of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing in New Zealand, and at least half of the cases are now thought to be community acquired.

There is evidence that co-trimoxazole is effective against MRSA, although further clinical trials are needed.[2]

Patients with a non-healing wound or an infected surgical wound that is not responding to first-line antibiotics should have a wound swab taken to check for the presence of MRSA and to guide antibiotic choice. Depending on susceptibility, appropriate treatments in the community include co-trimoxazole, clindamycin (requires specialist endorsement) and tetrayclines.

are contraindicated, or antibiotic sensitivities indicate that co-trimoxazole is the appropriate choice. Antibiotics are not always indicated in the first instance for some of these infections, e.g. otitis media, sinusitis, salmonellosis, and other second-line antibiotics may be preferable to co-trimoxazole (Table 1).

N.B. Second-line antibiotics usually have less predictable susceptibility against the likely pathogens causing a clinical syndrome, e.g. *Streptococcus pneumoniae* susceptibility to co-trimoxazole is unpredictable; in 2011 resistance was 29% across New Zealand.[4]

Prescribing co-trimoxazole

Co-trimoxazole (trimethoprim and sulfamethoxazole in fixed ratio 1:5) is available as:

- Tablets – 80/400 mg (trimethoprim 80 mg + sulfamethoxazole 400 mg)
- Oral liquid – 40/200 mg/5 mL (trimethoprim 40 mg + sulfamethoxazole 200 mg in 5 mL)
- Injection (not subsidised) – 80/400 mg/5 mL (trimethoprim 80 mg + sulfamethoxazole 400 mg in 5 mL)

Table 1: Second-line indications for the use of co-trimoxazole

Infection	First-line antibiotic	Other second-line antibiotics	Notes for using co-trimoxazole
Acute exacerbations of chronic bronchitis	Amoxicillin	Doxycycline	Only if evidence of sensitivity to co-trimoxazole
Pneumonia in adults	Amoxicillin	Erythromycin, roxithromycin, doxycycline	Can be used as monotherapy if a history of penicillin allergy
Otitis media in children	Amoxicillin	Cefaclor, erythromycin	Only if antibiotics are required
Sinusitis	Amoxicillin	Doxycycline, cefaclor	Only if bacterial infection suspected
Cellulitis	Flucloxacillin	Erythromycin, roxithromycin, cefaclor	If a history of penicillin allergy
Diabetic foot complications	Amoxicillin + clavulanic acid	Cefaclor	Use with metronidazole to cover polymicrobial infection
Salmonellosis	Ciprofloxacin	-	Antibiotic treatment usually unnecessary, treat only if severe symptoms
Acute pyelonephritis	Ciprofloxacin	Amoxicillin + clavulanic acid	Refer to hospital if moderate to severe symptoms

For treatment of an infection the following doses are suitable:[1]

- Child aged six weeks – five months – 20/100 mg (2.5 mL), twice daily
- Child aged six months – five years – 40/200 mg (5 mL), twice daily
- Child aged six – 12 years – 80/400 mg (10 mL or one tablet), twice daily
- Child aged over 12 years and adults and –160/800 mg (two tablets), twice daily

Alternatively, the co-trimoxazole dose for children can be calculated by body weight:[5]

- Child aged 6 weeks – 12 years – 0.5 mL/kg oral liquid, twice daily

Co-trimoxazole should be avoided in infants aged under six weeks, due to the risk of hyperbilirubinaemia.

Co-trimoxazole is contraindicated in people with a previous hypersensitivity reaction or severe hepatic damage. Severe renal impairment, bone marrow depression and agranulocytosis are also contraindications to use of co-trimoxazole, unless these can be closely monitored for and the clinical need outweighs the risk.

If co-trimoxazole is being taken long-term, a full blood count is recommended monthly, especially in patients who are poorly nourished or who may be folate deficient.[6]

Silver sulfadiazine for burns: no longer recommended

In the past, topical silver sulfadiazine 1% cream was a common treatment for superficial and mid-dermal burns treated in primary care. It is still an effective treatment, however, newer occlusive dressings are associated with faster healing, decreased pain, fewer dressing changes and improved patient satisfaction.[3]

Double-check and prescribe clearly: is it mg of trimethoprim, or mg of co-trimoxazole?

