BEST PRACTICE

24

NOVEMBER 2009

Anticonvulsant medications for epilepsy

Seasonal allergic rhinitis

Breast screening – achieving equity

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better medicine

This magazine is printed on an environmentally responsible paper managed under the environmental management system ISO 14001, produced using Certified ECF pulp sourced from Certified Sustainable & Legally Harvested Forests.

We would like to acknowledge the following people for their guidance and expertise in developing this edition:

Dr David Abernethy, Wellington

Dr Peter Bergin, Auckland

Dr Vincent Crump, Auckland

Dr Celia Devenish, Dunedin

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Dr Nina Scott, Wellington

Professor Mark Thomas, Auckland

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Best Practice Journal (BPJ)

ISSN 1177-5645

BPJ, Issue 24, November 2009

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

Bpac^{nz} Ltd is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

We develop and distribute evidence based resources which describe, facilitate and help overcome the barriers to best practice.

Bpac^{nz} Ltd is currently funded through contracts with PHARMAC and DHBNZ.

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CONTENTS

CONTENTS

Supporting the PHO Performance Programme

PHO
PERFORMANCE PROGRAMME

CONTENTS

Essentials

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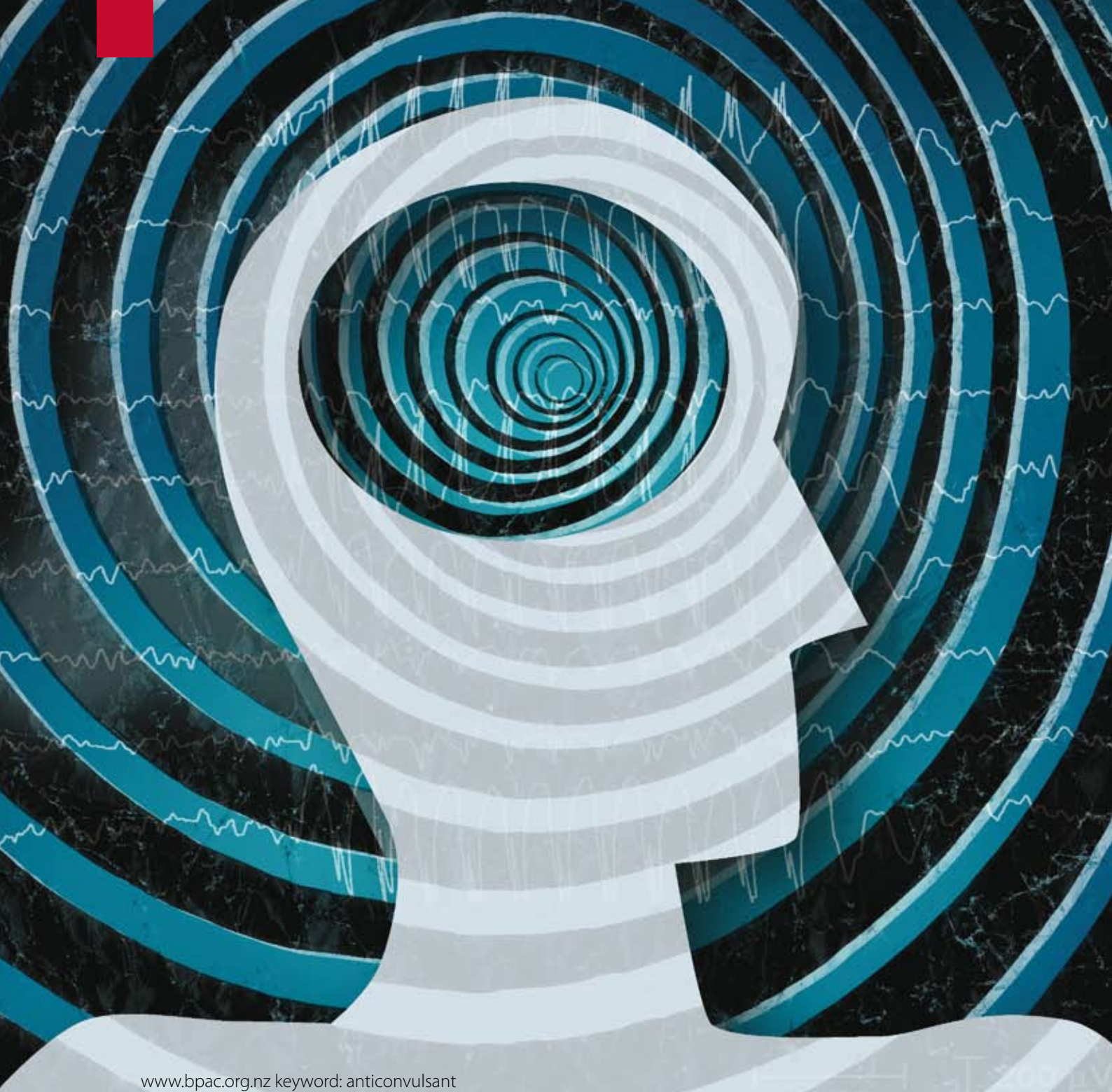

www.bpac.org.nz keyword: anticonvulsant

Prescribing issues associated with

anticonvulsant medications for EPILEPSY

Anticonvulsant medications are primarily used for the treatment of epilepsy, but may also have a place in the treatment of neuropathic pain, bipolar affective disorder and migraine prophylaxis.

Treatment with anticonvulsant medication is usually initiated after a history of two seizures, when further seizures are likely and when the benefit of treatment is anticipated to outweigh the adverse effects of medication. There is some evidence that initiating anticonvulsants after a single seizure may not result in improvement in the long term prognosis and may not reduce the risk of injury or mortality.[1,2]

Selection of an anticonvulsant is generally guided by the type of epileptic seizure, the risk of adverse effects and the presence of co-morbidities. Sodium valproate is used first line for generalised epilepsy syndromes. However, in women of child bearing potential, low dose lamotrigine (<200 mg/day) or carbamazepine are preferred because of the teratogenicity associated with sodium valproate (see page 11 for more information).[3] For patients with partial seizures, lamotrigine or carbamazepine are the preferred initial treatment choices.[4]

The goal of successful pharmacological treatment in epilepsy is the complete control of seizures. However for some people this may not be achievable without intolerable adverse effects.[5] Table 1 (over page) summarises the prescribing issues associated with common anticonvulsant medications.

Key concepts:

- Sodium valproate is used first line for generalised epilepsy syndromes except in women of child bearing potential
- For people with partial seizures and for women of child bearing potential lamotrigine or carbamazepine are the preferred initial treatment choices
- All anticonvulsant medications are associated with adverse effects which in rare circumstances can be potentially life-threatening
- An increased risk of anxiety, depression and suicidality has been associated with the use of anticonvulsants
- Some anticonvulsants, particularly phenytoin and carbamazepine, induce and increase the production of hepatic enzymes which can result in clinically significant drug interactions
- Routine therapeutic drug monitoring of anticonvulsants has limited clinical use

Table 1: Prescribing issues associated with common anticonvulsant medications[1, 6, 7, 8]

Multiple drug interactions and adverse effects may occur with all anticonvulsants. This table highlights the key areas of concern only. Seek further information if required.

Type of epilepsy	Adverse effects	Interactions	Monitoring	Notes
Sodium valproate				
All types of epilepsy First-line for generalised epilepsies	Common – weight gain, tremor, GI disturbance and hair loss (usually mild) Thrombocytopenia Hepatic failure Pancreatitis Other blood dyscrasias	Interacts with: ▪ Most other anticonvulsants, in general raising blood levels (particularly lamotrigine) ▪ TCAs ▪ Benzodiazepines ▪ Warfarin ▪ Aspirin (combination may result in easier bruising)	CBC, LFT, electrolytes at baseline, at three months and then annually Repeat tests if clinical suspicion of haematological or hepatic damage If warfarin commenced, check INR after 5–7 days (warfarin dose decrease may be required)	Avoid in women of childbearing potential Regarded as less sedating than other anticonvulsants
Carbamazepine				
Partial epilepsies (first-line), also in generalised or mixed epilepsies May worsen absence or myoclonic seizures	Common - nausea and vomiting, sedation, dizziness and ataxia Allergic rash (may be severe) Leucopenia Hyponatraemia (action not required if sodium stable above 125 mmol/L) Hepatotoxicity Other blood dyscrasias	Increased plasma concentration (increasing the risk of toxicity) if used with: ▪ Azole antifungals ▪ Macrolide antibiotics ▪ SSRIs e.g. fluoxetine Induces hepatic enzymes and reduces the effect of some medications including: ▪ Oestrogens and progestogens ▪ TCAs ▪ Warfarin ▪ Calcium channel blockers ▪ Statins	CBC, LFT, electrolytes at baseline Repeat tests if clinical suspicion of haematological or hepatic damage If warfarin commenced, check INR after 5–7 days (warfarin dose increase may be required)	Use slow release preparations Carbamazepine or lamotrigine are the anticonvulsant drugs of choice in pregnancy
Lamotrigine				
Most forms of epilepsy Alternate first-line for partial epilepsies	Common – allergic rash, headache, dizziness, blurred vision Serious allergic rash particularly: ▪ In children ▪ If dose increased rapidly ▪ If dose increased rapidly in combination with sodium valproate	Plasma concentration is increased by sodium valproate Plasma concentration is decreased by enzyme inducing anticonvulsants, oestrogens and progestogens	Not routinely indicated	Start low, go slow to avoid allergic rash Lamotrigine or carbamazepine are the anticonvulsant drugs of choice in pregnancy Avoid doses over 200 mg in women of childbearing potential

Type of epilepsy	Adverse effects	Interactions	Monitoring	Notes
Phenytoin				
Most forms of epilepsy May worsen absence or myoclonic seizures	Common - headache, tiredness, nausea, dizziness, drowsiness and insomnia Allergic rash (may be severe) Hirsutism, coarsening of facial features, acne and gingival hyperplasia Hepatotoxicity Blood dyscrasias	Induces hepatic enzymes and reduces the effect of some medications including: ▪ Oestrogens and progestogens ▪ TCAs ▪ Warfarin ▪ Calcium channel blockers ▪ Statins	CBC, LFT, electrolytes at baseline, at three months and then annually Repeat tests if clinical suspicion of haematological or hepatic damage If warfarin commenced, check INR after 5–7 days (warfarin dose increase may be required)	Therapeutic drug monitoring is useful due to non-linear pharmacokinetics e.g. when adjusting dose or adding additional medications with potential for interaction No longer widely used (narrow therapeutic index, long term toxicity)
Gabapentin				
Partial and secondarily generalised tonic-clonic seizures May worsen absence or myoclonic seizures	Common – dizziness, tiredness and nausea Weight gain, peripheral oedema Allergic rash (may be severe)	No clinically important drug interactions	Not routinely indicated	More widely used for neuropathic pain than epilepsy
Topiramate				
Generalised seizures Partial epilepsy	Common – ataxia, confusion, dizziness, tiredness Weight loss Acute angle closure glaucoma Kidney stones Cognitive impairment (up to 15%) particularly if used with sodium valproate	Can decrease serum concentration of digoxin and oral contraceptives by about 30%	Not routinely indicated	Often used as adjunctive therapy Patients should be advised to have adequate fluid intake

Notes:

Phenobarbitone and **primidone** are effective in most forms of epilepsy except absence seizures. However they are no longer widely used due to multiple adverse effects particularly on the CNS and respiratory system. Their use is associated with tolerance, dependence and in elderly people, with falls, osteoporosis and fractures. Primidone can be effective for essential tremor.

Ethosuximide is only effective for absence seizures. It may worsen generalised tonic clonic seizures. It is not widely used.

Vigabatrin is used in treatment of epilepsy (via special authority) that is not well controlled with other anticonvulsants. It may worsen absence or myoclonic seizures. Its use has been limited by the risk of concentric irreversible visual field defects, which are seen in 30–40% of patients.[9] These defects are usually initially asymptomatic and begin with bilateral nasal field loss. Refer for baseline visual field testing by perimetry with follow up tests every six months.[10]

Levetiracetam is only available by specialist application to the Special Access Panel. It is effective as adjunctive treatment of partial onset seizures with or without secondary generalisation.

Pregabalin is effective in the treatment of partial seizures with or without secondary generalisation. It is indicated in New Zealand as adjunctive therapy for patients with this type of epilepsy and also for neuropathic pain, however it is not subsidised.

Oxcarbazepine is not subsidised in New Zealand and therefore not widely used.

