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"The Christmas Message"

The following is a transcript of the first Royal Christmas Message, broadcast live on radio from Sandringham House, written by Rudyard Kipling and delivered by King George V, 1932.

"Through one of the marvels of modern Science, I am enabled, this Christmas Day, to speak to all my peoples throughout the Empire. I take it as a good omen that Wireless should have reached its present perfection at a time when the Empire has been linked in closer union. For it offers us immense possibilities to make that union closer still.

It may be that our future may lay upon us more than one stern test. Our past will have taught us how to meet it unshaken. For the present, the work to which we are all equally bound is to arrive at a reasoned tranquillity within our borders; to regain prosperity without self-seeking; and to carry with us those whom the burden of past years has disheartened or overborne.

My life's aim has been to serve as I might, towards those ends. Your loyalty, your confidence in me has been my abundant reward.

I speak now from my home and from my heart to you all. To men and women so cut off by the snows, the desert or the sea, that only voices out of the air can reach them; to those cut off from fuller life by blindness, sickness, or infirmity; and to those who are celebrating this day with their children and grandchildren. To all - to each - I wish a Happy Christmas."

So much has changed since this first broadcast of the Royal Christmas Message in 1932, yet so much has remained the same. The Wireless Radio – the communication tool of the future, joining people together, reaching the masses, allowing a common message to be heard by all. Of course wireless has a rather different meaning in 2010, but the concept remains the same. Results from the World Internet Project in 2009 found that over 80% of New Zealanders classified themselves as internet users, with almost all using the internet every day and most rating it as "important" to their everyday life.[1]

In 1932, the people marvelled over their "wireless", the new way forward in communication and in 2010 we do the same. Prescribing information at your fingertips, electronic decision support, e-resources, e-therapy, the answer to those tricky questions and of course, a way for patients to communicate instantly with their health providers... well perhaps not all technology is good! Interestingly, the World Internet Project found that there is a small but persistent population of ex-technology users that is slowly growing every year. Has technology reached its plateau? Is everybody online that ever will be? What will be our marvellous tool for communication in the future? Will we shun our wireless for the old-fashioned face-to-face?

Technology has its limitations. It will never be able to match the clinician's judgement in the assessment of a patient whose lip quivers as they tell you they are fine, the elderly gentleman who is burdened by caring for his ailing wife but is too proud to ask for help, the infant who cannot speak, but stares at you with pleading eyes. Healthcare is easier, quicker and arguably smarter, with the tools and gadgets of the 21st century. However, true healthcare must still be delivered with the same compassion that existed in 1932, to reach out and help those who are prevented from leading a fuller life through sickness and infirmity.

We have aimed to provide you the knowledge, to help clinicians navigate the sea of healthcare information. Thank you for listening to our point of view. To quote the words of King George V, albeit written for him by a Nobel Prize winner in literature, "Your loyalty, your confidence in us, has been our abundant reward".

Merry Christmas from the team at bpac^{nz}

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Pharmacogenomics for General Practitioners:

Time for clinical application

Contributed by **Dr Patrick Gladding**

Pharmacogenomics tests are not yet available to general practice. The purpose of the following article is to inform primary care clinicians about the existence of such tests and to generate discussion about what role, if any, they may play in future medical practice. – Professor Murray Tilyard, Editor-in-chief, Best Practice Journal

Most medical practitioners will be aware of the variable nature of medication response. Until recently prescribing the correct medicine, at the correct dose, to the right patient has largely been empirical. Skilled prescribers take into account age, body weight and other co-morbidities when making a treatment choice. However, there are many other important factors that can be considered, such as genetics.

Pharmacogenomic testing will soon be available to GPs and encompasses what has previously been out of reach, the molecular dimension of patient care. The exciting promise of genomics and other molecular technologies is to make medicine more predictive, preventative and personalised.

What is pharmacogenomics?

The field of pharmacogenomics has existed for several decades, however, its clinical application has been limited by a number of factors. Although good science and clinical data exists to support the use of the technology, there are barriers to its implementation. These include cost, availability, speed of turnaround in results, education and opposition from industry. Since the completion of the human genome project in 2003, the cost of genotyping has reduced exponentially. Alongside this, there has been an explosion in the methods to perform genotyping and sequencing. A complete genome is not necessary to make important clinical decisions – single individual genetic variants (also known as single nucleotide polymorphisms, "SNPs") can be useful tests in isolation. The cost of testing

SNPs has now dropped to under $200 and each test needs to be performed only once in an individual's lifetime.

Pharmacogenomic testing generally involves the testing of a number of SNPs within key genes that encode for metabolic pathways, transporter systems or drug targets. Alterations in SNPs may alter the function of an enzyme or protein to make it more or less active, contributing to the phenotype or physical characteristics of an individual. It is important to understand that the genotype does not always correlate perfectly with the phenotype.

Considerations for healthcare professionals

As personalised medicine enters primary care, it will be important for it to be understandable and relevant to both the patient and practitioner. Unfamiliar data for general practitioners will be potentially confusing. For a SNP test to be worthwhile, it has to provide a result that is able to be actioned and also must provide additional benefit compared to current management strategies.

Pharmacogenomic tests fall into two categories (though some may provide information on both):

1. **Predictive tests** that are actionable and change treatment. These tests provide information about a patient's response or non-response to a medication.

   Examples of this include:

   a) Warfarin – genetic information combined with clinical information provides an accurate maintenance dose estimate (within 0.5 mg). In the future those at high risk for bleeding may be prescribed dabigatran.[1]

   b) Clopidogrel – provides the ability to identify non-responders who are at higher risk for stent thrombosis and death. Non-responders can be given alternative treatments when they become available in New Zealand.[2]

2) **Prognostic tests** that assess risk.

   Examples of this include:

   a) Simvastatin – provides a relative risk for the development of myopathy on 80 mg of simvastatin. Homozygotes are at a sixteen times higher risk of myopathy.[3]

   b) Abacavir - provides a risk for developing Steven's Johnson syndrome.[4, 5]

   c) Carbamazepine - provides a risk for developing Steven's Johnson syndrome in Asian people.[6]

Two considerations for the prescriber about pharmacogenomic testing are:

1. What is the likelihood of the adverse event?

   In the instance of statin myopathy the clinical trial event rate is uncommon and testing every patient may not be cost-effective.

2. How common is the genetic variant in the population I am testing?

   In some populations genetic variants that code non-response are more prevalent, meaning that testing may be more cost-effective.

Ethics and privacy

Genetic testing may be viewed as discriminatory by some groups. This concern is well founded as employers and insurance companies have shown an interest in using genetic information to assess prospective employees and load policies. General practitioners need to be aware that entering genetic information into patient's clinical notes may allow them to be viewed by third parties. Also, a non-functioning or deficient enzyme could quite easily be considered a label of a "deficient individual."

Other concerns with genetic testing include racial ancestry and paternity. Rare variants that are common in some ethnic

Current and future personalised medicine tests available in New Zealand

Biomarker test	Provider/Developer	Utility and Accuracy	Cost	Benefits
Stool-based molecular diagnostic test	Exact Sciences	Detects the presence of bowel cancer and adenomatous polyps	Unknown	Higher uptake of screening Improved specificity compared to faecal occult blood test
Renin[8]	Diagnostic Medlab	Predicts success of monotherapy to antihypertensive treatment (chlorthalidone vs atenolol)	Low	Avoids cycling through therapy and may reduce number of pills needed
Urine-based molecular diagnostic test	Pacific Edge Biotechnology Ltd	Detects the presence of bladder cancer	Unknown	Screening tool for bladder cancer, allows early diagnosis and treatment
Clopidogrel pharmacogenetic test	Theranostics Lab	Predicts risk of adverse events and efficacy	$150	Prompts treatment increase or change in treatment to reduce stent thrombosis
Statin pharmacogenetic test	Theranostics Lab	Predicts myopathy risk	$150	Improved adherence to treatment
Warfarin pharmacogenetic test	Theranostics Lab	Dose prediction and bleeding risk	$150	Reduced bleeding events
ACE inhibitor pharmacogenetic test	Theranostics Lab	Prediction for ACE inhibitor-related cough	$150	Prevents ACE cough, patients could possibly switch to ARB treatment

Notes: Other genetic tests of note include TPMT for azathioprine, KRAS for cetuximab and BRAF for melanoma treatment (see Phase III study from Plexxikon). Pharmacogenetic testing for SSRIs and tamoxifen are also emerging areas. Clopidogrel and warfarin tests have proven cost-effectiveness.

groups may be used as a surrogate for race. Presence or absence of a variant may imply paternity. Discussing genetic results with patients can be fraught with problems and genetic counselling is advised for any genetic test that has the potential for significant psychological impact to an individual and their family. Genetic testing of an individual, in effect, is also indirectly testing family members.

The future of personalised medicine

It is clear that the future of medicine is heading in the direction of personalised risk and treatment decisions. Historically the practice of medicine has largely focused on the physical (or phenotypic) manifestations of disease. However, many diseases begin at earlier stages that may not be apparent to most modern methods of diagnosis. These disease stages are sometimes detectable using molecular methods of diagnosis. Pharmacogenomics is the first in a number of scientific fields that is emerging as clinically valuable. The goal for these fields is to improve on the efficiency of current medical practice, rather than add to their cost. An example of this is a recently developed molecular stool-based test for bowel cancer screening (sensitivity 85%, specificity 90%). This test potentially may increase adherence to screening programmess and reduce negative colonoscopies.[7] In addition, genomic medicine is revealing highly targeted therapies, such as a new melanoma treatment produced by the company Plexxikon.

Cost is an important consideration when reviewing all of these new technologies. Making medicine more efficient by identifying high risk individuals using genomics, and applying non-invasive molecular screening tools, should lead to reduced cost, which is currently consumed by procedures and specialists applying healthcare that is not widely accessible. A smaller market for the pharmaceutical industry is unattractive and drugs developed for a few may unfortunately cost a lot, putting them out of reach for patients in New Zealand. General practitioners are likely to be at the very forefront of personalised medicine which seeks to provide a more global and holistic approach to healthcare.

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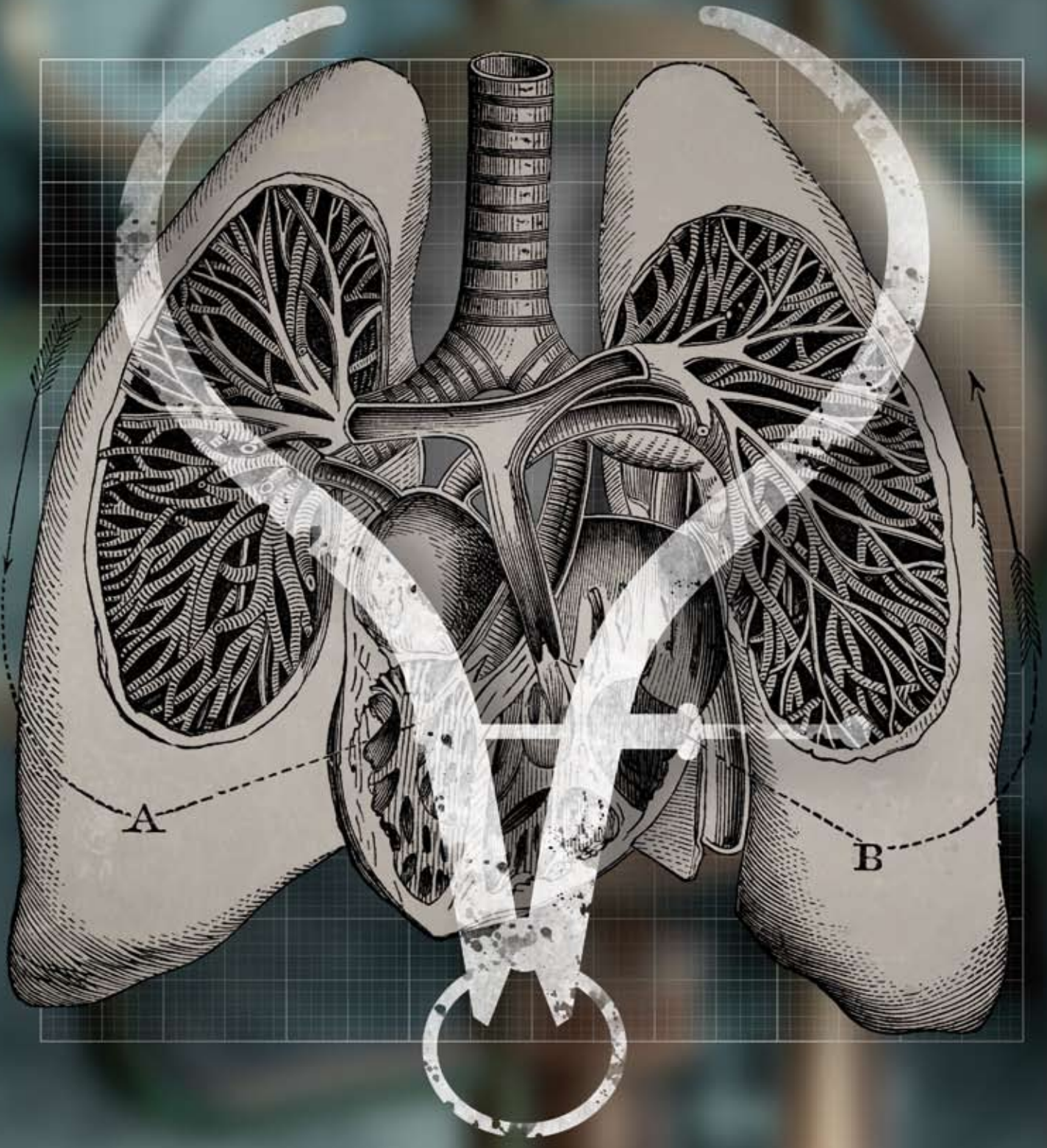
Competing interests: Dr Gladding has a patent pending on clopidogrel pharmacogenomics with treatment strategies and is the founder of a non-profit translational research company.

