BEST PRACTICE

18

DECEMBER 2008

ANAPHYLAXIS

OPIOIDS

PREGNANCY

SCIENCE BEHIND LIFESTYLE INTERVENTIONS

bpac nz
better medicine

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

Dr Lisa Houghton, Dunedin

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Dr Kath Ryan, Bournemouth, UK

Dr Richard Steele, Wellington

Dr Wendy Stevens, Auckland

Dr Neil Whittaker, GP Reviewer, Nelson

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Contact us:
Mail: P.O. Box 6032, Dunedin
Email: editor@bpac.org.nz
Free-fax: 0800 27 22 69

www.bpac.org.nz

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INTRODUCTION

Welcome to BPJ 18

In the introduction to the last issue we said we were interested in your feedback to help guide the selection of topics to cover. As a result, in this issue we look at a diverse range of subjects from mastitis to methadone, suggested by you, our readers.

The exception is Upfront which highlights an area in which Māori lead the world, the incidence of lung cancer. Clearly there are numerous factors which contribute to this sad statistic. However the high proportion of people with lung cancer who first access secondary care through the emergency department suggests there are still some significant barriers to accessing primary care. While not all these can be solved by practices, some can and in this article we describe practical strategies that we would encourage you to consider.

One of the reasons we continue to highlight these disparities is because what you do can, and does, make a difference. In fact Professor James O'Donnell[1] suggests that the way we have learnt to save and extend lives by combining the scientific method with care for human beings is the greatest invention of the last 2000 years. To back this up he suggests the following thought experiment: review your own life and imagine what it would be like without late-twentieth-century healthcare. Would you still be alive today?

(It should be noted in the interests of balance that others have suggested hay is the greatest invention of the last 2000 years but we prefer to concur with Professor O'Donnell).

Finally we appreciate that the "festive season" is far from a holiday for many health care professionals. To those of you working while the rest of us are on holiday - thank you. And to those taking a well earned break – enjoy!

1. O'Donnell J. The Greatest Inventions of the Last 2000 Years. Brockman J Ed, Weidenfeld & Nicholson. 2000.

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All web links in this journal can be accessed via the online version.

www.bpac.org.nz

Christmas is that time of year that lets us reflect on what we've done,
The ghosts of Christmas past, Christmas present and Christmas yet to come.

Metabolic syndrome is out, Type 2 diabetes is no longer a disease,
Generic medicines are filling the shelves, patient consultations by email if you please.

"Quit smoking", "eat healthy", "lose weight" never change,
Nor lipids, blood pressure or glucose in normal range.

We wait in anticipation for the magic pill,
One swallow, ten ingredients to cure every ill.

So now this story is half way done,
Where have we been? What have we done?

We have brought you pain, depression and CVD,
Insomnia, head lice and some alternative remedy.

We covered the letters PCOS, HRT, DMARDs and IBD
We asked you to consider principles of prescribing, drug abuse and disparity.

You filled out our quizzes and wrote us a letter,
New topics are waiting, it will only get better.

The story has ended, let's finish here,
Thank you for being part of our wonderful year

Merry Christmas from the team at bpac^{nz}

Best Practice Journal

Dear bpac,
It's amazing how hard it is to let some things that you value, enjoy, and that have become motifs for what you do and who you are, finally go. But my medical life is in the past now. Almost exactly two years ago I took the decision not to renew my Practising Certificate, so I've been retired for that length of time. However, over all this time I've had the pleasure of continuing to receive all your wonderful stuff through the mail. I love reading it, rarely complete the quiz, and file it away in a part of my filing cabinet that says bpac, with a wistful "just maybe".

At last I feel it only right to set the record straight as it were, and let you know of these changed circumstances. If this means, as I'm sure it will, the end of our association, sadly, so be it. I want to record my sincere thanks to you for providing what, over my last several years of practice, were some of my best references tools, and sources of excellent, reliable information. I'm sure bpac has made a huge difference to the New Zealand medical landscape.

Sincere thanks and warm regards

Dr Geoff Bradley, GP, Retired
Canterbury

Neuropathic pain

Dear bpac,
Thank you for producing such an interesting and useful magazine as "Best Practice". I always enjoy reading it.

I have a slight issue with your management of neuropathic pain on page 14, in Issue 16, September 2008. If one followed the protocol for nortriptyline to the maximum of 75mg and then carbamazepine to the full dose, it would require 12 weeks which it is felt is too long.

Would it not be better to explain the side effects, but raise the doses much more quickly. In the same way as in a depressed patient you would not raise the nortriptyline over seven weeks?

GP, Wellington

Thank you for your question. In the management of neuropathic pain it is possible, and may be desirable, to escalate the doses more quickly than indicated in the article. So, why the cautious approach? To answer this, consider the contrasting therapeutic goals when prescribing for chronic pain and depression.

Firstly, in depression the aim is to reach the therapeutic dose as quickly as possible and then wait for the lag in clinical effect. The expectation is that at therapeutic doses the majority of patients will find relief from their symptoms but that at lower doses there will be no significant clinical effect. Thus, there is nothing to be gained by waiting at the lower doses and the dose should be raised to maximum as quickly as possible.

In contrast, chronic pain management,[1] while including medication to reduce pain, also involves patient education regarding the natural history of their condition and explaining the realistic treatment expectations. The aim of pharmacological treatment is optimal pain control without troublesome side effects and this is best achieved by starting with a low dose and then increasing this slowly according to response and tolerance. This allows pain control to be assessed and even a partial response may significantly improve quality of life. Rapid dose escalation may not provide better pain control but a dose which is unnecessarily high is likely to be more poorly tolerated.

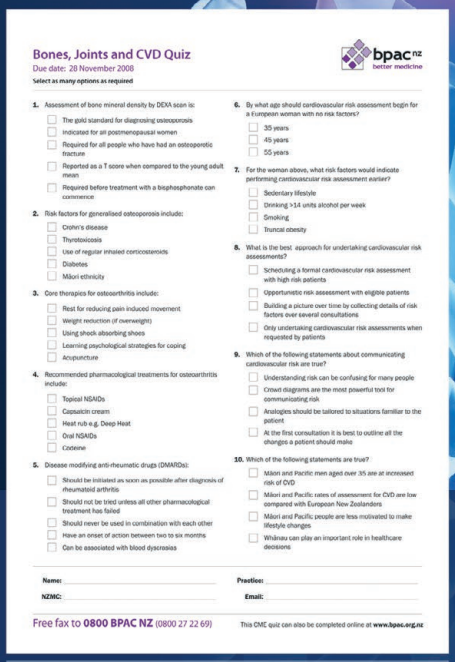
Not all neuropathic pain seen in general practice will fall into the chronic pain category. For example in newly diagnosed shingles it would be reasonable to increase the dose more rapidly with the aim of controlling pain in the shortest possible time. Similarly in palliative care rapid control of pain is often required.

Reference

1. Gilron I, Watson PN, Cahill CM, Moulin DE, Neuropathic pain: a practicle guide for the clinician. CMAJ 2006;175(3):265-75.

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

Quiz feedback for BPJ 17



Bones, Joints and CVD Quiz

Due date: 28 November 2008

bpac nz better medicine

Select as many options as required

1. Assessment of bone mineral density by DEXA scan is:
   - The gold standard for diagnosing osteoporosis
   - Indicated for all postmenopausal women
   - Required for all people who have had an osteoporotic fracture
   - Reported as a T score when compared to the young adult mean
   - Required before treatment with a bisphosphonate can commence
2. Risk factors for generalised osteoporosis include:
   - Crohn's disease
   - Thyrotoxicosis
   - Use of regular inhaled corticosteroids
   - Diabetes
   - Māori ethnicity
3. Core therapies for osteoarthritis include:
   - Rest for reducing pain induced movement
   - Weight reduction (if overweight)
   - Using shock absorbing shoes
   - Learning psychological strategies for coping
   - Acupuncture
4. Recommended pharmacological treatments for osteoarthritis include:
   - Topical NSAIDs
   - Capsaicin cream
   - Heat rub e.g. Deep Heat
   - Oral NSAIDs
   - Codeine
5. Disease modifying anti-rheumatic drugs (DMARDs):
   - Should be initiated as soon as possible after diagnosis of rheumatoid arthritis
   - Should not be tried unless all other pharmacological treatment has failed
   - Should never be used in combination with each other
   - Have an onset of action between two to six months
   - Can be associated with blood dyscrasias
6. By what age should cardiovascular risk assessment begin for a European woman with no risk factors?
   - 35 years
   - 45 years
   - 55 years
7. For the woman above, what risk factors would indicate performing cardiovascular risk assessment earlier?
   - Sedentary lifestyle
   - Drinking >14 units alcohol per week
   - Smoking
   - Truncal obesity
8. What is the best approach for undertaking cardiovascular risk assessments?
   - Scheduling a formal cardiovascular risk assessment with high risk patients
   - Opportunistic risk assessment with eligible patients
   - Building a picture over time by collecting details of risk factors over several consultations
   - Only undertaking cardiovascular risk assessments when requested by patients
9. Which of the following statements about communicating cardiovascular risk are true?
   - Understanding risk can be confusing for many people
   - Crowd diagrams are the most powerful tool for communicating risk
   - Analogies should be tailored to situations familiar to the patient
   - At the first consultation it is best to outline all the changes a patient should make
10. Which of the following statements are true?
    - Māori and Pacific men aged over 35 are at increased risk of CVD
    - Māori and Pacific rates of assessment for CVD are low compared with European New Zealanders
    - Māori and Pacific people are less motivated to make lifestyle changes
    - Whānau can play an important role in healthcare decisions

Name: Practice:

NZMC: Email:

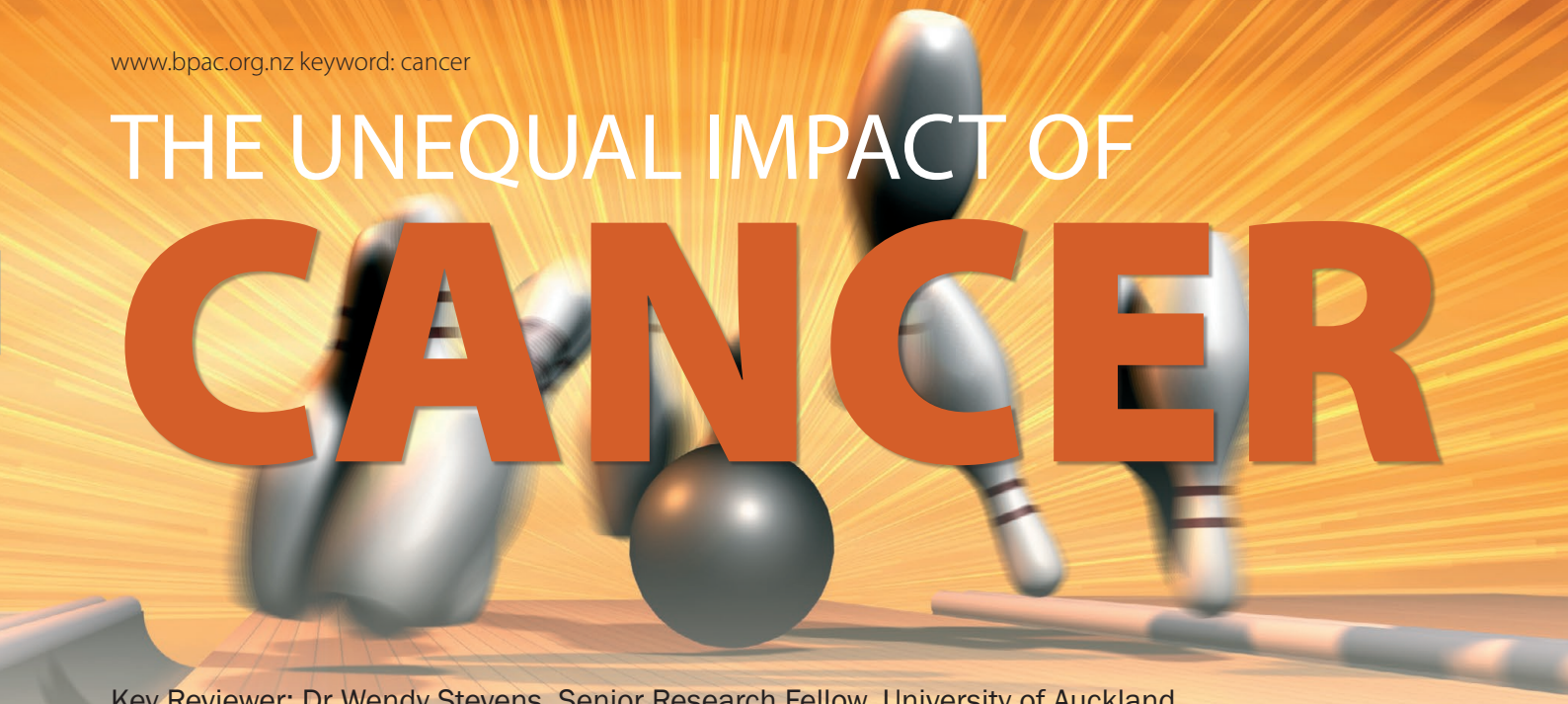
Free fax to **0800 BPAC NZ** (0800 27 22 69) This CME quiz can also be completed online at **www.bpac.org.nz**

Quiz feedback from BPJ 17 (Bones and Joints/ CVD risk assessment) will be available online in the new year - check out **www.bpac.org.nz** (search by publication type "**CME quiz feedbacks**").

A summary of the quiz answers along with expert commentary will appear in the next issue of BPJ.

www.bpac.org.nz keyword: cancer

THE UNEQUAL IMPACT OF CANCER



Key Reviewer: Dr Wendy Stevens, Senior Research Fellow, University of Auckland

Cancer has a significant and disproportionate impact on Māori and there are significant disparities in experiences, quality of health care from diagnosis to treatment and resulting outcomes. This suggests that focused interventions for Māori are needed.

There is greater incidence and mortality for all cancers in Māori compared to non-Māori.[1, 2] Inequalities in cancer death rates are increasing and this is a major reason for the significant gap in life expectancy (8.2 years[3]) between Māori and non-Māori.[4, 5] Survival rates for Māori diagnosed with cancer are poorer[6, 7, 8] and there are disparities in access to all cancer services.[9]

Māori are nearly twice as likely to die from cancer, even though they are only 18% more likely to have cancer. One reason for this may be that Māori are more likely to be diagnosed with cancer at a more advanced stage.[10]

Māori have the highest rate of lung cancer in the world

New Zealand survival rates from lung cancer are one of the poorest in the developed world. Lung cancer is the leading cause of cancer deaths with a five year relative survival rate of 10.2%,[11] considerably worse than Australia (14%)[12] and the USA (15.5%).[13]

The incidence of lung cancer in Māori is the highest in the world. The mortality rate for Māori from lung cancer is three times higher than for non-Māori and the average age of death is lower (63 years compared to 70 years). The five year relative survival rate for Māori is just 5.4%.[10]

Recent studies of lung cancer in New Zealand found that:[15,16]

- High mortality from lung cancer is largely due to late presentation, delays in treatment and low surgical rates for early stage disease.
- The most common method of entry to secondary care was through the emergency department (Pacific 52%, Māori 38%, European 32%, Asian 26%).
- A high proportion of people with lung cancer are not managed within recommended timeframes.
- Timely access to specialist oncology services was associated with improved outcomes.
- Māori were more likely to have delays in receiving treatment.
- Māori were four times less likely than Europeans to receive curative treatment.
- Treatment for Māori was aimed at relieving symptoms.

The high proportion of patients with lung cancer entering secondary care through the emergency department suggests that access barriers (e.g. financial, cultural, geographic) may still exist in the primary care sector. However, there may be other factors influencing late presentation such as patient fear. Presentation to the emergency department are associated with severe presenting symptoms, late stage disease, and Māori and Pacific ethnicity. The differences between Māori and non-Māori in types of treatment received may reflect the stage of cancer at presentation and higher rates of comorbidity (e.g. renal disease, cardiovascular disease) for Māori, which would preclude the use of curative treatments.

Planning and efforts to eliminate barriers, improve access and ensure earlier presentation to primary care services along with timely appropriate referral to secondary services when necessary, is required. An increase in the early detection of lung cancer and subsequent treatment would have an immediate benefit to the patient and their whānau.

BPJ 13 – Improving Māori health detailed the following practical solutions that can be used to assist in eliminating disparities in your practice:

1. Plan to improve Māori health

Change does not happen by accident, it needs to be planned.

2. Set realistic practice goals

You don't have to change everything at once. Prioritise and develop achievable goals that can be measured.

The first goal may be as simple as correctly recording ethnicity or smoking status.

3. Invest time in establishing relationships

Invest time in building trusting therapeutic relationships with patients and whānau.

An effective therapeutic relationship may mean that patients are more likely to attend regularly, enabling identification of early symptoms such as persistent cough.

4. Engage patients in their health issues

Consider each contact as an opportunity to educate and engage patients in their health care and address wider issues.

Encouraging young Māori not to start smoking and offering smoking cessation advice for those that do smoke are important factors in reducing the incidence of lung cancer.

5. Agree on realistic patient-centred health goals

Break up the health issue into manageable pieces. Agree on achievable treatment goals, activity goals and lifestyle changes.

Encouraging a smoke-free environment at home may be the first step towards smoking cessation.

6. Make it easy for patients to come back

Give patients a reason and create an expectation to return. Use reminders. Make the environment welcoming. Offer solutions for any barriers that may exist. Ensure you validate their attendance, encourage and arrange for them to return.

Not every presentation of cough in a patient who smokes will be cancer, but it is useful to let patients know that cough is an important symptom in smokers, without being judgemental.