Adverse effects of anticonvulsant medication

All anticonvulsant medications are associated with adverse effects which may significantly impact on quality of life, contribute to non-compliance and in rare circumstances be potentially life-threatening.

Common dose related adverse effects

Initiation of anticonvulsants is associated with a number of very common dose related adverse effects including:

- Sedation, tiredness, dizziness, ataxia, tremor, slurred speech, confusion, decreased coordination
- Dry mouth, nausea, diarrhoea, GI disturbance

Typically these effects are of mild to moderate severity, are dose related and resolve within the first few weeks of treatment.

Adverse effects may be minimised by:[5]

- Choosing a slow release formulation when practical to avoid rapid rises in serum concentration
- Starting with a low dose and slowly increasing at one or two week intervals
- Using monotherapy if possible

Allergic rash is common with phenytoin, carbamazepine and lamotrigine. Gradual introduction of carbamazepine and lamotrigine is thought to significantly reduce the incidence of this. In general if a rash develops the medication should be withdrawn as allergic rashes have the potential to progress to severe skin and systemic reactions.

Mild haematological reactions can occur, e.g., leucopenia with carbamazepine and thrombocytopenia with sodium valproate. These changes are usually transitory, dose related and require no intervention, however in rare cases they may be life threatening.[11,12]

Potentially life-threatening adverse effects

Rare, life-threatening adverse effects with anticonvulsants include:[11,12]

- Skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Systemic reactions e.g. hypersensitivity resulting in multi-organ failure
- Haematological reactions including thrombocytopenia, aplastic anaemia, agranulocytosis and leucopenia
- Hepatic failure

Routine monitoring has not been shown to be of value in identifying these conditions. Instead patients should be advised of the risks and asked to report any warning signs such as rash, fever, bruising and other signs of infection such as sore throat.

Abrupt withdrawal of any anticonvulsant medication has the potential to precipitate seizures or status epilepticus. Before an anticonvulsant medication is stopped e.g. because of a serious adverse effect, an additional anticonvulsant should first be added that can quickly obtain therapeutic levels. Consultation with a specialist is recommended.

Anticonvulsants and suicidality

An increased risk of anxiety, depression and suicidality has been associated with the use of anticonvulsants. It is recommended that all patients taking anticonvulsants for any indication are routinely assessed for symptoms of these conditions. This recommendation is based on a recent FDA meta-analysis of clinical trials involving 11 anticonvulsant drugs, reporting that patients taking these drugs had twice the risk of suicidal thoughts and behaviours than those patients taking a placebo (0.43% compared to 0.22%).[13]

See BPJ 14, June 2008 “Anticonvulsants associated with suicidality”.

Anticonvulsants and osteoporosis

Anticonvulsant medications (particularly phenytoin, sodium valproate, carbamazepine, primidone and phenobarbitone) are associated with a reduction in bone mineral density and an increased fracture risk.[14, 15]

Many guidelines recommend that all patients taking any anticonvulsant medication should be offered lifestyle and dietary advice to reduce the risk of osteoporosis.[14, 16] Vitamin D supplementation should be considered for patients who have additional risk factors for osteoporosis.[17]

See BPJ 17, October 2008 "Prevention of osteoporosis".

Dose adjustments

Dose adjustments may be required for patients with impaired hepatic function

Most anticonvulsant medications are metabolised by the liver. If hepatic function is impaired, lower doses may be required to avoid elevated serum drug levels. Gabapentin, pregabalin, levetiracetam and vigabatrin are excreted without metabolism by the liver and should not require dose adjustment in patients with impaired hepatic function.

Dose adjustments may be required for patients with impaired renal function

A reduction in renal excretion of some anticonvulsants and/or their active metabolites may result in an increase in adverse effects or toxicity and doses may need to be reduced.

Dose adjustment in elderly people

In many elderly people, changes in renal or hepatic function and altered pharmacodynamic response may increase the likelihood of adverse effects. Therefore lower doses of anticonvulsants may be required.

Enzyme induction

Some anticonvulsants, particularly phenytoin and carbamazepine induce and increase the production of hepatic enzymes. This can result in clinically significant drug interactions by increasing the metabolism of some co-administered drugs e.g. oral contraceptives, warfarin, calcium channel blockers and many antipsychotic and antidepressant drugs.

Enzyme induction can be associated with an increase in gamma-glutamyl transferase (GGT). An isolated increase in GGT (up to 1.5 – 2 times upper limit of normal) is not usually of concern unless it is associated with increases in transaminases which may signal hepatotoxicity, requiring further investigation. Alcohol use can increase the GGT level further.

Other enzyme inducing anticonvulsants include phenobarbitone and primidone. Topiramate and oxcarbazepine are inducers at high dose but at lower doses have some inhibiting properties.[6] Sodium valproate is an inhibitor of specific isoenzymes and typically increases the concentrations of other anticonvulsants, particularly lamotrigine and the active metabolite of carbamazepine. Doses of lamotrigine should be halved while taking sodium valproate.

Routine therapeutic drug monitoring of anticonvulsants has limited clinical usefulness (except phenytoin)

Therapeutic drug monitoring (TDM) has traditionally been used to guide treatment decisions for patients with epilepsy.[7, 18] However, there have been no randomised studies that demonstrate that TDM has a positive impact on clinical outcomes in patients with epilepsy.[7] It is now recognised that the usefulness of routine TDM has been overemphasised and that optimal treatment should rely primarily on a careful assessment of the patient's clinical state.[7, 19]

Despite this, TDM may be of benefit in some circumstances for some patients, because of the pharmacokinetic

variability of anticonvulsant medications and the often unpredictable nature of epilepsy.[7] However, a clinical decision should usually not be made based on the serum concentration alone.

TDM may be beneficial in the following specific clinical situations;[7]

- When pharmacokinetics (and consequently, dose requirement) alter, e.g. in children, in elderly people, in pregnancy, in people with co-morbidities or when a drug interaction is suspected
- When increasing the dose of an anticonvulsant with non-linear pharmacokinetics e.g. phenytoin (see sidebar)
- If seizures persist despite an apparently adequate dosage
- If toxicity is suspected or when it is difficult to assess this clinically, e.g. in children or people with mental disability

The importance of steady state

If TDM is to be clinically useful and comparable, samples should be taken after steady state has been reached and should be collected at the same time of day e.g. usually just prior to the next dose. The time to reach steady state varies widely for anticonvulsants and additionally there are diurnal fluctuations in the serum concentrations of drugs which have short elimination half lives (e.g. carbamazepine. sodium valproate).

For further information see Best Tests, July 2009, "Practical considerations for therapeutic drug monitoring".

Phenytoin and non-linear pharmacokinetics

Most drugs used in clinical practice exhibit linear pharmacokinetics. That is, they have a constant half-life and, at steady state, the dose rate is directly proportional to the plasma concentration. In linear pharmacokinetics, if the dose is doubled the resultant plasma concentration is doubled. Phenytoin, however, exhibits non-linear pharmacokinetics as its metabolism becomes saturated at plasma concentrations associated with therapeutic use. Increases in phenytoin dose should be made cautiously in small increments to avoid toxicity, e.g. a dose increase of 30 mg. After each dose increase, monitor clinical effect and plasma concentration.

Special issues in the management of epilepsy

Females with epilepsy

For women of child bearing potential with epilepsy, the main concerns are adequate contraception and when pregnancy is planned, safety during pregnancy and labour. GPs can be actively involved in helping educate women with epilepsy about the pros and cons of treatment with anticonvulsants and provide advice on contraception and pre-conception care.

Anticonvulsants and contraception

Several anticonvulsants, in particular carbamazepine and phenytoin, increase the metabolism of oestrogen and progestogen and therefore reduce the effectiveness of the combined oral contraceptive (COC). Topiramate and lamotrigine may also reduce the effectiveness of the COC to a lesser extent. Sodium valproate does not affect oestrogen metabolism.

It is recommended that women taking enzyme inducing anticonvulsants who require contraception, be prescribed a COC containing at least 50 µg of oestrogen. Mid cycle bleeding can be an indication that the oestrogen dose is inadequate. In this situation the options are to advise that:[16]

- The oestrogen dose can be increased by taking two 30 µg pills per day (and in some cases up to two 50 µg pills per day)

and/or

- The COC can be taken continuously for three months with a four day break between cycles

and/or

- A barrier form of contraception be used concurrently

or

- An alternative method of contraception may be more appropriate.

The use of enzyme inducing anticonvulsant medications (e.g. carbamazepine, phenytoin) may also reduce the effectiveness of the progesterone only pill (POP). The POP therefore is not recommended for women who are taking anticonvulsants.

Barrier methods, depot medroxyprogesterone acetate (DMPA, Depo-Provera), standard intrauterine contraceptive devices (IUCD) and the levonorgestrel intrauterine system (Mirena) are effective and may be suitable choices.[20] However, because both DMPA and some anticonvulsants are associated with weight gain and lower bone mineral density with long term use, DMPA may not be a first line choice in some women.[20,21] If DMPA is used, it is recommended that the interval between injections is shortened to ten weeks.[11]

If emergency contraception is required for women taking enzyme inducing anticonvulsants, it is usually recommended that twice the normal dose of the progesterone-only emergency contraceptive pill should be taken.[16, 21] An IUCD fitted within five days of unprotected intercourse could be offered as an alternative.[20]

Pre-conception care

As many anticonvulsants are associated with an increased risk of neural tube defects, it is recommended that all women of child bearing potential who are taking anticonvulsants take folic acid 5 mg/day.[11,22] Once pregnant, folic acid (5 mg daily) should be continued for the first trimester.

Women with epilepsy who are planning a pregnancy should be referred for specialist advice. The combined input of both a neurologist and an obstetrician is usually required.

Anticonvulsants and pregnancy

Carbamazepine, or lamotrigine in doses under 200 mg/day, when used as monotherapy, are the anticonvulsant drugs of choice in pregnancy.[23, 24]

The use of the majority of anticonvulsant medications increases the risk of teratogenicity. The risk of major congenital malformation in the general population is approximately 2–3% compared to 4–7% in women taking anticonvulsant medications.[22] The risk is higher for the older anticonvulsant medications (especially sodium valproate) when combination therapy is required or when anticonvulsants are taken at higher doses.[22, 23]

The type of congenital malformation varies with the type of anticonvulsant medication, e.g., sodium valproate is associated with neural tube, craniofacial, skeletal, cardiovascular and urogenital defects. Exposure of the foetus to sodium valproate may also be associated with development delay and cause cognitive impairment.[25]

In some women, anticonvulsant treatment can be safely withdrawn before pregnancy, although this should be confirmed by a specialist. If tonic clonic seizures are likely to occur during pregnancy then an anticonvulsant should be continued because these seizures are likely to be harmful to both mother and foetus.

The challenge is to strike a balance between the risk of uncontrolled seizures and the risk of teratogenicity. Ideally, use a single anticonvulsant at the lowest possible dose to maintain seizure control.

Anticonvulsants and breast feeding – guidelines advise that most women taking anticonvulsants can breast feed safely.[16]

Limited alcohol is usually acceptable

Alcohol is a CNS depressant and lowers seizure threshold. Although a very small amount of alcohol can be enough to trigger a seizure in some people with epilepsy, the majority can safely consume a limited amount of alcohol. Excess consumption of alcohol, binge drinking or acute withdrawal from alcohol can induce seizures, even in a patient with no history of epilepsy.

A small to modest intake (one to two drinks per occasion, totalling no more than three to six drinks per week) is suggested as a safe upper level of alcohol intake. This amount has been shown not to alter serum concentrations of anticonvulsants and not to increase the frequency of seizures.[26]

Best practice tip: It is safer to advise patients that some alcohol is allowed while on anticonvulsant medication, rather than risk a situation where patients do not take their medication when they drink.

Epilepsy and driving

Any person who has a seizure, irrespective of cause, should receive advice about driving.

Patients who have had a single seizure, without a diagnosis of epilepsy, are subject to the same driving restrictions as patients with a formal diagnosis of epilepsy.

A patient with epilepsy controlled by treatment may still be able to hold a licence to drive a private motor vehicle. However, a diagnosis of epilepsy for a driver of a commercial vehicle will result in the permanent loss of this class of licence, in most circumstances.

A medical practitioner is required to notify the Director of Land Transport Safety if they are aware that a patient with uncontrolled seizures continues to drive. This should be discussed with the patient first who should be offered the opportunity to seek a second opinion if required.

Full information can be found in "Medical aspects of fitness to drive – A Guide for Medical Practitioners" which is available online at: **www.landtransport.govt.nz/licensing/docs/medical-aspects.pdf**

This guide has recently been updated and there have been some minor changes to the section on epilepsy.