Assessing cardiovascular risk: **what the experts think**



Risk factors for cardiovascular disease

Cardiovascular disease is the leading cause of mortality in New Zealand, accounting for 40% of deaths annually.[1] Many cardiovascular-related deaths are premature and preventable.

The development of cardiovascular disease is associated with risk factors that an individual may be able to change or improve (i.e. modifiable) as well as factors that are fixed (i.e. non-modifiable). Modifiable risk factors include; smoking, lipid levels, physical activity, diet, blood pressure, alcohol intake, psychosocial stress and obesity. Non-modifiable risk factors include; age, gender, genetics, ethnicity and socioeconomic status. Knowledge of which risk factors are present can help target appropriate interventions and monitor response.

In addition to these risk factors, certain co-morbidities can also increase cardiovascular risk, including diabetes, chronic kidney disease, rheumatoid arthritis and depression.

Despite much being known about cardiovascular risk assessment, there are still areas which remain contentious and are not supported with conclusive evidence. Therefore we invited a group of practitioners, with expertise and interest in cardiovascular disease, to discuss some of these issues.

Questions focused on:

- Risk assessment tools in the current New Zealand guidelines – are they still appropriate to use? How up to date and relevant are they? Can they be used with confidence?
- Risk factors – how are factors such as obesity, ethnicity and renal function included in a risk assessment?
- Surrogate risk markers – e.g. lipoprotein (a) and high sensitivity C-reactive protein, is there any evidence for their use?

The experts:

Dr Sisira Jayathissa, General Physician and Geriatrician, Clinical Head of Internal Medicine, Hutt Valley DHB, Wellington.

Professor Jim Mann, Human Nutrition and Medicine, University of Otago, Consultant Physician (Endocrinology), Dunedin.

Associate Professor Stewart Mann, Cardiovascular Medicine, University of Otago, Wellington.

Professor Norman Sharpe, Medical Director, National Heart Foundation of New Zealand.

So, what did they say?

A summary of advice from the experts

The risk assessment tools included in the current New Zealand guidelines are well supported. Tools based on Framingham data are robust and take into account the essential elements for cardiovascular risk assessment. When used as outlined in the New Zealand guidelines, risk prediction can be performed with confidence for the majority of people.

- Do the basics and do them well for everybody. Use the current cardiovascular risk assessment tools without getting too tied up in the arguments about alternative tools and the use of emergent risk factors and surrogate markers.
- Use the available assessment tools as a prompt and use your clinical judgement at an individual level.
- Be definite in setting goals and reassessing time frames. Rather than saying to a patient: “Next time I see you, we will measure your blood pressure”, instruct them to: “Make an appointment in three months time to have your blood pressure checked”.
- Significant effort needs to go into lifestyle changes including smoking cessation. Acknowledge to the patient that it can be hard to maintain diet and exercise changes but that they are very important and worth persevering with.

- Beware of giving people false reassurance – clinicians have to give a true picture of the patient's cardiovascular risk. Remember not everybody understands numbers in the same way. You may need to explain risk in a variety of different ways to ensure it is understood.

Best Practice Tip: The Heart Foundation "Know Your Numbers" programme is a very useful tool for engaging with patients in primary care and motivating change, particularly as it shows the future lifetime risk trajectory and how high risk can be improved with lifestyle interventions and treatments. This programme is available online at: **www.knowyournumbers.co.nz**

Current cardiovascular risk assessment tools are supported

There has been some question over whether Framingham based tools should still be used for cardiovascular risk assessment and whether alternative tools should be used.

In the United Kingdom there is no consensus about which risk calculator should be used, rather a number are available including the Framingham risk score, QRISK®2 (based on a primary care cohort from the United Kingdom) and ASSIGN. Clinicians are advised to select the tool that is best suited to their requirements.[2]

QRISK®2 calculator available at: **http://qrisk.org**

ASSIGN calculator available at: **www.assign-score.com**

Current New Zealand guidelines for primary prevention of cardiovascular disease recommend risk management based on the Framingham risk score. It is available in different formats including risk charts and electronic calculators.

In your opinion are the current cardiovascular risk assessment tools outlined in the New Zealand Cardiovascular Guidelines Handbook (based on Framingham score) still up to date based on latest evidence?

"The Framingham engine may appear a little crude as it requires only basic information from patient history and easily available tests. However, it remains a powerful tool for population prediction and it is difficult to show significant improvement by allowing for inclusion of any one new risk factor."– Stewart Mann

"Most cardiovascular risk assessment tools are based on Framingham data, therefore the debate about which is better probably has little merit. There is no good evidence that any of the other tools currently available perform any better than that in current use in New Zealand."– Jim Mann

"An ideal tool for New Zealand would be based on our own population data including ethnic sub-groups."– Sisira Jayathissa

The Framingham score is used to predict the absolute risk of coronary events in populations free of cardiovascular disease. Risk calculators based on Framingham data are the most widely used and researched. Validation studies have demonstrated that the Framingham risk prediction is well calibrated for New Zealand, Australia and the United States. Although in New Zealand a 5% additional risk is added for certain ethnicities, e.g. Māori, Pacific peoples and people from the Indian subcontinent. In Europe and the United Kingdom risk prediction is poorer due to over-estimation.[3]

Clinical judgement can account for limitations in risk prediction

There are limitations associated with the use of any of the available risk prediction tools. Interpretation of the calculated risk requires clinical judgement to adjust for other known factors that the risk calculator does not take into account. Once the risk elements have been

incorporated into the prediction tool; age, gender, blood pressure, cholesterol, smoking and diabetes, then each patient should be evaluated on an individual basis. The factors that need to be kept in mind include:

- Family history of premature cardiovascular disease
- Obesity
- Ethnicity
- Socioeconomic factors
- Renal function
- Age <35 years and >75 years

What are the main limitations of the current assessment tools?

"Underestimation of risk in certain groups may occur, especially in people with a family history of premature cardiovascular disease, in people who are obese and in certain ethnic groups. It has been suggested that such individuals might be moved up the risk scale. The extent to which this improves the risk estimate has not been established but could be taken into account when discussing risk with individual patients." – Jim Mann

"The identification of 'at risk' people is critical. Assessment tools should be viewed as a prompt to enable this. Doctors need to consider additional risk factors relevant to each patient such as abnormal renal function and obesity."– Sisira Jayathissa

The Framingham risk score (the basis for the New Zealand risk charts) calculates risk based on age, gender, blood pressure (systolic), cholesterol level (total cholesterol:HDL cholesterol ratio), smoking status and presence of diabetes mellitus. In addition, the New Zealand risk charts allow for adjustments to be made in groups where underestimation of risk is likely, e.g. for certain ethnic groups and family history.[4]

Many studies have attempted to identify additional risk factors that could improve prediction beyond the Framingham risk score. However, some commentators believe that issues with study design, analysis or reporting cast some doubt on the strength of these factors as predictors.[5]

Possible additional risk factors include:

- Body mass index, waist circumference, waist-hip ratio
- Deprivation, living standards
- Alcohol intake (excessive or binge drinking)
- Surrogate markers including; high sensitivity CRP, lipoprotein (a), uric acid

Triglycerides have been included in studies of risk factors, however, they have only a weak effect on cardiovascular risk assessment. Apart from one or two rare disorders, they are likely to be, for the most part, an indirect measure of poor lipid particle clearance, e.g. insulin resistance.

Some risk factors are not independent. For example, social deprivation, smoking, stress and alcohol misuse are interrelated, as are ethnicity, obesity, dyslipidaemia and diabetes. The strength of the relationship between dependent factors is unknown.[2]

Family history

The New Zealand guidelines account for family history of cardiovascular disease by adding an additional 5% to the calculated five-year cardiovascular risk. Family history is defined as premature coronary heart disease or ischaemic stroke in a first-degree relative (father or brother <55 years, mother or sister <65 years).[4]

"Caution is required with family history as there are widely different interpretations of what qualifies for a positive family history. Both the Framingham and INTERHEART studies showed that family history added virtually nothing to prediction once the classic risk factors had been included."– Stewart Mann

The INTERHEART study found nine risk factors that collectively accounted for over 90% of the population-attributable risk of an initial acute myocardial infarction. The factors were; abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables and alcohol and regular physical activity.[6]

The study also found that 90.4% of myocardial infarctions could be attributed to the risk factors described above and this only rises to 91.4% when family history is added. This indicates that although family history is an independent risk factor for myocardial infarction, most of the attributable risk can be accounted for through the other risk factors studied. Family history appeared to be a more significant risk factor in younger people.[6]

Obesity

Obesity needs to be considered in conjunction with other risk factors, such as raised blood pressure, glucose and lipid levels. If these factors are also present then management can include addressing these factors along with lifestyle issues. However, if the patient is obese without other associated factors then management could be based on diet and exercise alone.

"Some co-morbidities of obesity will be detected through standard cardiovascular risk assessment. Others, most importantly pre-diabetes, will not. Obese patients require measurements in addition to those routinely recorded as part of cardiovascular risk assessment. The most appropriate clinical measurements for assessing obesity are BMI in conjunction with waist circumference. It is a false assumption that higher BMIs are acceptable in some ethnic groups, particularly Maori and Pacific peoples."–Jim Mann

"Obesity appears to exert an influence on calculable risk when it is associated with higher blood pressure or glucose intolerance (which of course is not infrequent). The preferred index for obesity remains controversial. The waist circumference (or waist-to-hip ratio) is likely to prove more predictive but may be as much of a risk marker (indicating a genetic dysmorphic pattern associated with other risks such as low HDL/high triglyceride) as a usefully modifiable risk factor."– Stewart Mann

Ethnicity

New Zealand cardiovascular guidelines identify Māori, Pacific peoples and people from the Indian subcontinent as high-risk groups that should be targeted for risk assessment. It is recommended that risk assessment should be started ten years earlier than for New Zealand Europeans and that an upward adjustment of 5% in five-year cardiovascular risk is made for these ethnic groups.

There are differences in cardiovascular risk factors between ethnic groups such as rates of smoking and diabetes, and possibly differences in blood pressure and lipid levels. There is work being undertaken to develop New Zealand specific cardiovascular risk prediction equations which consider ethnicity.[7]

Socioeconomic factors

"Socioeconomic factors are undoubtedly important and should be kept in mind. Framingham may not have measured these well enough. The INTERHEART study did include them and identified them as important. Some socioeconomic factors will be accounted for by ethnicity and some track closely with other classic risk factors (studies from the United Kingdom have shown that the main reason for the socioeconomic gradient is a correlated prevalence of the classic risk factors). Hopefully, local studies will include this and be able to weight it as an independent variable appropriately."– Stewart Mann

The Living Standards and Health Survey 2006/07 found that adults experiencing severe hardship were 60% more likely to have coronary heart disease than those with good or very good living standards or experiencing no deprivation. They were also twice as likely to be current smokers and 20–25% more likely to be obese.[8]

One-quarter of Pacific people (24%), approximately 16% of Māori, 7% of Europeans and 6% of Asians reported any degree of hardship. Over 5% of Pacific and 3% of Māori reported severe hardship; this response was much less prevalent (approximately 1%) among the European and Asian ethnic groups.[8]

Renal Function

The link between chronic kidney disease and increased cardiovascular disease is not always recognised. The estimated glomerular filtration rate (eGFR) is now automatically reported by most laboratories in New Zealand and can be used to screen for chronic kidney disease. The eGFR can be considered in the overall cardiovascular risk assessment.

> "Impaired renal function is clearly a risk factor but numbers have not been large enough to include in population equations."– Stewart Mann

It is increasingly recognised that chronic renal dysfunction alone is an independent risk factor for the development of cardiovascular disease.[9]

The eGFR can be used to screen for chronic kidney disease. Most patients with an eGFR <60 mL/min/1.73 m^2 die of cardiovascular causes and not due to progression to end stage renal disease.[10] An eGFR <60 mL/min/1.73 m^2 indicates the need for measures to reduce cardiovascular risk.[2]

A meta-analysis found that people with an eGFR <60 mL/min/1.73 m^2 had a 43% greater risk of stroke than those with a normal eGFR and that Asians were at higher risk than those of non-Asian ethnicity.[10] This supports the use of a low baseline eGFR as a risk marker. When eGFR is <60 mL/min/1.73 m^2, established strategies such as blood pressure reduction should be used to prevent future strokes and reduce cardiovascular risk in people with renal insufficiency.

See "Making a difference in chronic kidney disease", BPJ 22 (Jul, 2009).