7. Form partnerships

Find out who is taking responsibility for a patient's healthcare – it may be another whānau member.

Involve Māori health providers and encourage community initiatives e.g. smoke free marae. Cancer is a whānau condition.

What methods have worked for you?

We are interested in hearing about successful initiatives for improving Māori health in your practice. Contact **peter@bpac.org.nz**

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The management of **ANAPHYLAXIS** in primary care

Key Reviewer: Dr Richard Steele, Clinical Immunologist and Immunopathologist, Wellington Hospital and Aotea Pathology

Anaphylaxis treatment algorithm

Confirm anaphylaxis*

Is onset of symptoms acute?

Are there life-threatening airway, breathing or circulation problems?

Are skin changes present?

Call for help/Dial 111

Treat ABC

Lie patient flat and raise their legs (or place in a sitting position if breathing difficulties).

Remove the trigger if possible e.g. stop delivery of any drug, remove a bee sting. Do not induce vomiting after food-induced anaphylaxis.

Administer adrenaline

Recommended adrenaline dose: 10 micrograms/kg (0.01 mL/kg) up to a maximum of 500 micrograms (0.5 mL)

Age if body weight under 10 kg or weight unknown	IM adrenaline dose	mL of 1:1000 adrenaline
< 2 years	100 micrograms	0.1 mL
2 – 4 years	200 micrograms	0.2 mL
5 – 11 years	300 micrograms	0.3 mL
≥ 12 years	500 micrograms	0.5 mL

If skills and equipment available:

Establish airway

Monitor pulse oximetry, blood pressure, ECG

Administer high flow oxygen

Gain IV access

Administer IV fluids (0.9% saline)

Consider an antihistamine or hydrocortisone

Adapted from the UK Working Group of the Resuscitation Council[1] and and the Immunisation Handbook, 2024[8]

*Anaphylaxis is a severe allergic reaction. Patients with signs and symptoms indicative of a mild to moderate allergic reaction (swelling of lips, face or eyes, hives or welts, tingling mouth, abdominal pain or vomiting) should be closely observed for deterioration and treated symptomatically.

Recognising anaphylaxis

Anaphylaxis is a potentially fatal hypersensitivity reaction, characterised by rapid onset of life-threatening respiratory and cardiovascular symptoms. Most episodes are triggered by an allergen interaction with immunoglobulin E (IgE), however reactions may occur in the absence of any obvious trigger (idiopathic anaphylaxis).[2]

Anaphylactoid reactions are distinguished from true anaphylaxis as they are not IgE mediated, but this distinction is not clinically relevant for treatment as both types of reaction cause the same symptoms and are treated in the same way.[2]

Allergic triggers in anaphylaxis

Food — egg, cows' milk (and dairy foods), peanuts, tree nuts, seeds (e.g. sesame), seafood, fruit (e.g. kiwifruit, banana). Sensitivity to food additives rarely causes anaphylaxis.

Insect venom — bees, wasps.

Medication — antibiotics (e.g. penicillin), aspirin/NSAIDs, muscle relaxants, herbal products.

Other — latex (e.g. balloons, gloves, condoms), blood products, radio contrast media, storage mite (found in stored grains e.g. flour), exercise, exposure to cold air or water.

Signs and symptoms of anaphylaxis may vary

Symptoms, severity and time of onset may vary between patients and from one episode of anaphylaxis to another.[3] Symptoms usually occur within five to 30 minutes after exposure to a trigger, however reactions can occur up to several hours later, or symptoms can build up over time, beginning as a mild allergic reaction. Exposure to an intravenous trigger usually results in a more rapid onset of symptoms, followed by stings, then orally ingested allergens.[1]

If untreated, anaphylaxis can cause death within minutes due to cardiovascular collapse (more common in adults) or respiratory tract obstruction (more common in children).[2,4]

Risk factors for mortality include;

- Age – adolescents and younger adults are at the highest risk for fatal anaphylaxis from foods, especially peanuts. Venom-induced deaths are more frequent in middle-aged adults and older adults account for most cases of fatal medication-induced anaphylaxis.
- Asthma – especially if not well controlled
- Cardiopulmonary disease
- Delayed or no administration of adrenaline

Diagnosing anaphylaxis

Diagnosis is based on history and observations at the time of the event and may be difficult due to the range of signs and symptoms that can occur. However, anaphylaxis is more likely when a certain combination of factors are present.[1]

Criteria for suspecting anaphylaxis[1]

Anaphylaxis is likely when all three of the following criteria are met:

1. Sudden onset and rapid progression of symptoms
2. Life threatening airway, breathing or circulatory problems
3. Skin and/or mucosal changes

Exposure to a known allergen supports the diagnosis.

Note that:

- Skin or mucosal changes alone are not a sign of anaphylactic reaction
- Skin or mucosal changes can be subtle or absent in some reactions (approximately 12%)
- Gastrointestinal symptoms may also be present

Differential diagnosis

Other conditions which may mimic the signs and symptoms of anaphylaxis include:[1]

- Life threatening asthma, especially in children
- Septic shock – hypotension, petechial or purpuric rash
- Vasovagal episode (faint) e.g. after immunisation
- Panic attack – may occur in people who have had a previous anaphylactic reaction, if they think they have been exposed to the same trigger
- Breath-holding in children
- Idiopathic urticaria or angioedema
- Foreign body in the airway
- Reaction to MSG or sulphites
- Flushing due to menopause or drug reactions (e.g. vancomycin)

Signs and symptoms of anaphylaxis

Life-threatening symptoms:

Airway — pharyngeal or laryngeal oedema, hoarse voice, stridor, swallowing difficulties.

Breathing — dyspnoea, increased respiratory rate, wheeze, bronchospasm, hypoxia, pulmonary oedema, cyanosis and respiratory arrest.

Circulation — shock (pale, clammy), tachycardia, hypotension, dizziness, collapse, deterioration when sitting or standing, decreased consciousness, myocardial ischaemia, ECG changes, cardiac arrest.[1]

Other symptoms:

Skin — erythema, urticaria, flushing, itching, angioedema.

Gastrointestinal — abdominal pain, cramps, vomiting, diarrhoea.

Nervous system — anxiousness, confusion, agitation.

Treating anaphylaxis

Adrenaline is the core treatment

Adrenaline (also called epinephrine) should be given immediately to all patients with life threatening features of anaphylaxis.[2] Adrenaline prevents and relieves laryngeal oedema and circulatory collapse, provides bronchodilation and reduces the release of histamine and other mediators.

It is important not to give adrenaline inappropriately e.g. for allergic reactions just involving the skin, vasovagal reactions or panic attacks.[1] However many cases of fatal anaphylaxis are caused as a result of the reaction not being recognised and adrenaline not delivered promptly enough or not used at all.[1]

Intramuscular injection is used in most cases

Intramuscular (IM) injection of adrenaline is usually the most appropriate method of delivery in a primary care setting.[5] The best site for IM injection is the anterolateral aspect of the middle third of the thigh, ensuring that the needle is long enough to reach the thigh muscle. IM adrenaline is not recommended after cardiac arrest has occurred.[1]

Intravenous (IV) use of adrenaline is usually reserved for the hospital setting for those experienced in its use. IV injection can be administered when there is no response to IM adrenaline and when cardiovascular collapse is impending. This should be given by controlled infusion rather than a bolus.[2]

Subcutaneous injection of adrenaline is not recommended as absorption is slow and unreliable.[5] Inhaled adrenaline is also not recommended as there is insufficient delivery for treating anaphylaxis.[1]

Doses of adrenaline for the emergency treatment of anaphylaxis. *Adapted from the Immunisation Handbook, 2024.*[8]

Recommended adrenaline dose: 10 micrograms/kg (0.01 mL/kg) up to a maximum of 500 micrograms (0.5 mL)		
Age if body weight under 10 kg or weight unknown	**IM adrenaline dose**	**mL of 1:1000 adrenaline**
< 2 years	100 micrograms	0.1 mL
2 – 4 years	200 micrograms	0.2 mL
5 – 11 years	300 micrograms	0.3 mL
≥ 12 years	500 micrograms	0.5 mL

The dose should be repeated at five minutes if there is no improvement. Further doses can be given at five to ten minute intervals according to response.[1]

Beta blockers reduce the efficacy of adrenaline. Patients using beta blockers may need IV glucagon or atropine in addition to adrenaline.

Use of adrenaline should not be withheld because of adverse effects

Transient palpitations, tremor and pallor may occur after injection of adrenaline.[7] More serious cardiovascular effects (arrhythmia, myocardial infarction) may occur with adrenaline overdose, an inadequately diluted dose or a too rapid rate of infusion. Elderly people and people with hypertension, arteriopathies or ischaemic heart disease have the highest risk of adverse effects. Adrenaline should not be withheld but these groups of people should be monitored more closely for cardiac effects. Note that anaphylaxis itself also causes adverse cardiac events.[2]

Adrenaline in New Zealand is available in 1 in 1000 (1 mL) or 1 in 10000 (10 mL) injection strengths. It should be stored in a cool, dark place, but should not be refrigerated.

Other treatments for anaphylaxis

Fluids are given IV (adult 500-1000 mL, child 20 mL/kg). They can be given rapidly but monitor response. Give further doses as necessary. A 0.9% saline solution is appropriate.

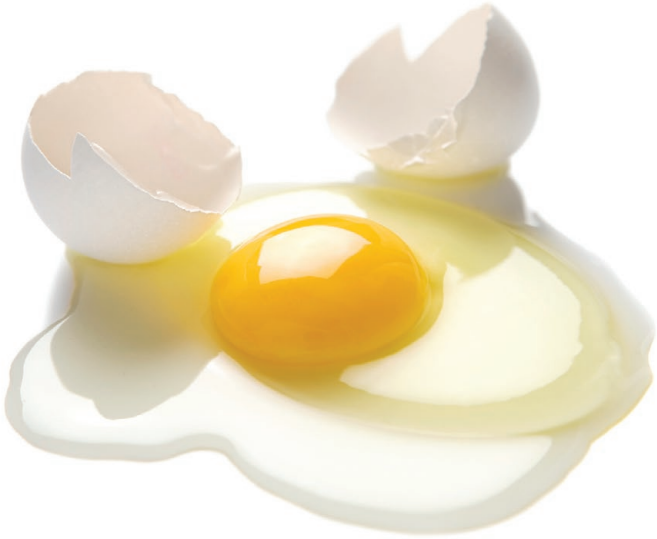
Oxygen is given using the highest concentration possible and at a high flow (> 10 L/min^{-1}).[1,4]

H1-antihistamines (e.g. loratadine or cetirizine) are sometimes used for anaphylaxis to down-regulate the allergic response and minimise the clinical impact of histamine release.[4] H1-antihistamines may relieve itching, hives, other cutaneous symptoms and rhinorrhoea. After oral administration, onset of action is one to two hours. First generation sedating antihistamines (e.g. promethazine) should be avoided. IM preparations are not generally used.

Corticosteroids may help to shorten reactions. Recommended dose: Inject hydrocortisone slowly IV or IM. Adults 200 mg, children 6 – 12 years 100 mg, children 6 months to 6 years 50 mg, children less than 6 months 25 mg.[1]

Bronchodilators such as salbutamol (inhaled or IV), ipratropium (inhaled) or aminophyline (IV) can be considered for people with severe breathing difficulties.[1]

H2-receptor antagonists (e.g. ranitidine) are also sometimes used in anaphylaxis, however there is little evidence to support their effectiveness.[1, 4]



Signs and symptoms of mild to moderate allergic reaction

Swelling of lips, face or eyes

Hives or welts

Tingling mouth

Abdominal pain, vomiting

Mild to moderate allergic reaction

If life-threatening respiratory and cardiovascular features of anaphylaxis are not present, but there are other features of a systemic allergic reaction (e.g. skin changes, abdominal pain or vomiting), the patient should be closely observed for deterioration and given symptomatic treatment such as oral antihistamines and if clinically indicated, oral steroids (e.g. prednisone 20 mg).

Refer all patients with anaphylaxis to hospital care

All patients who have had an anaphylactic reaction should be referred to hospital care and monitored and observed for up to 24 hours.[1]

Situations in which the risk of recurrence of symptoms (biphasic reaction) is higher include:[1]

- Severe reactions which were slow in onset after exposure to the trigger
- Reactions in people who have severe asthma or with a severe asthmatic component
- Reactions in which the allergen may continue to be absorbed
- Previous history of biphasic reactions

Antihistamines and oral steroid therapy may be given for up to three days after an anaphylactic reaction. This is useful for treating any remaining symptoms (e.g. urticaria) and may decrease the chance of further reaction.[1] Long-term use of antihistamines does not prevent anaphylaxis.

Risk reduction

After any anaphylactic reaction, consider referral for identification of the trigger and implementation of a plan to reduce the risk of future reactions.[1] There are only a small number of allergy specialists and clinical immunologists available via the public or private health systems in New Zealand. In areas where allergy clinics or specialists are not available, patients can be referred to paediatric, medical or dermatology specialists. A list of allergy specialists can be found at **www.allergy.org.nz**

Principles of long-term management:[7]

- Refer to a specialist for identification of triggers – this may include allergy testing or food/drug challenge.
- Provide education about avoiding triggers – avoidance is the only means of prevention for many causes of anaphylaxis.
- Assess the risk of a recurrent reaction – implement risk reduction measures.
- Write up an emergency anaphylaxis action plan – essential for first aid management.
- Reassess regularly – determine whether the allergy is still present and review prevention strategies and first aid plans.

Identifying triggers

An allergy specialist or clinical immunologist may perform tests for allergen specific IgE (skin or blood tests) to help confirm or exclude a trigger. Other methods of allergy testing (e.g. hair analysis) are not recommended and may provide unreliable or misleading results.[7]

Education about avoiding triggers

Education about avoiding triggers is essential as this is often the only effective measure to prevent an allergy.[7] It is important that concerns and anxieties about anaphylaxis are also addressed. Having an allergy can be debilitating and restrictive and can affect well-being and quality of life.[9]

GPs may also be asked to work with parents to help educate the child's teachers or carers and provide relevant medical information.

Information and practical suggestions for avoiding triggers, especially for food allergies, can be found online at the Australasian Society for Clinical Immunology and Allergy website (click on "anaphylaxis resources"): **www.allergy.org.au**

Assessing and reducing risk

In some cases people may be able to easily avoid the trigger that puts them at risk of anaphylaxis e.g. a specific drug or easily identifiable food such as shellfish. For others, reducing their risk is not as easy.

When the risk of anaphylaxis is not able to be easily managed, safety measures such as carrying an **adrenaline auto-injector** should be considered. An adrenaline auto-injector is recommended for:

- People with a history of idiopathic reaction
- People with continued risk from food or venom related reactions which are difficult to avoid
- People with known allergy who have concurrent asthma or ischaemic heart disease (increases risk of severe reaction)
- People who live in remote areas

EpiPen is the only type of auto-injector available in New Zealand and is not funded.* In comes in 0.3 mg (for adults and children over 20 kg) and 0.15 mg doses (for children 10 kg – 20 kg) and can be ordered directly from a distributor by the GP, purchased by the patient from a pharmacy, or ordered over the internet. It is essential

* Funding may be available from ACC for people with anaphylaxis due to insect stings or bites

that patients and their families are shown how to use the device correctly. Practice auto-injectors may be useful – these devices do not contain adrenaline or a needle and are usually available wherever auto-injectors are sold.

A **Medical Alert bracelet** or emblem should also be considered, especially for allergies to medicines and latex that need to be avoided in an emergency medical situation.

For drug allergies, patient details should be submitted to the Centre for Adverse Reactions Monitoring (CARM) so information can be entered into the national patient alert system.

Further risk reduction can be achieved by identifying patients who have a food allergy and also have **asthma** and ensuring that their asthma is well controlled.

Any patient who has had a systemic reaction to insect venom should be referred to a specialist who may recommend **venom immunotherapy** (desensitisation), which reduces the risk of anaphylaxis with subsequent exposure.

Anaphylaxis action plan

An anaphylaxis emergency action plan is a written document completed by the GP that includes information on allergic triggers, family contact details, signs and symptoms, and indicating when to call for medical assistance or use an adrenaline auto-injector if available. As symptoms of anaphylaxis often vary, it is important to have individual action plans with specific instructions. Copies of action plans should be kept by the patient, GP, allergy specialist and school/workplace.

Action plans for anaphylaxis that can be completed by doctors for their patients are available online from the Australasian Society for Clinical Immunology and Allergy (click on "anaphylaxis resources"): **www.allergy.org.au**

Regular review

Some food allergies can resolve with age e.g. allergy to dairy products, soy, wheat and egg, so children should be reviewed regularly by a specialist to determine whether the allergy is still present. This also includes people who may have been incorrectly diagnosed. Unnecessary food avoidance can adversely affect nutrition, particularly in children.[7]

Severe allergies to multiple foods and allergies to tree nuts, peanuts or seeds are less likely to resolve. Allergy to seafood, insect venom and medications is usually a lifelong problem.[7] However it is important that any allergy is properly diagnosed.

GPs should regularly review action plans and provide re-education on adrenaline auto-injector use, also checking with the patient that the medication has not expired.

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Unusual cases of anaphylaxis in New Zealand

Contributed by Dr Richard Steele

"Pancake" anaphylaxis

Storage mites, of which multiple species are present in New Zealand, are microscopic insects that are found in stored grains (e.g. wheat and corn). Sensitisation to these mites is associated with worsening symptoms of asthma, eczema and rhinitis as well as anaphylaxis.[1] Sensitisation is most common in people living in humid environments and living near or working in grain storage facilities due to increased exposure to the mite.