Dosing recommendations of co-trimoxazole vary, particularly in paediatric references, with some using milligrams of the trimethoprim component alone and other using milligrams of both components combined. Administration errors can easily occur, and most often result in significant under-dosing of co-trimoxazole.

Adverse effects of co-trimoxazole

Adverse effects with sulfonamide antibiotics are relatively common, occurring in approximately 3% of people taking a course of treatment.[7] Nausea, vomiting, anorexia, diarrhoea and hyperkalaemia are the most commonly reported adverse effects, but co-trimoxazole is also rarely associated with serious hypersensitivity reactions and blood dyscrasias (bone marrow depression and agranulocytosis) especially in elderly people.[1]

Hypersensitivity reactions

It is estimated that 0.09% of people experience a hypersensitivity reaction after taking a sulfonamide antibiotic, although the frequency is much higher among people with HIV and AIDS.[8] Reactions include; anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like syndrome, lupus-like syndrome, multi-organ hypersensitivity syndrome, pneumonitis, hepatitis, interstitial nephritis, systemic vasculitis and pancytopaenia.[9]

Patients with a hypersensitivity reaction may present with fever, painful macropapular rash, lesions in mucous membranes, cough, sore throat or difficulty breathing. A "hypersensitivity" syndrome characterised by hypotension, fever, rash and pulmonary infiltrates has also been associated with sulfonamides.[8] Hypersensitivity symptoms usually develop within one to three weeks after starting treatment, and resolve within one to two weeks after ceasing treatment.[8, 10]

Anaphylaxis typically occurs within thirty minutes of the first dose, but is more common with parenteral administration.[8] Urticaria or isolated angioedema can occur within minutes to days after the first dose.[8]

Hypersensitivity reactions to sulfonamide antibiotics are not completely understood but are thought to be related to the drugs' sulphur moiety (the sulphur part of the drug molecule) and the presence of an arylamine group.[8] There is no well-validated diagnostic test for sulfonamide sensitivity.

If a hypersensitivity reaction occurs, sulfonamide antibiotics should be avoided, unless the benefit outweighs the risk. A history of Stevens-Johnson syndrome, toxic epidermal necrolysis or anaphylaxis would be a contraindication to using a sulfonamide antibiotic.[8]

Risk of cross-reactivity with other sulfonamides is low

Other sulfonamide medicines, such as thiazide diuretics, do not contain the arylamine group and are less likely to cause severe hypersensitivity reactions.[8] Cross-reactivity between sulfonamide antibiotics and other sulfonamide medicines is also unlikely.[7]

Despite this low risk, many practitioners take a cautious approach, and avoid prescribing all sulphur-containing medicines in a patient who has had a reaction after taking a sulfonamide antibiotic. There are a limited number of case reports which support this advice. However, a large cohort study found that allergy to a sulfonamide antibiotic was a risk factor for allergy to medicines in general, rather than cross-reactivity to other sulfonamides. The authors concluded that patients with a history of allergic reaction after taking sulfonamides (or penicillins) should be considered at increased risk for allergy to any medicine.[11]

Practical advice would be to avoid prescribing other sulfonamide medicines (and sulphur-containing products) in patients with serious allergic reactions to sulfonamide antibiotics. Sulfonamide medicines could be prescribed in patients with only mild reactions if there was no other alternative, and the patient was monitored for signs of an adverse reaction.[7]

Older people are more at risk of adverse effects

Older people are generally more susceptible to adverse reactions when taking any medicine, and these effects are more likely to have serious consequences. This is compounded by multiple medicine use and the presence of impaired renal or hepatic function.