Younger (<35 years) and older (>75 years) people

Risk calculators become less accurate at the extremes of age (under 35 years and over 75 years).

> "The Heart Foundation's 'know your numbers' tool is very useful for dialogue with young people at high relative but low absolute risk where efforts should concentrate on lifestyle rather than medicines." – Stewart Mann
>
> "Future health promotion efforts should be focussed on targeting 'at risk' people at very young ages as atheroma deposition and changes to the brain start below age 35 years. Older people need to be assumed as having high risk due to their age and associated co-morbidities". – Sisira Jayathissa

Caution with surrogate markers – they may be unproven or obsolete

It may be tempting to include additional factors such as lipoprotein (a), homocysteine or high sensitivity C-reactive protein (hsCRP) into a calculation of cardiovascular risk. However, these factors are not supported with conclusive evidence of improved risk prediction and priority should be given to the basic risk factors as in Framingham.

What is the current thinking on the role of cardiovascular risk markers such as lipoprotein (a), homocysteine and hsCRP?"

Lipoprotein (a)

"Lipoprotein (a) is still not widely measured but high levels are associated with higher risk. We do not appear to have specific tools to deal with it effectively."– Stewart Mann

"If someone has a family history of premature cardiovascular disease and no obvious risk factors, measurement of lipoprotein (a) is an appropriate, though costly, test. Nicotinic acid is currently the only available therapeutic agent to treat elevated lipoprotein (a) levels and large doses are required. A slow release preparation is now available and is relatively free of adverse effects. Because of the difficulty in treating raised levels of lipoprotein (a) it is important to ensure that other risk factors are effectively treated."– Jim Mann

Routine measurement of lipoprotein (a) is not indicated as part of a cardiovascular risk assessment in primary care.

Lipoprotein (a) is a modest, independent risk factor for atherosclerotic cardiovascular events, especially myocardial infarction. There are no clinical trials that have adequately tested the hypothesis that lipoprotein (a) reduction reduces the incidence of first or recurrent cardiovascular events. Lipoprotein (a) levels are also difficult to alter. Therefore, widespread screening for elevated lipoprotein (a) is not indicated and treatment of lipoprotein (a) levels should only be considered in specific circumstances.[11] A high level would usually prompt a more aggressive approach to other risk factors, rather than treating the level itself. If the clinical approach is otherwise clear based on other definite risk factors, then measuring lipoprotein (a) has little additional value.

Homocysteine

"Three very large trials have shown no benefit from reducing homocysteine levels with folate supplementation to lower cardiovascular risk."–Stewart Mann

Routine measurement of homocysteine is not indicated as part of a cardiovascular risk assessment in primary care.

It is hypothesised that high homocysteine levels cause endothelial damage and contribute to progression of cardiovascular disease. Treatment with folic acid (0.5 to 5 mg/day) lowers homocysteine, and therefore a decreased risk or slowing of cardiovascular disease progression would be expected. However, results from meta-analyses show that folic acid supplementation fails to decrease cardiovascular events despite homocysteine lowering. Folic acid supplementation actually appeared to increase cardiovascular risk in patients with high homocysteine levels at baseline. This suggests that folic acid may affect atherosclerotic disease progression through pathways that are independent of homocysteine lowering.[12] Folic acid supplementation is not recommended as a means to prevent or treat cardiovascular disease or stroke.[12]

Vitamin B supplements; cyanocobalamin (B12), folic acid (B9) and pyridoxine (B6), are also used to lower homocysteine levels. However, there is also no evidence to support their use in lowering homocysteine levels to prevent cardiovascular events.[13]

High sensitivity CRP

"HsCRP is undoubtedly a powerful risk marker (and may act as a useful surrogate for calculated absolute risk). However, genetic variations in hsCRP levels are not associated with variations in risk. Treatments for other risk factors, e.g. statins, tend to reduce hsCRP as well and we do not have a pharmaceutical that reduces it alone and specifically to test its relevance as a risk factor." – Stewart Mann

Routine measurement of hsCRP is not indicated as part of a cardiovascular risk assessment in primary care.

Inflammatory processes significantly contribute to atherogenesis (plaque formation in the aterial lining). It is unclear whether hsCRP is a non-specific marker that is increased in response to the inflammation or whether it directly contributes to the progression of atherosclerosis and its clinical consequences. Observational studies, although inconclusive, have suggested that hsCRP has only a small, or no, incremental contribution to cardiovascular risk prediction compared to traditional risk factors.[14]

HsCRP may be temporarily raised by inflammation and in addition, there is significant biological variation in levels (approximately 30–40% compared with most other lipid markers such as cholesterol and HDL which are 6–10%). Therefore, a raised level should be followed up with a repeat test when the patient is well.

Effect of calcium supplementation and low vitamin D levels is still unclear

Recent studies have raised concern that calcium supplementation (without vitamin D) may increase cardiovascular risk. Other observational studies have shown an association between low vitamin D levels and increased risk of cardiovascular events, in particular stroke. Many older people receive calcium or vitamin D supplements or both. It is therefore important to understand their effects on overall cardiovascular risk.

What is the current advice about the use of calcium supplements in patients with cardiovascular disease? Is vitamin D protective?

"Some studies have suggested adverse cardiovascular outcomes with calcium supplementation but this is not universally accepted. A systematic review showed neutral effects of calcium on cardiovascular disease.[15] It may be reasonable to avoid calcium supplements in patients with established cardiovascular disease until further evidence becomes available." – Sisira Jayathissa

"Calcium supplements should be avoided in general, in favour of a healthy balanced diet, and particularly so in people with cardiovascular disease or those at high risk. They remain a consideration for older people with high fracture risk where the benefits for some individuals in terms of bone health may outweigh any small increase in cardiovascular risk."–Norman Sharpe

"Vitamin D deficiency is common and we know improvement in vitamin D level is good for bones, muscles and other bodily functions. However, based on current evidence it is difficult to recommend routine vitamin D supplementation for cardiovascular protection."– Sisira Jayathissa

The evidence is limited as no randomised trials have focused primarily on the effect of vitamin D and calcium supplementation on cardiovascular end-points. The best evidence comes from trials that were designed to explore other issues. The available secondary and observational evidence suggests a possible cardiovascular disease prevention benefit of vitamin D (at moderate to high doses) and no benefit of calcium supplementation (either alone or in combination with vitamin D).[15,16]

While vitamin D supplementation may be associated with reduced cardiovascular disease risk, the evidence is limited and not sufficient to justify widespread vitamin D supplementation.[16]

A systematic review provides some reassurance that calcium supplements are unlikely to be associated with cardiovascular harm,[15] as suggested by local New Zealand studies, which found an increased risk of cardiovascular events in people receiving calcium without vitamin D.[17,18]

Further studies are required to establish the potential role of calcium and vitamin D supplementation in the prevention of cardiovascular disease.[15]

Aspirin for primary prevention is not routinely indicated for patients with diabetes

Recent studies have cast doubts on the widespread use of aspirin for primary prevention and its routine indication in people with diabetes.

Is there a place for aspirin in primary prevention, particularly in patients with diabetes?

"Aspirin is not generally recommended for primary prevention but is still a consideration for those identified at high risk in discussion between patient and doctor."–Norman Sharpe

"Aspirin should not be used routinely in primary prevention of cardiovascular events in diabetes. Good quality clinical trials and meta-analyses have shown lack of benefit of aspirin in primary prevention. However, aspirin could be considered on an individual basis if the patient has very high cardiovascular risk."– Sisira Jayathissa

"Recent studies showing little benefit of regular prophylactic aspirin in primary prevention have included large numbers of people at low absolute risk. It is still likely that people at higher risk, e.g. >15% five-year cardiovascular risk, may benefit and the Heart Foundation recommendations are to continue this practice here. Other trials are in process to examine this. The cardiovascular risk in diabetes has, in my view, been overplayed as evidenced by cardiovascular disease rates in some recent trials being a fraction of what was initially predicted. The concept that a diagnosis of diabetes confers equivalent risk to a cardiovascular event is not tenable. Many diabetics are therefore at low or intermediate risk, although a significant number have other risk factors which might well render aspirin useful."–Stewart Mann

See "Aspirin for primary prevention of cardiovascular disease", BPJ 25 (Dec, 2009).

A meta-analysis of randomised controlled trials, evaluating the benefits and harms of low-dose aspirin in people with diabetes and no cardiovascular disease, has shown no clear benefit of aspirin use. Until further research evidence becomes available, at present the use of low dose aspirin in the primary prevention of major cardiovascular events in people with diabetes remains unproven.[19]

Dietary inclusions and nutritional supplements may have value as part of lifestyle and diet modification

There is evidence that some dietary inclusions, e.g. nuts, may have a beneficial effect on reducing cardiovascular risk, however use of such products is not widely advocated.

Is there any evidence for nutritional supplements targeted at reducing cardiovascular risk such as flaxseed, walnuts or omega-3 fatty acid?

"All these products and others may have some value in improving the quality of the diet as a part of lifestyle modification."– Sisira Jayathissa

"A diet that favours significant contributions from fruit, vegetables and unprocessed nuts confers some lowering of risk. There is an absence of evidence (and in some cases, evidence of absence) of 'benefits' from nutritional supplements, which should be clearly stated on product information."– Stewart Mann

"There is no doubt that a healthy lifestyle including an appropriate dietary pattern is a cornerstone of treatment of all those at risk of cardiovascular disease. However, there is little evidence for unique benefits of individual foods. Nuts may be the single exception. There is evidence that those regularly consuming nuts may be at reduced risk of subsequent cardiovascular events, an effect which seems to be independent of potentially confounding factors. They have a favourable effect on several clearly described risk factors though if recommending nuts patients should be advised to avoid heavily salted and roasted nuts. They are sometimes roasted in saturated fat!

There is limited evidence that omega 3 fatty acids given as supplements, as well as the regular consumption of oily fish, may reduce subsequent cardiovascular events in those with established cardiovascular disease. There is no convincing evidence of benefit of any other nutrient supplements. " – Jim Mann

A mean daily consumption of 40 g to 100 g of raw nuts, e.g. almonds, walnuts, hazelnuts, pecans, pistachios and peanuts* may reduce cardiovascular risk and reduce blood lipid levels.[20]

Nut consumption improves blood lipid levels, particularly among people with higher LDL-cholesterol or with lower body mass index. It is not clear why nuts are less effective in lowering blood cholesterol concentration among people who are obese.[20]

The cardiovascular disease prevention benefits of nuts are likely to be due to a number of effects in addition to cholesterol lowering. Other beneficial effects include improved endothelial function and lowered oxidative stress. Nut consumption is also associated with a lower risk of developing type 2 diabetes and research has shown that frequent, moderate raw nut consumption does not lead to weight gain.[20]

Increasing the consumption of nuts as part of a healthy diet can be expected to favourably affect blood lipid levels (at least in the short-term) and has the potential to lower cardiovascular risk.[20]

* Peanuts are members of the legume family, but have a comparable nutrient profile to nuts and are associated with the same beneficial cardiovascular effects.[20]

Looking ahead

"The New Zealand Cardiovascular Risk Assessment Guidelines were updated as outlined in the Cardiovascular Guidelines Handbook 2009. The assessment of absolute risk is still based on the Framingham data and this has been validated for New Zealand. However, within the next year or two we will have the opportunity to rewrite the risk equation using New Zealand specific data obtained from primary care. These data have linked risk assessment with outcomes in a large population sample aggregated in recent years. Beyond that, the remaining challenge is to move beyond risk assessment to effective management and ensure that high risk individuals do indeed have effective long term intervention and support to reduce their absolute risk and improve their outlook."– Norman Sharpe

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Some questions remain unanswered

Some issues in cardiovascular risk assessment remain controversial and there is not always a clear or universally accepted viewpoint.

The influence of current cardiovascular medication on risk assessment

"The role of treatment in re-assessment of risk level is an unanswered (and possibly unanswerable) question. It is no longer possible to study an untreated population comparable to a treated one. Past studies have shown that some risks are reduced immediately and completely by effective treatment, e.g. stroke risk in hypertension, but others, e.g. coronary disease in hypertension, may take longer to reduce. Certainly, studies of people with treated hypertension show that they remain at higher risk than those with comparable levels of blood pressure who were never hypertensive, but there could be many confounding factors here." – Stewart Mann

Uric acid as a risk marker

"This issue (using serum uric acid as a marker of cardiovascular risk) is still somewhat controversial. Some studies have shown independent association of uric acid and increased cardiovascular risk but other studies have come to a different conclusion. The main link between raised uric acid levels and cardiovascular disease is hypertension. In a small study of young adults, reduction in uric acid levels has produced improvement in hypertension. Uric acid has been linked to metabolic syndrome and diabetes. There is not sufficient evidence to consider treating isolated high uric acid levels in low risk adults. Doctors should instead focus on treating the known risk factors."– Sisira Jayathissa

"Gout appears to be increasing in Māori and Pacific peoples so uric acid as a risk marker is perhaps important in these groups." – Jim Mann

Research surrounding the link between uric acid, allopurinol and hypertension is currently underway, which may provide new data to help understand this association.

See "Genes, fructose, allopurinol and gout" BPJ 32 (Nov, 2010) and "Gout in the Māori community" BPJ 13 (May, 2008).