Anaphylaxis to storage mite is also called "pancake" anaphylaxis, as it usually presents in patients who have eaten homemade baked goods made of flour that has been stored at home for a prolonged period of time.[2] Most patients have a history of atopy.[3] Skin prick test or specific IgE to house dust mite is an important clue as most patients are positive due to the high cross-reactivity between storage and house dust mite. Many of the patients are also sensitive to aspirin.[3] The mites can be identified through microscopic examination of the ingredient in question, although experience is required to do this and is limited in New Zealand.

Management can be problematic and is not evidence based. Patients are usually counselled to avoid homemade food containing flour.[3] They are also advised to eat foods from commercial sources where the turnover of ingredients is much shorter and ingredients are less likely to become contaminated with mites. All grains and flour stored at home should be kept in sealed containers in the fridge and for a short period of time.

Anisakis in the South Pacific

Anisakis simplexis is a parasite found in many New Zealand fish species and is able to infect humans.[4] The main risk factor for infection is eating raw or partially cooked fish.[5] Occupational exposure in fish workers has also been documented. The acute illness is usually self limiting with severe abdominal pain, vomiting and diarrhoea.[5]

In New Zealand, allergic reactions to *Anisakis* are predominantly seen in those of Pacific Island origin. The patient usually presents with acute reaction (urticaria, angioedema and anaphylaxis) after eating infected seafood. Skin and specific IgE testing to seafood is usually negative. Specific IgE to *Anisakis* is available in New Zealand, and this is usually positive. Confusion can arise as the reaction after ingestion of *Anisakis* tends to be more delayed compared to other reactions to food.

Management is essentially similar to other forms of anaphylaxis. Patients should be advised to avoid all fish and cephalopods (e.g. octopus, squid). Crustaceans (e.g. prawns, shrimps) and shellfish can usually be eaten. Avoidance is problematic as the reactions to fish usually only occur intermittently depending upon whether there is infestation. Eating fish may be an important part of life for the patient and therefore education and negotiation is very important. If the patient elects to eat fish, the risks are likely to be reduced by suggesting that only the flesh (muscle) of the fish be eaten. Whole fish and the abdominal contents of the fish should be avoided. Fish should be obtained from fresh sources, and should be gutted quickly to avoid contamination of the muscle. Heating the fish to 60°C or freezing to –20°C (for at least 48 hours) is also recommended. Although the dead parasites remain allergenic after freezing this process is likely to reduce the risk of anaphylaxis.[6] Fresh water fish are much less likely to be parasitized unless they have been fed untreated fish waste. Injectable adrenaline should be offered to those at risk of further exposure.

Food dependant exercise induced anaphylaxis (FDEIA)

FDEIA is another form of anaphylaxis that can easily be missed. It requires two triggers; the ingestion of foods or drugs followed by some from of exercise. The symptoms can vary from mild rhinitis/urticaria to severe anaphylaxis. The history of exercise can be missed, as it can be triggered, for example, by a vigorous walk. It is more common in children, and men are affected more than women. About 40% of cases have atopy.[7] The mechanisms for FDEIA are unknown but may involve release of mediators during exercise which reduce the threshold of mast cells to activate and increased absorption of allergens from the GI tract.[8]

The most common food trigger is wheat[9] but a variety of other food allergens have also been implicated. Skin and specific IgE testing can be helpful in giving a clue to the suspected allergen, however the gold standard test is to ingest the food in question and exercise under medical supervision. This is clearly not without risk and in practice in New Zealand this is usually not performed. In addition, challenge tests are resource intensive and can only confirm the diagnosis of FDEIA in up to 70% of patients.

More recently it has been shown that a combination of foods, drugs and other factors maybe required to precipitate a reaction. The most important groups of drugs to consider are NSAIDs, particularly aspirin.[10] COX-2 inhibitors have been reported not to lower the threshold for anaphylaxis.[10] Other reported triggers included the strength/duration/type of exercise, timing after food ingestion, alcohol, atmospheric/seasonal conditions, fatigue, sleep, infection, stress, house dust mite ingestion[11] and menstruation.

Management focuses on patient education. If a particular food can be pinpointed, then it should be avoided between four to six hours prior to any exercise. In many cases the combination of factors cannot be fully elucidated and some patients will react regardless of the food eaten. In this situation all food should be avoided four to six hours prior to exercise. This may not be possible for a particular patient and therefore fitting this advice into a particular lifestyle and clinical presentation is needed. Patients should be advised to carry both injectable adrenaline and antihistamines. Antihistamines are potentially useful as a prophylactic measure or to treat non-life-threatening problems such as urticaria and angioedema, but should not take the place of adrenaline in the event of anaphylaxis. Patients should also be encouraged to exercise with others and in areas where medical help is accessible. It is important to stress that most of these patients can be managed effectively and should be encouraged to exercise as part of a healthy lifestyle.

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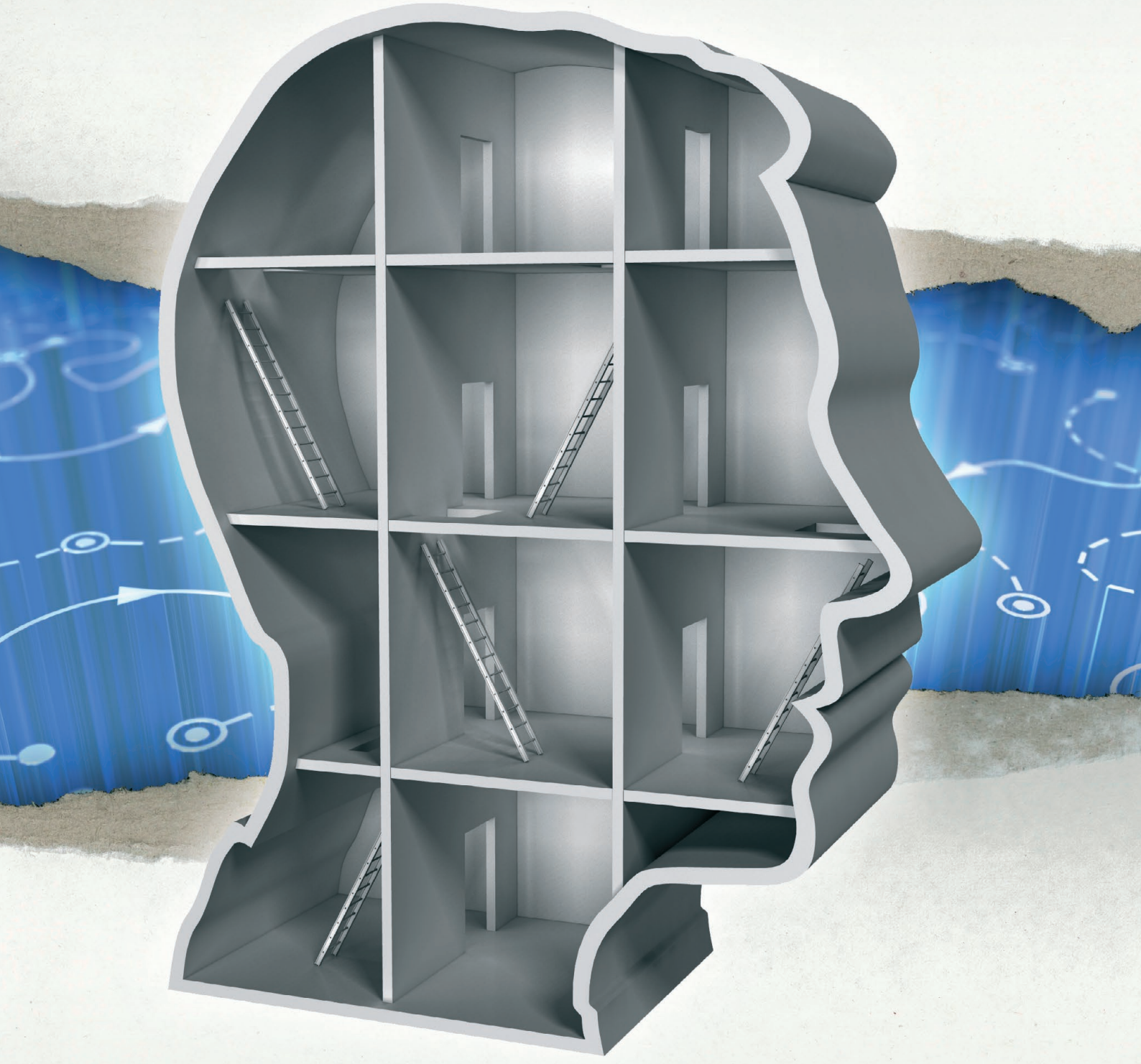
WHO Analgesic Ladder: which weak opioid to use at step two?



In BPJ 16 (September 2008) we discussed the management of chronic pain. The World Health Organisation (WHO) analgesic ladder is the framework used to guide the pharmacological treatment of pain in chronic pain and palliative care patients.

In general, at step one, paracetamol and NSAIDs are recommended. At step two weak opioids are introduced and at step three the weak opioid is stopped and a strong opioid started. Another option is to start low doses of a strong opioid, such as morphine, at step two.

Chronic opioid therapy may have fewer life-threatening risks than long-term daily use of NSAIDs

Recent guidelines for treating musculoskeletal pain, for example osteoarthritis and low back pain, recommend NSAIDs and COX-2 inhibitors only in strictly defined circumstances, at the lowest effective dose and for the shortest possible time. It is now considered that, especially for many elderly people, chronic opioid therapy may have fewer life-threatening risks than the long-term daily use of NSAIDs. Recent guidelines focus more on the use of paracetamol and opioids. This has led to more interest in how to choose between the opioids available, particularly at step two.

Opioids at step two – comparing apples with pears

All opioids are not the same. They differ in their pharmacodynamics and pharmokinetics, and clinically in their range of effects (Table 1).

Table 1: Commonly used opioid analgesics compared to morphine

	Codeine & dihydrocodeine	Tramadol	Morphine
Metabolised by	CYP2D6 to morphine	CYP2D6 and CYP3A4	glucuronidation
Main action	mu-opioid	mu-opioid & monoaminergic	mu-opioid
Constipation	●●●	●	●●
Nausea & vomiting	●●	●●●●	●●
Sedation	●●●	●●●●	●●●
Dizziness	●●	●●●	●●
Addiction risk	●●	●	●●
Respiratory depression	●●	●	●●
Serotonin toxicity		●●	
Seizures	●	●●	●
Major contraindications		MAOIs history of seizures	
Maximum daily dose	240 mg/day = morphine 24 mg	400 mg/day* = morphine 80 mg	no practical limit

Adapted from Rodriguez et al

*300 mg/day in people aged >75 years

Codeine is a prodrug that must be metabolised to morphine by the liver enzyme CYP2D6 to achieve most of its analgesic effect. Because of genetic differences some individuals (e.g. 6–10% of Caucasians) lack the enzyme CYP2D6 and cannot metabolise codeine effectively and therefore obtain limited pain relief while experiencing all the adverse effects.

Dihydrocodeine is similar to codeine in both its structure and its analgesic effect. It is primarily metabolised by CYP2D6 and CYP3A4 to dihydromorphine and nordihydrocodeine, however it is unclear whether the parent drug, metabolites or a combination of both result in dihydrocodeine's analgesic activity.

Tramadol is chemically unrelated to morphine. Tramadol is also metabolised by CYP2D6 and CYP3A4. Similar to codeine and dihydrocodeine some individuals tolerate tramadol poorly and may have increased adverse effects.

Tramadol and its metabolites have combined opioid and monoaminergic properties. Less than half of the analgesic effect is via the mu-opioid receptors. The remainder is from inhibiting the re-uptake of noradrenaline and serotonin. This dual action produces a different analgesic effect compared with the simple opioid analgesics and less respiratory depression or risk of addiction compared with the strong opioids. However, there is also a wider range of side effects, with the additional risk of serotonin toxicity (see BPJ 8 for details) and a reduced seizure threshold. For this reason tramadol is contraindicated in individuals taking MAOIs and those with epilepsy. It should also be used with caution, or avoided if possible, in those already taking a serotonergic medication (e.g. most antidepressants) or in people taking drugs that reduce seizure threshold (e.g. TCAs). In general, tramadol is associated with less constipation but increased nausea and vomiting, sedation, dizziness and orthostatic hypotension when compared to other step two opioids.

Is tramadol an option at step two?

Tramadol has been shown to be no more effective than other weak opioids but adverse effects may be problematic and drug interactions need to be considered. Tramadol is not currently subsidised and so cost to the patient is also a factor.

The most recent Scottish Intercollegiate Guidelines Network (SIGN) publication for the treatment of cancer pain suggests that there is still insufficient evidence available to make a recommendation on the use of tramadol.

For many patients, codeine when used concurrently with paracetamol will be as effective as tramadol and may be better tolerated.

Strong opioids such as morphine are more effective for severe pain and this combined with the fact that tramadol has a ceiling dose of 400 mg/day means that it is not considered an alternative to morphine for severe pain.

The choice

The final choice of which opioid to prescribe, after contra-indicated drugs are excluded, will come down to a balance between possible adverse effects and the desired analgesic effect.

Although it is often not possible to predict beforehand how an individual will tolerate a particular opioid, asking about response to previous trial of codeine may help exclude codeine and tramadol in those patients who are poor metabolisers. For these patients starting on a low dose of morphine may be the preferred option.

All step two opioids have active metabolites that are excreted renally and therefore require reduced doses and increased monitoring in elderly people and in people with reduced renal function.

As with all opioids "start low and go slow".
Remember **ABC**:
Antiemetic for the first week,
Breakthrough medication
Laxatives for **C**onstipation

see BPJ 16 for further information on the treatment of chronic pain.

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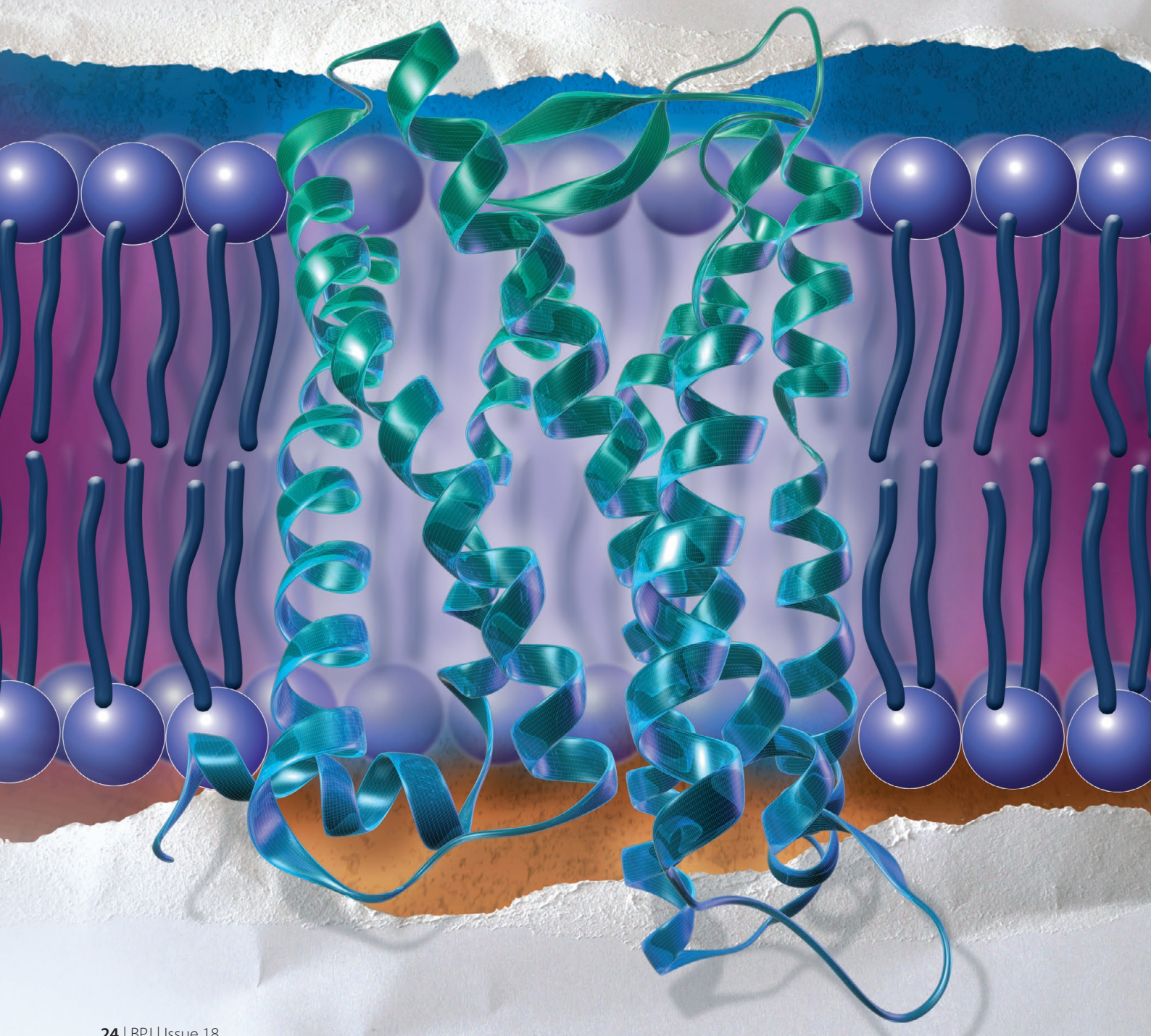
WHO Analgesic Ladder: Step 3

Methadone – safe and effective use for chronic pain



Methadone is a strong opioid

In BPJ 16 (September 2008), we provided guidance about the management of chronic pain. The three step pain ladder was recommended for managing pain; start with a non-opioid analgesic, add a weak opioid if pain is uncontrolled, and finally change to a strong opioid if pain continues to be uncontrolled.