ACKNOWLEDGMENT Thank you to **Dr David Abernethy**, Neurologist and Senior Lecturer, School of Medicine, University of Otago, Wellington and **Dr Peter Bergin**, Neurologist, Auckland DHB for their expert guidance in developing this article.

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www.bpac.org.nz keyword: hayfever

SEASONAL ALLERGIC RHINITIS

MANAGING HAY FEVER

Key concepts:

- Seasonal allergic rhinitis can significantly affect the quality of life for many people
- Assess for asthma as this often co-exists with allergic rhinitis
- For mild symptoms, try intranasal antihistamines first
- For moderate to severe symptoms, try intranasal corticosteroids, which are the most effective medicine class for managing symptoms of seasonal allergic rhinitis
- If standard treatment fails, immunotherapy may be considered

Seasonal allergic rhinitis, also known as hay fever, is caused by an immune mediated reaction to seasonal environmental aeroallergens (i.e. pollen).[1] Symptoms are usually seen in spring and early summer, depending on weather conditions and local plant species.[2]

Hay fever can have a significant impact on peoples' lives. It can affect sleep, work performance, learning ability and participation in social activity. Allergic rhinitis often co-exists with asthma, eczema, conjunctivitis and other sinus conditions.[2]

There are a wide range of effective treatment options available. Aim for symptom control with the lowest dose and number of medications.

Diagnosing seasonal allergic rhinitis

Seasonal allergic rhinitis may affect up to 30% of adults and 40% of children. Prevalence is higher in Western countries including New Zealand, Australia, Canada, USA and UK.[3] Pollen sensitivity begins between age six months and two years, although symptoms do not generally develop until age two to seven years.[1]

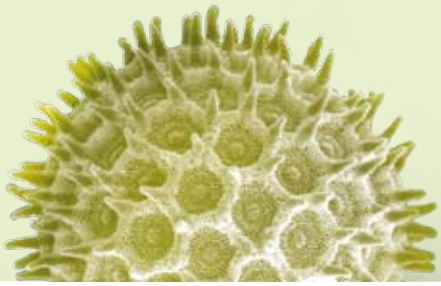
Family history of atopy is a known risk factor, but it is unclear whether early childhood exposure to infections, animals and tobacco smoke plays a role in allergic rhinitis.[1]

For a positive diagnosis of seasonal allergic rhinitis, the timing of symptoms should be related to exposure to environmental aeroallergens.

Symptoms are characterised by sneezing (especially paroxysmal), congestion, watery anterior rhinorrhoea, itchy nose, eyes and throat, sinus pressure, facial pain and decreased sense of smell or taste. Signs in children may include tiredness, daytime sleepiness, sniffing, blinking, eye rubbing, speech problems, snoring and dark circles under the eyes ("shiners").[1, 3, 4]

Types of rhinitis[2]

- **Seasonal allergic rhinitis** – associated with spring and early summer, triggered by pollen (outdoor allergens)
- **Perennial allergic rhinitis** – symptoms all year round, triggered by house dust mite, pets and mould (indoor allergens)
- **Occupational rhinitis** – symptoms worsened at work, triggered by chemicals, irritants and dust
- **Non-allergic rhinitis** – triggered by strong smells, change in temperature, viral infections, pregnancy, hypothyroidism or rarely medications e.g. some antihypertensives



Symptoms **not** usually associated with allergic rhinitis include: unilateral symptoms, nasal obstruction without other symptoms, mucopurulent rhinorrhoea, posterior rhinorrhoea with thick mucuous, recurrent epistaxis.[3]

Towards the end of pollen season, symptoms may worsen. This is known as allergen priming where after repeated challenges, the amount of allergen required to induce a response decreases.[1]

An annual pollen calendar for plant species in New Zealand can be found at:

www.allergy.org.nz/site/allergynz/files/Annual%20Pollen%20Calendar.pdf

Ask about:

- Pattern, chronicity and seasonality of symptoms
- Response to medications
- Occupational exposure
- Environmental history
- Identification of precipitating factors
- Effect on quality of life

Assess for:

- Co-existing asthma

Allergic rhinitis is significantly associated with asthma (the "united airways disease" concept). Allergic rhinitis occurs in 75–80% of patients with asthma and conversely, 20–30% of patients with known allergic rhinitis are subsequently found to have asthma. Studies have shown that in patients with both asthma and allergic rhinitis treatment of allergic rhinitis with intranasal steroids reduces the risk of asthma-related emergency department visits and hospitalisations.[3]

Many people have both seasonal and perennial allergic rhinitis

In reality many people are allergic to both indoor and outdoor allergens, and their symptoms are perennial, with seasonal exacerbations. The World Health Organisation along with the Allergic Rhinitis and its Impact on Asthma group (ARIA)[3] have developed a new classification of rhinitis based on frequency and severity of symptoms, as these are the major factors involved in determining treatment.

Patients are classified by both:

1. **Duration of symptoms :**
   - Intermittent – symptoms less than four days per week or four weeks at a time
   - Persistent – symptoms greater than four days per week or four weeks at a time

2. **Severity of Symptoms**
   - Mild – no troublesome symptoms with normal sleep and normal daily activities
   - Moderate to severe – troublesome symptoms with abnormal sleep and impairment of daily activities (e.g. school, work, sport)

The ARIA classification works very well in New Zealand where most people with seasonal rhinitis are allergic to more than one type of pollen. For example, people allergic to only birch pollen will have symptoms lasting for only three to four weeks, whereas, most people with hay fever are probably allergic to grasses, trees and weeds, and their hay fever season will last up to nine months.

Skin prick testing

Referral for skin prick testing may be considered, if the diagnosis is in doubt, if the patient wishes to determine possible sensitivity to a specific allergen or when expensive avoidance measures or immunotherapy are being contemplated. A positive reaction to an extract does not necessarily mean that this allergen causes the patients symptoms, but it provides supportive evidence as part of an overall exposure history.

Extracts used for testing should be carefully selected to match allergens that the patient is normally exposed to.[2] N.B. atopic individuals may get false positive results with skin prick testing because of sensitivity of their skin to any trauma (dermographism). However this should be apparent if the negative saline control is also positive.

Managing seasonal allergic rhinitis

Management of hay fever should be individualised depending on specific patient factors and symptoms. In most cases, begin with one treatment and assess response and adverse effects. If the patient is compliant with the medication but symptoms are not controlled, consider substitution with another class of medication or addition of a medication in a step wise approach.

See Table 1 (page 21) for information on medicines recommended for use in hay fever.

For mild symptoms try antihistamines first

Intranasal antihistamines may be used as first-line treatment for people with occasional mild symptoms, who wish to gain rapid relief (rescue therapy).[5] They are equal to or more effective than oral antihistamines for the treatment of rhinitis symptoms, although less effective than intranasal corticosteroids. They are not as effective for the treatment of symptoms related to the eye and throat.[6] They have a rapid onset of action so may be used on an "as needed" basis for symptom relief.[1] If treatment fails, or symptoms worsen, proceed to intranasal corticosteroid treatment.

Some formulations may cause drowsiness. Intranasal antihistamines are not suitable for children aged less than five years.[5]

Oral antihistamines can be considered if a spray formulation is not acceptable. They may be used as needed but are more effective if used continuously throughout the pollen season. Oral antihistamines are less effective for nasal congestion than intranasal antihistamines or corticosteroids, but more effective than intranasal antihistamines for eye symptoms.[1]

Second-generation antihistamines (e.g. loratadine, fexofenadine, cetirizine) should be used as they are less sedating and less associated with anticholinergic effects. Of the second generation antihistamines, none have been found to be superior over the other for symptom control.[1] However, cetirizine may cause drowsiness, particularly when the dose is increased above 10 mg daily.

Sedating antihistamines are contraindicated for the treatment of allergic rhinitis in children, even for night time use as somnolence can continue through to the next day and affect cognitive function.

For moderate to severe symptoms try intranasal corticosteroids first

For most patients, if their symptoms are significant enough to seek medical advice, it is likely that they require more effective treatment than antihistamines.

Corticosteroid nasal sprays are considered to be the most effective medicine class for controlling the four main symptoms of hay fever – sneezing, itching, rhinorrhoea and nasal blockage. The onset of action of intranasal corticosteroids is usually within 12 hours, but the effect can be more rapid for some people (three to four hours). Maximum efficacy may take up to two weeks.[5, 6] Treatment can be started prior to the anticipated beginning of the pollen season and regular use throughout the season is ideal.

Clinical response does not appear to vary significantly between different products, regardless of potency, therefore use the lowest dose possible to control symptoms.[1, 2] There are two methods for achieving the optimum dose – either start low and step-up the dose as dictated by symptoms[5] or start with the maximum dose for the patients age and step down the dose at one week intervals to the lowest effective dose.[7] If symptoms still remain uncontrolled, or for "breakthrough symptoms", consider the addition of an oral antihistamine.[6]

Intranasal corticosteroids may be absorbed systemically to some extent but they are not generally associated with adverse effects and are considered a safe long-term treatment (including during pregnancy and breast feeding[5]). Nasal irritation and bleeding may occur.

If patients find it difficult to use the spray, check their technique (see box below).[2] Be aware of total steroid load in patients also using inhaled corticosteroids.

Best practice tip: If a nasal saline spray is used before the steroid, it can clear mucous and improve mucosal contact with the steroid and potentially reduce the dose required for efficacy.[2]

Other medications

Saline spray/drops are less effective than intranasal corticosteroids but can relieve nasal congestion and dryness. They are associated with minimal adverse effects and may be considered for younger patients or those who cannot tolerate other medications.[1] There are several commercial saline sprays available. A home-made salt water solution could also be used for irrigation – mix ¼ tsp salt with two cups of cooled, boiled water. The solution can be administered using a small spray bottle, nasal dropper or syringe.[4]

Intranasal decongestants may be used to reduce significant nasal congestion. However due to the risk of rhinitis medicamentosa (rebound nasal congestion), they should only be used short-term (<10 days) and intermittently.

Oral decongestants such as pseudoephedrine and phenylephrine are generally not recommended for use in hay fever. They are associated with insomnia, irritability, hypertension and palpitations so should be used with caution in older people and people with cardiac conditions and should not be used in children under six or in the first trimester of pregnancy.[1]

Oral corticosteroids may be considered for very severe or intractable nasal symptoms or nasal polyps. Use a short course of five to seven days only,[1] 20–40 mg per day in adults and 10 mg per day in children.[5] Continue intranasal corticosteroid during treatment.[6]

Parenteral corticosteroid injections are not recommended due to the risk of long-term corticosteroid adverse effects and the availability of more effective treatments.[1, 5]

Intranasal anticholinergics e.g. ipatropium bromide can be used as an "add-on" treatment to intranasal corticosteroids and antihistamines to reduce rhinorrhoea, but it has no effect on other nasal symptoms.[1, 4, 6]

Intranasal sodium cromoglycate may be effective in preventing onset of symptoms in some patients but for most people, it is less effective than intranasal corticosteroids.[1] The four times daily dosing and the delayed onset of action (up to three weeks) of the cromoglycates contribute to the overall reduced compliance and effectiveness. It is a safe treatment to use in young children and during pregnancy.[6]

Patient advice on administering intranasal sprays (adapted from Scadding et al 2008)[6]

1. Shake bottle well
2. Look down at the floor (do not tilt head back)
3. Using the right hand for the left nostril, put the nozzle just inside the nose and aim to the side (away from the septum)
4. Squirt once or twice as directed
5. Do not sniff as this may result in the drug being swallowed (indicated by an unpleasant taste in the mouth) and is a cause of treatment failure
6. Change hands and repeat for the other side (i.e. use the left hand for the right nostril)

Oral anti-LT agents (anti-leukotriene receptor antagnosists) such as monteleukast are used in some countries for treating hay fever. They are less effective than intranasal steroids and antihistamines and are not generally recommended.[1, 4, 5]

Medications for eye symptoms

If allergic conjunctivitis is the dominant symptom, antihistamine eye drops are most effective.[6] Saline eye drops, sodium cromoglycate eye drops, intranasal corticosteroids and/or oral antihistamines can also be used.[5]

Patients should be advised to avoid rubbing their eyes as this can cause worsening of symptoms. Frequent use of artificial tears during the day can help to dilute and remove allergens.[8]

Follow-up and specialist referral

If a patient with moderate to severe allergic rhinitis fails to improve after four weeks of adequate treatment (nasal corticosteroids and oral antihistamines), patient compliance or the diagnosis must be re-assessed. In such cases, if the diagnosis is in doubt a nasal endoscopy is necessary, to exclude other potential causes of nasal obstruction.