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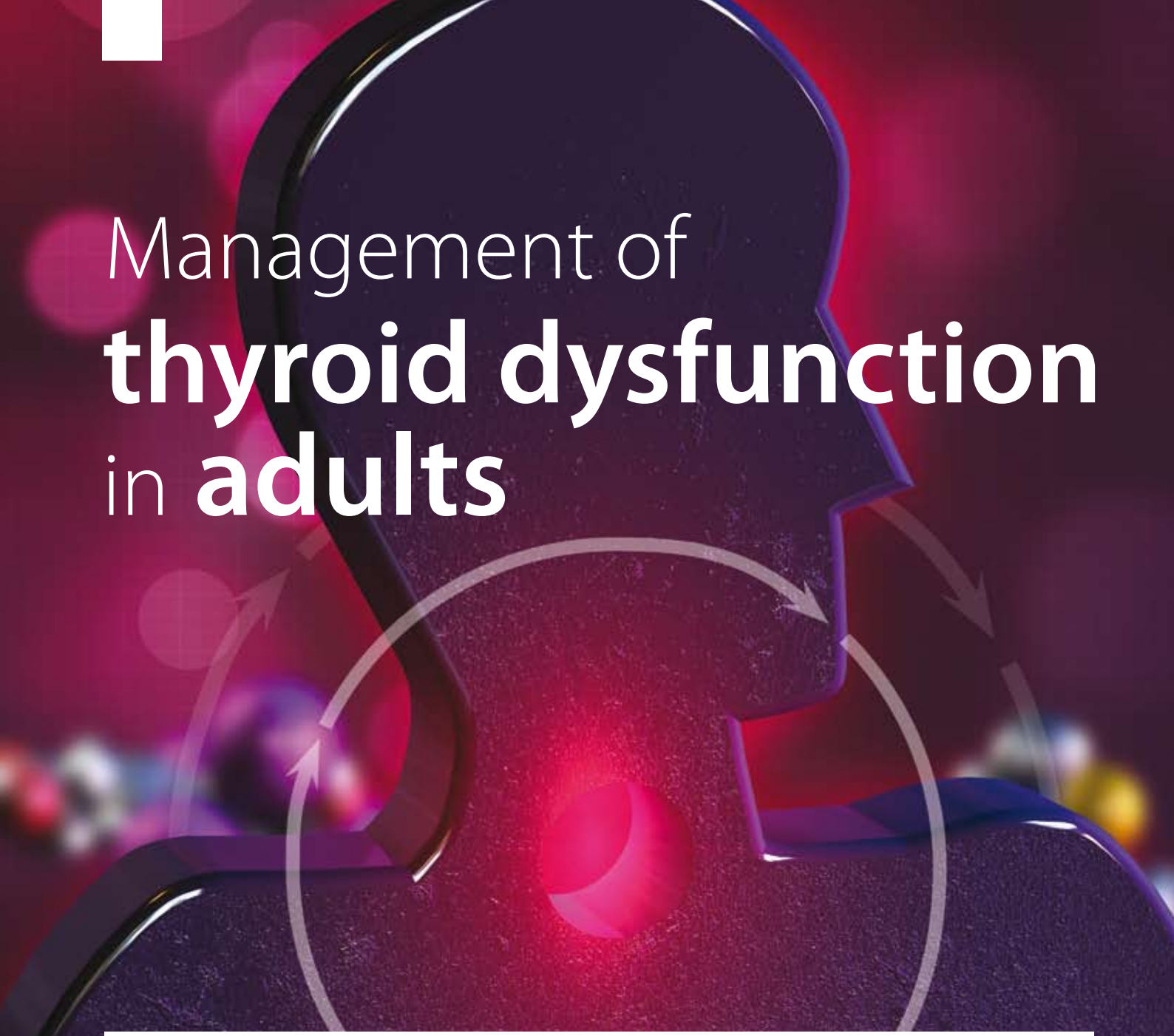


Management of **thyroid dysfunction** in **adults**

Key concepts

- Routine screening for thyroid dysfunction is not recommended unless there are symptoms and signs of thyroid disease
- TSH is the best initial test and an abnormal result will trigger laboratory reflex testing of additional thyroid function tests as indicated, in most laboratories
- Thyroid dysfunction (hypo- or hyperthyroid) can be classified as overt or subclinical and treatment is guided by TSH results and the clinical situation
- Levothyroxine is the treatment of choice for hypothyroidism
- Carbimazole is most often the initial choice of treatment for Graves' hyperthyroidism
- Other treatment options for hyperthyroidism include β-blockers, radioactive iodine and surgery
- Screening for thyroid dysfunction in pregnant women is not routinely recommended in New Zealand, however, testing should be considered if there are symptoms of thyroid disease or in women who are at increased risk of hypothyroidism

Diagnosis of thyroid dysfunction

Conditions that affect the thyroid gland are common, affecting 5% of women and 1% of men in New Zealand.[1] The incidence of thyroid dysfunction (particularly hypothyroidism) tends to increase with age.[2,3]

Clinical assessment and judgement should guide initial testing when a diagnosis of thyroid dysfunction is suspected. The common symptoms and signs are presented in Box 1. A family history of thyroid dysfunction may also increase clinical suspicion. There is a lack of evidence to support routine screening in asymptomatic people, therefore testing for thyroid dysfunction is not recommended unless there are symptoms and signs of thyroid disease.[4,5]

TSH can be used as the initial measure of thyroid function in most cases

In most situations serum thyroid stimulating hormone (TSH) can be used as the initial measure of thyroid function.[6] If further tests, such as serum free thyroxine (FT4), free triiodothyronine (FT3) or thyroid antibodies (see over page) are required following an abnormal TSH result, these may be added to the original request without the need for the patient to have a second blood test. Most laboratories do this automatically following an abnormal TSH result ("reflex" testing) or the additional tests may be added by the clinician. To assist the laboratory it is useful to include relevant clinical details and medications on the request form.

Box 1: Symptoms and signs of thyroid dysfunction (adapted from "Investigating Thyroid Function", bpac^{nz}, 2005)

	Hypothyroidism	Hyperthyroidism
High suspicion	Goitre Delayed reflexes	Goitre Thyroid bruit (secondary to increased blood flow) Lid lag Proptosis (bulging eyes)
Intermediate suspicion	Fatigue Weight gain/difficulty losing weight Cold intolerance Dry, rough, pale skin Constipation Facial swelling (oedema) Hoarseness	Fatigue Weight loss Heat intolerance/sweating Fine tremor Increased bowel movements Fast heart rate/palpitations Staring gaze
Low suspicion **Non-specific symptoms**	Coarse, dry hair Hair loss Muscle cramps/muscle aches Depression Irritability Memory loss Abnormal menstrual cycles Decreased libido	Nervousness Insomnia Breathlessness Light or absent menstrual periods Muscle weakness Warm moist skin Hair loss

In summary: the use of thyroid function tests for investigation

Asymptomatic patients:

- Do not test for thyroid dysfunction unless specifically indicated

Patients with symptoms or signs of thyroid dysfunction:

- Request TSH
- During a non-thyroidal illness (sick euthyroid syndrome), there may be transient changes in TSH, FT4 and FT3. If possible defer thyroid function testing until this illness has resolved.

Patients on medicines that can affect thyroid function:

- Amiodarone – patients on long-term therapy should have six monthly TSH tests
- Lithium – use TSH once a year to check thyroid function

See Page 28

Request both TSH and FT4:

- During pregnancy
- If there is suspected non-adherence to the thyroid replacement regimen
- When a patient is suspected of having pituitary failure (a low FT4 with an inappropriately normal TSH is usually seen)

Specific groups of people are at higher risk of developing hypothyroidism (Box 2) and some recommend screening these people every one to two years or if there are symptoms or signs of thyroid disease.

Box 2: People who may be at increased risk of hypothyroidism (adapted from Vaidya, 2008)[5]
Those with other autoimmune disease, e.g. type 1 diabetes, Addison's disease, coeliac disease
Those with a genetic condition such as Down or Turner syndromes
Those who have had treatment with radioactive iodine therapy or surgery for hyperthyroidism
Those who have had radiotherapy to the neck for head and neck cancer
Those with a history of postpartum thyroiditis

"Thyroid antibodies" is a non specific term that encompasses the tests for thyroid peroxidase antibodies (TPO-Ab) and the less common anti-thyroglobulin antibodies. TPO antibodies were previously referred to as microsomal antibodies. TPO antibodies are a risk factor for autoimmune thyroid disorders. In subclinical disease, the presence of TPO-Ab increases the long-term risk of progression to clinically significant thyroid disease by approximately two-fold. Almost all people with autoimmune hypothyroidism and up to 80% of those with Graves disease have TPO antibodies, usually at high levels, although they are also found in a small number of people who are euthyroid.[4]

Thyroid dysfunction can be classified as overt or subclinical

Primary hypothyroidism

Overt hypothyroidism affects approximately 1–2% of women and 0.1% of men and is characterised by a TSH concentration above the normal reference range and a FT4 concentration below the reference range.[4, 6]

Untreated overt hypothyroidism can cause fatigue, weight gain, abnormal lipid profile, heart failure, and, in children, can retard growth and mental development.[7] Myxoedema coma is a rare complication of hypothyroidism most often

occurring in elderly people with undiagnosed disease or in patients who are poorly compliant with treatment.[4]

Subclinical hypothyroidism affects women more than men and occurs more frequently with increasing age – up to 10% of women over 60 years of age have elevated TSH levels.[4] It is characterised by a TSH concentration that is increased above the reference range but FT4 concentration within the normal range. Patients with subclinical hypothyroidism may develop overt hypothyroidism.

Hyperthyroidism

Overt hyperthyroidism affects 1.9% of women and 0.16% of men and is characterised by a TSH level lower than the reference range and FT4 and/or FT3 levels above the normal reference range.[8] Complications include Graves' opthalmopathy, thyrotoxic crisis, atrial fibrillation, loss of bone mass and congestive heart failure.[8]

Subclinical hyperthyroidism affects approximately 2% of adults and increases with advancing age with 3% of adults over 80 years of age being affected.[3] It is characterised by TSH lower than the reference range but FT4 and FT3 levels within the normal reference range.

Management of hypothyroidism

The most common cause of hypothyroidism is autoimmune thyroid disease (Hashimoto's thyroiditis and atrophic thyroiditis),[9, 10] although in many parts of the world iodine deficiency remains a major cause of hypothyroidism. Other causes include thyroidectomy, radioiodine ablation, drug induced hypothyroidism and congenital hypothyroidism.[5]

In most cases GPs diagnose and manage hypothyroidism. Replacement treatment with levothyroxine is appropriate for symptomatic patients with TSH above 10 mIU/L. However, the decision to treat may depend on the clinical situation, e.g. a lower threshold to treat in a young woman, particularly if she may become pregnant, than in a very elderly patient. It is good practice to request a second TSH to confirm the diagnosis, as treatment is usually life-long.[5]

Levothyroxine is used to treat hypothyroidism

Levothyroxine is a synthetic form of the natural hormone thyroxine (T4), and is the treatment of choice for hypothyroidism because it reliably relieves symptoms, stabilises thyroid function tests and is safe.[6] The body converts levothyroxine to liothyronine (T3) as necessary. The dose of levothyroxine is dependent on body weight and age. Most adults will achieve euthyroidism with a dose of approximately 1.6 mcg/kg/day.[5, 10] For example, in an adult weighing 60 kg the dose required would be approximately 100 mcg/day and for an adult weighing 80 kg, approximately 125 mcg/day.

Young, otherwise healthy patients can usually start with the expected full dose.[5, 6, 11] Long standing bradycardia due to hypothyroidism can mask substantial asymptomatic coronary artery disease.[5] Treatment with levothyroxine also carries a small risk of inducing cardiac arrhythmias, angina or myocardial infarction.[11] Therefore, for people older than 60 years and those with ischaemic heart disease, it is recommended that low initial doses are used, i.e. start on 12.5 mcg to 25 mcg daily with dose increases of 25 mcg, approximately every six weeks, as guided by TSH results, until euthyroidism is achieved.[5, 11]

Hypothyroid symptoms generally improve within two to three weeks, however, it can take several months before a patient feels back to normal health after biochemical correction of hypothyroidism.[5] Once the target TSH has been reached, a further TSH test in three to four months is often helpful to ensure the TSH is stable. Patients on long-term, stable replacement treatment usually require only an annual TSH, unless pregnant (see Page 31). If for any reason a dose adjustment takes place, TSH testing will be required after approximately six to eight weeks.

There are currently several different brands of levothyroxine funded in New Zealand. The active ingredient, levothyroxine, is the same in all brands but some of the other tablet constituents differ and may affect absorption of levothyroxine. If a patient switches brands, TSH should be repeated six weeks later.

Liothyronine and whole thyroid extract

Liothyronine is a synthetic thyroid hormone which replaces T3. It is not funded on the Pharmaceutical Schedule in New Zealand, however, can be obtained via section 29.* Combined use of liothyronine and levothyroxine is promoted on some websites, however, there is no convincing evidence that such a regimen is better than levothyroxine alone, and it may even be harmful.[12]

Whole thyroid extract is produced from dried thyroid gland from domesticated animals (usually pigs). It contains both T3 and T4. There have been no clinical trials published to determine its effectiveness or safety.[5]

* Section 29 of the Medicines Act 1981 permits the sale or supply to medical practitioners of medicines that have not been approved, and requires the "person" who sells or supplies the medicine to notify the Director-General of Health of that sale or supply in writing, naming the medical practitioner and the patient, describing the medicine and the date and place of sale or supply.