Methadone is a strong opioid and may be suitable for people whose pain is uncontrolled with morphine (e.g. neuropathic pain) or who are unable to tolerate morphine (e.g. idiosyncratic reactions, or in renal failure).

Methadone has complex pharmacokinetics and pharmacodynamics

Methadone has a long half-life (30 hours) and displays wide variations between individuals. The duration of analgesic effect is much shorter. Methadone takes five to seven days to reach steady state and so is a difficult analgesic to titrate. If the dose is titrated too rapidly, accumulation and toxicity can occur. In the community, there is a high risk of unobserved respiratory depression and death if doses are escalated too quickly.

Because of the potential for fatal respiratory depression, it is recommended to never use methadone for breakthrough pain.

Key concepts

- Methadone may be suitable for people whose pain is uncontrolled with, or who are unable to tolerate, morphine
- Methadone has complex pharmacokinetics and pharmacodynamics and requires careful dosing and monitoring
- The general rule for dosing methadone in opioid naïve patients is “start low, go slow”
- Methadone interacts with other drugs, be especially aware of a change in therapeutic effect that may indicate an interacting drug is being used concurrently
- Monitor for adverse effects, especially respiratory depression
- Educate patients about the safe and effective use of methadone

Despite these issues, methadone is an excellent analgesic for complex pain and is increasingly being used as a first, rather than second or third-line opioid. With precautions methadone can be safely introduced in the community.

Methadone is a NMDA antagonist

Aside from its agonist activity at the mu opioid receptor, methadone has other actions that are believed to contribute to its unique analgesic activity.

Compared to morphine it is an agonist to a broader spectrum of opioid receptors and is also an antagonist at the N-methyl-D-aspartate (NMDA) receptor and inhibits the re-uptake of both noradrenaline and serotonin. These actions are believed to contribute to its increased analgesic efficacy for patients with chronic pain syndromes, hyperalgesia and neuropathic pain.

Example of methadone titration

Week 1	2.5 mg twice daily
Week 2	5 mg twice daily
Week 3	7.5 mg twice daily
Week 4	10 mg twice daily
Week 5	10 mg three times daily or 15mg twice daily
Week 6	20 mg twice daily or 10 mg four times daily

Many patients gain good analgesic control with once daily or twice daily regimens especially once a steady state is achieved. In situations where patients develop pain prior to their next dose, methadone given three or four times daily may be more effective.

Rapid titration

Quicker titration regimens are available but because of the risk of respiratory depression are not recommended in the community and inpatient admission is required. There are conversion regimens that can fully titrate methadone doses in about a week. Specialist advice/input is recommended.

Other opioids for breakthrough pain may be required

Patients who require extra analgesia outside of their methadone regimen can be initially prescribed either, codeine 30–60 mg as required, maximum four times per day, or morphine 2.5–5 mg as required (doses depend on clinical factors such as age, renal function and previous response to codeine).

Safe methadone dosing in the community

Methadone for opioid naïve patients – start low, go slow

When therapy with methadone is started, patients need to be carefully monitored for signs of toxicity, especially respiratory depression. This will require daily monitoring in the first days of treatment. Home visits may not be necessary and telephone calls may be adequate if the health professional can talk to a reliable adult. Ask about confusion, excessive drowsiness and control of pain. The patient should not be left home alone for the first five to seven days.

For patients who have not been taking regular opioids, a safe starting dose is 2.5 mg every 12 hours or 5 mg once daily. If pain is not controlled, and methadone is tolerated, doses can be increased slowly every five to seven days (see sidebar for an example).[1]

Methadone for opioid tolerant patients – ratios change based on current opioid dose

Because the analgesic effect of methadone is a result of more than its opioid effects, the conversion ratios with morphine are not linear but change with increasing doses. Various conversion ratios for morphine to methadone have been developed (see Table 2 for an example).

If the previous dose of morphine is much higher than 300 mg/day the ratio increases even further. When converting at these doses it may be more suitable to do this in an inpatient setting where the patient can be monitored more closely.

Table 1: Morphine equivalent doses

Opioid	Equivalent to 10 mg morphine (oral)	Conversion factor
Codeine	100 mg	0.1
Dihydrocodeine	100 mg	0.1
Tramadol	50 mg	0.2
Oxycodone	5 – 7.5 mg	1.5 – 2

Table 2: Suggested safe and effective starting doses when changing patients from oral morphine to oral methadone[3]

Morphine dose (mg/day)	Morphine to methadone equianalgesic dose ratio	Methadone starting dose
30–90	4:1	e.g. 90 mg morphine per day = 22.5 mg methadone per day
90–300	8:1	e.g. 200 mg morphine per day = 25 mg methadone per day
>300	12:1	maximum = 30 mg methadone per day as outpatient

It is recommended to not start higher than 30 mg of methadone per day unless the patient is in hospital.

To convert a patient from another opioid to methadone:[1]

Step 1. Assess current daily opioid dose – add up all long-acting and short-acting doses.

Step 2. If the current opioid is not morphine, convert this to a daily morphine equivalent dose.

Step 3. Based on this estimated daily equivalent morphine dose, work out the recommended methadone dose using the ratio.

Clinical scenario 1. Patient currently taking morphine for musculoskeletal pain associated with hemiplegia. Appears to be suffering thalamic pain. Plan change of opioid to methadone.

Step 1. Current opioid use: morphine 90 mg per day

Step 2. Not required

Step 3. Methadone dose: Divide the total daily morphine dose by the appropriate equianalgesic dose ratio (Table 2). In this case the equianalgesic dose ratio is 4:1.

90 mg morphine divided by 4 = 22.5 mg methadone per day given as 7.5 mg three times daily or rounded down to 10 mg twice daily.

Breakthrough analgesia is usually 1/6th of the total daily opioid dose. For this example, continue with previous breakthrough analgesia – morphine 90 mg/6 = 15 mg (morphine syrup) as required.

Clinical scenario 2. Patient currently taking oxycodone for pain from spinal stenosis. On increasing dose has developed severe itch. Plan change of opioid to methadone.

Step 1. Current opioid use: oxycodone 150 mg per day

Step 2. Morphine equivalent dose: Convert to a daily morphine equivalent dose (see Table 1 for morphine equivalent ratios). Equivalent morphine dose 150 mg x 2 = 300 mg morphine per day. Practitioners may be surprised at this equivalency.

Step 3. Methadone dose: Divide the total daily morphine dose by the appropriate equianalgesic dose ratio (Table 2). In this case the equianalgesic dose ratio is 8:1.

300 mg morphine equivalent divided by 8 = 37.5 mg methadone per day. As the maximum starting dose recommended is 30 mg methadone per day, start at 15 mg twice a day or 10 mg three times a day.

Breakthrough – continue with previous breakthrough analgesia e.g oxycodone 150 mg/6 = 25 mg as required.

In all cases review daily to check the effects until a stable dose is reached. Doses may be adjusted depending on the effect e.g. with signs of toxicity (drowsiness/

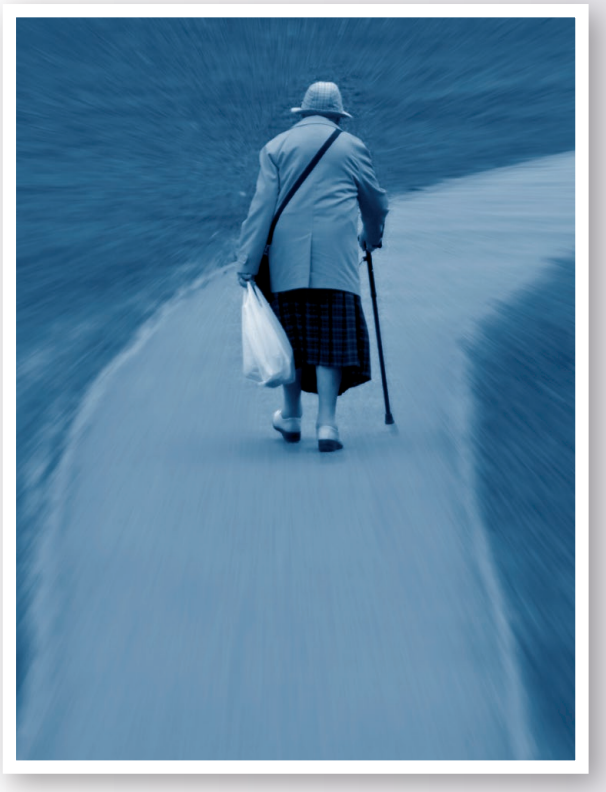
Methadone dosing in special populations

Liver disease and renal dysfunction

The dose of methadone does not need to be adjusted in stable liver disease and does not accumulate in people with renal dysfunction, although dosage adjustment may be required in end-stage renal disease.

Elderly people

Elderly people are more susceptible to the side effects of confusion, drowsiness and respiratory depression. It is recommended to start with once daily dosing in this population e.g. 2.5 mg once daily. For frail elderly people an even smaller starting dose can be used e.g. 1 mg once daily (0.5mL of methadone oral liquid 2 mg/mL).[2] Dose changes should not occur faster than once weekly in this group.



respiratory depression) reduce dose. If pain is poorly controlled, increase the dose by 30-50% with extreme caution. Monitor for drowsiness and confusion.

Drug interactions

Methadone has a number of interactions that are not seen with morphine. It is mainly metabolised by CYP3A4 along with other CYP enzymes. Drugs that inhibit or induce these enzymes will affect the plasma concentration and therapeutic effect of methadone. Azole antifungals (e.g. fluconazole) inhibit CYP3A4 and may increase the concentration of methadone and increase the likelihood of adverse effects and overdose. Drugs that induce these enzymes, e.g. St John's Wort and some anticonvulsants (e.g. phenytoin, carbamazepine), may reduce the plasma concentration of methadone decreasing its therapeutic effect.[4]

Concomitant use of drugs that affect the CNS, for example, alcohol, benzodiazepines, or other opioids, may increase the likelihood of adverse effects such as sedation and respiratory depression.[4]

Methadone can cause QT prolongation which may lead to the development of potentially fatal arrhythmias. This is particularly associated with higher doses (e.g. >150 mg/day). Other risk factors include concomitant use of drugs that also prolong the QT interval, and use in patients with cardiac disease. ECG monitoring is recommended for these patients.[5, 6]

Large dose changes of methadone are not often required after initial titration unless the clinical picture changes. If therapeutic effect changes during treatment, consider whether the potential addition of another drug has altered the plasma concentration of methadone and therefore its therapeutic effect.[1]

Adverse effects – monitoring for respiratory depression is especially important

Constipation, drowsiness and respiratory depression are potential adverse effects. Respiratory depression is a

particular concern and patients should be monitored on a daily basis during the initial titration period. Consider hospital admission for a patient with a respiratory rate of less than 12 breaths per minute.

Methadone causes significant constipation as do other opioids. A stimulant/softener laxative should always be prescribed concurrently.

Patient education

Educate patients about the safe and effective use of methadone:

- Effective pain relief can take several days.[1] Advise that the initial dose may not provide adequate pain relief but reduces the chance of adverse effects, and the dose will be titrated to an effective level.[2]
- Use of methadone in combination with other opioids, other drugs or alcohol can be fatal.
- Frequent monitoring is required during initiation and maintenance of treatment. Patients should be instructed to immediately report any increasing or intolerable adverse effects.
- Constipation is a common adverse effect so advise patients to take laxatives as prescribed, eat a well-balanced diet containing plenty of fibre and drink adequate fluids.
- Patients may be aware that methadone is used to treat opioid addiction and may be concerned about the social stigma. Reassure them that this is an accepted pain medication and explain the difference between dependence and addiction.

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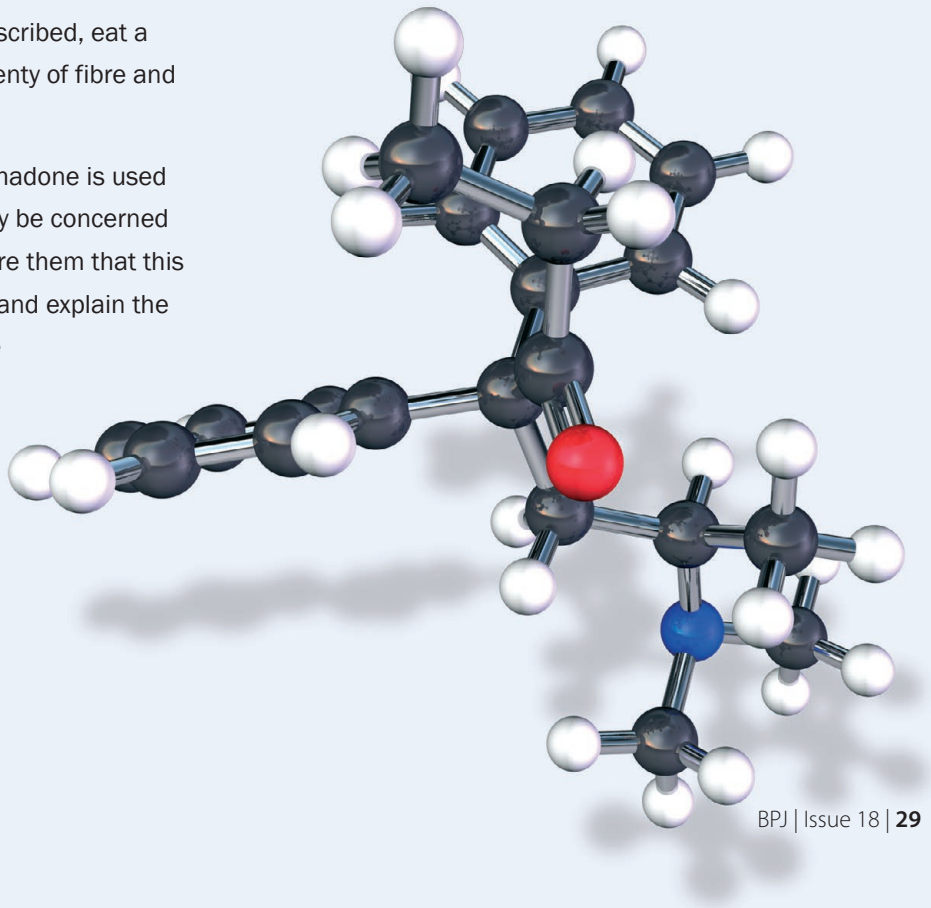


The science behind lifestyle risk factors for **cardiovascular disease**

Key Reviewer: Professor Rod Jackson, Clinical Epidemiology & Biostatistics
School of Population Health, University of Auckland

www.bpac.org.nz keyword: cvd

When it comes to providing advice to patients about cardiovascular risk, most doctors understand that the cornerstones of lifestyle advice are: stopping smoking, improving diet, exercise and losing weight. What might be less well known is how each of these factors contributes to cardiovascular risk.

This article examines how modifiable lifestyle factors contribute to cardiovascular risk, and some of the benefits of lifestyle intervention.

Smoking

Some of the advantages of smoking cessation are almost immediate, while others take time. After a myocardial infarction stopping smoking is potentially the most effective of all preventative measures.[1] In some studies platelet aggregation has been demonstrated to improve in two weeks following smoking cessation. For a person who stops smoking, after five years their personal CVD risk is the same as a person who has never smoked.

Smoking and CVD

Approximately 22% of New Zealanders aged 15 to 64 years are cigarette smokers.[3] Cigarette smoking is estimated to cause approximately 5000 deaths per year with about 70% of these being from CVD. There are approximately another 400 deaths per year attributable to second hand smoke.[4] Cigarette smoking is associated with an increased rate of myocardial infarction and fatal CVD. Active smokers have approximately an 80% higher risk of CVD compared to non-smokers, while non-smokers who are regularly exposed to environmental smoke have a 30% increase in CVD.[5]

Smoking increases the risk of CVD in two key ways: by increasing the rate of atherosclerosis and by increasing the incidence of thrombosis. It is widely believed that these two mechanisms work together, with coagulation being initiated after exposure of blood to tissue factors present in artheromatous plaques.

There is a range of pathophysiology caused by the toxic effects of smoking. These changes do not occur independently of each other, and in some cases effects can cascade. The effects are dose related, depending on the degree of cigarette exposure. When a person stops smoking the decrease in thrombotic risk is almost immediate, whereas the effect on atherosclerosis takes some years to reverse.

Some of the pathological consequences of smoking include:[2]

- Damage to the endothelium in vessel walls. This has been demonstrated in the endothelium of the macrovascular bed of the coronary arteries.
- Altered lipid profile (increases cholesterol, triglyceride and LDL, but decreases HDL). Smoking has been shown to immediately increase serum free fatty acids,[6] with long term smoking leading to hyperlipaemia.
- Inflammation in the blood and vessel walls. The leucocyte count of smokers is estimated to be 20 – 25% higher than non smokers.
- Increased prothrombotic factors and decreased fibrinolytic factors. People who smoke have been demonstrated to have higher fibrinogen (prothrombotic) levels than non-smokers, but these will return to normal if the person stops smoking.
- Platelet dysfunction (increased aggregability). People who smoke show increased potential for platelet aggregation, lower platelet survival rate and increased excretion of thromboxane metabolites (involved with platelet release).

Composition of cigarette smoke

Cigarette smoke can be divided into two phases: a tar phase and a gas phase. The tar phase is the material predominantly trapped in the filter. The gas phase is the material that passes through.[2]

Cigarette smoke intentionally inhaled is known as mainstream smoke, while sidestream smoke is the smoke emitted from the burning end. Sidestream smoke has not passed through a filter and therefore contains a higher proportion of the tar phase, which contains more harmful free radicals than the gas phase, therefore is more hazardous.