Consider referral to an ear, nose and throat specialist if:[3]

- The patient has constant unilateral obstruction
- There are complications such as resistant obstruction, anosmia, sinus disease, ear problems, persistent purulent discharge
- A polyp is unresponsive to inhaled corticosteroid treatment

Environmental management of seasonal allergic rhinitis

Pollen counts are generally the highest in the morning and on sunny, windy days with low humidity, although this is difficult to predict.[1, 6]

There are many tips about how to minimise pollen exposure. Unfortunately many of these are not practical. Some practical pollen avoidance measures include:[2, 4, 9]

- Use a clothes dryer to finish drying bedding – this reduces the amount of pollen that may have settled while on the washing line
- Wear glasses/sunglasses outdoors to reduce pollen contact with the eyes
- Use air conditioning (on recycle mode) in the car
- Use a dehumidifier to reduce indoor humidity
- If possible avoid mowing lawns or raking leaves (or wear a mask)
- Have lawns mowed frequently to avoid flowering
- Select garden species which are low pollen producers (usually native plants, ask at your local garden store)

Consider referral to an allergy specialist for patients who have:

- Inadequately controlled symptoms with maximum doses of medications
- Reduced quality of life
- Adverse reactions to medications
- A desire to identify the allergens to which they are sensitised
- Serious co-morbid conditions such as uncontrolled asthma

Immunotherapy

Immunotherapy involves subcutaneous injection of increasing doses of an identified allergen (or combined allergens), eventually resulting in desensitisation.[9] This is an effective treatment for allergic rhinitis which can be considered for patients who are unable to tolerate the amount of medications required to control their symptoms and the associated adverse effects, or for those who have medication failure.

Allergen immunotherapy may prevent the development of new sensitivities and reduce the risk of developing asthma. In one study, patients who had subcutaneous immunotherapy showed a 50% reduction in symptoms and an 80% reduction in the need for medication, compared to those receiving placebo.[10]

Patients receive weekly increasing doses of the vaccine for 12 weeks, up to a maintenance dose, and then monthly injections of the maintenance dose for three to five years. Treatment can be costly, but clinical benefit is usually sustained for many years. There is no specific upper or lower age limit for treatment.[6]

Sublingual immunotherapy is an alternative method of desensitisation, however it is currently not widely used outside Europe.

ACKNOWLEDGMENT Thank you to **Dr Vincent St Aubyn Crump**, Allergy Specialist, Auckland Allergy Clinic for expert guidance in developing this article.

Table 1: Common medications used for seasonal allergic rhinitis

Notes:

1. Medications are ordered based on efficacy and adverse effects, however cost and patient preference are also important factors in choice of medicine.
2. For pregnant or breastfeeding women use intranasal corticosteroid first-line (e.g. budesonide), if not tolerated or additional treatment is required, prescribe an oral antihistamine (e.g. loratadine), also consider the use of saline nasal spray as a "drug-free" alternative.[5]

	Adults	Pregnant/breastfeeding	Children
Intranasal antihistamines	Azelastine 0.14 mg/spray, one spray per nostril, twice daily (**Azep** NS) Levocabastine 0.5 mg/mL, two sprays per nostril, twice daily (**Livostin** NS)	Azelastine – B3 Levocabastine – B3	From age five years: Azelastine 0.14 mg/spray, one spray per nostril, twice daily (**Azep** NS)
Oral antihistamines	Loratadine 10 mg once daily (**Loraclear Hayfever Relief** FS) Fexofenadine 120–180 mg once daily (**Telfast** PS) Cetirizine 5–20 mg once daily (**Zetop** FS) (sedating above 10 mg daily)	Loratadine – B1 Cetirizine – B2 Fexofenadine – B2	From age two years: Loratadine 1 mg/mL, 5 mL once daily (age >6 years, 10 mL) (**LoraPaed** FS) From age two years: Cetirizine 1 mg/mL, 5 mL once daily (age >6 years, 10 mL) (**Cetirizine AFT** FS)
Intranasal corticosteroids	Fluticasone 50–100 mcg/nostril once daily (**Flixonase, Nasaclear** NS) Triamcinolone 55 mcg/nostril twice daily (**Telnase** NS) Beclomethasone 50–100 mcg/nostril twice daily (**Alanase** FS) Budesonide 50–100 mcg/nostril once daily (**Butacort Aqueous** PS)	Budesonide – A Beclomethasone – B3 Fluticasone – B3	From age 12 years: Fluticasone 50 mcg/nostril once daily (**Flixonase, Nasaclear** NS) From age six years: Budesonide 50 mcg/nostril once daily (**Butacort Aqueous** PS)

FS = Fully subsidised, PS = Partly subsidised, NS = Not subsidised

	Adults	Pregnant/breastfeeding	Children
Intranasal decongestants	Xylometazoline 0.1%, one spray/nostril two to four times per day, maximum five days (**Otrivin spray** or **drops** NS) Oxymetazoline 0.5 mg/mL (**Drixine** NS)	Xylometazoline Not recommended unless benefit outweighs risk (**Category C**)	Xylometazoline 0.05%, one spray/nostril two to three times per day, max five days (**Otrivin Junior spray** or **drops** NS)
Oral corticosteroid	Prednisone 20–40 mg once daily for five to seven days	Prednisone – A	Prednisone 10 mg once daily for five to seven days
Intranasal anticholinergic	Ipratropium bromide 0.03% two sprays, two to three times daily (**Apo-Ipravent** FS)	Ipratropium bromide – B1	From age 12 years: Ipratropium bromide 0.03% two sprays, two to three times daily (**Apo-Ipravent** FS)
Intranasal sodium cromoglycate	Sodium cromoglycate Nasal Spray 4%, one spray/nostril two to four times per day FS	Sodium cromoglycate – A	From age six years: Sodium cromoglycate Nasal Spray 4%, one spray/nostril two to four times per day FS
Ocular antihistamines	Levocabastine, one drop per eye, three times per day (**Livostin eye drops** PS) Lodoxamide, one drop per eye, four times per day (**Lomide** PS) Olopatadine, one drop per eye, two times per day (**Patanol** NS) Ketotifen, one drop per eye, two times per day (**Zaditen** NS) Naphazoline + pheniramine (**Visine, Naphcon-A** NS) Antazoline + naphazoline (**Albalon-A** NS) **N.B.** naphazoline can cause rebound hypaeremia (redness) if used for longer than ten days	Lodoxamide – B1 Olopatadine – B1 Ketotifen – B1 Levocabastine – B3	From age six years: Levocabastine, one drop per eye, three times per day (**Livostin eye drops** PS From age four years: Lodoxamide, one drop per eye, four times per day (**Lomide** PS) From age three years: Olopatadine, one drop per eye, two times per day (**Patanol** NS) From age three years: Ketotifen, one drop per eye, two times per day (**Zaditen** NS)

Australian Drug Evaluation Committee classification of drugs in pregnancy (summarised)[11]

Category A	No evidence of harmful effects to the human foetus.
Category B1	No evidence of harmful effects to the human foetus observed, but limited number of human studies. Animal studies have shown no increased risk of foetal harm.
Category B2	No evidence of harmful effects to the human foetus observed, but limited number of human or animal studies.
Category B3	No evidence of harmful effects to the human foetus observed, but limited number of human studies. Animal studies have shown evidence of increased risk of foetal harm, the significance of which is uncertain in humans.
Category C	May cause, or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. Drug should only be used if benefit outweighs risk

FS = Fully subsidised, PS = Partly subsidised, NS = Not subsidised

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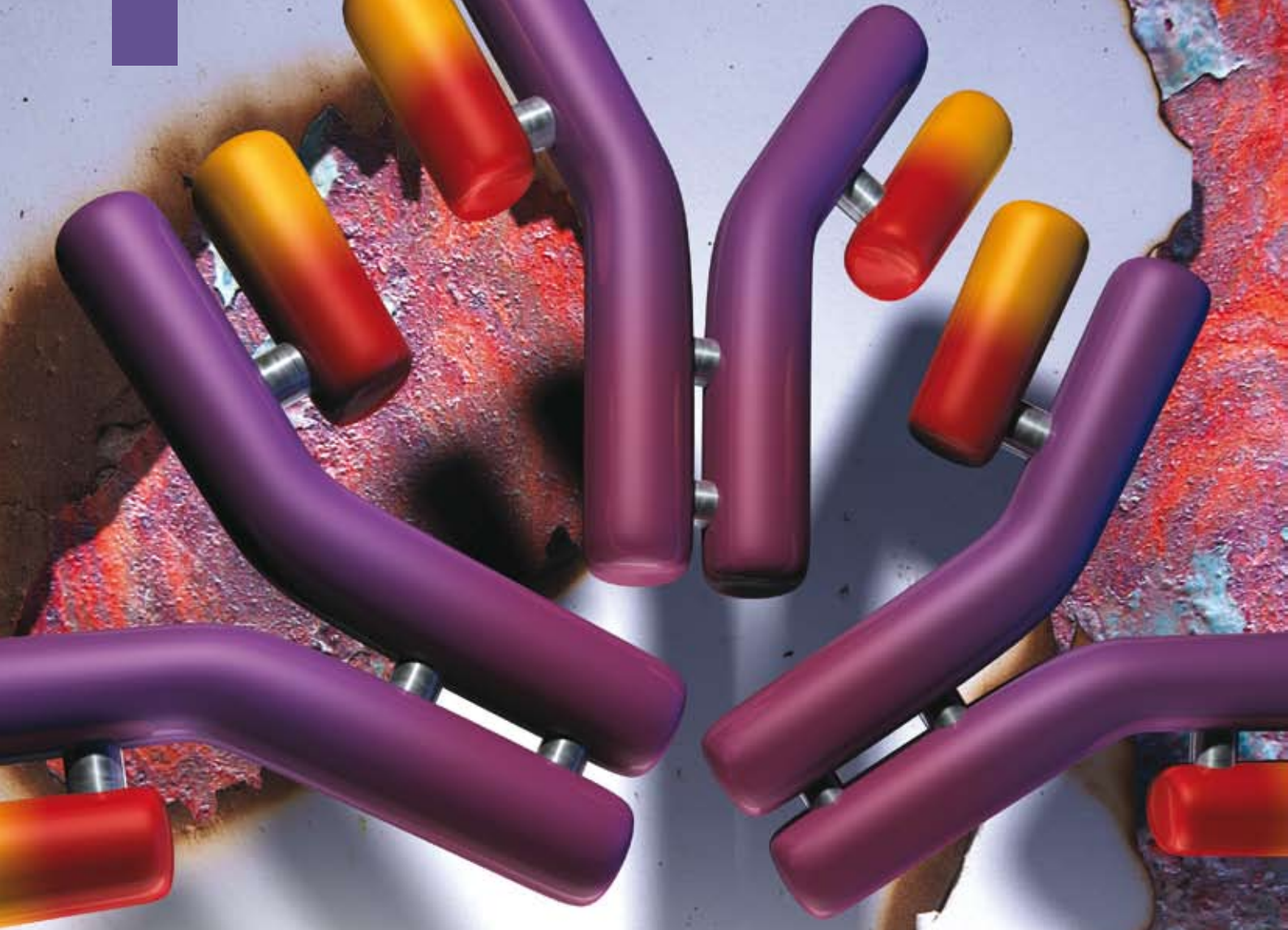

www.bpac.org.nz keyword: TNF

TNF inhibitors: an update

Tumour necrosis factor

Tumour necrosis factor (TNF) is an inflammatory cytokine involved in the pathogenesis of a number of inflammatory or immune mediated conditions.

TNF inhibitors available in New Zealand

Adalimumab (Humira) and infliximab (Remicade) are both monoclonal antibodies active against TNF. They neutralise the inflammatory effect of TNF by binding to it and inhibiting binding with its target receptor.

Adalimumab contains only human proteins and is administered by subcutaneous injection, usually every two weeks. Infliximab contains both human and mouse proteins and is administered by intravenous infusion every eight weeks.[1]

Etanercept (Enbrel) is a genetically engineered human soluble TNF receptor that works by binding to TNF and blocking its activity.[2] It is given by subcutaneous injection twice weekly.

Place in therapy

TNF inhibitors are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, severe psoriasis, Crohn's disease and juvenile idiopathic arthritis when there is high disease activity despite a full trial of conventional therapies.