Levothyroxine adverse effects and interactions

Adverse effects with the appropriate use of levothyroxine are rare, however, they may occur when excessive doses are taken.[6] Excessive doses may result in symptoms of hyperthyroidism such as fatigue, arrhythmias, sweating, tremor, heat intolerance, diarrhoea, muscle cramps and muscle weakness. These effects usually resolve with dose reduction or discontinuation.[4]

Calcium, iron, aluminium hydroxide (antacids) and cholestyramine reduce the absorption of levothyroxine, therefore these are best taken at least four hours apart from levothyroxine.[13] For maximum absorption, levothyroxine is best taken on an empty stomach before breakfast,[13] although if the patient forgets, the tablet should still be taken to encourage compliance. Levothyroxine has a long half-life of approximately seven days,[13] so in practice if a tablet is missed the patient will be unlikely to be aware of any noticeable change.[5]

Some anticonvulsants, e.g. phenytoin and carbamazepine, and oestrogen therapy, such as hormone replacement therapy, can increase levothyroxine requirements, therefore TSH should be rechecked six weeks after commencing treatment.[13] There are a number of other medications that may also affect the absorption of levothyroxine. For further information, refer to the medicine datasheet.

Use TSH for monitoring with levothyroxine

TSH is the most appropriate test when monitoring patients receiving levothyroxine for the treatment of hypothyroidism.[6] It should be measured no sooner than six to eight weeks after the start of treatment. If thyroid function needs to be assessed before this time, FT4 should be used, as TSH will not have plateaued at this stage. FT3 has little value in monitoring patients with primary hypothyroidism on replacement treatment as it may be affected by other factors such as illness.

The usual goal of treatment is for TSH to be within the reference range and symptoms to improve. Age and the presence of co-morbidities may guide the target TSH level

and the rate at which it is achieved, e.g. slower attainment of target TSH in elderly people and conversely more rapid in younger people.

Specialist referral may be required for some patients with hypothyroidism

It may be appropriate to refer patients for specialist care in the following circumstances:[4, 5]

- Patients who have TSH levels persistently above the normal reference range despite full doses of levothyroxine being taken. However, first check compliance and drug interactions and consider excluding coeliac disease (which may cause malabsorption) as there is some evidence that these two autoimmune conditions may co-exist.[5]
- Patients whose symptoms do not respond or worsen after treatment with levothyroxine
- Patients who are pregnant or postpartum
- Children aged less than 16 years
- Patients with co-morbidities, e.g. unstable ischaemic heart disease

If secondary hypothyroidism (from pituitary or hypothalamic disease) is suspected, then referral is always indicated.[4]

Treatment of subclinical hypothyroidism

For patients with **TSH less than 10 mIU/L**, treatment with levothyroxine may be considered if symptoms of hypothyroidism develop. Treatment may also be considered in patients with a rising TSH or in those who have goitre. If treatment is initiated then it should be for a sufficient length of time, e.g. three months, to assess whether there is symptomatic benefit.[4, 11] Patients not treated with levothyroxine should be monitored using TSH every 6–12 months or if symptoms develop.[4, 11]

A common cause of subclinical hypothyroidism is autoimmune Hashimoto's thyroiditis and many of these patients subsequently develop overt hypothyroidism

In summary: the use of thyroid function tests for monitoring patients on levothyroxine

Men and non-pregnant women:

- Wait at least six weeks to test TSH after any adjustment of the dose of levothyroxine
- Monitor stable patients annually with TSH only

Women planning pregnancy:

- Check TSH of women with past TSH elevation or positive thyroid antibodies (whether or not on treatment)

Pregnant women:

- Check TSH and FT4 early in pregnancy, four weeks later, four to six weeks after any change in the dose of levothyroxine, and at least once each trimester

Postpartum:

- The levothyroxine dose can be reduced to the usual (pre-pregnancy) maintenance dose postpartum with TSH checked six weeks later

(approximately 5% per year), especially if thyroid antibodies are strongly positive. For patients with strongly positive thyroid antibodies and TSH persistently above 7 mIU/L, levothyroxine therapy is sometimes commenced.

For patients with **TSH persistently greater than 10 mIU/L** (i.e. TSH ≥ 10mIU/L on repeated testing at least three months apart), treatment with levothyroxine should be considered depending on the clinical situation.

Management of hyperthyroidism

Common causes of hyperthyroidism are Graves' disease and toxic nodular goitre. Graves' disease generally appears in people aged 20 to 40 years, whereas the prevalence of toxic nodular goitre increases with age. Thyroiditis is another important cause of hyperthyroidism which commonly occurs in women who are postpartum,[19] as well as in people with viral-type symptoms and neck pain, referred to as "subacute thyroiditis".

Amiodarone and lithium can cause thyroid dysfunction

Amiodarone

Amiodarone can cause thyroid dysfunction (either hyper- or hypothyroidism) in 14–18% of patients due to its high iodine content (75 mg organic iodine per 200 mg tablet)[14] and its direct toxic effect on the thyroid.[15] Although treatment with amiodarone causes an initial rise in TSH because of the effect of the excess iodine, levels return to within the normal range after three months. Amiodarone inhibits the peripheral conversion of T4 to T3 and therefore during treatment FT4 is usually increased and FT3 normal or decreased.[15,16]

Recommendations for monitoring thyroid function in patients on amiodarone vary, but the best marker of amiodarone-induced thyroid dysfunction appears to be TSH. In the majority of laboratories, TSH results that are outside the normal reference range will trigger reflex testing of FT4 and if TSH is low, FT3. TSH testing is therefore recommended at baseline and then six monthly for patients taking amiodarone. Amiodarone has a long half-life so monitoring is required up to 12 months after cessation of treatment.[15]

Clinical monitoring for symptoms and signs of thyroid dysfunction is also required as often amiodarone induced hyperthyroidism can develop rapidly.[16] If new signs of arrhythmia appear, consider hyperthyroidism as the potential cause.[17] Patients with multinodular goitre are at increased risk of developing amiodarone-induced hyperthyroidism.

Pre-existing Hashimoto's thyroditis and/or the presence of TPO antibodies increase the risk of developing hypothyroidism during treatment with amiodarone therefore some experts recommend testing for TPO antibodies before amiodarone is initiated.[16]

 Previous guidance on monitoring amiodarone has recommended that both TSH and FT4 are tested. It is now standard practice to monitor only TSH, as abnormal results will trigger reflex testing.

Lithium

Lithium-associated hypothyroidism is common and can appear abruptly even after long-term treatment. Females and people with positive TPO antibodies are at increased risk of this.[18]

Lithium-associated hyperthyroidism is rare and occurs mainly after long-term use.[18]

It is recommended that for monitoring patients on lithium, TSH and FT4 are tested at baseline, then TSH only at three months and annually thereafter. Patients should also be monitored for signs of thyroid dysfunction and should have thyroid function tests earlier if symptoms develop.

The management of hyperthyroidism depends of the cause and severity of disease, patient's age, goitre size, concurrent medication or co-morbidities and, especially in Graves' disease (where there may be a choice of treatment), patient preference.[9] Anti-thyroid medicines, radioactive iodine and surgery are the main options for treatment of persistent hyperthyroidism. β-blockers, e.g. propranolol, may be used as a treatment adjunct to control symptoms such as tremor and tachycardia.[8,20]

Patients who are systemically unwell or who have severe symptoms and signs of hyperthyroidism, e.g. fever, agitation, heart failure, confusion or coma, may require hospital admission.[8]

Carbimazole is often used for the first episode of Graves' disease

Anti-thyroid drugs, such carbimazole (a thionamide), are normally used for the first episode of Graves' disease. Thionamides, however, are not indicated for thyroiditis where there is no excessive production of thyroid hormones.[19]

Carbimazole decreases thyroid hormone synthesis by interfering with the organification (oxidation and binding) of iodine.[20,21] Treatment with carbimazole may be started in primary care. In patients where the diagnosis is uncertain, referral to an endocrinologist is recommended.

Carbimazole is usually given at a dose of 15 to 40 mg daily until the patient becomes euthyroid, usually after four to eight weeks. The dose is then gradually reduced to a maintenance dose of 5 to 15 mg.[22] A block and replace regimen has been used where high doses of a thionamide are used in combination with levothyroxine. However, there is no clear benefit to this method[19] and it is not suitable in pregnancy.[22]

Prolonged use for 12 to 18 months provides the best chance of sustained remission in Graves' disease.[19] However, relapse occurs in approximately 50% of patients.[9] Relapse is more likely in patients who smoke, who have large goitres or who have suppressed TSH levels at the end of therapy.[19,23]

Monitoring patients on thionamides

It is recommended that thyroid function be monitored every four weeks using FT4 and TSH to adjust the dose until the TSH normalises and clinical symptoms have improved. The patient can then be monitored every two months using TSH only.

N.B. some patients can have T3 toxicosis where monitoring of TSH, FT4 and FT3 is necessary – advice from an endocrinologist is recommended.

Adverse effects of thionamides

Minor adverse effects such as rash, fever and gastrointestinal disturbances occur in up to 5% of patients taking thionamides and can often be treated symptomatically without the need to discontinue treatment. Bone marrow suppression resulting in agranulocytosis is a rare but serious adverse effect of thionamides occurring in 0.1 to 0.5% of patients taking these medicines (see sidebar over page).[20,21]

β-blockers provide rapid relief of adrenergic symptoms

β-blockers, such as propranolol, provide rapid relief of adrenergic symptoms, e.g. tachycardia, tremor, heat intolerance and anxiety. They can be initiated in most patients, as soon as a diagnosis of hyperthyroidism is made, to provide symptomatic relief while waiting for test results. β-blockers can be continued until the patient becomes euthyroid. They are also used to provide symptomatic relief in patients with thyroiditis where thionamides are not appropriate.[9]

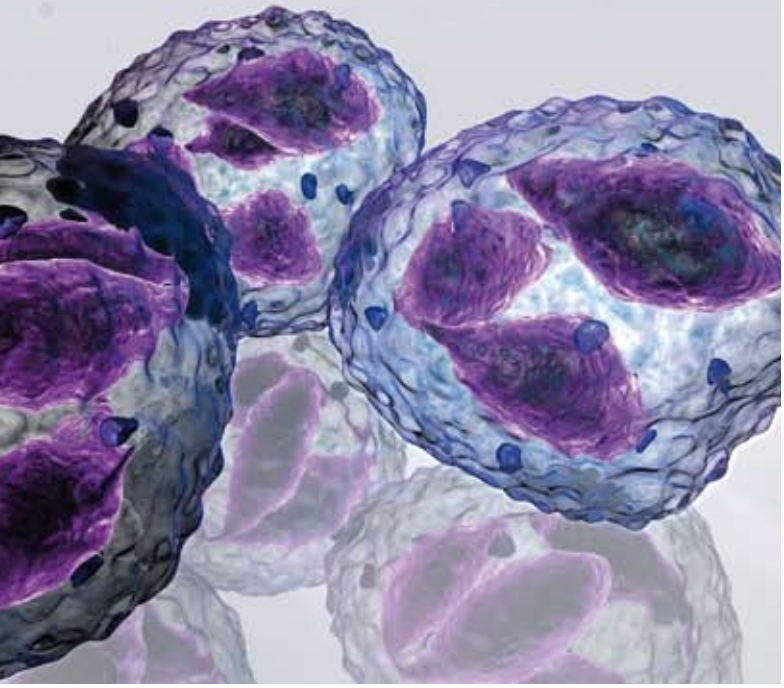
Other treatments – radioactive iodine and surgery

Relapses of hyperthyroidism due to Graves' disease are usually treated with radioactive iodine, or occasionally surgery, as repeat courses of drugs rarely lead to

Risk of agranulocytosis with thionamides

All patients on thionamides should be warned about the rare but serious complication of agranulocytosis. Patients should be instructed to stop their anti-thyroid medication and consult a doctor if fever, sore throat or other infection develops. Patients should have an urgent white blood cell count performed, looking for evidence of neutropenia.[22] Because the onset of agranulocytosis is abrupt, and the occurrence is rare, routine full blood counts are not recommended for patients on thionamides.[9]

Best Practice Tip: When writing a prescription for a thionamide, include instructions for the patient to report fever, sore throat or infection that will be printed on the medication label. Some patient management systems will allow for this information to be stored in "preferred medication prescription instructions" so it does not have to be typed in on an individual basis.



remission.[7] These options may also be an appropriate first choice treatment for toxic nodular goitre because remission is rare when it is treated with anti-thyroid drugs.[9, 19] In some countries, such as the United States, radioactive iodine is used as a first-line treatment for both Graves' disease and toxic multinodular goitre.[20]

Radioactive iodine is an effective treatment with 80–90% of patients becoming euthyroid after a single dose.[19] There is a risk of worsening hyperthyroidism shortly after treatment due to pre-formed thyroid hormone leaking from the damaged thyroid.[19] Patients may be prescribed anti-thyroid medicines that are taken before or shortly after treatment with radioactive iodine in an attempt to prevent this. Although there is a small risk that this may increase treatment failure.[19,24]

The risk of permanent hypothyroidism increases with the dose of radioactive iodine and with time.[9] Most patients will eventually develop hypothyroidism after treatment with radioactive iodine and therefore lifelong annual monitoring of TSH is recommended.[9,19]

Surgery is an appropriate choice for patients with a goitre causing local compression[9] and for selected patients with Graves' thyrotoxicosis, for example in a patient with very large goitre and patients with severe ophthalmopathy (which may be exacerbated by radioiodine).[19,20]

Subclinical hyperthyroidism

Common causes of subclinical hyperthyroidism include excessive levothyroxine replacement, autonomously functioning multi-nodular goitre and subclinical Graves' disease. These patients are at increased risk of developing atrial fibrillation and possibly osteoporosis. Further investigation and treatment should be considered for patients with an undetectable TSH on repeated testing.