It is estimated that two thirds of the smoke from a burning cigarette is not inhaled and enters the environment. Environmental smoke is a mixture of sidestream smoke and exhaled main stream smoke and inhalation of this is known as passive or second-hand smoking.

Nutrition

Most guidelines advise overall healthy eating plans that include a variety of fruits, vegetables, grains, low-fat or non-fat dairy products, fish, legumes, poultry and lean meats. There is a wealth of information of the health benefits in following this type of diet, including reductions in cardiovascular risk but there is a lack of information about the biological mechanisms by which this type of diet contributes to decreased risk.

Fats

The traditional New Zealand diet is high in saturated and total fat and this is considered a key contributor to CVD.[7] A diet rich in saturated and trans fats is associated with adverse changes in lipid profile, including increased levels of LDL and decreased levels of HDL (Table 1).

Saturated fats are found in animal products such as butter and fatty meat. Leaner cuts of meat should be used and butter should be replaced with margarines and oils which contain unsaturated, polyunsaturated and monounsaturated fats. Olive and canola oils and nuts are monounsaturated while soybean and sunflower oils are sources of polyunsaturated fat.

Trans fats have the most adverse effect on the lipid profile. They are oils that have been hydrogenated to turn them into semi-hard fats. As awareness of the adverse effects of trans fat has increased over recent years, a number of food manufacturers in New Zealand have voluntarily lowered the trans fat in their food production.

Omega-3 and omega-6 are essential fatty acids, which may have a beneficial effect on lipid profile. They are obtained from polyunsaturated fats. Fish is the best source of omega-3, while omega-6 is found in corn, soybean and safflowers oils.

Sterols are a component of the structure of plant cell membranes. When consumed they block absorption of cholesterol into the blood stream and can be useful in lowering LDL levels.

Fruit and vegetables

Probably the most consistent dietary advice given over recent years is the “5+ a day” campaign to encourage consumption of five or more portions of fruit or vegetables per person per day.

Table 1: Fats and their effect on lipid profile

Type of fat	Dietary sources	Effect on LDL	Effect on HDL	Effect on triglyceride
Trans	Commercially fried foods, prepared snacks and baked goods	Increases	Slight decrease	No effect
Saturated	Red meat, cheese, butter, palm oil.	Increases	No effect	No effect
Monounsaturated	Nuts, olives, avocado, olive and canola oils	Decreases	No effect	No effect
Polyunsaturated **Omega-6**	Corn, soybean and safflower margarine and oils	Decreases	May decrease	Unknown
Polyunsaturated **Omega-3**	Salmon, mackerel, herring, flax seed, walnuts, soybean	Variable	No effect	Decreases
Sterols	Margarine with added plant sterols	Decreases	No effect	No effect

The beneficial effect of fruit and vegetables is thought to be associated with components such as fibre, antioxidants, potassium and folate. Higher fruit and vegetable consumption can often be associated with other healthy behaviours such as not smoking and exercising more frequently.

There is a lack of consensus on whether fruit juice can be included as a serve of fruit or vegetables. Fruit juice offers no nutritional advantage over whole fruit, and may lack the fibre contained in whole fruit.

Antioxidants have been shown to protect cells from the effects of free radicals. The main danger of free radicals is the damage they can do when they react with important cellular components such as DNA, or the cell membrane. A higher intake of certain antioxidants has been shown to lower the incidence of heart disease. Polyphenols are the most abundant antioxidants in the diet and include vitamin E, beta-carotene and vitamin C. The main dietary sources are fruits, dry legumes, cereals, chocolate and plant-derived beverages such as fruit juices, tea, coffee, red wine.

Salt

Hypertension is a well recognised risk factor for cardiovascular disease. There is a strong association between hypertension and salt intake. Controlling salt intake can lower blood pressure, as well as lowering the risk of a cardiovascular event.[8] It is thought that increased sodium intake also adversely effects the cardiovascular system independently of blood pressure.

The way that food products are labelled may make it more difficult for people to understand how much salt they are eating.[9] Dietary recommendations are given in terms of maximum levels of salt (sodium chloride) intake, whereas the nutritional information on most food packaging tends to be indicated by sodium content. To estimate sodium chloride content, the sodium content has to be multiplied by 2.5. People should not consume more than 6g of salt per day.

Fibre

Dietary fibre is either soluble or insoluble, with both types derived from plants. Insoluble fibre (e.g. wheat, bran, potato skin) passes through the body mostly unchanged but absorbs water and swells which helps to soften stool and increase bulk, and reduce gut transit time. Soluble fibre (e.g. peas, apples, carrots, oats) is broken down once it reaches the large bowel where gut flora feed and multiply contributing to softer, bulkier stools.

The protective mechanism of dietary fibre in CVD risk is unknown, but individuals that consume higher levels of dietary fibre have:[10]

- Lower BMI and less likelihood of being overweight
- Reduced risk of hypertension
- Decreased levels of apolipoprotein (apo) B, cholesterol and homocysteine.

It is recommended that people should consume at least 25 g/day of dietary fibre, although levels of up to 35g/day can be expected to provide even more benefit.

Alcohol

Small amounts of alcohol may protect against CVD. This is distinct from the effect of antioxidants in some drinks such as red wine. The protective effect of alcohol is primarily explained by an increased HDL, decreased platelet aggregability and promotion of fibrinolysis, although there are probably a number of other mechanisms. This may include the possibility that people who only drink moderately have generally healthier lifestyles.[11]

Detrimental alcohol-related effects begin to counteract the benefits from alcohol consumption above an intake of around 10g of alcohol per day (one standard drink).[12] Therefore while light to moderate drinking is unlikely to cause significant harm, non-drinkers should not be advised to take up drinking to improve their cardiovascular health.

Exercise

Physical exercise has been shown to provide a wide variety of benefits for all individuals, whether or not they have had a previous cardiac event. A sedentary lifestyle is said to carry approximately the same risk for the development of coronary artery disease as the more traditional risk factors of cigarette smoking, hypertension and hypercholesterolemia.[13] Although the precise mechanism by which exercise reduces coronary risk remains unknown, exercise training induces physiological changes that may be cardioprotective and also favourably modifies other coronary risk factors.

In the Harvard Alumni Study, men who were physically active had a 25% lower risk of death from any cause and a 36% lower rate of death from coronary heart disease compared to less active men.[14]

The most constant benefit of exercise training in both healthy individuals and people with coronary artery disease is an improvement in exercise tolerance. This results in:

- An increase in maximal oxygen uptake
- Higher resting and exercise stroke volumes
- Lower resting heart rate
- Beneficial adaptations in skeletal muscle
- Slowed age related cardiac decline

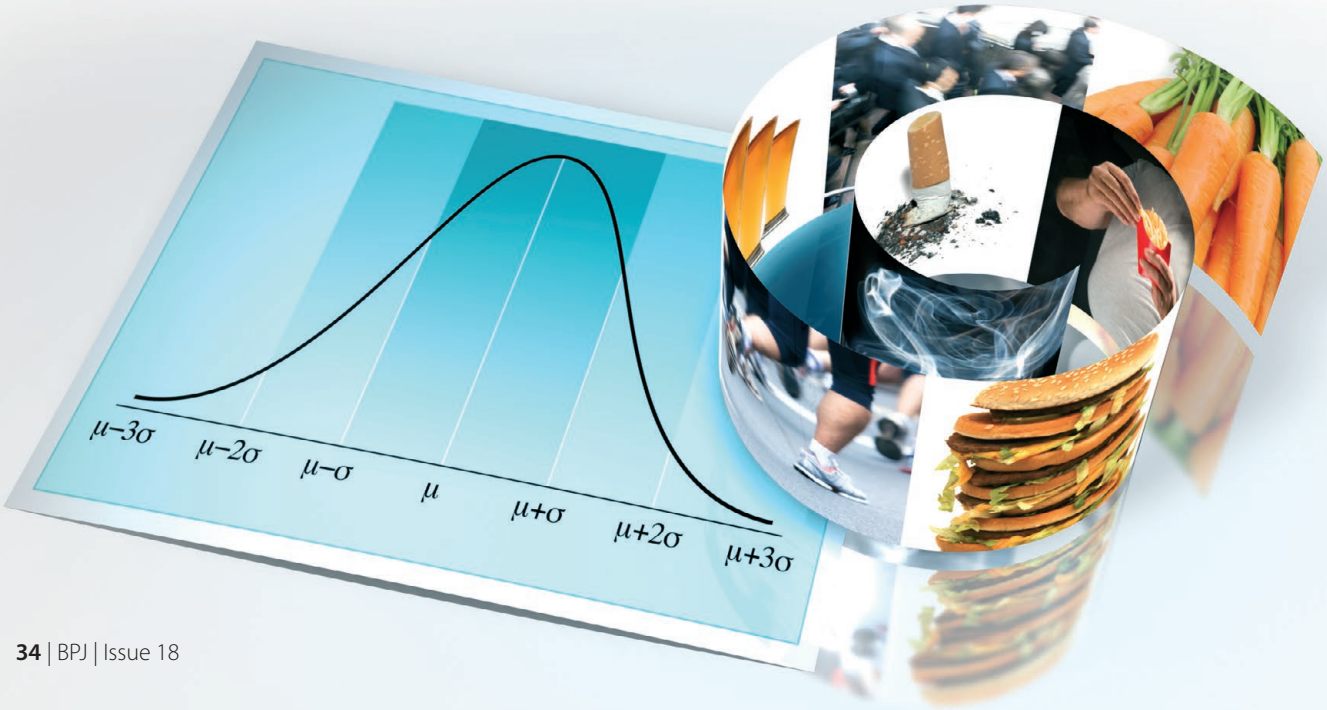
Obesity

Obesity is influenced by a combination of genetic, behavioural and environmental factors. The incidence of obesity is increasing world wide, mainly attributable to an increase in sedentary lifestyles and high fat diets.

Recent studies have demonstrated that the distribution of adipose tissue is more important for determining cardiovascular risk than total body weight. Increased intra-abdominal fat (see sidebar) has been demonstrated to be strongly associated with increased cardiovascular risk.

Tools for estimating obesity include body mass index, waist circumference or waist-hip circumference ratio.[15] Although BMI is less prone to measurement error, increasing waist circumference and waist-hip circumference ratio have been shown to be more strongly associated with increased cardiovascular risk. The World Health Organisation and the American Heart, Lung and Blood Institute recommend the use of waist circumference as an additional indicator of CVD risk.

To reduce measurement error, it is important waist circumference is measured midway from the lower rib margin to the anterior superior iliac crest.



The impact of increased adipose tissue mass on CVD

There are a number of mechanisms by which being overweight or obese contributes to increased cardiovascular risk.[17] Although adipose tissue tends to be less vascular than other tissues, it is surrounded by a significant capillary network, thereby increasing overall fluid levels in an overweight person. This increased blood volume along with the increased metabolic demand, caused by the extra weight leads to an increased cardiac output. The increased cardiac volume is produced by increased stroke volume, rather than an increase in heart rate and this may eventually lead to ventricular chamber dilation and left ventricular hypertrophy.

Left ventricular hypertrophy is often associated with ventricular diastolic dysfunction, particularly in people who are morbidly obese. In addition, longer periods of obesity are associated with poorer left ventricular systolic and diastolic function.

In obesity, fat deposits can occur in a number of organs, including the heart. Organ function can be reduced due to cell dysfunction or cell death, a phenomenon known as lipotoxicity. If this occurs in the heart, this may contribute to obesity cardiomyopathy.

Fat, particularly visceral fat, is capable of synthesising a number of compounds, such as angiotensin II, C-reactive protein, fibrinogen, which can exert a negative effect on the cardiovascular system.

Individual variability

It is worth remembering that these lifestyle factors occur on a background of inherited individual susceptibility. There will always be exceptions, people who ignore this advice and live to an old age. These exceptions should not be accepted as evidence that change is not needed.

Types of adipose tissue

Adipose tissue is present in two main forms: visceral (or intraabdominal) and subcutaneous. Men tend to gain weight in the classic “apple” shape as a result of accumulation of both subcutaneous and visceral fat abdominally. Women tend to develop the classical “pear” shape, due mainly to the accumulation of subcutaneous fat in buttocks and thighs. Following menopause, women are more likely to accumulate more visceral fat.

Obesity in New Zealand

The New Zealand Health Survey (2006/2007) reported the age-standardised obesity prevalence rate for the population aged 15 years and over as 25%. This was similar to the 2002/2003 rate of 24% but a significant increase from the 1997 rate of 19%.[3]

The study also reported that 8% of children aged 5 to 14 years were obese, a prevalence rate similar to that of 2002 (9%). Obesity in adolescence is a strong predictor of adulthood obesity.[16]

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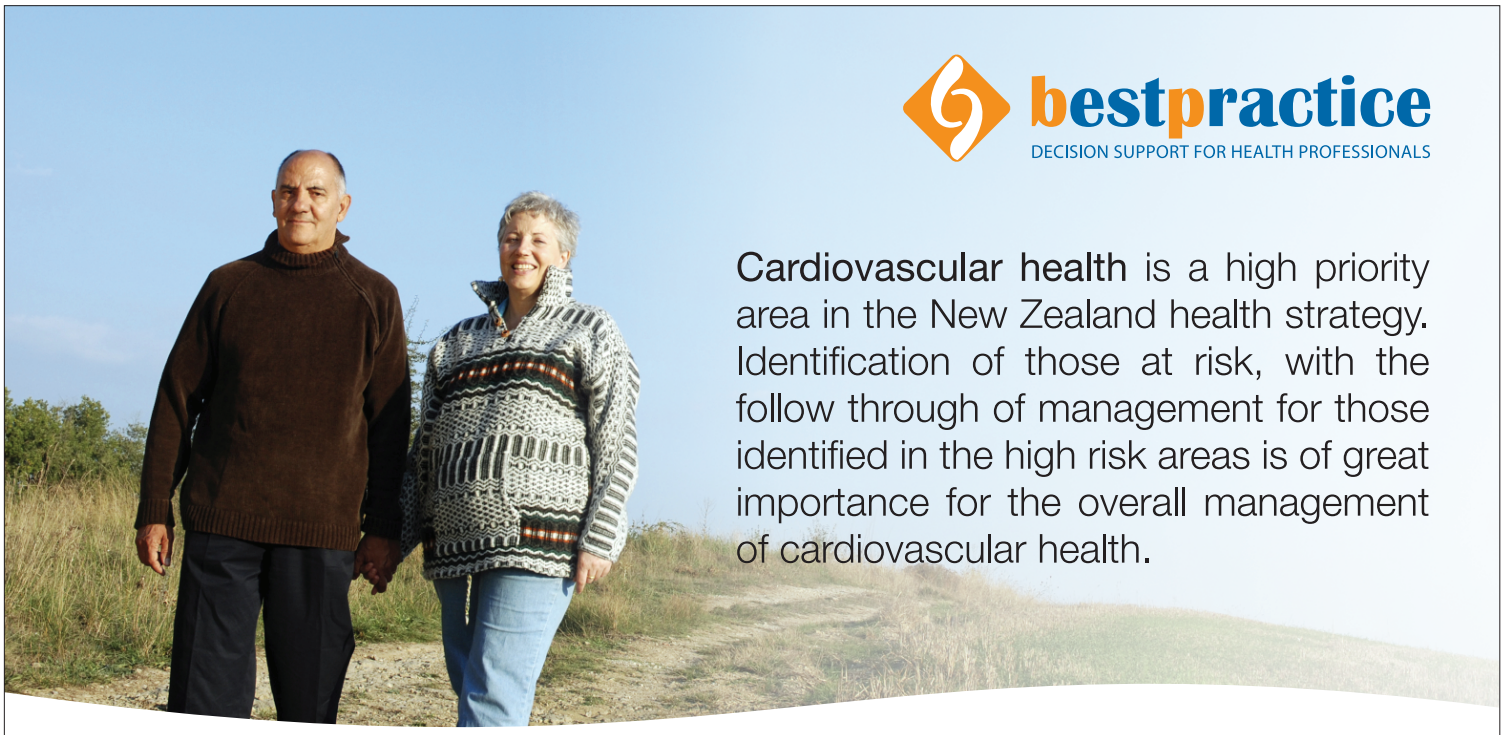


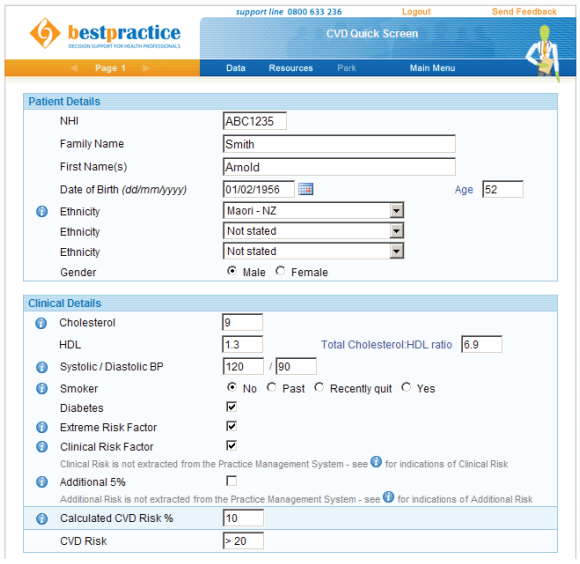
Cardiovascular health is a high priority area in the New Zealand health strategy. Identification of those at risk, with the follow through of management for those identified in the high risk areas is of great importance for the overall management of cardiovascular health.