Contraindications to TNF inhibitor use

TNF inhibitors are not suitable for people who have :[1]

- Severe active infections (e.g. infected prosthesis, severe sepsis)
- Untreated active or latent tuberculosis
- Moderate to severe congestive heart failure
- Multiple sclerosis or optic neuritis

Adverse effects

Common adverse effects

The most common adverse effect with TNF inhibitors injected subcutaneously is **injection site reactions**. Injection site reactions can be lessened with pre-treatment antihistamines or treated with local application of ice or topical corticosteroid unless infection is present on the skin.

Infusion reactions may occur with infliximab. They can often be prevented by premedication with a sedating antihistamine and paracetamol.[4]

Rare but serious adverse effects

Reactivation of tuberculosis (TB) is most likely to occur in the first 12 months of treatment therefore extra vigilance is required during this time. British guidelines suggest screening all patients for TB prior to commencing treatment with a TNF inhibitor.[5] This includes taking a history to check for any prior TB infection or treatment and performing a clinical examination and a chest x-ray. Patients who are found to have latent or active TB should be treated prior to commencing a TNF inhibitor.

Adalimumab funded for more indications

In addition to being subsidised for the treatment of severe rheumatoid arthritis, access to subsidised adalimumab (Humira) has recently become widened to include last-line treatment of ankylosing spondylitis, Crohn's disease, severe chronic plaque psoriasis and psoriatic arthritis. Funding for all subsidised indications is subject to Special Authority criteria being met.

Adalimumab has been shown to:[3]

- Reduce signs and symptoms of ankylosing spondylitis, psoriatic arthritis and rheumatoid arthritis
- Inhibit progression of structural damage in rheumatoid and psoriatic arthritis
- Reduce signs and symptoms and maintain clinical remission in Crohn's disease
- Decrease epidermal thickness and inflammatory infiltration in plaque psoriasis

Note: Etanercept is still funded, subject to Special Authority criteria, for juvenile idiopathic arthritis and infliximab will still be available for treatment in hospital (if funded by the hospital).

Monoclonal antibody naming conventions

Generic drug names are intended to make drugs identifiable and to avoid confusion with other drug names. All monoclonal antibodies are recognisable from their suffix stem of –mab (e.g. infliximab, adalimumab). They also have a specific sub stem that reflects the species origin of the antibody:[2]

Sub-stem	Origin of antibody	Example
-o-	Mouse	No examples in New Zealand
-xi-	Chimeric (e.g. mouse + human)	Infliximab
-zu-	Humanised	Palivizumab
-u-	Human	Adalimumab

Patients who qualify for TNF inhibitor therapy in New Zealand have usually trialled multiple DMARDs previously. Tuberculin skin tests (Mantoux test) are significantly affected by immunosuppressive therapy therefore their value in this setting is questionable.[6]

Serious opportunistic infections

TNF inhibitors should not be initiated in the presence of serious infections and extreme caution should be used in patients with increased risk of infection, e.g., bronchiectasis, history of chronic leg ulcers and history of septic arthritis.

Infection developing in patients on TNF inhibitors can quickly become severe and lead to life-threatening or fatal sepsis.

Best practice tip: In patients taking TNF inhibitors it is important to treat any infections early, even if minor,[7] Patients should be advised of the increased risk of infection and the need to consult their GP if signs of infection occur.

Therapy should be discontinued if a serious infection develops but can be restarted once it has completely resolved.

To minimise the risk of infection in patients who are undergoing major surgery, TNF inhibitor therapy should be withheld for two to four weeks prior to surgery and can be resumed post-operatively if there are no signs of infection and wound healing is sufficient.[5]

Malignancy, heart failure and demyelinating disease are other potential adverse effects

Malignancies, including lymphoma, have been reported in association with TNF inhibitors however the risk does not seem to be elevated above the risk of malignancy associated with rheumatoid arthritis. Caution should be exercised in patients with current or recent malignancy. Until there is conclusive evidence of safety it would be advisable to avoid TNF inhibitors in patients with a history of lymphoma.

TNF inhibitors may be associated with congestive heart failure. They are contraindicated in moderate to severe heart failure (NYHA class III/IV) and should be discontinued if heart failure develops or worsens.[5]

Demyelinating disease has been associated with TNF inhibitor use. Symptoms of demyelination include confusion, ataxia and changes in sensation. TNF inhibitor therapy should be discontinued in patients who develop symptoms of demyelination and are best avoided in people who have conditions associated with demyelination such as multiple sclerosis.[4]

Drug induced lupus erythematosus

See Research Snippets (page 48) for further information.

Monitoring

Monitoring may vary depending on whether other DMARDs are used in conjunction with TNF inhibitors but as a guide test the following at baseline, then monthly for six months and then every three to six months thereafter:

- Complete blood count - stop therapy and seek advice for WBC < 3.5 x 10^9/L, neutrophils < 2 x 10^9/L, platelets < 150 x 10^9/L
- Liver function tests - seek advice if ALT level greater than twice the upper limit of normal[8]

ACKNOWLEDGMENT Thank you to **Dr Andrew Harrison**, Rheumatologist and Senior Lecturer, School of Medicine, University of Otago, Wellington, for expert guidance in developing this article.

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www.bpac.org.nz keyword: oxycodone

Oxycodone
– Place in therapy

Key concepts:

- Oxycodone is a strong opioid and is a second line option (after morphine) for use at step three on the WHO analgesic ladder
- Morphine remains the first-line strong opioid and oxycodone should be reserved for specific situations
- Oxycodone can be considered if morphine is poorly tolerated
- Oxycodone is not a substitute for codeine at step two on the analgesic ladder. If the response to codeine is unsatisfactory, morphine should be considered (i.e. step three)
- Oxycodone has a number of potentially significant drug interactions that do not occur with morphine
- Oxycodone is not completely safe in renal impairment

Oxycodone use is increasing

The use of oxycodone has been steadily increasing over the last three to four years (Figure 1).

This trend is similar to patterns observed in other countries such as the UK and Australia and corresponds with a prominent marketing campaign suggesting that oxycodone should be the preferred opioid analgesic for the treatment of moderate to severe persistent pain. Oxycodone is more expensive than morphine, has a similar side effect profile and there is no clinical evidence to support its use first-line.

Oxycodone is a strong opioid similar to morphine

Oxycodone is a semi-synthetic opioid with effects similar to morphine. It is an alternative to morphine for severe pain at step three on the WHO analgesic ladder

See BPJ 16, September 2008 “Pharmacological management of chronic pain”.

Clinical trials indicate that oxycodone is as effective as morphine at controlling cancer pain but with no significant difference in overall tolerability. There is no evidence that oxycodone is superior to morphine for chronic, non-cancer pain.

There is some evidence that there is individual variation in analgesic response and sensitivity to the adverse effects of opioids.[1] Oxycodone can be considered for the small number of patients who experience allergy or ongoing neurotoxic adverse effects to morphine, such as hallucinations. Oxycodone may have a place in the management of complex pain syndromes.

Oxycodone is not a substitute for codeine at step two on the analgesic ladder

One possible reason for the increased prescribing of oxycodone is that it is being used in place of codeine. From its name (oxycodone) it may be perceived as being similar to codeine (a weak opioid), but in fact oxycodone is a strong opioid twice as potent as morphine and with similar adverse affects. If pain is not controlled adequately with a step two analgesic, including codeine, progress to step three might be indicated with morphine as the first line choice.

Precautions

Potential drug interactions

Oxycodone shares the same drug interactions as the other opioid analgesics. However, in contrast to morphine, the enzymes CYP2D6 and CYP3A4 are involved in the hepatic metabolism of oxycodone, and there is the potential for drugs which inhibit these enzymes (e.g. fluoxetine, erythromycin) to increase oxycodone plasma concentrations. There appears to be little evidence at present that these potential interactions are clinically significant, but as with any drug it is important to check the interaction profile prior to prescribing.

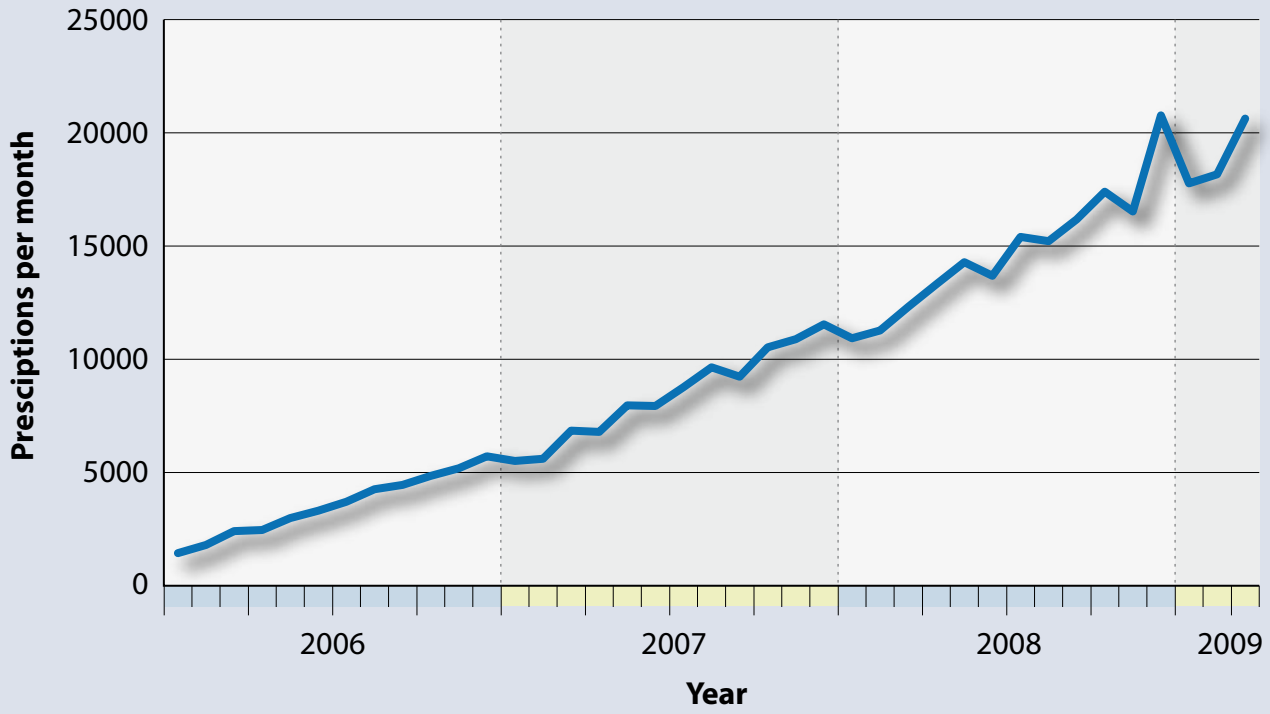

Figure 1: Number of oxycodone prescriptions in New Zealand 2006 to 2009 (Pharmaceutical Warehouse data)

Promotion of oxycodone

Oxycodone preparations have been heavily marketed over the last few years but advertisements do not provide useful information to guide its rational and appropriate use.

- The wording in the advertisements strongly suggests to the prescriber that oxycodone is generally superior to other opioid analgesics, but does not provide any evidence to support this.
- All statements supporting the use of oxycodone could be equally applied to morphine.
- When the trials that are cited to support the efficacy of oxycodone are analysed, it is found that they do not describe any benefits over other opioid analgesics. For example, the statement "proven efficacy in providing long acting relief from moderate to severe persistent pain" is supported by three references:
  - A comparison between modified release and normal release oxycodone for chronic back pain (equally effective)[2]
  - A controlled trial of oxycodone versus placebo for osteoarthritis pain (oxycodone superior to placebo) [3]
  - A comparison of controlled release morphine with controlled release oxycodone in cancer pain (equally effective)[4]
- None of these trials indicate that oxycodone is anything other than an effective second-line alternative to morphine.

Adverse effects

Oxycodone is not a safer alternative to other opioid analgesics and it has the same spectrum of adverse effects. Of greatest concern is the potential for respiratory depression when used at too high a dose or when combined with other CNS depressants such as benzodiazepines and alcohol. Combination with other opioids is potentially lethal and care should be taken to avoid this, especially if people might have access to a supply of both, e.g. after switching from morphine.

Dosage adjustment still required in renal impairment

Oxycodone has a better profile in renal impairment as, unlike morphine, it does not have active metabolites that are renally excreted. However, caution is still required as the half-life of oxycodone is increased with renal impairment and dosage adjustment is required.