Management of thyroid dysfunction in pregnancy

Hypothyroidism in pregnancy

Screening for thyroid dysfunction in women planning pregnancy, and those who are pregnant, is not routinely recommended in New Zealand. However, it is known that subclinical hypothyroidism may be associated with ovulatory dysfunction and infertility. Undetected subclinical hypothyroidism during pregnancy may be associated with adverse outcomes such as hypertension, pre-eclampsia, premature delivery and a risk of cognitive impairment in the infant.[4,25]

Thyroid testing should be considered if there are symptoms of thyroid disease or in women who are at increased risk of hypothyroidism, such as those with type 1 diabetes, a personal or family history of thyroid disease or those with goitre.[4]

TSH may be temporarily suppressed during the first trimester of pregnancy, due to the thyroid stimulating effect of hCG. FT4 levels tend to fall slowly in the second half of pregnancy.

In women with previous mildly elevated TSH who are considering pregnancy, TSH should be checked. If TSH is elevated, thyroid function should be restored to within the reference limit prior to conception if possible.

In hypothyroid pregnant women receiving treatment, the goal should be normalisation of both TSH and FT4. The majority of women receiving levothyroxine need a dose increase during pregnancy, usually during the first trimester. A "pro-active" dose increase of 30% has been recommended once pregnancy is confirmed.[26] This is most easily done by asking the woman to double her maintenance daily dose of levothyroxine on two days each week. Dose requirements stabilise by 20 weeks and then fall back to non-pregnant levels in a short time after delivery. FT4 should be maintained above the 10th percentile of the range (about 11–13 pmol/L) from week six to week 20. There is strong observational evidence that this approach allows optimal foetal neurological development. TSH and FT4 should be checked early in pregnancy then every six to eight weeks during pregnancy and at the start of trimesters two and three. More frequent re-testing is sometimes indicated, e.g. four weeks after adjustment of levothyroxine dose.

Hyperthyroidism in pregnancy

Pregnant women with hyperthyroidism may be at increased risk of foetal loss, pre-eclampsia, heart failure, premature labour and having a low birth-weight infant.[26]

Thionamides are the preferred treatment choice in pregnancy. It is appropriate to use the lowest possible dose needed to control symptoms and achieve euthyroidism. In the last trimester many women can cease their anti-thyroid medication. Aiming for a FT4 in the upper third of the normal reference range for non-pregnant women may minimise the risk of foetal hypothyroidism.[26]

Of the thionamides, propylthiouracil is preferred (but is only available via the Exceptional Circumstances scheme*) as carbimazole has been associated with rare teratogenic effects. Propylthiouracil has rarely been associated with significant liver toxicity and some guidelines recommend changing from propylthiouracil back to carbimazole after the first trimester. A block and replace regimen is not suitable in pregnancy because thionamides cross the placenta in excess of levothyroxine and may result in foetal hypothyroidism and goitre.[26]

Graves' thyrotoxicosis frequently relapses postpartum. Monitoring of TSH at six weeks postpartum and if symptoms recur is appropriate.

Radioactive iodine is contraindicated in pregnancy and for six months pre-conception.[26]

* Propylthiouracil is not listed on the Pharmaceutical Schedule, but can be made available for patients meeting specific criteria, where there is no suitable alternative.

ACKNOWLEDGEMENT Thank you to **Dr Penny Hunt**, Consultant Endocrinologist, Canterbury DHB, Senior Lecturer, Christchurch School of Medicine, University of Otago, Christchurch for expert guidance in developing this article.

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ANTIMICROBIALS Where are we now?

Contributed by **Dr Rosemary Ikram**, Clinical Microbiologist, MedLab South

Two previous articles in this series have outlined the main issues related to antimicrobial resistance within the community in New Zealand (BPJ 30, BPJ 31). This article will review the data we have available now. This enables interventions to be targeted towards issues which are local and current.

Bacterial resistance in the New Zealand community

Surveillance of antimicrobial resistance is currently co-ordinated through the Institute of Environmental Science and Research (ESR) and reports are made available on its website. The following organisms will be discussed in more detail: methicillin resistant *Staphylococcus aureus* (MRSA), extended spectrum β-lactamase producing Enterbacteriaceae (ESBL-E), *Streptococcus pneumoniae* (*S.pneumoniae*), *Neisseria gonorrhoeae* (*N. gonorrhoeae*) and *Haemophilus influenzae* (*H.influenzae*).

MRSA

Initially this organism was detected mainly in hospitals as a result of healthcare associated infection (HA-MRSA). Strains of MRSA more closely associated with community acquisition (CA-MRSA) have now been recognised. An epidemic MRSA (EMRSA) first emerged in New Zealand hospitals in 2000. This strain was imported from the United Kingdom most likely by both patients and staff.

The situation as it was at the end of 2009 is shown in Figure 1 and the distribution of strains among DHBs is shown in Figure 2. EMRSA–15 is a healthcare associated infection, but the other named types (WSPP and AK3 MRSA) are community acquired. This data suggests that the amount of EMRSA-15 is decreasing, however, the number of community strains is increasing. This pattern of change is similar to that experienced in other countries.

ESBL-E

ESBL-E produce a β-lactamase that renders them resistant to all penicillins and cephalosporins. Many of these organisms are resistant to other groups of antimicrobials as well and are classified as multi-drug resistant organisms, i.e. resistant to three or more classes of antimicrobial.

Figure 3 shows the annual/annualised incidence of ESBL-E from 2000 to 2009, demonstrating a rapid increase in isolates since the beginning of the decade. Figure 4 shows the annualised incidence of ESBL-E-producing infections by

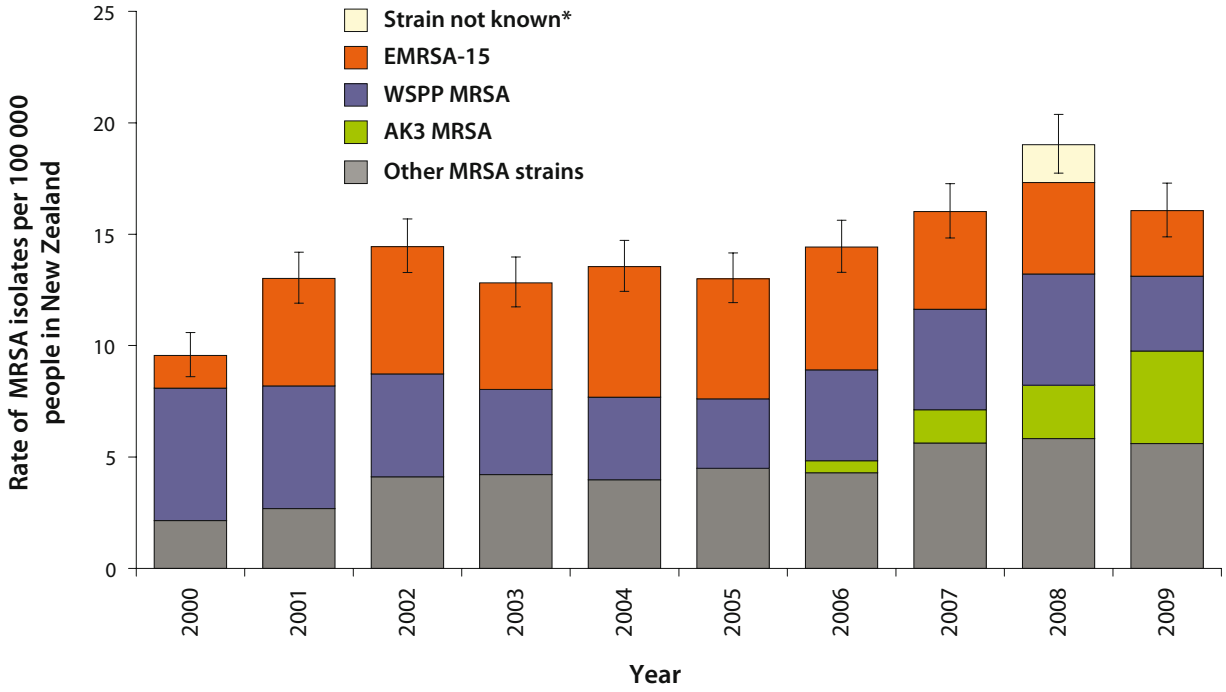

Figure 1: MRSA point-prevalence rates, 2000–2009, showing 95% confidence intervals (ESR data)[1]

*The category "Strain not known" for 2008 represents the number of people identified with MRSA by Middlemore Hospital laboratory which did not refer the isolates to ESR for strain identification.

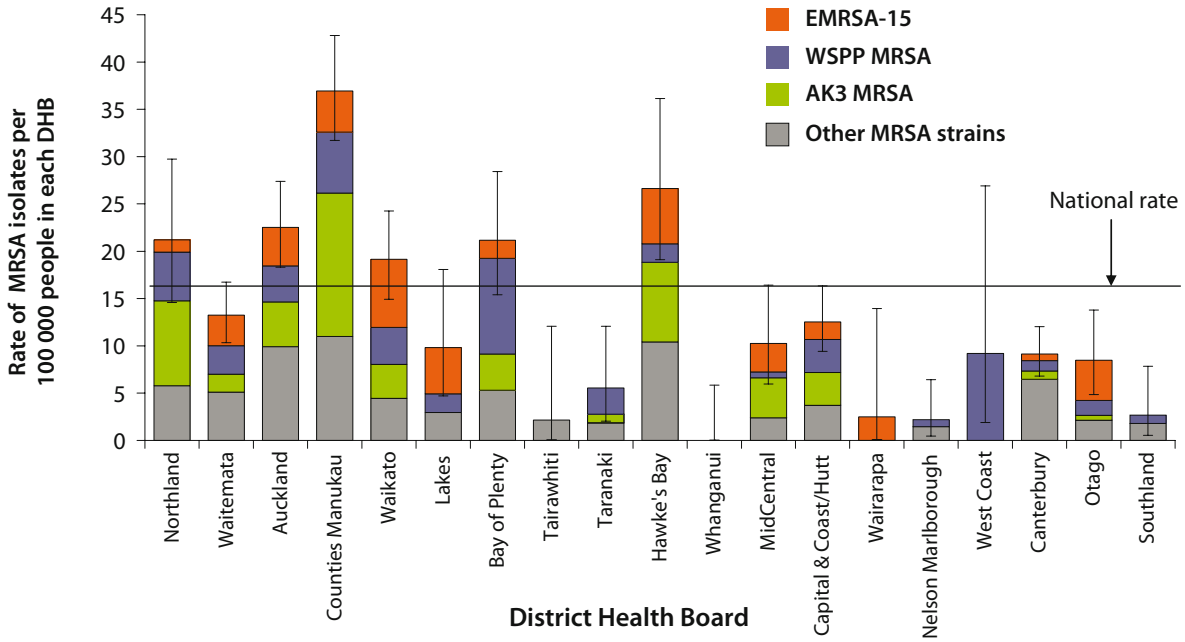

Figure 2: Point-prevalence rates of MRSA by district health board, 2009, showing 95% confidence intervals (ESR data).[1]

N.B Data for the Capital & Coast and Hutt District Health Boards (DHBs) is combined as "Capital & Coast/Hutt", and data for the Canterbury and South Canterbury DHBs is combined as "Canterbury".

DHB in 2009. This distribution shows that more infections are encountered in the North Island compared with the South Island. Community onset was assigned for 36% of these infections.

N.B. In the ESR data, healthcare-associated infection includes samples referred from emergency departments, outpatient clinics or residential care facilities.

Streptococcus pneumoniae

In 2008 a survey of community isolates of *S.pneumoniae* was performed to provide baseline serotype and susceptibility data on community isolates, prior to the addition of the 7-valent conjugate vaccine (PCV-7), Prevenar, to the vaccination schedule. Isolates were collected by two community laboratories - Diagnostic Medlab in Auckland and MedLab South in Christchurch. Overall 17% of isolates were resistant to penicillin and 13.8% were resistant to penicillin and erythromycin. A total of 12.7% were multidrug resistant. The only difference in the prevalence of susceptibility between Auckland and Christchurch was the susceptibility to chloramphenicol which was 4% in Christchurch isolates and 0.7% in Auckland. With the introduction of the PCV-7 vaccination programme, it would be expected that *S.pneumoniae* will be more susceptible because most of the resistant serotypes are present in the vaccine.