Cardiovascular Disease Modules

CVD Risk with Management

The ***CVD Risk Assessment and Management*** module is based on the *New Zealand Cardiovascular Guidelines Handbook*, June 2005. The module utilises the *Framingham Equation* for determining a persons five year cardiovascular risk with the additional 5% calculations as per the *New Zealand Cardiovascular Guideline*, plus identifying those patients with metabolic syndrome who have a high risk for both diabetes and cardiovascular disease.

After determining CVD risk, the module then provides management options customised to the patient from the information already gathered, with supporting clinical information and patient education resources.



CVD Quickscreen

The new ***CVD Quickscreen*** module calculates 5-year CVD Risk using only the minimal number of fields required by the *Framingham Equation*. Because many of these fields are prepopulated by the PMS, a CVD Risk can usually be determined in seconds.

Contact:
Murray Tilyard or **Kaye Baldwin**
***bestpractice* Decision Support**
Level 8, 10 George Street, PO Box 6032, **Dunedin**
phone: 03 479 2816 **email**: murray@bpac.org.nz or kaye@bpac.org.nz

Is a vegetarian diet healthy for a child?

Key Reviewer: Dr Lisa Houghton, Lecturer, Department of Human Nutrition, University of Otago

Key concepts:

- A well balanced vegetarian diet that includes adequate amounts of essential vitamins and minerals can be a healthy option for a child.
- Vegetarian diets in children are associated with leaner body weight and may be protective against diabetes, heart disease, hypertension and obesity in adulthood.
- The greatest concern with a vegetarian diet is deficiency. If dietary intake of vitamin D, vitamin B12, calcium and iron is inadequate, consider checking for deficiency and recommending supplements.

In BPJ 15 (August 2008) we covered the topic of vitamin and mineral deficiencies. We received feedback that further information would be useful about what deficiencies a child eating a vegetarian diet would be at risk of.

Vegetarianism is becoming an increasingly popular dietary choice. A well-planned vegetarian diet can be healthy and nutritious for an adult but many families considering this diet for their children may seek advice on the safety of this practice.

Whether vegetarian or not, it is vital that children have a well balanced diet. This is particularly important in the pre-school years as this is a time of rapid growth and development.

Lacto-ovo is the most common type of vegetarian diet and describes someone who excludes meat from the diet but consumes eggs and dairy products.

Vegan describes someone who abstains from eating all animal products, sometimes even honey.

Vegetarian diets can be healthy and nutritionally adequate for children but food intake needs to be planned carefully to include adequate protein, iron, vitamin B12, folate, zinc, riboflavin and essential fatty acids that can be harder to obtain from plant sources.

Children and adolescents that follow a properly designed vegetarian diet grow and develop normally. In fact, studies have shown that children who follow a vegetarian diet have a lower intake of cholesterol and fat and a higher intake of fruit and vegetables and are leaner than children who have a non-vegetarian diet. A vegetarian diet adopted at an early age is also thought to be protective against diabetes, cardiovascular disease, hypertension and obesity in adult life.[1]

Most concerns about vegetarian diets in children surround vitamin B12, vitamin D and calcium deficiencies. A recent study of 215 adolescents found that those with a vegetarian diet had lower levels of serum vitamin B12.[2] Another study of 100 children found that a vegetarian diet was associated with an inadequate dietary intake of calcium and vitamin D, with potential implications on bone turnover rate.[3] However there are many non-vegetarian children with inadequate diets that are equally at risk from these deficiencies.

Energy

Young children need lots of nutrient dense foods for growth and energy. Sometimes a vegetarian diet is so bulky that a child can not eat enough to get the calories needed. A critical time is during the weaning stage when a baby is switching from high-fat, high-calorie mother's milk to a less calorific dense diet.

If some animal products are allowed in a child's diet such as eggs and dairy products then energy intake is not as much of a concern. However if parents wish to raise the child on a vegan diet, advice should be that they perhaps wait until the child is older and has better gastrointestinal capacity to eat the bulky volume of food required. Advice from a paediatric dietitian is highly recommended.

Protein

The main source of protein in a vegetarian diet is from eggs and dairy products. Plant sources include legumes (beans, peas, lentils), soy (tofu) and nuts. One cup of cooked beans has the same amount of protein as approximately 50g meat.[4] It may be difficult to get small children to eat adequate amounts of plant-based protein. Nuts also contain high calories so should not be used as a main protein source in the diet. In general, children require two to three servings of protein per day. Because amino acids have a lower absorption from plant foods, vegetarians may require a higher intake of protein (up to 30% more).[1, 5]

Iron

The best source of iron is red meat, but the iron content of a vegetarian diet can be adequate. Breakfast cereals (18%) and breads (12%) provide the greatest proportion of iron to the diet of New Zealand children.[6] Iron is also present in legumes, dried fruit, whole grains, soy foods and green leafy vegetables, although in a form (non-heme) which is harder for the body to absorb. In general, people eating a vegetarian diet require almost two times more iron daily than people who eat meat because of this difference. Vegetarian diets should include a source of vitamin C as this aids absorption of non-heme iron.[1, 4]

Iron is a very important nutrient for children and deficiency, through lack of iron-rich food in the diet, may result in anaemia. A small study looking at the dietary intake of vegetarian children aged 7 to 11 years compared with age-matched meat eaters, showed them to have significantly lower haemoglobin levels.[7] Supplementation with iron could be offered to a child presenting with iron-deficiency anaemia.

Vitamin B12

Vitamin B12 is especially important during periods of rapid growth in childhood. It is found naturally only in animal products, so children eating a vegan diet are at risk of deficiency. Vitamin B12 sources in a vegetarian

Vegetarian food sources of nutrients[5]

Nutrient	R.D.I (based on 10 year old child)	Food source	Amount per serve
Iron	8 mg/day	Tofu ½ cup	6.6 mg
		Pumpkin seeds ¼ cup	5.2 mg
		Soybeans ½ cup	4.4 mg
		Lentils ½ cup	3.3 mg
		Sesame tahini 2 Tbsp	2.7 mg
Zinc	6 mg/day	Pumpkin seeds ¼ cup	2.6 mg
		Navy beans (most baked beans) ½ cup	2.3 mg
		Soybeans, dry ½ cup	2.1 mg
Calcium	1000 mg/day	Bok choy 1 cup	167–188 mg
		Cheddar cheese 20 g	153 mg
		Yoghurt, ½ cup	137–230 mg
		Cows' milk ½ cup	137–158 mg
		Figs, dried 5	137 mg
Riboflavin	0.9 mg/day	Yeast flakes, 1 Tbsp	1.9 mg
		Egg, large	0.6 mg
		Almonds ¼ cup	0.3 mg
Vitamin B12	1.8 mcg/day	Yeast flakes, 1 Tbsp	1.5 mcg
		Egg, large	0.5 mcg
		Cows' milk ½ cup	0.4–0.5 mcg
Linolenic acid (omega-3)	1.0–1.2 g/day	Walnuts ¼ cup	2.7 g
		Flaxseed oil, 1 Tbsp	2.7 g
		Canola oil, 1 Tbsp	1.3–1.6 g

diet include milk, eggs, soy milk, yeast extract and fortified cereals. Children who do not eat enough of these foods are recommended to take a vitamin B12 supplement.

Calcium

For children on a lacto-ovo vegetarian diet, calcium intake may actually be higher than non-vegetarians due to the dependence on dairy products for calories and protein. However the diets of vegan children have been found to meet only 40% of a child's calcium needs.[7] Non-dairy sources of calcium include calcium fortified cereals, soy foods, legumes and some green vegetables (e.g. bok choy, broccoli). Factors that enhance calcium absorption include adequate vitamin D and protein.[5]

Vitamin D

Very few foods naturally contain vitamin D. Fish such as salmon, tuna and mackerel, and cod liver oil are among the best sources. Small amounts of vitamin D are found in beef liver, cheese and egg yolks. Vitamin D is not permitted

to be added to breakfast cereals in New Zealand.[8] Levels of vitamin D found naturally in milk are very low and there is no mandatory fortification of milk, margarines or butters in New Zealand – only a few products have been fortified.

Another source of vitamin D is skin exposure to sunlight. Sun exposure to face and arms for 15 to 20 minutes per day is adequate. Children with darker skin require approximately three to four times more exposure to gain the same benefit.

Children who have inadequate sun exposure and are unable to consume enough vitamin D rich foods may require vitamin D supplementation.[4] Supplementation may be problematic for children following a vegan diet as vitamin D3 (cholecalciferol) is of animal origin (from irradiation of animal skins or sheep lanolin). Vitamin D2 (ergocalciferol) is a form acceptable to vegans, however it is less bioavailable than vitamin D3.[9]

Zinc

Zinc from animal products is more easily absorbed than zinc from plants. Children eating a vegetarian diet need up to two times more zinc to make up for the bioavailability difference. Plant sources of zinc include fortified grains, legumes, nuts and soy foods.[4]

Omega-3 fatty acids

Preformed long-chain omega-3 fatty acids are most commonly found in fish and eggs, therefore vegetarian or vegan diets may be deficient. Long-chain omega-3 fatty acids are able to be synthesised by the body from plant-based α-linolenic acid obtained from flaxseed oil, canola oil, walnuts and soybeans.[1] Children not consuming fish and eggs require increased amounts of α-linolenic acid.

Riboflavin

Riboflavin is a B group vitamin that is essential for the metabolism of fats, carbohydrates and proteins. Plant based sources include almonds, asparagus, bananas, legumes and yams. Dairy products, fortified cereals and soy milk may also provide riboflavin.

Bottom line

A vegetarian diet can be healthy for a child as long as it is well balanced and adequate amounts of essential nutrients and vitamins are consumed. In fact, researchers are currently trialling vegetarian diets as a management strategy for obesity in children. A vegan diet for a child is more complicated to manage in terms of gaining essential nutrients and vitamins. Prescribing multiple supplements for children to overcome dietary deficiencies is not as desirable as a well balanced diet. Parents should take this into consideration when making dietary choices for their child. Advice from a nutritionist should be sought.

In children with a vegetarian or vegan diet, consider the possibility of vitamin D, vitamin B12, calcium and iron deficiency; consider supplementation if the child is unable/unwilling to consume enough of these nutrients from dietary sources.

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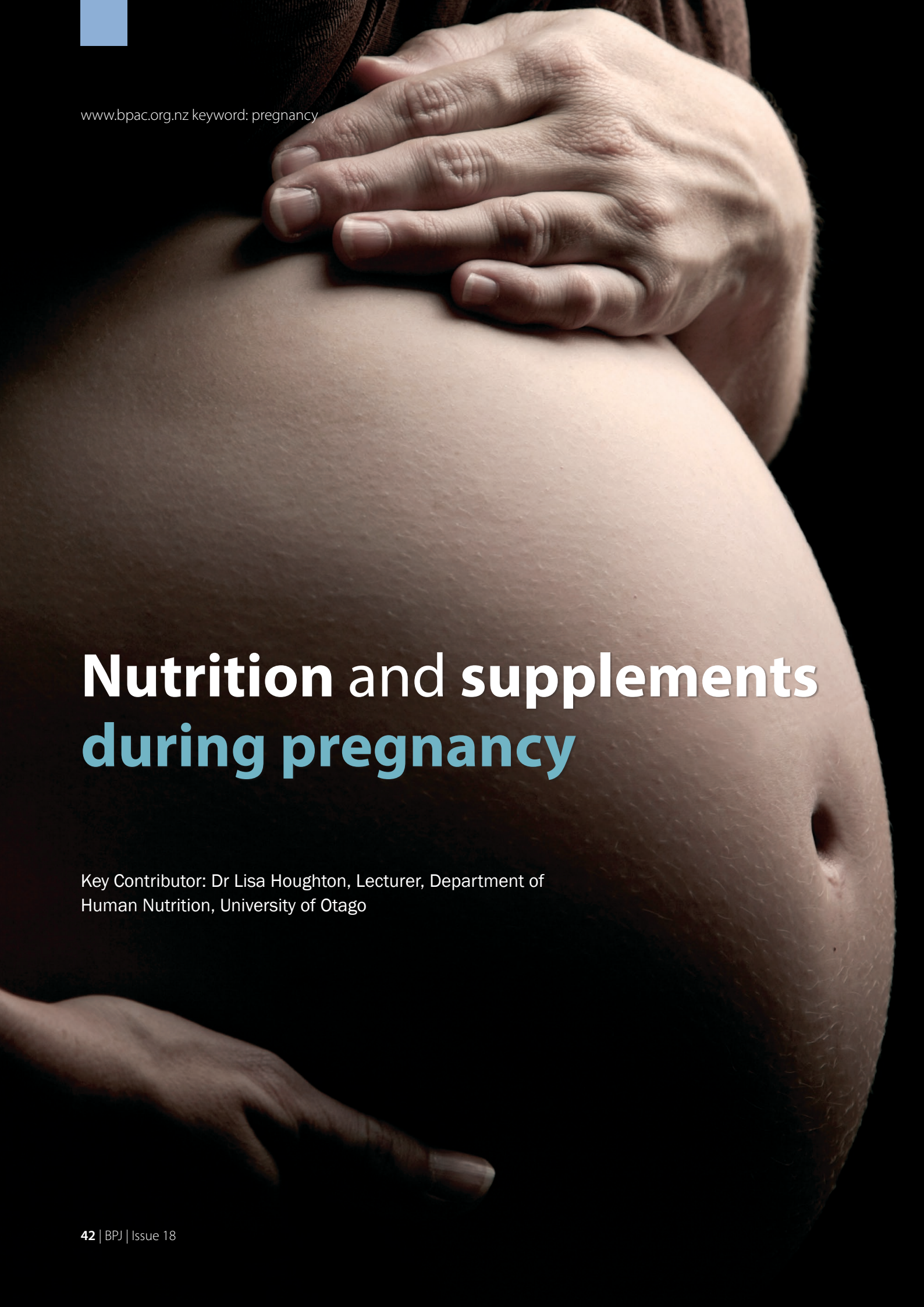

Nutrition and supplements during pregnancy

Key Contributor: Dr Lisa Houghton, Lecturer, Department of Human Nutrition, University of Otago

IN BPJ 15 (AUGUST 2008), we covered the topic of vitamin and mineral deficiencies. GPs tell us that they would like more information on what supplements or additional foods they should be prescribing or recommending for women who wish to become pregnant or those who are pregnant.

The importance of ensuring good maternal health during pregnancy is widely recognised while an increasing body of evidence suggests that nutritional status prior to pregnancy strongly influences foetal and infant outcomes. In view of this, the goal is to ensure that women attain good nutritional status before, during and between pregnancies to optimise their own health and reduce the risk of pregnancy complications, birth defects and the onset of chronic diseases in their children.

Attention to pre-conception nutrition improves pregnancy outcomes

Improving nutritional status before pregnancy is challenging because about half of pregnancies in New Zealand are not planned.[1,2] Even among women planning pregnancy, few seek medical or nutritional advice prior to conception, and most women do not have their first prenatal care visit until well into the first trimester.

Key concepts:

Health professionals can improve pregnancy outcomes by advising women to:

- Achieve a healthy body weight prior to conception and maintain appropriate weight gain during pregnancy according to pre-pregnancy BMI
- Take a daily supplement of 800 mcg of folic acid beginning before becoming pregnant and continuing throughout the duration of pregnancy (400 mcg folic acid is adequate but funded tablets are available in 800 mcg or 5 mg strengths)
- Take a low dose iron supplement in their second and third trimester
- Use iodised salt when cooking and at the table, and to choose foods that are sources of iodine e.g. low-fat milk, eggs
- If consuming a multivitamin and mineral supplement during pregnancy, choose a supplement containing folic acid, iron, and potassium iodide and be careful not to take excess vitamin A.

Folate reduces risk of neural tube defects

It is well established that folate decreases the risk for neural tube defects. Women planning a pregnancy, or who are in the early stages of pregnancy, are advised to take a daily folic acid supplement of 800 mcg for at least four weeks before, and up to 12 weeks after conception (although women are recommended to continue with this supplement throughout pregnancy). Higher doses (5 mg daily) are recommended for those who have had a previous neural tube defect affected pregnancy, a family history of neural tube defects, or are taking anticonvulsant drugs. Supplementing with 400 mcg of folic acid is sufficient to reduce the risk for women who have no history of neural tube defects, however only 800 mcg or 5 mg tablets are currently available as registered medicines in New Zealand. Mandatory folic acid fortification of bread next year will ensure that all women who become pregnant – planned or unplanned – will receive some preconceptional folic acid.

Sub-optimal iron stores are difficult to replenish once pregnant

A substantial amount of iron is required during pregnancy to meet foetal and maternal needs. About 40% of women aged 15–44 years in New Zealand have an inadequate intake of iron. Adequate pre-pregnancy iron stores may play a role in reducing risk for iron deficiency and anaemia during pregnancy. Sub-optimal iron stores are difficult to replenish once pregnant.