Prescribing oxycodone

The pharmacodynamics of morphine and oxycodone are comparable and equivalent formulations can be used in similar ways. Oxycodone is available as:

- OxyNorm = normal release liquid (5 mg/5 mL) and capsules (5 mg/10 mg/20 mg)
- OxyContin = modified release tablets (5 mg/10 mg/20 mg/40 mg/80 mg). The modified release tablets have a biphasic release profile, which gives an onset of analgesia within an hour of dosing and a duration of action of 12 hours
- Parenteral formulation (OxyNorm 10 mg/mL) for subcutaneous or intravenous injection or infusion. This is 1.5 to 2 times more potent than oral oxycodone.

Changing from oral morphine

Oral oxycodone is approximately twice as potent as oral morphine. To convert from oral morphine to oxycodone it is necessary to halve the dose e.g. 10 mg morphine is equivalent to 5 mg of oxycodone. It is important to note

that conversion rates are an approximate guide and patient response should be carefully monitored.

Starting oxycodone in an opioid naïve patient

It is uncommon to commence oxycodone in an "opioid naïve" patient. One reason to consider this would be in a "morphine phobic" patient who can be convinced to trial an opioid with a different name.

If opioid treatment with oxycodone is commenced, one possible approach is:

1. Start with normal release formulation to find the daily dose required. As the half-life of the OxyNorm is slightly longer than the half-life of morphine it may be dosed at six hourly rather than four hourly intervals.

   Example of a prescription for an "opioid naïve" patient with normal renal function:

   Oxynorm 2.5 mg to 5 mg four to six hourly

   Plus

   A = antiemetic e.g. haloperidol 1.5 mg nocte or as required for first five to seven days

   B = breakthrough Calculate the "as required" dose (prn) at 1/6th to 1/10th of the 24 hour regular prescription. For example if taking Oxynorm 2.5 mg four hourly (= 24 hour dose of 15 mg), prescribe prn dose of 2.5 mg (maximum one extra dose, two hourly)

   C = constipation Start regular laxatives e.g. Laxsol one to two tablets twice daily and alter the dose depending on effect

2. Titrate up. If requiring extra doses, or in pain, increase the regular and the prn dose by 30–50% by going from 2.5 mg to 5 mg, to 7.5 mg, to 10 mg, to 15 mg, to 20 mg, to 30 mg, to 40 mg etc.

3. Once the dose is stable, and the pain controlled, add up all the doses required in a 24 hour period (regular and prn) and divide by two to find the modified release twice daily dose.

For example Oxynorm 10 mg, six doses each day, which adds up to 60 mg, is equivalent to Oxycontin 30 mg twice daily.

Reassess:

A– Any nausea should be settled by the first week.

B – Always prescribe equivalent breakthrough e.g. if taking Oxycontin 30 mg twice daily, prescribe Oxynorm 5 mg to 10 mg prn (maximum one extra dose, two hourly)

C – Remember to reassess bowel function and readjust laxative dose as appropriate

An alternative approach is to start with a low dose of modified release oxycodone (Oxycontin). This may be particularly appropriate for benign chronic pain where the goal is not complete pain control but improvement in function. For example, start with 5 mg every 12 hours. The dose can then be titrated to effect as necessary.

Key resource:

Christchurch Hospital Palliative Care Service. Palliative Care Guidelines. Canterbury District Health Board, 2009. Available from: **www.cdhb.govt.nz/documents/palliative-care-manual/palliative-care/Pal_Care_Guidelines.pdf** (Accessed September 2009).

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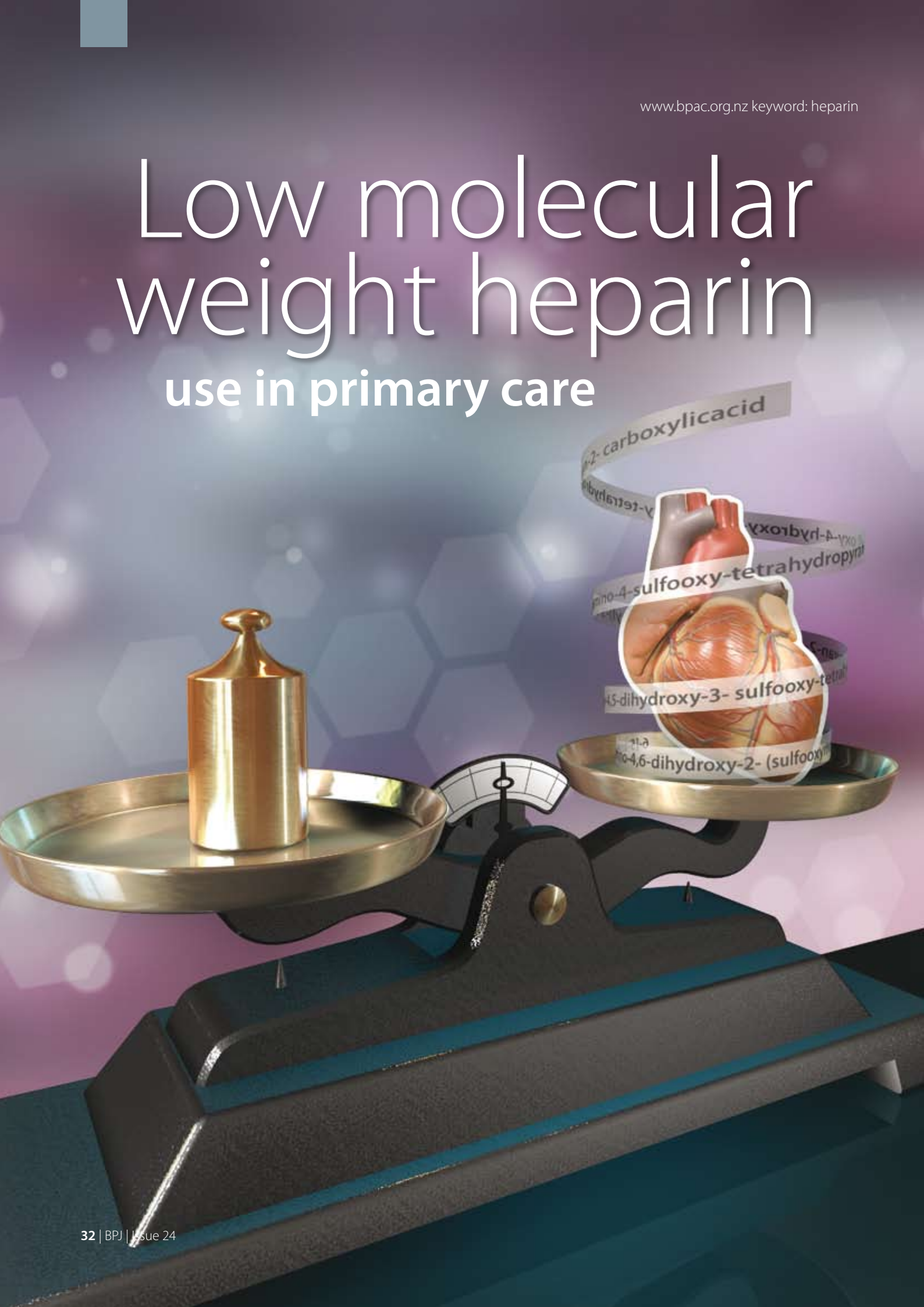
Low molecular weight heparin

use in primary care



Enoxaparin (Clexane) is a low molecular weight heparin (LMWH) used in the treatment of acute coronary syndromes and in the treatment and prevention of thromboembolic disorders.

Access to enoxaparin, has recently been widened, and GPs may become increasingly involved in its use. For many conditions, treatment with enoxaparin is started in hospital, however GPs may be involved in its initiation as well as the continuation of treatment.

In acute deep vein thrombosis without pulmonary embolism, enoxaparin can be used in the out-of-hospital setting (in conjunction with warfarin) because it can be administered by subcutaneous injection and generally does not require routine laboratory monitoring.

Initiation of enoxaparin

Contraindications to enoxaparin

Enoxaparin is contraindicated for people with an allergy to enoxaparin or other LMWHs as well as for people with active bleeding and conditions with a high risk of haemorrhage such as recent haemorrhagic stroke.[1]

It is also contraindicated if platelet count is less than, or equal to 50×10^9/L, in bacterial endocarditis, uncontrolled or severe hypertension, severe hepatic or renal disease, angiodysplasia or following recent eye or CNS surgery (less than one month prior).

Prior to commencing enoxaparin

Prior to commencing therapy with enoxaparin it is recommended that all patients:[2]

1. Are weighed
2. Have their creatinine clearance calculated using the Cockcroft- Gault formula. The eGFR calculated by the laboratory can be used as an indicator of renal impairment but the creatinine clearance equation should be used to guide dosage adjustment

Subsidised enoxaparin on special authority

Enoxaparin is available fully subsidised via special authority for pregnant women who require treatment with a low molecular weight heparin or for the treatment of venous thromboembolism where the patient has a malignancy.

It is also available fully subsidised via special authority for one month:

- For the short-term treatment of venous thromboembolism prior to establishing a therapeutic INR with oral anticoagulant treatment
- For the prophylaxis and treatment of venous thromboembolism in high risk surgery
- To enable cessation/re-establishment of existing warfarin treatment pre/post surgery
- For the prophylaxis and treatment of venous thromboembolism in acute coronary syndrome surgical intervention
- To be used in association with cardioversion of atrial fibrillation

3. Have blood tests to make sure they have a normal coagulation profile (INR, APTT), platelet count and normal liver function

Enoxaparin dosing

See Table 1 for dosing volumes.

Patients without renal impairment:[1]

Prophylaxis of venous thromboembolism: 40 mg daily

Treatment of venous thromboembolism:* 1.5 mg/kg once daily or 1 mg/kg twice daily

* Significant pulmonary embolus is usually treated with twice daily dosing.

Patients with renal impairment:

Prophylaxis of venous thromboembolism: 20 mg daily

Treatment of venous thromboembolism: An initial standard dose of enoxaparin based on the patient's actual body weight is used so that an effective concentration is achieved rapidly. However, for patients with reduced renal function (i.e. creatinine clearance less than 30 mL/min), subsequent doses require adjustment because of the risk of over-coagulation and bleeding.

For patients with creatinine clearance less than 30 mL/min enoxaparin should be dosed at 1 mg/kg once daily.[2]

Patients who are at extremes of weight

Dosing based on body weight is acceptable up to 150 kg, however there is evidence that a dose based on lean body weight may be more appropriate.[4] Once daily treatment is not recommended in patients over 100 kg (maximum syringe size is 150 mg).

Enoxaparin administration

Do not expel the air bubble from the syringe before the injection. The volume to be injected should be measured precisely by holding the syringe needle down to dispel any excess enoxaparin without expelling the air bubble.[1]

The whole length of the needle should be introduced vertically (at a 90° angle to the skin) into a skin fold gently held between the thumb and forefinger. The skin fold should be held throughout the duration of the injection.[1]

Monitoring of enoxaparin may be appropriate for those who are underweight or overweight and for those with impaired renal function

Anti-factor Xa may be used to monitor the anticoagulant effect of enoxaparin in patients with significant renal impairment or those at extremes of weight (e.g. below 45 kg or above 150 kg).[1] However anti-factor Xa monitoring is best managed by a specialist because it is not routinely available and results can be difficult to interpret.[2]

Adverse effects of enoxaparin

Haemorrhage

The risk of a significant bleed when using low molecular weight heparins is increased with:[5]

- Reduced creatinine clearance
- Number of enoxaparin doses received
- Increasing age
- Female gender
- Low body weight (< 45kg)
- Concurrent use of other drugs that affect haemostasis including aspirin, clopidogrel, warfarin or NSAIDs
- Previous peptic ulcer disease

Table 1: Volumes of Clexane required for each prescribed dose

120 mg and 150 mg syringes		80 mg and 100 mg syringes	
Syringe concentration is 150 mg/mL, each graduation is 0.02 mL = 3 mg		Syringe concentration is 100 mg/mL so each graduation is 0.025 mL = 2.5 mg	
Doses should be rounded to the nearest multiple of 3 mg		Doses should be rounded to the nearest 2.5 mg (or possibly 5 mg)	
Dose (mg)	**mL**	**Dose (mg)**	**mL**
150	1.00 (use 150 mg syringe)	**100**	1.00 (use 100 mg syringe)
147	0.98	97.5	0.975
144	0.96	95	0.95
141	0.94	92.5	0.925
138	0.92	90	0.90
135	0.90	87.5	0.875
132	0.88	85	0.85
129	0.86	82.5	0.825
126	0.84	**80**	0.80 (use 80 mg syringe)
123	0.82	77.5	0.775
120	0.80 (use 120 mg syringe)	75	0.75
117	0.78	72.5	0.72 5
114	0.76	70	0.70
111	0.74	67.5	0.675
108	0.72	65	0.65
105	0.70	62.5	0.625
102	0.68	60	0.60

Impaired renal function and prolonged use of enoxaparin were found to be significant predictors of bleeding in one New Zealand study. The authors suggested that current guidelines for dosing adjustment in renal impairment may be inadequate to minimise bleeding risk.[6] Consider discussing treatment with a specialist for patients who have impaired renal function or require prolonged treatment with enoxaparin.