Neisseria gonorrhoeae

Regular surveillance reports on the susceptibility of *N.gonorrhoeae* started in 2005. Since that time, ciprofloxacin resistance has increased from 15% to 25% (2008 data). However, there is considerable local variation in susceptibility in smaller centres. For example, in an outbreak of infection in South Canterbury over the December to January period 2009/2010, none of the isolates were susceptible to ciprofloxacin.

The rate of penicillin resistance has remained relatively low although intermediate susceptibility to penicillin rose from 55% in 2005 to 81% in the April to June quarter in 2008. Currently no ceftriaxone resistant isolates have been found.

Haemophilus influenzae

The susceptibility of invasive strains of *H.influenzae* has been monitored since 2000. On an annual basis, relatively

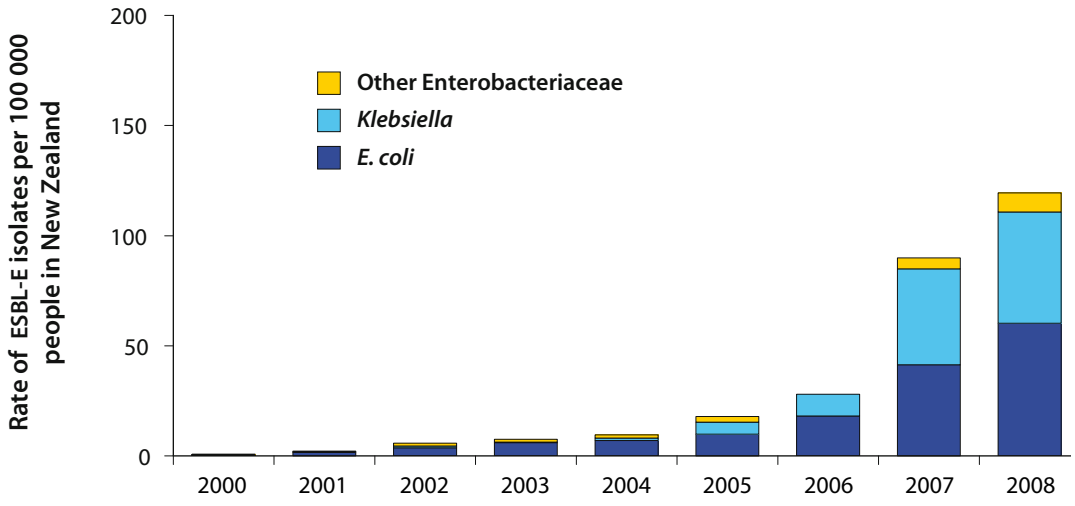

Figure 3: Annual/annualised incidence of ESBL-producing Enterobacteriaceae, 2000-2009 (ESR data).[2]

small numbers of organisms have been tested. The proportion of organisms which were ampicillin resistant by virtue of β lactamase production has varied from about 11% to 34%. Latest data from 2009 showed resistance at 17.2%.

Another type of ampicillin resistance is β-lactamase negative ampicillin resistance (BLNAR). This was uncommon before 2005, but now accounts for approximately half of the ampicillin resistant isolates. In 2008, of the reported non-invasive isolates, 24.7% were ampicillin resistant and 3.7% amoxicillin clavulanate resistant. These latter isolates represent the BLNAR *H.influenzae*, therefore this type of resistance seems to be less common in less invasive organisms.

Antimicrobial use in New Zealand

There is some variability in the number and type of antibiotics dispensed around New Zealand. Figure 5 shows the number of antibiotic prescriptions dispensed per 1000 population, by DHB area (indicated by different colour shading on the map). Bar charts show the percentage of these antibiotics by antimicrobial group. Figure 5 shows less antimicrobial scripts per 1000 population in the South Island compared to the North Island. This mirrors surveillance data from Europe, which shows that in general there is less antimicrobial resistance in areas where less antimicrobials are used.

A portrait of antimicrobial resistance

The surveillance information from ESR, along with patterns of antimicrobial use, highlights the current problem of antimicrobial resistance in New Zealand. This situation has changed, and will continue to change, over time. Infectious organisms are imported to this country and then spread, often in the healthcare setting first, before becoming established in the community. Reducing the use of antimicrobials has been shown to reduce the occurrence of these organisms overseas and this may well be the case in New Zealand too.

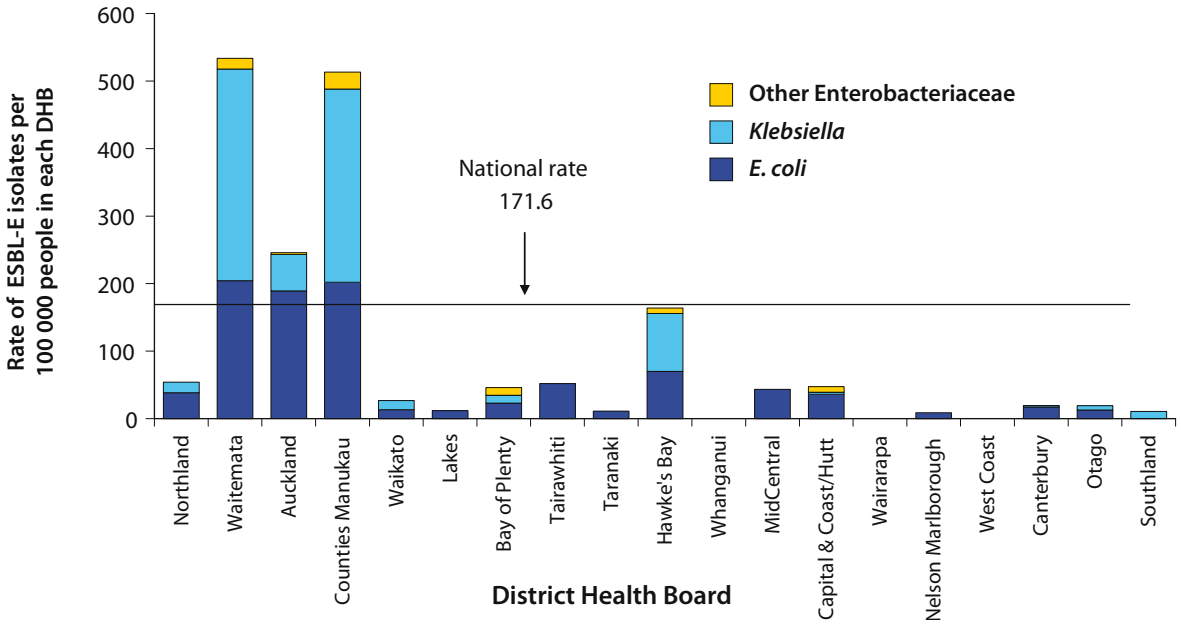

Figure 4: Annualised incidence of ESBL-producing Enterobacteriaceae infections by district health board, 2009 (ESR data).[2]

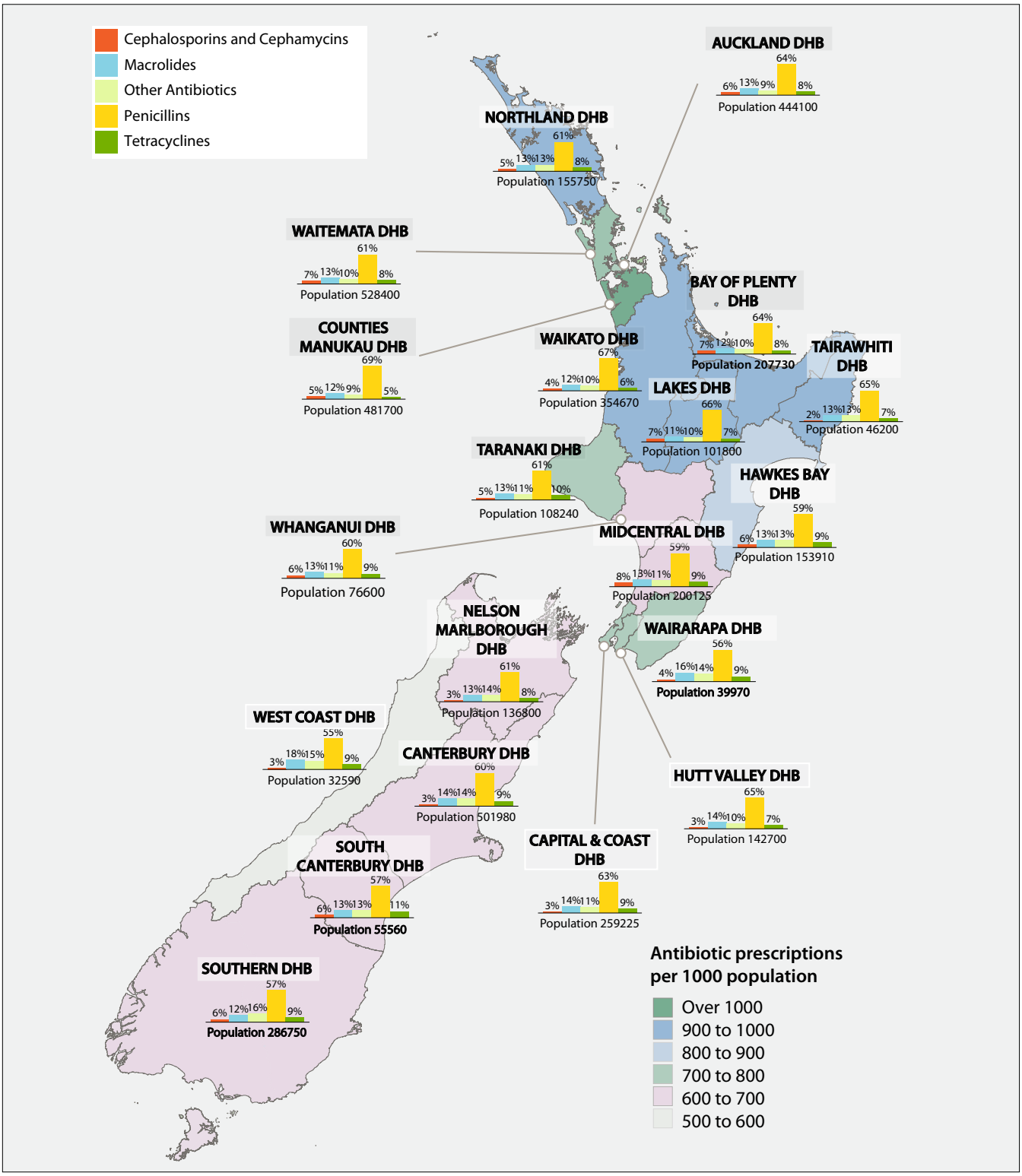

Figure 5: Antibiotic prescriptions dispensed per 1000 population, 2009.

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Update on
SMOKING CESSATION

Supporting the PHO Performance Programme

Key concepts

- The rate of smoking among New Zealanders is slowly reducing, however more work needs to be done to further reduce this number
- Brief advice about quitting smoking from a health professional increases the likelihood that someone who smokes will successfully quit and remain a non-smoker 12 months later
- There is no set manner in which the brief advice to quit needs to be given, although it should be personally relevant to the patient and describe the benefits to be gained from smoking cessation
- The main groups of pharmacological interventions for smoking cessation are nicotine replacement therapy, bupropion, nortriptyline and varenicline

Advice from primary care helps people who smoke to quit

Smoking has been identified as the major cause of preventable death in OECD countries.[1] One of the Ministry of Health targets for 2010/11 is: "Better help for smokers to quit".

The results of the 2009 New Zealand Tobacco Use Survey showed an encouraging reduction in the number of people smoking compared to statistics from previous years. At the time of the survey, 22% of people aged 15–64 years were current cigarette smokers. When results were first collected in 1986, this proportion was 30% (Figure 1). Although this is only an improvement of 8% over more than twenty years, it is estimated that each 1% reduction in the population aged 15–64 years who smoke, represents about 30,000 fewer smokers.[2]

PHO performance programme goals for smoking cessation

The smoking cessation indicators for the PHO Performance Programme (PPP) are:

- % of the enrolled practice population who have had their smoking status recorded
- % of the enrolled practice population whose most recent smoking status is recorded as "current smoker"
- % of current smokers who have been given brief advice in the last 12 months
- % of current smokers who have been given or referred to cessation support services in the last 12 months

The Programme has identified two data sets that will enable collection and analysis of data for these indicators:

1. Recording of smoking status
2. Recording the delivery of brief advice and cessation support

Smoking status and, if relevant, smoking cessation advice should be recorded for each patient in their computerised medical record, using an appropriate code.

Nicotine withdrawal

Nicotine use creates a chemical dependency, therefore tobacco users can usually expect to experience withdrawal symptoms when quitting smoking.

Withdrawal symptoms may include:

- Headache, fatigue, restlessness
- Anxiety, irritability, sleep disturbance, mood swings
- Sweating, dizziness
- Increased appetite,* nausea, stomach cramps
- A craving for more tobacco

* On average, people may expect to gain between four to five kilograms in the first year of abstinence.[4] Patients should be advised to concentrate on achieving and maintaining abstinence from smoking, before managing any weight gain.