Healthy pre-conception bodyweight improves outcomes

Being underweight or overweight prior to conception can affect birth outcome. Evidence from observational studies suggests that low pre-pregnancy body mass index (BMI, <19.8 kg/m^2) is associated with reduced infant birth weight, and increased incidence of preterm delivery.[3] Obese women have an elevated risk for pre-eclampsia, gestational diabetes, neural tube defects and stillbirth, as well as giving birth to a large for gestational age infant.[3,4] More than one quarter of all New Zealand women are obese.[4]

Weight gain during pregnancy influences infant birth weight and health

The U.S. Institute of Medicine recommendations for appropriate weight gain during pregnancy (Table 1) are based on pre-pregnancy BMI and uphold a slightly different range of weight gain for each BMI category. Weight gains within these guidelines are associated with optimal birth weight (between 3000 g and 4000 g) and best labour and delivery outcomes. Women who gain more weight in pregnancy than recommended have a significantly increased risk of having an infant weighing greater than 4000 g.[5] High birthweight infants tend to be taller and heavier children with increased risk of obesity and metabolic problems in later life.[6] Excessive prenatal weight gain also places the mother at risk for long-term obesity post-delivery.[7]

There are currently no data available to indicate how much weight New Zealand women are gaining during pregnancy. Survey work conducted in the United States and Europe indicates that only a small proportion of women gain within the recommended ranges with excessive weight gain being more prevalent than inadequate weight gain.[5] Reports indicate that pregnancy weight gain is influenced by recommendations of health care providers so it is important this advice is accurate. Many women receive no prenatal weight gain advice.[8,9]

Table 1: Current recommendations for weight gain during pregnancy[6]

Pre-pregnancy BMI category	Recommended total gain (kg)
Low (<20)	12.5 – 18.0
Normal (20 – 25)	11.5 – 16.0
High (>25 – 29)	7.0 – 11.5
Obese (>29)	≥7.0

A healthy diet meets most nutrient requirements during pregnancy

Many questions remain unanswered regarding how the mother's nutritional status influences pregnancy outcome. Consequences of deficient or excessive nutrient intakes are difficult to determine, and assessment of vitamin and mineral status during pregnancy is not easy due to a lack of pregnancy-specific laboratory values. Based on available evidence, a healthy and varied diet can provide adequate energy and meet the mother's requirements for most nutrients. Selected vitamin and minerals that are likely to be limited in the diets of pregnant women are briefly highlighted.

Folate requirements are high during pregnancy

In addition to reducing neural tube defects, lack of folate during pregnancy is associated with increased risk of preterm delivery, low birth weight and poor foetal growth. The recommended intake of dietary folate is 600 mcg per day. Survey data of pregnant women in New Zealand indicate that dietary intakes of folate are well below recommended levels.[4]

400 mcg folic acid or 600 mcg dietary folate?

The 400 mcg recommendation to reduce neural tube defects is based on folic acid (synthetic form of folate) only. The 600 mcg recommended during pregnancy is in the units of Dietary Folate Equivalents (DFE) (food folate = 1 mcg DFE and folic acid = 1.7 mcg DFE). So essentially the 400 mcg folic acid tablet recommended preconceptional is worth 680 mcg DFEs and pregnant women then meet both recommendations by taking a supplement. Post-closure of the neural tube (after the first trimester) it is recommended that women intake 600 mcg DFEs. It is possible to obtain this all from the diet but this would involve large amounts of foods such as broccoli and spinach. Therefore women are recommended to continue with a folic acid supplement in addition to a folate rich diet for the entire pregnancy. This recommendation stands regardless of fortification of the food supply.

Iron requirements increase throughout pregnancy

Additional iron requirements during pregnancy increase substantially from the first trimester to the third trimester. A recommended dietary intake of 27 mg per day for the entire duration of pregnancy builds iron stores in early pregnancy for the third trimester.

Although women should be encouraged to consume plenty of iron rich foods during pregnancy, obtaining the recommended intake from diet alone is difficult. Survey data of pregnant women in New Zealand indicate mean

iron intakes between 11–14 mg per day.[4] The highest prevalence of low iron stores, iron deficiency and iron-deficiency anaemia is among New Zealand Māori women, particularly aged 15–24 years.[4] Maternal anaemia is associated with infant mortality and premature delivery.

Post-delivery, a woman who has been iron deficient during pregnancy should have further follow-up as postpartum anaemia is associated with emotional instability, depression and stress.[10]

For those who consume no or small amounts of animal source food, or when low iron stores are suspected, a low-dose iron supplement (30 mg ferrous iron per day) taken at bedtime or between meals is advised. When iron deficiency with or without anaemia is diagnosed, larger doses of iron supplements (~100 mg ferrous iron per day) may be advised to improve iron status as early in pregnancy as possible.[6] Although there is currently insufficient evidence to recommend for (or against) routine iron supplementation of all pregnant women, the U.S. Institute of Medicine, recognises that many women have suboptimal iron stores and advise daily low-dose iron supplementation (30 mg) to all women in the second and third trimesters.

Iodine requirements increase in pregnancy

Requirements for iodine increase in pregnancy due to a marked change in thyroid function. Despite the upcoming mandatory fortification of bread with iodine in 2009, pregnant women will likely have intakes below the recommended level of 220 mcg per day. Median iodine intakes of New Zealand pregnant women are estimated between 60 to 70 mcg per day.[11] Iodine deficiency during pregnancy can negatively affect both maternal and infant thyroid function and cognitive development of the infant.

Despite lack of clinical data on the effect of iodine supplementation on birth outcomes in mild to moderately deficient pregnant women,[12] several health authorities recommend that pregnant women consume 150 mcg per day of potassium iodide to prevent deficiency.[13, 14] Currently there are no single oral iodine preparations available as registered medicines in New Zealand. Seaweed and kelp tablets should not be used as the iodine content in these products is extremely variable and can be toxic.

Low vitamin D levels can affect foetal bone

During pregnancy, the lack of vitamin D may adversely affect foetal bone and accumulation of newborn vitamin D stores.[15] Vitamin D increases intestinal absorption of calcium. Rickets is a clinical marker of poor pre- and postnatal bone health caused by vitamin D deficiency. There have been reports that rickets is re-emerging though its prevalence in New Zealand is unknown.

Dietary sources of vitamin D are limited and the main source is skin synthesis on exposure to sunlight. The most recent national survey indicated a high prevalence of vitamin D insufficiency in New Zealanders.[16] Plasma concentration of 25-hydroxyvitamin D is a marker of vitamin D status. A level below 25 nmol/L indicates risk of vitamin D deficiency. A survey of pregnant women from a general practice population in Wellington reported that 87% of women had 25-hydroxyvitamin D below 50 nmol/L.[17]

Many experts agree that the recommended adequate intake for vitamin D of 200 IU per day during pregnancy is grossly underestimated.[18] Studies are currently underway to address the effect of vitamin D supplementation during pregnancy on the nutritional vitamin D status in both mother and foetus.

There is little evidence to support other supplements

For all other vitamin and minerals in pregnancy, there is little evidence to support routine supplementation unless inadequate nutrient intakes are suspected.

Women who are taking multivitamin/multimineral supplements should be cautioned to avoid exceeding intake of 10,000 IU (3,330 RE) of vitamin A (retinol) per day.

See Table 2 (over page) for a comparison of ingredients of some commonly used pregnancy multivitamins.

Fully funded supplements in pregnancy:

Iron

Ferrous fumarate

Tab 200 mg – Ferro-tab
Approximate elemental iron = 65 mg

Ferrous fumarate with folic acid

Tab 310 mg with folic acid 350 mcg – Ferro-F-Tabs
Approximate elemental iron = 100 mg

Ferrous gluconate with ascorbic acid

Tab 170 mg with ascorbic acid 40 mg – Healtheries Iron with Vitamin C
Approximate elemental iron = 20 mg

N.B: Ferrous sulphate preparations are available but subject to a part charge

Folic acid

Tab 5 mg – Apo-Folic Acid

Tab 0.8 mg – Apo-Folic Acid

Vitamin D

Alfacalcidol

Cap 0.25 mcg; Cap 1 mcg; Oral drops 2 mcg per mL

Table 2: Commonly used pregnancy multivitamins – comparison of ingredients (per recommended daily dose)

	Elevit	Blackmores Pregnancy and Breastfeeding Gold	Clinicians PregaVit	Solgar Prenatal Vitamins
Dose	One tablet daily	One tablet daily	Three capsules twice daily (6 caps/day)	Two tablets daily
Calcium	125 mg	59 mg	265 mg	650 mg
Folic Acid	800 mcg	250 mcg	300 mcg	400 mcg
Iodine	nil	125 mcg	50 mcg	75 mcg
Iron	60 mg	5 mg	nil	14 mg
Vitamin A*	nil	2880 mcg (carotenoids) = 2400 IU	225 mcg (retinol) = 750 IU	1800 mcg (beta carotene) + 4.8 mcg (carotenoids) = 3004 IU
Vitamin B12	4.0 mcg	1.5 mcg	25 mcg	2 mcg
Vitamin C	100 mg	30 mg	42 mg	25 mg
Vitamin D (cholecalciferol)	12.5 mcg = 500 IU	6.25 mcg = 250 IU	2.5 mcg = 100 IU	2.5 mcg = 100 IU

* 1 mg retinol = 0.5 mg beta carotene = 0.08 mg carotenoids

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Thompsons Pregnacare	Radiance Pregnancy Multivitamin	Bronson Prenatal	Recommended daily intake (RDI) in pregnancy[19] (obtained through diet and supplementation if required)
One tablet twice daily	One capsule daily	One chewable tablet daily	
400 mg	300 mg	125 mg	RDI = 1000 mg/day. Do not exceed 2500 mg/day.
300 mcg	200 mcg	400 mcg	RDI = 400 mcg for prevention against neural tube defects. Do not exceed 1000 mcg/day.
nil	37.5 mcg	75 mcg	RDI = 220 mcg/day. Do not exceed 1100 mcg/day. A supplementary intake of 150 mcg/day is recommended.
10 mg	9 mg	25 mg	RDI = 27 mg/day. Do not exceed 45 mg/day. A supplementary intake of 30 mg/day is suitable for all women in the second and third trimesters.
3000 mcg (beta carotene) = 5000 IU	1500 mcg (beta carotene) = 2500 IU	600 mcg (retinol) = 2000 IU	RDI (retinol) = 800 mcg/day (2667 I.U.). Do not exceed 10,000 IU/day.
12 mcg	5 mcg	7.5 mcg	RDI = 2.6 mcg/day. There is no upper level of intake.
160 mg	30 mg	60 mg	RDI = 60 mg/day Do not exceed 1000 mg/day.
5 mcg = 200 IU	2.5 mcg = 100 IU	5.0 mcg = 200 IU	RDI = 200 IU/day. Do not exceed 3200 IU/day.

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Key Reviewer: Dr Kath Ryan, Reader in Maternal and Perinatal Research, Bournemouth University, UK

Mastitis and sore nipples while breastfeeding

In BPJ 15 (August 2008), we emphasised that breast feeding was the best option for infant nutrition. Here we outline the management of two conditions that commonly, but unnecessarily, lead to discontinuation of breast feeding.

Mastitis

Mastitis is inflammation of the breast, occurring primarily in lactating women. It presents as warmth, redness and swelling in one area of the breast. When infection is involved, the inflammation is often accompanied by systemic flu-like symptoms (see box). If not quickly and properly treated, in extreme cases, a breast abscess can result.

One in five breastfeeding mothers will experience mastitis

It has been reported that up to 20% of breastfeeding mothers will experience mastitis at some point.[1] Some risk factors for its development include: cracked or sore nipples, infant attachment difficulties, missed feeds or changed routines, milk stasis including from restrictive clothing or straps, candida infection, maternal fatigue, previous mastitis or use of a manual breast pump.[2]

Management: maintaining breastfeeding is important

Should mastitis occur, maintaining breastfeeding is important. If breastfeeding is stopped, milk stasis will increase and make it more likely that a breast abscess will occur. Breastfeeding also provides the best removal of milk from the breast and allows for continued feeding after mastitis has resolved. In the first 24 hours, in the absence of systemic signs of infection, continued breastfeeding along with gentle breast massage, hot compresses and rest is recommended.[1]

In practice, often a mother may have already been experiencing pain for 24 hours when they present to their GP, so antibiotics will be given straight away.

Feeding from an infected breast can continue without the concern of passing the infection to the infant because the infant is usually infected with the same organisms at the time mastitis develops. The milk from the infected breast may contain anti-inflammatory components that are beneficial to the infant. If the baby is not feeding well, breast milk will need to be expressed regularly.[2]

Medication: if required

Paracetamol or an NSAID such as ibuprofen may be used for pain and inflammation and are safe to use while breastfeeding.[3]

Antibiotics are required for women whose symptoms have not improved in 24 hours or who have systemic symptoms. One of the most common infecting organisms is *Staphylococcus aureus* and for that reason, flucloxacillin 500 mg four times daily for seven days is recommended.[1-3] Penicillins are considered safe for use during breastfeeding, however they may cause loose bowel motions in the infant.[3]

Complications – breast abscess

Breast abscess has similar symptoms to mastitis except that there is a firm area of the breast. It can be identified by breast ultrasound. Breast abscess is treated by surgical drainage or needle aspiration.[2] Breastfeeding can usually continue except where the mother is severely unwell or the drainage incision inhibits breastfeeding.

Common symptoms of infective mastitis

- Localised, painful inflammation of the breast
- Temperature over 38.5 degrees celsius
- Chills
- Headache
- Systemic flu-like symptoms (e.g. fever, malaise)

Sore nipples

There are many causes of sore nipples including; normal tenderness in the initial days to weeks of breastfeeding, poor positioning and attachment of baby, or infection in the nipple.[1] Breastfeeding should not hurt. Pain is a sign that there is a problem.

The treatment of sore nipples depends on the cause

- Normal tenderness – reassure mother and make sure positioning and attachment are correct.
- Treat any nipple infection – Use flucloxacillin for bacterial infections such as *Staphylococcus aureus*. For candida infection, oral antifungal liquid such as nystatin for the baby and topical antifungals (e.g. clotrimazole or nystatin) for the mother are often effective. Oral fluconazole may be required in more severe and painful cases. Use is unlicensed, suggested dose is a 400 mg loading dose followed by 200 mg/day for at least 10 days. If topical treatments are applied, excess cream should be removed from the nipple before breastfeeding.
- Paracetamol or ibuprofen can be used to relieve pain.

The Ministry of Health breastfeeding website is a good resource for mothers, partners, whānau/families and health practitioners and is available at: **www.moh.govt.nz/breastfeeding**

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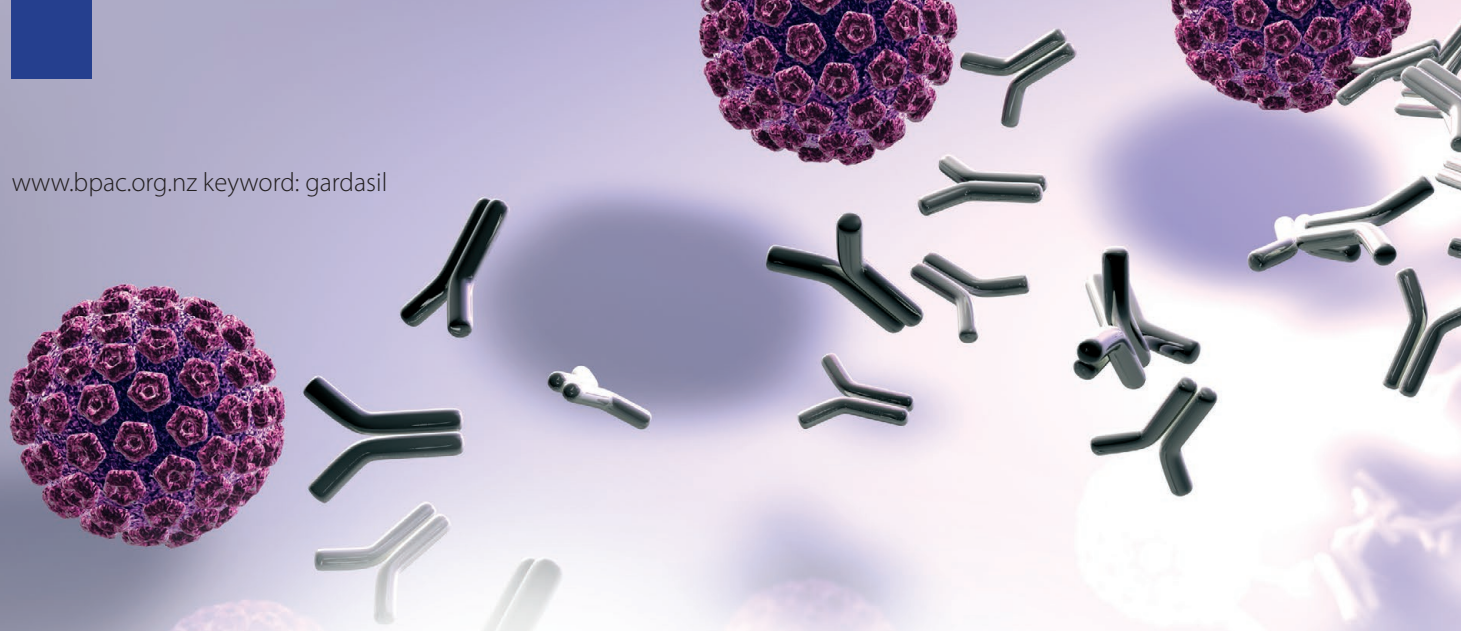

Gardasil vaccine: Update

Human Papillomavirus (HPV) vaccines were discussed in BPJ 12 (April 2008), but since then a number of changes have occurred:

- Gardasil has been added to the National Immunisation Schedule.
- Gardasil is currently funded for women born on or after January 1st, 1990.
- From January 2009, Gardasil will be funded for females aged between 12 and 18 years old.
- As part of a catch up programme, 17 and 18 year old women have been eligible for vaccination from 1st September 2008.
- An advertising campaign is planned from the Ministry of Health from January 2009.

The vaccine course comprises of three doses, given over six months and can be delivered by primary care practitioners or through school-based programmes (these will be phased in over 2009 and 2010). All three doses of vaccine need to be given for adequate seroconversion.[1]

CSL Biotherapies (NZ) Ltd has created a reminder programme using email and text messages. Young women receiving the vaccine can fill out a form to consent to receive reminders for when her next dose is due.