Although a rare adverse effect, there appears to be an increased risk of thrombocytopenia (with or without purpura) in older people who are prescribed co-trimoxazole and who are currently taking a diuretic such as a thiazide.[6]

Avoid co-trimoxazole in early and late pregnancy

Co-trimoxazole is a folate antagonist. Although its inhibitory effect is more selective for bacteria, co-trimoxazole should be avoided in women who are in the first trimester of pregnancy (as folate is essential during this period). Co-trimoxazole should also be avoided in women after 32 weeks gestation, as it is associated with an increased risk of neonatal haemolysis and methaemoglobinaemia.[1]

Co-trimoxazole may be used in women who are breast feeding, but only if the infant is aged one month or older.[1]

Medicine interactions with co-trimoxazole

Several clinically important medicine interactions can occur with co-trimoxazole (Table 2), which are more significant in elderly people and those taking multiple medicines.

References

1. New Zealand Formulary (NZF). NZF v6. NZF; 2012. Available from: www.nzf.org.nz (Accessed Dec, 2012).

2. Goldberg E, Bishara J. Contemporary unconventional clinical use of co-trimoxazole. Clin Microbiol Infect 2012;18:8–17.

3. Lloyd E, Rodgers B, Michener M, Williams M. Outpatient burns: prevention and care. Am Fam Physician 2012;85(1):25–32.

4. Environmental Science and Research (ESR). Antibiotic resistance data from hospital and community laboratories, 2011. ESR: Wellington; 2012.

5. BMJ Group. British National Formulary for Children. The Royal Pharmaceutical Society of Great Britain and RCPCH Publications Ltd; 2012.

6. Mylan New Zealand Ltd. Trisul Medicine Datasheet. Medsafe; 2011. Available from: www.medsafe.govt.nz (Accessed Nov, 2012).

7. Sweetman S, editor. The complete drug reference. London: Pharmaceutical Press, 2011.

8. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. Immunol Allergy Clin North Am 2004;24(3):477–490.

9. Adelaide: Australian Medicines Handbook Pty Ltd, 2011. Australian medicines handbook.

10. Cairns B, Rich M. Fever, rash and peeling skin. J Fam Pract 2011;60(11):9–12.

11. Strom B, Schinnar R, Apter A, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Eng J Med 2003;349(17):1628–35.

12. Ho J, Juurlink D. Considerations when prescribing trimethoprim-sulfamethoxazole. CMAJ 2011;183(16):1851–8.

Table 2: Known drug interactions involving co-trimoxazole[1, 12]

Drug	Mechanism of interaction	Complication	Management
Warfarin	CYP450 2C9 inhibition	Increased INR and haemorrhage	Monitor INR a few days after starting co-trimoxazole, and again after stopping
Sulfonylureas e.g. gliclazide, glipizide	CYP450 2C9 inhibition, CYP450 2C8 inhibition, and a direct effect on pancreatic cell release of insulin	Hypoglycaemia, which will take longer to resolve in renally impaired people	Consider reducing dose of gliclazide or glipizide when starting co-trimoxazole if creatinine clearance is less than 30 mL/min; increase blood glucose monitoring
Methotrexate	Organic anion transporter inhibition in the renal tubule, anti-folate effect	Methotrexate toxicity (cytopenia, hepatotoxicity, mucositis)	Monitor full blood count; may need to reduce dose of methotrexate (with specialist advice)
ACE inhibitors **ARBs** **Spironolactone**	Trimethoprim-induced antikaliuretic effect due to chemical structure similarities	Hyperkalaemia	Monitor potassium levels a few days after starting co-trimoxazole if person is elderly, or has impaired renal function; review any potassium supplementation
Phenytoin	CYP450 2C9 and 2C8 inhibition (also metabolized by 2C19)	Phenytoin toxicity	Monitor for clinical signs of phenytoin toxicity; fever, rash, bradycardia, gingival hyperplasia, neurological effects, and monitor FBC, LFT, electrolytes
Clozapine	Additive effect of bone marrow supression	Blood dyscrasias and potentially fatal agranulocytosis	Increased frequency of monitoring white cell count

For further information about drug interactions, see Stockley's alerts, accessed from the New Zealand Formulary: **www.nzf.org.nz**

Using the New Zealand Formulary: Guide for switching antidepressants

In most cases, selective serotonin re-uptake inhibitors (SSRIs) are the first-line pharmacological treatment for depression. They are better tolerated and have a wider safety margin than tricyclic antidperessants (TCAs) and irreversible non-selective monoamine oxidase inhibitors (MAOIs). However, choice of antidepressant is also based on individual patient factors, and different medicines may need to be trialled to find the most effective and well-tolerated treatment.