A patient who has received LMWH and is clinically bleeding, may be administered protamine in hospital. While protamine reverses approximately 70% of the activity of LMWH, it does reduce clinical bleeding. If enoxaparin was given within eight hours, then a dose of 1 mg of protamine per 1 mg of enoxaparin is given. Smaller doses are recommended if it is greater than eight hours since enoxaparin was administered (0.5 mg protamine for 1 mg enoxaparin).[3]

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is diagnosed when HIT antibodies are detected in conjunction with any of the following events: a decrease in platelet count of

greater than or equal to 50%, venous or arterial thrombosis, skin reactions occurring at heparin injection sites or acute systemic (anaphylactoid) reactions that occur after IV heparin bolus administration.[7]

HIT occurs rarely with the use of LMWH, occurring three fold less frequently than with heparin.[3] The frequency of HIT is highly variable and is influenced by: the reason the patient is receiving heparin (the risk is greatest post-surgery followed by use for medical patients, and lowest when used during pregnancy), duration of heparin exposure and gender (the risk is greater for females than males).

For people who are at higher risk of HIT (e.g. post-surgery, prolonged exposure, female) platelet count should be checked before initiation of enoxaparin, then regularly (every three to five days) during the initial stage of treatment. If HIT has not developed within the first month of treatment it is unlikely to occur.

For people at low risk of HIT, less frequent (or no) platelet count monitoring may be appropriate. All patients receiving enoxaparin should be instructed to contact their GP promptly if signs or symptoms of venous thromboembolism (the most common complication of HIT) occur or painful skin lesions develop at the injection sites.[7]

ACKNOWLEDGMENT Thank you to **Dr Paul Harper**, Haematologist, Midcentral DHB, Palmerston North, for expert guidance in developing this article.

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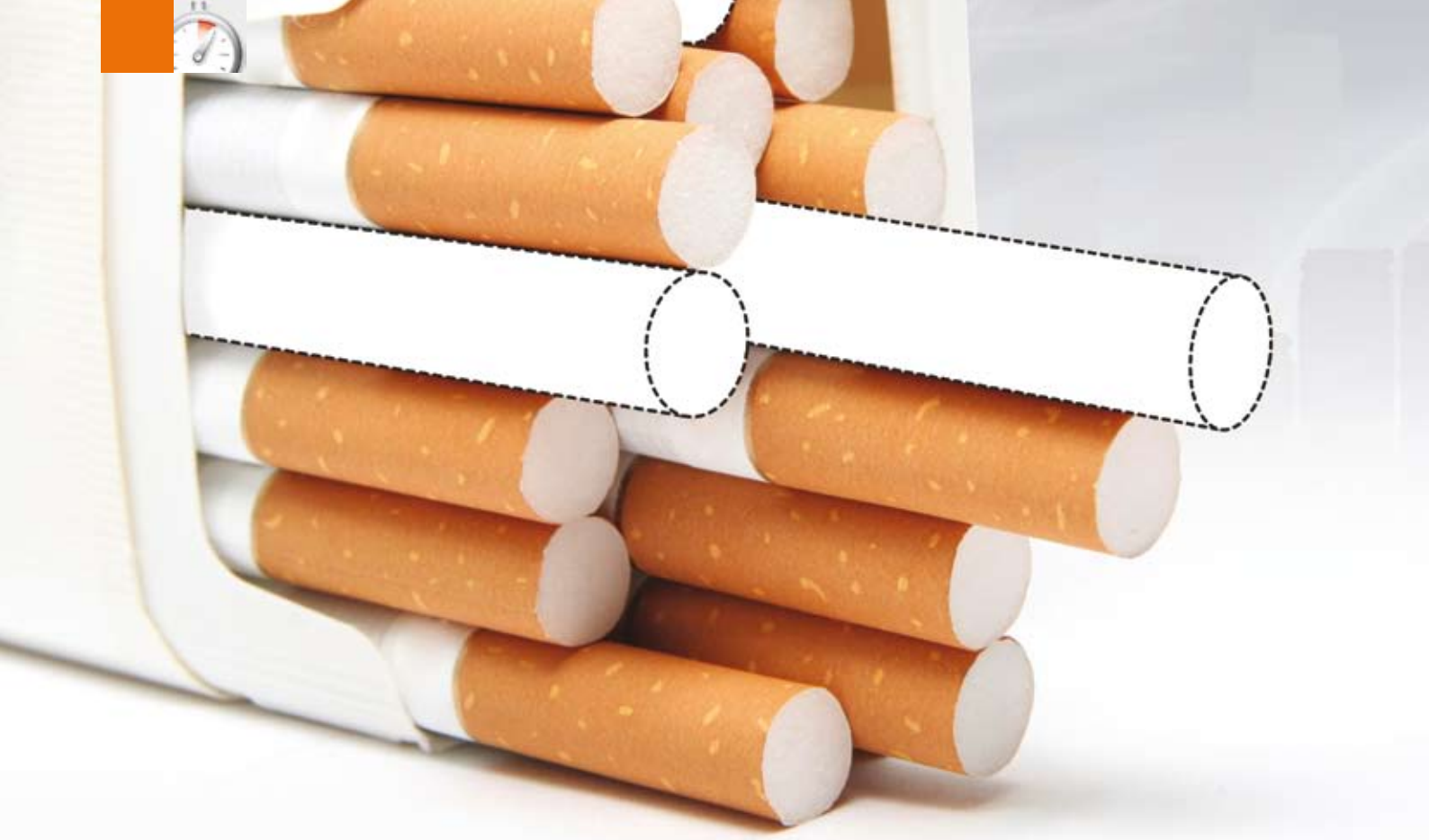

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DECISION SUPPORT FOR HEALTH PROFESSIONALS

Breast screening
– achieving equity

Key concepts:

- Māori and Pacific women have lower rates of breast screening and as a result have a higher mortality rate from breast cancer
- General practice can play a key role in addressing this inequality by ensuring all eligible women are assisted to enrol and participate in the breast screening programme
- Practices that have made a commitment to increasing breast screening rates for Māori and Pacific women are finding they can make significant improvements in screening rates

PHO PERFORMANCE PROGRAMME

Breast cancer is the most commonly diagnosed cancer in women and is a leading cause of cancer death in New Zealand women. A woman's chance of developing breast cancer increases with age. Approximately 70% of women diagnosed with breast cancer are aged over 50 years and of those who die from breast cancer, 80% are aged 50 years and over.[1]

The incidence of breast cancer is similar for all women. However Māori and Pacific women are over 1.5 times more likely to die as a result of breast cancer compared to other women in New Zealand (Figure 1).[2] Māori and Pacific women are diagnosed later than other ethnic groups with larger, higher grade tumours with more lymph nodes involved.[3]

The national target for breast screening is for 70% of all eligible women to have been screened within a two year screening interval. This target has not been met for any ethnic group, and there are significant differences in screening rates between Māori and Pacific women, and other women (Figure 2).

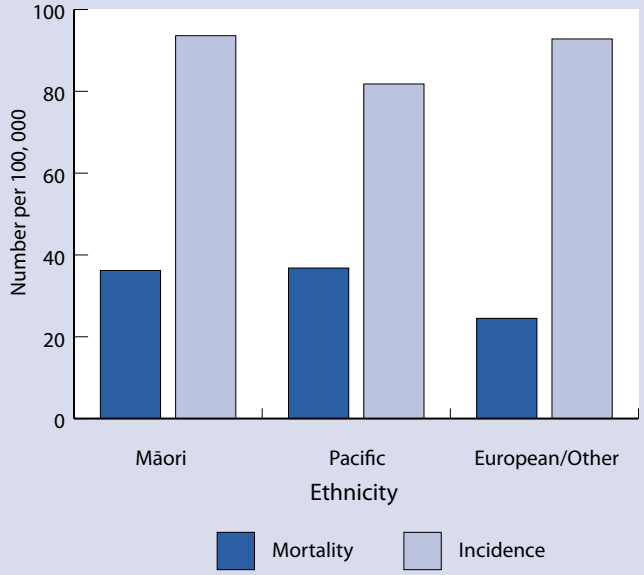

Figure 1: Breast cancer incidence and mortality[2]

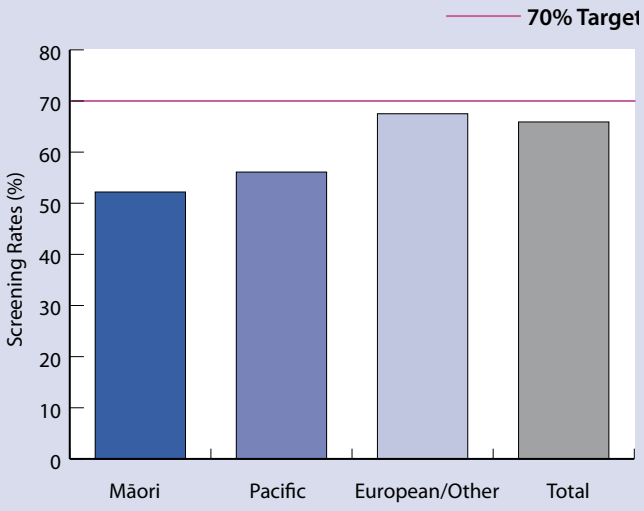

Figure 2: Breast screening coverage by ethnicity (women aged 50 to 69 years, June 2007–09)

General practice has a key role in improving breast screening rates in Māori and Pacific women

The aim of breast screening is to identify breast cancers at an early stage, allowing treatment to commence sooner, leading to reduced morbidity and mortality. Many women miss out on breast screening because there is no national system available which identifies and enrols them for screening as they become eligible.

The challenge, in the absence of a national system is for individual general practices to commit to ensuring all eligible women in their practice population are encouraged and assisted to enrol in the breast screening programme.

Who is eligible for breast screening in New Zealand?

As part of the New Zealand breast screening programme, a mammogram is performed every two years. This is provided throughout the country by BreastScreen Aotearoa and is free of charge. To be eligible women must:[4]

- Be aged 45 to 69 years of age
- Have no symptoms of breast cancer
- Have not had a mammogram in the previous 12 months
- Not be pregnant
- Be eligible for public health services in New Zealand (**www.moh.govt.nz/eligibility**)

Women who have had breast cancer in the past, but now meet the above requirements can enter or re-enter the BreastScreen Aotearoa programme, five years from when their breast cancer was first diagnosed.

What can your practice do?

Be able to identify and contact eligible women in your practice:

- Use your practice management system to identify and flag eligible women
- Send invitations that encourage women to enrol for breast screening
- Ask women about their breast screening status and record it in their notes in a way that is accessible/ searchable

Reflect on barriers that may prevent women accessing screening. Strategies to overcome some of the common barriers include:

- Encourage all practice staff to have an understanding of the barriers to breast screening and be aware of the practice's strategies to overcome these barriers
- Actively assist women to enrol with BreastScreen Aotearoa and to make an appointment for a mammogram

PATIENT INFORMATION supporting the breast screening programme, in a variety of languages, and free of charge and can be ordered online at: **www.healthed.govt.nz**

- Ensure eligible women know that breast screening is free
- Provide women with appropriate information about breast screening
- Allow enough time to talk through a woman's concerns
- Support women who are shy or apprehensive
- Ensure women know they can bring a support person

Ensure your practice is aware of breast screening services in your area:

- Do you know when the next mobile breast screening vehicle is in your area? This information is available from **www.nsu.govt.nz/Health-Professionals/1388.asp**

  Click on your region, then select "mobile screening unit schedule" to bring up a list of times, dates and locations of mobile screening. Consider printing this out and ensuring all practice staff are aware when the mobile screening unit is in your community.

Consider coordinating with other practices as it is important to ensure the potential of the mobile breast screening unit is maximised when it is in your community.

Ensure practice staff are aware of transport options in your area. Your PHO may have a financial assistance programme which could be used to help cover the cost of transport, if this is a barrier.