HPV vaccine uptake

At present in New Zealand approximately 160 women are diagnosed with cervical cancer each year and 60 women die from it. Māori women are almost twice as likely to get cervical cancer and almost three times as likely to die of it compared to non-Māori.

Māori currently have the lowest immunisation rate of any ethnic group in New Zealand. School based vaccination programmes are associated with higher coverage rates and reduced inequalities compared to vaccine delivery in other settings.[2]

Soon after Gardasil first became available for females aged 17 and 18 years in September 2008, there were some reports that the uptake of the vaccine was low, however more recent reports suggest that uptake levels are promising.

Potential issues surrounding Gardasil use

- Young women who are already sexually active may be unsure if it is still worthwhile having the vaccine or may be worried that they will be asked about their sexual activity.

- Some parents may be concerned that the vaccine could encourage their daughters to engage in sexual activity at a younger age.
- Young women born before January 1st 1990 or males may enquire about whether they can be vaccinated with Gardasil.
- Some parents may be concerned about the safety of Gardasil as it is a new vaccine.
- People may ask about the effectiveness of Gardasil and how long protection lasts.
- Women may ask if they still need cervical smears.

Sexual activity

The vaccine is most effective when administered before the onset of sexual activity but benefit may still be derived after this as the woman may not have been exposed to the HPV types that the vaccine protects against (subtypes 6, 11, 16 & 18).

Young women will not be asked if they are sexually active before receiving the vaccine.

Research in other countries has not found that the vaccine is linked to sexual activity occurring at a younger age.[1]

Non-funded vaccine use

Women born before January 1st 1990 and males may still receive the vaccine but it is not funded. It would normally cost approximately $450 for the three doses, in addition to any consultation fee that may apply.

Safety concerns

Clinical trials have shown that Gardasil is not associated with serious adverse events. Since the vaccine has been licensed the most common reports to the Vaccine Adverse Events System (VAERS) have been local injection site reactions and some cases of fainting after vaccination. As with all vaccines a 15–20 minute post-vaccination waiting period is advisable.[3]

Vaccine effectiveness

Cervical cancer develops over ten or more years and HPV subtypes 16 and 18 are implicated in approximately 70% of cervical cancers. Gardasil vaccine targets these HPV subtypes and current evidence from clinical trials suggests that it provides immunity for at least five years with no evidence of reducing effectiveness. Continued monitoring of longevity of immunity is underway. If boosters are needed in the future this would not change any recommendation for initial vaccination.[3]

Gardasil is expected to reduce future cervical cancer rates by up to 70% if young women are vaccinated before their first sexual intercourse. It is estimated that Gardasil has the potential to prevent cervical cancer in the future for approximately two women per week in New Zealand saving 30 lives per year.[1] In the shorter term, it is expected to reduce the incidence of genital wart infection (HPV subtypes 6 and 11 are implicated in 90% of genital warts) and abnormal cervical changes.

Cervical smears are still required

Gardasil will not replace the cervical cancer screening programme as approximately 30% of cervical cancers are caused by HPV subtypes not present in the vaccine. In addition, women with exposure to HPV prior to vaccination still need to be monitored.

see BPJ 12 (April 2008) for more information about HPV vaccines.

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Anticholinergics for COPD

Anticholinergics and cardiovascular safety

Two recent studies have raised concerns that the use of the anticholinergics ipratropium and tiotropium for COPD is associated with an increased risk of cardiovascular events. However, a large randomised controlled trial conducted over four years did not show an increase in cardiovascular risk when tiotropium was compared with placebo. The consensus is that tiotropium remains a safe and effective treatment for most patients with COPD.

Two studies showed an increased cardiovascular risk

The results of a large meta-analysis of randomised controlled trials suggests that ipratropium and tiotropium increase the risk of cardiovascular events in people with COPD compared with placebo, inhaled corticosteroids or beta-agonists.[1] The use of anticholinergic agents for more than 30 days was associated with an increased risk of cardiovascular events (RR 1.58, 95% CI, 1.21 – 2.06). The limitations of this study include the mix of treatments in the control arm and the fact that differences in cardiovascular risk factors (e.g. diabetes, smoking history, use of statins) was not accounted for. None of the randomised controlled trials included in the meta-analysis were designed to investigate differences in cardiovascular outcomes.

A case control study, published around the same time, showed that ipratropium was associated with an increase in all cause mortality and cardiovascular deaths compared with reference treatment (no treatment or short-acting beta-agonist).[2] The study can only show a possible association as there are a number of possible confounders. However, a well designed randomised controlled trial is required to investigate this association further. To date there have been no international or national recommendations to change the step one management of COPD, which is the use of a short-acting bronchodilator; either ipratropium or a beta-agonist.

A large long term trial showed no increased risk

The latest study (UPLIFT) was a randomised controlled trial which investigated almost 6000 patients given either tiotropium or placebo and then followed over four years.[3] No significant differences in all cause mortality, myocardial infarction or stroke were found between the groups. The results of the UPLIFT study may provide reassurance of the cardiovascular safety of tiotropium.

Neither Medsafe or the Asthma and Respiratory Foundation are currently recommending any significant changes to practice in response to these study results. However, it is suggested that patients with ischaemic heart disease and unstable angina should have their anticholinergic treatment reviewed as they are already at very high risk of a cardiovascular event.[4]

Tiotropium is associated with fewer COPD exacerbations but does not slow decline in lung function

The UPLIFT study also looked at COPD exacerbations and the rate of decline in FEV1 compared with placebo. Patients treated with tiotropium experienced fewer exacerbations of symptoms than those on placebo (RR 0.86, 95%CI 0.81 – 0.91). However, over the four year study period, there was no difference in the rate of decline in FEV1 between the tiotropium and placebo groups. Smoking cessation remains the only intervention that can slow the rate of decline in lung function.

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www.bpac.org.nz keyword: metabolicsyndrome

Metabolic Syndrome: useful or not?

Debate about the clinical usefulness of metabolic syndrome has been ongoing since it was first described in the late 1980's. Proponents of the syndrome encourage its use as a clinical tool to help identify people who may be at higher risk of cardiovascular disease and diabetes.[1] Critics however, suggest that making a diagnosis of metabolic syndrome is no more useful than an assessment of the individual risk factors alone.[2]

What there is agreement on is that:

- There is an association of certain metabolic factors that is not due to chance alone
- These risk factors, either by themselves or in combination, are associated with an increased risk of cardiovascular disease and diabetes
- There is no definitive treatment for metabolic syndrome

Metabolic syndrome is characterised by the presence of the following risk factors:

- Hypertension
- Insulin resistance
- Dyslipidaemia – increased triglycerides and decreased HDL
- Abdominal obesity

This clustering of risk factors with a metabolic origin is not thought to be grouped by chance alone and may be seen frequently in day to day practice.[1,4]

Those supportive of the syndrome suggest that it may help to:[1, 3]

- Focus both patients and clinicians attention on the need for lifestyle intervention
- Identify future risks of cardiovascular disease and type 2 diabetes
- Focus attention on a number of relatively minor abnormalities that add up to a significant cardiovascular disease risk; in other words a synergistic effect of multiple risk factors
- Encourage regular follow up

Those who argue against the syndrome suggest that:[3, 5]

- There is an ongoing debate regarding the terminology, definition and diagnostic criteria for the syndrome
- There is a lack of a biological basis for the diagnostic algorithm
- It fails to include other important risk factors for cardiovascular disease such as age and smoking
- Treatment of individual risk factors is as good as treatment of metabolic syndrome
- Using a label of metabolic syndrome may detract from the real issues such as cardiovascular disease or diabetes

The latest research from an analysis of longitudinal data from two population based studies has shown that having a diagnosis of metabolic syndrome has a weak or negligible association with cardiovascular disease and that a fasting blood glucose test alone is better at predicting future diabetes.[5]

It seems that the arguments for and against will continue to be debated in the clinical literature for some time. In light of the latest research the only value of the syndrome may be that it is useful simply as a basis for guiding risk assessment and promoting lifestyle interventions.[6]

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Evidence That Counts

Exposure to antipsychotics and risk for stroke

Journal Watch, Vol. 28, No.19, October 1, 2008

During 2002, analysis of clinical trial data raised concerns that exposure to the atypical antipsychotic drug risperidone led to excess stroke risk in dementia patients. However, whether stroke risk associated with antipsychotic drug exposure differs among people with or without dementia is unknown. Using a large database that predated these concerns, U.K. investigators compared stroke incidence during periods of exposure and nonexposure to antipsychotic drugs within individual patients who had, or did not have, dementia.

Of 6790 patients who had first strokes and were prescribed antipsychotic drugs between 1988 and 2002, 6334 were prescribed at least one typical drug (most commonly phenothiazines), and 905 patients were prescribed at least one atypical drug (most commonly risperidone). The median age at first exposure to any antipsychotic drug was 80, and the median age at first stroke was 81. Exposure to any antipsychotic drug was associated with significantly higher risk for stroke (rate ratio, 1.73); excess risk was noted for both typical drugs (RR, 1.69) and atypical drugs (RR, 2.32). In patients with dementia, exposure to any antipsychotic drug was associated with a rate ratio for stroke of 3.50, whereas, in patients without dementia, the rate ratio was 1.41. In all analysed groups, the rate ratios decreased towards 1.0 during the five months after treatment ended.

Comment

Exposure to antipsychotic drugs is associated with excess risk for stroke, and this risk appears to be higher among patients with dementia than among those without dementia. Notably, the mechanism by which these drugs raise stroke risk is unclear. Nevertheless, these results should serve as yet another red flag for clinicians, joining those of recent studies that showed minimal efficacy in patients with dementia who received antipsychotic drugs.

— Paul S. Mueller, MD, MPH, FACP

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Paracetamol and asthma in children

Journal Watch, Vol. 28, No.20, October 15, 2008

Observational studies suggest an association between use of paracetamol and the development of asthma in children. Investigators assessed the relation between paracetamol use during the first year of life or the 12 months before the study and development of wheeze, as recalled by parents or guardians, in 205,487 children aged 6 to 7 years in 31 countries.

In various analyses, controlling for numerous confounding variables and completeness of data, use of paracetamol during the first year of life was significantly associated with wheeze compared with no use (odds ratio, 1.46 in the most complete analysis). Use in the previous 12 months showed a significant dose-response association with asthma symptoms (ORs ranged from 1.61 for use once in the past year to 3.23 for monthly use). Paracetamol use also was associated with increased risk for eczema and rhinoconjunctivitis symptoms.

Comment

These authors rightfully state that the study size and consistency of findings in a range of countries suggest a relation between exposure to paracetamol and development of asthma. However, an association does not necessarily prove cause and effect. As noted in an editorial,

the analysis could not control for two important variables — reporting bias (parents of wheezing children might be more likely to give them paracetamol) and recall bias (parents of children with asthma might be more likely to recall giving the drug). I believe that these findings should not discourage the use of paracetamol when indicated.

— Howard Bauchner, MD

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Fluoroquinolone resistance among outpatient *E. coli* infections

Journal Watch, Vol. 28, No.22, November 15, 2008

Because of high rates of *Escherichia coli* resistance to trimethoprim-sulfamethoxazole, fluoroquinolones commonly are prescribed as initial therapy for urinary tract infections (UTIs). However, rising rates of *E. coli* resistance to fluoroquinolones have engendered new concerns.

In a Denver public hospital system with several community health centres, researchers assessed antimicrobial prescribing trends and *E. coli* resistance patterns. Until 1999, trimethoprim-sulfamethoxazole was the recommended agent for UTI treatment within the health system; in 1999, system physicians were advised to switch to fluoroquinolones as initial therapy. A central laboratory database was used to identify all outpatients in whom *E. coli* was isolated from any specimen; cultures were obtained at the discretion of physicians.

Fluoroquinolone use (for all indications) per 1000 visits increased from 3.1 prescriptions in 1998 to 12.7 prescriptions in 2005. During the same period, sulfonamide use dropped from 24 to 11.7 prescriptions per 1000 visits. The rate of levofloxacin resistance rose from 1.0% in 1999 to 9.4% (94% of the isolates from a urinary source; 6% from blood) in 2005. Among the 41 levofloxacin resistant *E. coli* isolates, 90% remained susceptible to amoxicillin-clavulanate, 95% were sensitive to ceftriaxone and nitrofurantoin, 76% were sensitive to gentamicin, and 34% were sensitive to trimethoprim-sulfamethoxazole.

Comment

This single-centre, retrospective study shows the parallels between the rising rate of *E. coli* resistance to fluoroquinolones and increasing fluoroquinolone use among outpatients. Given resistance patterns, the authors rightly advise switching from fluoroquinolones to nitrofurantoin as first-line therapy for outpatients with uncomplicated UTIs.

— Jamaluddin Moloo, MD, MPH

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Statin side effects — targets of ongoing research

Journal Watch, Vol. 28, No.22, November 15, 2008

Although statins generally are well tolerated, many clinicians believe that, in practice, statin-related side effects occur more commonly than was reported in randomised trials. Muscle symptoms, the most well-known statin side effect, can occur without elevated creatine kinase (CK) levels. Indeed, one study demonstrated

Evidence That Counts

reversible pathologic abnormalities on muscle biopsies in patients with normal CK levels who developed muscle pain or weakness while taking statins (JW Dec 1 2002 and Ann Intern Med 2002; 137:581). Recently, researchers identified a common variant of a gene on chromosome 12 that predisposes patients to statin myopathy.[1]

Determining whether a statin user's myalgias are related to the drug often is difficult. Thus, we would benefit by knowing whether statin users, as a group, experience muscle symptoms in excess of the background prevalence. In a recent study, in which researchers used the nationally representative NHANES database and excluded people with known arthritis, 22% of statin users and 17% of nonusers reported musculoskeletal pain. In a multivariable analysis, statin users exhibited significantly increased odds for musculoskeletal pain compared with nonusers (odds ratio, 1.5, after adjustment for many potentially confounding variables).[2] Although this cross-sectional analysis has limitations, it suggests that statin-associated muscular symptoms are not rare.

A point of controversy is whether statins cause cognitive problems in some people. This issue made national headlines in February 2008, when a Wall Street Journal article described patients who had developed problems with memory and other cognitive skills while taking statins. The article included testimonials by academic physicians and an affected patient.[3] Other experts have expressed concerns that these reports exaggerate statin risks and that negative publicity about statins will frighten patients unnecessarily.

Yet another concern about statins and cognition was raised in a recently published study. Canadian researchers used a national database to conduct a retrospective analysis of nearly 300,000 patients (age, ≥65) who had undergone elective surgery. Patients who had been prescribed statins during the previous 90 days had a significantly higher risk for developing postoperative delirium than did statin nonusers (OR, 1.3 after adjustment for many potential confounders). The database did not indicate when statin users last took statin drugs before surgery, ascertainment of delirium cases was incomplete, and hidden confounding that was not captured by the database is possible. Intriguingly, no other class of cardiovascular drugs was associated with postoperative delirium. The authors speculate that altered cerebral blood flow, resulting from the effects of statins on vascular smooth muscle, could be one mechanism for statin-induced postoperative delirium.[4] If this theory is borne out, it would compete with other data that suggest an association between perioperative statin therapy and lower postoperative mortality.[5]

The beneficial effects of statins in high-risk patient populations are indisputable. However, these drugs increasingly are being prescribed to asymptomatic people on the basis of somewhat arbitrary serum lipid thresholds, without regard to overall cardiovascular risk. Thus, gathering more information about potential adverse effects is imperative. One noteworthy effort comes from the University of California at San Diego, where researchers have conducted an NIH-funded randomised placebo controlled trial to gather detailed information about statin side effects. The study focused particularly on statins' effects on cognition and behaviour but also tracked other adverse effects.[6] Results should be available soon. In addition, the same group currently is conducting an observational study called the Statin Effects Study.

— Allan S. Brett, MD

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Marketing, disguised as research

Journal Watch, Vol. 28, No.21, November 1, 2008

"Seeding trials" are clinical studies that appear to answer a scientific question but whose main purpose is marketing of a drug. Researchers, who were paid to be consultants for plaintiffs, reviewed confidential documents that were made public as a result of litigation against Merck. The specific case involved a study in which rofecoxib (Vioxx®) was compared with naproxen for the stated purpose of evaluating gastrointestinal tolerability; study results were published in a peer-reviewed journal (Ann Intern Med 2003; 139:539).

Merck internal communications revealed that their marketing division had conceived the clinical trial, with the goal of encouraging physicians to gain experience with rofecoxib prior to and during its critical launch phase. The trial was designed to target "customers" (primary care physicians) to become investigators and to demonstrate the value of the drug to these physicians. Employees of Merck's marketing division collected, analysed, and disseminated the data (i.e., wrote the paper). They also tracked rates of rofecoxib prescribing by study physicians. But, physician-investigators, study participants, the U.S. FDA, and institutional review boards were not informed of marketing objectives; they all were told that the purpose was to evaluate gastrointestinal safety of rofecoxib. A marketing employee wrote in an e-mail, "It may be a seeding study, but let's not call it that in our internal documents." A Merck research director wrote in an e-mail, "[This and other] marketing studies ...are intellectually redundant."

Comment

Editorialists note that "deception [regarding intent] is the key to a successful seeding trial," and that "shining a bright light on their existence may have already sown the seeds of their destruction." Clearly, physicians must be aware that seeding trials exist and must be alert to spot them. The findings of this investigation are remarkable — in fact, shocking — and they speak for themselves.

— Richard Saitz, MD, MPH, FACP, FASAM

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