Improvement in symptoms is usually seen within two weeks of starting an antidepressant at a therapeutic dose. If after approximately four weeks (or longer), there is no response or only minimal improvement, changing to a different antidepressant may be considered, along with adding or changing psychological therapies. Switching antidepressants may also be considered if the maximum dose of an antidepressant has been reached, with no further improvement in symptoms, or if adverse effects of a particular antidepressant cannot be tolerated.

There is no particular method in choosing which antidepressant to switch to, however, often switching to a medicine within the same class is tried, before switching to a medicine from a different antidepressant class. Patients should be very carefully monitored when switching, and should be assessed on an individual basis to determine how quickly a switch can be performed.

Factors to take into consideration when changing antidepressants include:

- The patient's severity of illness and the urgency of switching
- Co-morbidities
- Concurrent medicines; serotonin syndrome is more likely to occur if the patient is taking other medicines with serotonergic activity, e.g. triptans, pethidine, tramadol, lithium
- Current dose of antidepressant
- Duration of antidepressant treatment (if less than six weeks it may be possible to stop the antidepressant abruptly)
- The need for a "washout period" (antidepressant-free interval) to avoid interactions
- Tapering of doses, e.g. slowly reducing higher doses of an antidepressant before switching to a new antidepressant, which is started at a low dose and increased as required
- History of discontinuation reactions and management of discontinuation syndrome, should it occur. Symptoms may include dizziness, nausea, anxiety, vivid dreams and headache with SSRIs, and cholinergic rebound (hypersalivation, abdominal cramping, diarrhoea and sleep disturbance) with TCAs.

For further information see: "Pharmacological management of depression in adults", Best Practice Special Edition, July 2009.

A comprehensive table on how to safely and effectively switch between antidepressants is available in Section 4.3 ("Antidepressant drugs") of the New Zealand Formulary (NZF).

This table can be found by clicking on Section 4.3 in the left-hand navigation panel of the NZF. A "printer friendly" PDF version can also be downloaded.

Available from: **nzf.org.nz/nzf/resource/Antidepressant_Switching_Table.pdf**

Short acting SSRIs including citalopram, escitalopram, paroxetine and sertraline can generally be stopped without tapering, and a different SSRI started the next day.

Discontinuation symptoms are unlikely because SSRIs have the same mechanism of action, and any effects will be covered by the new SSRI, which should be started at a low dose.

Fluoxetine has a longer half-life than other SSRIs. Discontinuation symptoms are unlikely with fluoxetine, however, more vigilance is required when changing from this medicine. A four to seven day wash-out period is recommended to allow concentrations of fluoxetine and its active metabolite to decrease.

MAOIs and moclobemide should never be adminstered with another antidepressant, and clomipramine should never be administered with SSRIs or venlafaxine.