To enrol women with BreastScreen Aotearoa:

1. Telephone BreastScreen Aotearoa on **0800 270 200**
2. Complete the online form **at www.nsu.govt.nz/Current-NSU-Programmes/1528.asp**
3. Post or fax an enrolment form to the BreastScreen Aotearoa lead provider in your area

Raising the profile of breast screening in a practice

Practice Nurse, Waitemata DHB

"We have had huge success, working in partnership with BreastScreen Aotearoa. Before the mobile caravan is due to come to our area, we have regular meetings and brainstorms with other health providers on how to reach eligible women. Together with BreastScreen Aotearoa we do an audit of our 45-69 year old female patients that are not enrolled with BreastScreen Aotearoa each year. We then rule out the patients who have gone privately, declined, or have other health issues preventing them from having a mammogram through breast screening.

BreastScreen Aotearoa gives us appointment times and we then phone these woman and enrol then over the phone and book them an appointment on the spot. We target the high needs Māori and Pacific women first. This method has been very successful as it means the patients do not have to phone BreastScreen Aotearoa and arrange it themselves. We also ask if there are any transport issues and can arrange transport for them through our local Māori Health provider or other community initiatives. The initial phone contact is useful to allay some women's fears and to answer questions about mammograms. BreastScreen Aotearoa reimbursed the practice for the time and phone call costs to do this.

Through this initiative we have improved our screening rates dramatically and it continues to improve each year. BreastScreen Aotearoa provided all the staff in the practice with shirts and fleeces with BreastScreen Aotearoa and the age limits written on them. It was surprising how many patients saw the shirts and were prompted to ask questions and subsequently go for a mammogram. Raising the profile of breast screening and working closely together with BreastScreen Aotearoa and other community groups seems to be the key."

Increasing the uptake of breast screening in Māori women[5]

A general practitioner led initiative at the Te Whānau ā Apanui Community Health Service (TWAACH) in the Eastern Bay of Plenty, has been successful in increasing the uptake of breast cancer screening in a predominantly Māori community (approximately 90% Māori). Screening rates have increased from 45% of eligible Māori women in 2003 to about 98% in both 2005 and 2007.

The starting point was agreement from the general practice team to set a goal and a clear focus on improving breast cancer screening participation rates for their predominantly Māori population. Changes were achieved using the current staff and resources, but with local input, flexibility and collaboration between existing services.

The strategy had two broad aims – to increase local involvement and to reduce barriers to participation and included the following:

- The PMS system was used to create a master list of eligible women who were sent letters inviting them to enrol for breast screening
- TWAACH received agreement from Breast Screening Aotearoa to coordinate registration and make appointments. Staff were encouraged to be flexible and resourceful to ensure no one was turned away and all available appointments were filled. Staff were able to arrange group bookings for women who lived in the same household, whānau (family) group or area
- Two weeks prior to screening, telephone or face-to-face contact was made with all women who had not enrolled, breast screening discussed and enrollment encouraged
- The day before their appointment women were contacted to confirm the appointment time and assistance was offered if there were going to be difficulties in attending
- Women who “dropped in” were not turned away. Instead there was flexibility to allow them to be enrolled and screened
- Women who did not arrive were contacted and offered further assistance and a rescheduled appointment at another mobile unit or fixed site

Issues that were predicted to affect participation in the screening programme were identified through discussions with practice staff and patients. These included transport difficulties, travel time, inconvenience, concern, fear and the influence of negative reports from other women. A number of strategies were used by TWAACH to help overcome these barriers to participation. They found:

- Booking directly with women helped overcome issues with an unreliable rural mail delivery, literacy, and competing priorities
- Arranging group bookings for women who lived in the same household, whānau (family) group or area, helped with travel difficulties as well as providing support
- Providing a cup of tea afterwards allowed the opportunity for women to share and debrief with each other, resulting in positive feedback and encouragement of other whanau to attend.

TWAACH also followed up abnormal results.

Breast screening was strongly advocated in the community. The staff of TWAACH were encouraged to promote breast screening at any opportunity. The dates of the mobile unit visits were advertised repeatedly in the TWAACH newsletter, marae and local businesses.

Breast screening was promoted and information provided at a number of community events. Two well known women who had previously been diagnosed with breast cancer shared their stories and support of the breast screening programme. Registration forms were available at these events.

PHO performance programme and breast screening

Breast cancer screening coverage is included as one of the clinical indicators for the PHO performance programme. The overall goal is to achieve a breast screening rate of greater than 70% for all high needs women aged 50 to 64 years. A high needs woman is defined as an enrolee who is Māori, Pacific or living in a New Zealand deprivation decile area 9 or 10.

Make it count

Calculation of breast screening rates is made using data extracted from the PHO enrolment data base and the National Screening Unit breast screening data base. It is important all demographic information collected is as complete and accurate as possible.

Ethnicity

The key points of effective ethnicity data collection are:

- Patients must identify their own ethnicity
- Patients may choose multiple ethnicities
- Patients may choose not to answer the question
- Ethnicity data can be collected in person, by telephone, by post or by proxy
- The standard ethnicity question helps to maintain consistency of responses and quality of data

See BPJ 9, October 2007 "Making Ethnicity Data count".

NHI number: Ensure the NHI number is included. A valid NHI means the data can be matched with the NSU and PHO enrolment databases, to ensure it is counted.

Gender: Ensure gender is recorded, as an "unknown" gender is converted to "male", and will not be counted.

Declines: Women who decline to be screened are not counted. This should not affect achievement of targets, as they are based on improvement rather than absolute numbers.

Age band extension: The BreastScreen Aotearoa programme was extended to include women aged 45-49 and 65-69 from 1 July 2005. At this point in time there is insufficient data for measurement of these age bands. As a result, women aged 50 to 64 are only measured for this indicator.

ACKNOWLEDGMENT Thank you to **Dr Nina Scott**, Māori Strategic Advisor, National Screening Unit, Wellington for expert guidance in developing this article.

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PHO PERFORMANCE PROGRAMME

The full PHO indicator definitions are available from: **http://www.dhbnz.org.nz/Site/SIG/pho/Programme_Documents.aspx**

SNIPPETS

When should you prescribe amoxicillin clavulanate?

One of the focuses of bpac programmes this year has been on the rational use of antibiotics. We have had many letters from our readers about different scenarios of antibiotic use, with a large proportion relating to the use of amoxicillin clavulanate. It appears that there is a lack of clarity surrounding the indications for its use.

Overview

Amoxicillin clavulanate is an important and effective broad spectrum antibiotic that is used widely in general practice. The problem is not that it does not work, but rather the more it is used, the higher the likelihood that bacteria will become resistant to this drug. Most infections can be successfully treated with other types of antibiotics and amoxicillin clavulanate needs to be reserved for specific indications when it is really needed.

The most common first-line indications for amoxicillin clavulanate are for human or animal bites or clenched fist injuries and for diabetic foot infections. Common second-line indications (after treatment failure with a narrow spectrum antibiotic) include mild acute pyelonephritis and acute sinusitis.

While use of amoxicillin clavulanate in New Zealand is reducing, prescribing figures are still high compared to other countries. Amoxicillin clavulanate is familiar, it works well and it potentially saves a patient from having to return to their doctor after treatment failure. However convenience for an individual has to be weighed against preventing bacterial resistance for the entire community. Every time you think about prescribing amoxicillin clavulanate, consider whether an alternative would be better.

Your clinical scenarios answered

Is it appropriate to prescribe amoxicillin clavulanate with roxithromycin for the treatment of community acquired pneumonias?

Management of pneumonia is possible in the community when symptoms are not severe, and when the available care for an individual is satisfactory. The choice of which oral antibiotics to use is generally made on empiric grounds to cover the most likely causative organisms.

Community acquired pneumonia (CAP) is most commonly caused by *Streptococcus pneumoniae*. Even when showing relative resistance in vitro, at standard or high doses, amoxicillin is the most active available oral β-lactam antibiotic against *S. pneumoniae*.

The addition of the β-lactamase inhibitor clavulanic acid (as in amoxicillin clavulanate) adds nothing to the activity of amoxicillin versus *S. pneumoniae* but is associated with increased adverse effects such as diarrhoea.

Neither amoxicillin nor amoxicillin clavulanate cover the atypical organisms, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* or *Legionella sp*.

Most guidelines therefore suggest using amoxicillin as monotherapy for CAP with the addition of a macrolide or a tetracycline if there is high clinical suspicion of atypical pneumonia or if there is lack of clinical response in 24 – 48 hours:

> Amoxicillin* 1 g three times per day, for seven days
>
> + /-

Erythromycin 500 mg four times per day

or

Roxithromycin 300 mg once per day

or

Doxycycline 200 mg stat then 100 mg once per day

*Monotherapy with erythromycin, roxithromycin or doxycycline is an alternative for patients allergic to penicillin.

Treatment with amoxicillin clavulanate is appropriate for post viral/influenza pneumonia, where *Staphlococcus aureus* is often implicated, and to cover anaerobes in aspiration pneumonia,

H. influenzae and *M. catarrhalis*, although associated with exacerbations of COPD, are uncommon causes of CAP and therefore the extra cover provided by amoxicillin clavulanate is unnecessary.

The treatment guidelines for CAP cover a range of clinical scenarios from treating relatively well people at home to those who are critically ill and require hospitalisation. The recommended regimens for hospitalised patients with poor prognostic indicators differ from those appropriate for community level management.

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In some clinics, pelvic inflammatory disease (PID) is treated empirically with doxycycline and amoxicillin clavulanate. Is this ideal?

The majority of cases of PID are sexually acquired. Approximately two-thirds of cases are associated with chlamydia and/or gonorrhoea. Vaginal flora such as those present with bacterial vaginosis and Mycoplasma genitalium are also associated with PID.[1, 2]

Non-sexually acquired PID is rare but may arise after procedures that breach the protective cervical barrier such as interuterine device insertion, dilation and curettage and surgical termination of pregnancy. In terms of management, guidelines do not differentiate between these groups.

Treatment protocols are designed to reflect the common microbiological aetiologies and patterns of resistance. Amoxicillin clavulanate was traditionally used as part of a treatment regimen for PID, however due to increased resistance, it is no longer recommended. Resistance of *N. gonorrhoea* to penicillin is through two separate mechanisms: β-lactamase resistance, which can be countered by the use of amoxicillin clavulanate, or by altered penicillin binding proteins which results in resistance to amoxicillin clavulanate. Between April and June 2008 over 80% of isolates of *N. gonorrhoea* in New Zealand were found to have this second mechanism of resistance, making them resistant to amoxicillin clavulanate.[1]

A suggested regimen for PID is: [2, 3]

Doxycycline 100 mg twice per day for 14 days

or azithromycin 1 g stat (for chlamydia)

And ceftriaxone 250 mg IM stat (for gonorrhoea)

And metronidazole 400 mg twice per day for 14 days (for vaginal flora)

It is recommended that patients should be followed up at 72 hours and then four to six weeks post treatment.

N.B. In our Antibiotic report/express audit, May 2009, we gave advice that mild to moderate non-sexually acquired PID should be treated with amoxicillin clavulanate and doxycycline. However in practice, all PID is treated the same. Amoxicillin clavulanate is not indicated and the regimen of doxycycline, ceftriaxone and metronidazole should be used.

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What is the appropriate antibiotic(s) to use for perianal cellulitis to prevent abscess formation in adults? In view of the fact that anaerobic organisms are likely to be involved amoxicillin clavulanate is often used.

Perianal cellulitis is most commonly seen in young children and is mainly associated with group A streptococcus. In adults, this type of perianal cellulitis is very unlikely, however there are clinical situations where adults, usually males, present with signs of perianal pre-abscess.

There is a lack of evidence about the best early treatment to prevent the formation of an abscess. Isolates of abscess pus are commonly polymicrobial. Therefore if considering empirical treatment of a pre-abscess a broad spectrum antibiotic should be used. In this case amoxicillin clavulanate 500/125 mg three times per day for five to seven days, is appropriate. This regimen does not cover *N. gonorrhoea,* so depending on the patient's history, rectal swabs for gonorrhoea may be considered.

Once an abscess has formed, even if non-fluctuant, the recommended treatment is incision and drainage. In patients with no confounding risk factors (e.g. immunosuppression), antibiotics are of no benefit. The action of antibiotics is impaired by the abscess environment and their use has no effect on long-term prognosis such as fistulae.[1]

Reference:

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ACKNOWLEDGEMENT Thank you to **Assoc. Prof Mark Thomas**, Infectious Disease Specialist, **Dr Celia Devenish**, Obstetrician and Gynaecologist and **Dr Jill McIlraith**, GP and Sexual Health Clinician for expert guidance in developing this document.

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