Antidepressant Switching Table

Changing from \ Changing to	short-acting SSRI [a]	fluoxetine	TCAs [b]	venlafaxine	mirtazapine (or mianserin)	bupropion	moclobemide	irreversible nonselective MAOIs [c]
short-acting SSRIs [a]	Stop 1st SSRI [d] then start 2nd SSRI the following day	Stop 1st SSRI [d] then start fluoxetine	Cross taper cautiously with very low dose TCA [f] [g]	Stop SSRI [d] then start venlafaxine the next day at 37.5mg/day and increase very slowly	Withdraw before starting mirtazapine cautiously	Withdraw then start bupropion	Withdraw, wait 1 week, start moclobemide	Withdraw and wait 1 week
fluoxetine [h]	Stop fluoxetine, wait 4-7 days, start SSRI at low dose [e]	—	Stop fluoxetine, wait 4-7 days, start TCA at very low dose and increase very slowly [f][g]	Stop fluoxetine, wait 4-7 days, start venlafaxine at 37.5mg/day and increase very slowly	Stop fluoxetine, wait 4-7 days, start mirtazapine cautiously	Stop fluoxetine, wait 4-7 days, start bupropion	Stop fluoxetine, wait 5 weeks, start moclobemide	Stop fluoxetine and wait 5 weeks [h]
TCAs [b]	Halve dose, add SSRI, then slowly withdraw TCA [g]	Halve dose, add fluoxetine, then slowly withdraw TCA [g]	Cross taper cautiously	Cross taper cautiously starting with venlafaxine 37.5mg/day [g]	Withdraw, start mirtazapine cautiously	Cross taper cautiously	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
venlafaxine	Cross taper cautiously starting with low dose SSRI [e]	Cross taper cautiously starting with fluoxetine 20mg on alternate days	Cross taper cautiously with very low dose TCA [g]	—	Withdraw, start mirtazapine cautiously	Withdraw, start bupropion cautiously	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
mirtazapine/ mianserin	Withdraw then start SSRI	Withdraw then start fluoxetine	Withdraw then start TCA	Withdraw then start venlafaxine	—	Withdraw, start bupropion cautiously	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
bupropion	Withdraw then start SSRI	Withdraw then start fluoxetine	Withdraw then start TCA at a low dose.	Withdraw, start venlafaxine at 37.5mg and increase slowly	Withdrawn, start mirtazapine cautiously	—	Withdraw, wait 7 days, start moclobemide	Withdraw and wait 7 days
moclobemide	Withdraw, wait 24 hours, start SSRI	Withdraw, wait 24 hours, start fluoxetine	Withdraw, wait 24 hours, start TCA	Withdraw, wait 24 hours, start venlafaxine	Withdraw, wait 24 hours, start mirtazapine	Withdraw, wait 24 hours, start bupropion	—	Withdraw and wait 24 hours
irreversible nonselective MAOIs	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks	Withdraw and wait 2 weeks

[a] Short-acting SSRIs are citalopram, escitalopram, paroxetine, and sertraline.
[b] TCAs are amitriptyline, clomipramine (refer to note g), dothiepin, doxepin, imipramine, nortriptyline, trimipramine.
[c] Irreversible nonselective MAOIs (phenelzine or tranylcypromine) should be commenced with caution after all other antidepressants because of the risk of hypertensive crisis and serotonin toxicity. Allowance should be made for the washout period (5 half-lives) and individual patient differences in pharmacokinetics.
[d] Abrupt withdrawal is usually possible, however if patients are likely to experience problems with discontinuation symptoms then a slower withdrawal may be required.
[e] Low Dose= citalopram 10mg/day; escitalopram 5mg/day; paroxetine 10mg/day; sertraline 25mg/day; fluoxetine 20mg on alternate days
[f] If changing from paroxetine or fluoxetine, TCA concentration may be elevated for at least several weeks due to persisting SSRI-induced cytochrome P450 inhibition.
[g] Do not co-administer clomipramine with SSRIs or venlafaxine.
[h] Care is required when changing from fluoxetine to another antidepressant as it has a longer half-life than other SSRIs, leading to significant concentrations of fluoxetine or its active metabolite being present for about five weeks after cessation.

Visit: www.nzformulary.org

Can tetracyclines and penicillins be used together?

Dear Editor,
With regard to your article: "Appropriate use of tetracyclines" (BPJ 47, Oct 2012), I have always understood that as tetracyclines are bacteriostatic in action and penicillins act on the cell wall of actively growing bacteria they should not be used together, as the former will stop the latter working.

As you are recommending, amongst others, giving amoxicillin with doxycycline for some conditions, am I wrong in my understanding or is it just that it does not happen in practice?

Chris London, Pharmacist
Milton

In New Zealand there are four tetracyclines available, doxycycline (fully subsidised), minocycline (partially subsidised), lymecycline (not subsidised) and demeclocycline (available under section 29, not subsidised). You are correct that, in theory, tetracyclines may antagonise the bactericidal activity of beta-lactam antibiotics, which includes penicillins and cephalosporins. However, there is little evidence to suggest that this is a clinically significant interaction. This interaction is also not listed in major drug interaction resources, such as Stockley's Drug Interactions.[1]

In vitro studies have shown a strong synergistic relationship between amoxicillin and tetracyclines.[2] The empiric use of either a macrolide or a tetracycline to cover atypical bacteria in moderate to severe community-acquired pneumonia (CAP) is recommended by international guidelines.[3, 4] However, there are few studies that compare the efficacy of beta lactam and tetracycline combinations with other antibiotic treatments for CAP. One large Australian retrospective study published in 2012 compared the efficacy of beta-lactam + macrolide vs beta-lactam + doxycycline in 855 patients for the treatment of CAP. Both regimens demonstrated similar outcomes against CAP due to either atypical or typical pathogens.[5] This study provides further reassurance that this interaction is not clinically significant, and tetracyclines and amoxicillin may be safely used together.

References

1. Baxter K (ed). Stockley's Drug Interactions 9. London: Pharmaceutical Press; 2012. Available from: www.medicinescomplete.com (Accessed Nov, 2012).

2. Olajuyigbe O. Synergistic influence of tetracycline on the antibacterial activities of amoxicillin against resistant bacteria. J Pharm Allied Health Sci 2012;2:12-20.

3. Therapeutic Guidelines Limited. Therapeutic guidelines: Antibiotic. Version 14. Melbourne: Therapeutic Guidelines Limited; 2010.

4. Mandell L, Wunderink R, Anzueto A. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia in adults. Clin Infect Dis 2007;44(suppl 2):s27-72.

5. Teh B, Grayson ML, Johnson PD, Charles PD. Doxycycline vs macrolides in combinations therapy for treatment of community acquired pneumonia. Clin Microbiol Infect 2012;18(4): E71-3.

Recording of immunisations in Medtech

Dear Editor,
I would like to raise a concern that we have noted at our Health Centre over the last year or so, to draw it to the attention of other general practices who may not be aware of this issue.

When the Immunisation Schedule was changed in 2008, the 11-year-old vaccination was changed from DTaPIPV (diphtheria, tetanus, pertussis and polio) to DTaP, i.e. the polio was removed. I think the IPV component was phased out gradually. What we discovered was that the Medtech recall schedule for the 11-year-olds who had started on the previous schedule displayed DTaPIPV as the vaccination due, so our nurses recorded this as being given rather than cancelling this recall and entering DTaP separately. We managed to search for all the affected children and alter their records retrospectively but we are aware from incoming medical records that other practices may have fallen into the same trap.

It is not a major problem but we found that the children being vaccinated were being wrongly recorded as having received a dose of Polio vaccine at age 11 years, when their last one was actually at age four years. This may have implications for future overseas travel risks. The problem will obviously have a limited lifespan as children grow up adhering to the 2008 schedule, but it may recur when other changes to the Schedule are made in future.

Dr Phil White, General Practitioner
Dunedin

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

Thank you for bringing this to our attention. This issue has also been highlighted in two separate reports in the bpac[nz] "Patient safety incident reporting system". Clinicians are encouraged to regularly review these incident reports and use the comment function to provide feedback and generate discussion.

Visit: www.bpac.org.nz/safety/home.aspx

To locate the incident reports on the immunisation issue, click on "review individual reports" the select the "documentation" category.

News update: The catch-up period for immunisations has been extended

Children and adults, who have missed immunisations as recommended on the New Zealand Immunisation Schedule, are encouraged to "catch-up" on these vaccines.

The eligibility for funded catch-up immunisations has now been extended to include adolescents aged up to 18 years (from the previous age of eligibility of up to 16 years). All young people entitled to free or subsidised health care in New Zealand, e.g. citizens, residents, migrants and refugees, may receive funded catch-up doses or vaccines. Adults must meet the cost of catch-up immunisations themselves.

N.B. The eligible age for funded catch-up doses of the HPV vaccine for females is age 20 years.

For further information on the immunisation schedule or planning a catch-up immunisation programme, see: "How to plan a catch-up immunisation programme", BPJ 45 (Aug, 2011).