Primary care is well placed to help identify smokers and offer smoking cessation advice and referral to smoking cessation services. There is evidence that brief advice about quitting smoking from a doctor increases the likelihood that someone who smokes will successfully quit and remain a non-smoker 12 months later.[3]

Ask, Brief advice, Cessation support

Ask, Brief advice, Cessation support (ABC) has become the standard of care for helping people to quit smoking. The ABC format can be easily integrated into everyday practice of all health care professionals, so that smokers are presented with every opportunity to quit.

A – Ask whether the patient smokes

B – Give brief advice to quit

C – Offer evidence based cessation support

There is no set manner in which the brief advice to quit needs to be given. Most clinicians would agree that the brief advice should be personally relevant to the patient and describe the benefits to be gained from smoking cessation.

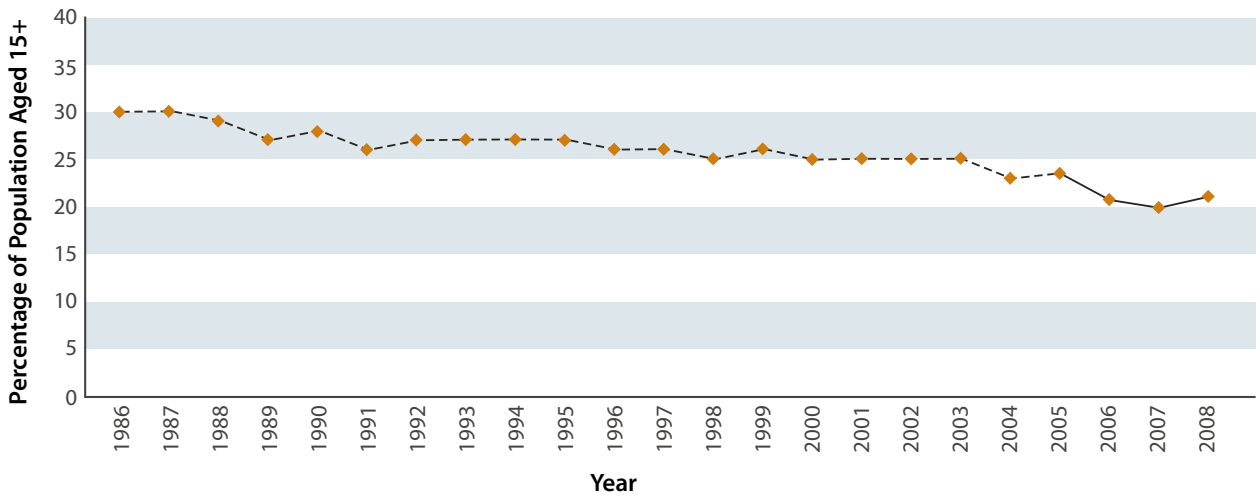


Figure 1: Prevalence of cigarette smoking in New Zealanders aged 15 years and over, 1986–2008 (Adapted from Ministry of Social Development, 2010)[1]

For younger patients it can be helpful to use the incentive that those who quit before the age of 35 years will have a normal life expectancy. For older patients it can be helpful to remind them that quitting increases life expectancy by reducing the risk of diseases such as lung cancer, cardiovascular disease and chronic obstructive pulmonary disease.[5]

Pharmacological interventions to aid smoking cessation

Many people who want to quit smoking will try to do so without any assistance, however, for most smokers quitting is a difficult process. Smoking cessation advice includes encouragement to quit as well as information about the different pharmacological treatments available to help.

The main groups of pharmacological interventions available include:

- Nicotine replacement therapy
- Nortriptyline
- Bupropion (Zyban)
- Varenicline (Champix)

Nicotine replacement therapy

To get the most out of NRT:

1. Explain what results may be achieved with NRT
2. Reassure that NRT is safe
3. Use enough NRT
4. Use NRT for a long enough time
5. Use NRT in a way that best suits the needs of the individual patient

Nicotine replacement therapy (NRT) is safe and cost effective. It can help people quit smoking by reducing the cravings that are linked with nicotine withdrawal and reduce relapse. It doubles the chances of long-term abstinence regardless of the amount of additional support provided. Despite this, initiation of NRT remains low and even when

"Ask about the elephant" smoking cessation e-learning tool

The "Ask about the elephant" programme uses the elephant metaphor to represent that smoking is something that should not be ignored or go unaddressed.

The tool:

- Provides practical information about ABC and nicotine replacement therapy
- Is endorsed by RNZCGP, awarding CME points
- Allows health professionals to print a certificate as evidence of professional development
- Allows non-prescribing health professionals to register as a Quit Card provider
- Takes 20 – 40 minutes to complete

It can be completed online at:
www.smokingcessationabc.org.nz

it is prescribed, insufficient duration of treatment and insufficient dosages are common. Poor utilisation rates may result from commonly held misperceptions about the safety and efficacy of nicotine and NRT. Correct usage is more likely when smokers' knowledge about the role of nicotine and the safety and efficacy of NRT is more accurate.[6]

From September 2009 NRT became available fully funded on prescription (in addition to the Quit card scheme). Different forms of NRT products are considered equally effective.[4]

The NRT products currently available in New Zealand are:

- Patches (7 mg*, 14 mg*, 21 mg* per 24 hours and 5 mg, 10 mg, 15 mg per 16 hours)
- Lozenges (1 mg*, 2 mg*)
- Gum (2 mg*, 4 mg*)
- NRT inhaler
- NRT nasal spray
- NRT sublingual tablets (2 mg)

*currently subsidised

Practice points for NRT use[4]

- There is a moderate advantage to using a combination of NRT products over just a single product. There are no safety concerns with combining NRT products.
- NRT should be used for 8 to 12 weeks, but a small number of smokers may need to use it for longer (5% may continue to use it for up to a year). There are no safety concerns with long-term NRT use.
- NRT is safe to use repeatedly with other attempts to stop smoking by people who have tried to stop but have not succeeded in the past.
- NRT can be used for "cutting down", to encourage reduction in cigarettes prior to quitting. Therefore it is safe to continue smoking while being treated with NRT, initially.
- International evidence shows that NRT is mainly effective in people who smoke ten or more cigarettes per day. However, it is the person's degree of dependency (anticipated difficulty in stopping smoking based on their degree of nicotine dependence, e.g. smoking within thirty minutes of waking) rather than the number of cigarettes they smoke that should be used to determine whether NRT is likely to be helpful.
- Contrary to product information, the New Zealand Smoking Cessation Guidelines state that it is appropriate for pregnant women to use NRT.[4] The use of NRT in pregnancy carries a small potential risk to the foetus, but NRT is safer than smoking. Intermittent NRT, e.g. gum or lozenges, should be used in preference to patches. Where the use of a patch is judged appropriate, the 16-hour patch is preferable.
- Some product information advises patients to wean off NRT patches, however there is no evidence that this is necessary. People can stop from a full-strength patch straight away, although some people may prefer to slowly reduce their dose.[6]
- There is insufficient evidence that the use of NRT by young people who smoke improves continuous six-month abstinence rates. However, expert opinion is that NRT may be used safely by young people (12–18 year of age) who are dependent on nicotine. N.B. NRT is not recommended for use in young people who occasionally smoke, such as those who smoke in social situations only.
- NRT can be safely used by people with cardiovascular disease, however, where people have suffered a serious cardiovascular event, e.g. myocardial infarction or stroke, in the past two weeks or have a poorly controlled disease, treatment should be discussed with a specialist. Oral NRT products are recommended, rather than longer-acting patches, for such patients.

NRT patches

Most smokers should start on a full-strength patch (21 mg), with the lower dose patches used for weaning-off (although this is not always necessary). Use of full-strength doses of both 16- and 24-hour patches, for at least eight weeks, have been found to be more effective than lower strength preparations for people who smoke more than 10 cigarettes per day.[4]

Patients should be advised to use a new site each day to apply the patch. Some common problems with the patches include skin reactions, patches falling off, headache or dizziness and sleeping disturbances such as vivid dreams or insomnia.[6]

NRT gum

To increase compliance with using NRT gum, it is important to carefully explain its use. NRT gum should not be referred to as chewing gum. The gum should be slowly chewed to release the nicotine, resulting in a hot peppery taste. The gum should then be parked between the cheek and gums so that the nicotine can be absorbed. After a few minutes, the gum can be chewed again and then parked (usually in a different area) and the process repeated for 20–30 minutes (although the gum can be chewed longer than this if desired). NRT gum takes approximately 20 minutes to reach peak concentration. Ten to 15 pieces of gum per day can be used, hourly if needed. Use is recommended for eight weeks.

Adverse effects reported with the use of the nicotine gum include sore throat, ears and jaw from chewing.[6] It is a good idea to prepare patients for the fact that oral NRT products may be unpleasant initially but will become more tolerable overtime.

NRT gum is available in 2 mg and 4 mg strengths. In practice, it is usually more effective to use the higher dose. Gum may also be used in combination with NRT patches.

N.B: Incorrect use, e.g, chewing NRT gum too vigorously, usually results in more nicotine being swallowed, which may cause irritation to the throat and mouth and hiccoughs.

NRT lozenges

NRT lozenges are sucked and slowly dissolved in the mouth. Nicotine reaches peak plasma concentration in approximately 20–30 minutes. Twelve to 15 lozenges can be used per day, as required.

NRT lozenges are available in 1 mg and 2 mg strengths. As with NRT gum, the higher dose would usually be prescribed. Lozenges can be used in combination with NRT patches.

NRT inhaler, nasal spray and microtabs

N.B. These products are not currently subsidised.

The NRT inhaler may be used for up to 10–20 minutes every hour. Ten puffs is equivalent to one puff from a cigarette. Each inhaler cartridge is equivalent to four cigarettes. Patients should aim to use six cartridges per day, although they may use less than this if their cigarette use prior to quitting was at a lower level. In cold weather, it is advisable to keep the inhaler warm to help the nicotine vapour be released from the cartridge.

The NRT nasal spray can be used up to hourly, with one spray per nostril.

Microtabs are placed under the tongue and slowly dissolve over approximately 30 minutes. It takes approximately 20 minutes for the nicotine to reach peak concentration. Hourly use is recommended to achieve the best effect, but the tablets can be used more frequently if desired. Up to 40 microtabs can be used per day.

See “Getting the most out of nicotine replacement therapy” BPJ 20 (Apr, 2009) for further information about prescribing NRT.

Bupropion

Bupropion is a dopamine-noradrenaline reuptake inhibitor which became available, fully subsidised, on the Pharmaceutical Schedule in July 2009. It approximately doubles the chances of long-term abstinence from smoking.[4]

Seizure risk with bupropion

The recommended dose of bupropion must not be exceeded, as it is associated with a dose-related risk of seizure. The incidence of seizure at doses up to 300 mg/day is approximately 0.1% (1 in 1000).

A maximum dose of 150 mg daily should be considered for the duration of treatment in patients with pre-disposing risk factors to a possible lowered seizure threshold, including:[7]

- Concomitant administration of other medicines known to lower the seizure threshold, e.g. antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic steroids, quinolones and sedating antihistamines
- Excessive use of alcohol or sedatives (also see contraindications)
- History of head trauma
- Diabetes treated with hypoglycaemics or insulin (If the diabetes is poorly controlled use NRT instead)
- Use of stimulants or anorectic products

Bupropion dosing

A quit date should be set for one to two weeks after commencing bupropion. The patient may smoke as normal up to their quit date and then should stop completely on this date.

- Days 1, 2 and 3: one tablet (150 mg) daily
- Day 4 onwards: one tablet (150 mg) twice a day, with at least eight hours between each dose
- A maximum daily dose of 150 mg is recommended for older people, people with renal or hepatic dysfunction and people with lowered seizure threshold (see sidebar)

A total course of 120 tablets can be prescribed, but it may be sensible to prescribe a smaller quantity initially so there is no wastage if the person experiences adverse events or does not manage to achieve abstinence. Patients should be treated for at least seven weeks but discontinuation should be considered earlier if the patient has not made significant progress towards abstinence by the seventh week of therapy, since it is unlikely that they will stop smoking during that attempt.[8]

Contraindications to bupropion use include: seizure disorders (or history of), CNS tumour, abrupt alcohol or sedative withdrawal, bulimia, anorexia nervosa (or history of), monoamine oxidase inhibitors use within 14 days, lactation.

Insomnia is a very common adverse effect associated with bupropion. Insomnia may be reduced by avoiding dosing at bedtime (provided there is at least eight hours between doses if an earlier dose is used) or, if clinically indicated, dose reduction.[8]

Practice points for bupropion use[4,8]

- There is insufficient evidence to recommend combining bupropion with any other smoking cessation medications
- Bupropion is considered safe and effective for use in people with stable cardiovascular disease

- Bupropion should be used with extreme caution in patients with severe hepatic cirrhosis – the dose should not exceed 150 mg on alternate days
- There is insufficient evidence to recommend the use of bupropion to women who are pregnant or breastfeeding, who smoke
- There is insufficient evidence to recommend the use of bupropion to young people aged under 18 years who smoke
- There is insufficient evidence to recommend the use of bupropion in preventing smoking relapse, i.e. long-term use is not recommended

Nortriptyline

Nortriptyline is a tricyclic antidepressant that has been shown to be as effective as bupropion and NRT in aiding smoking cessation.[4] However, adverse effects associated with nortriptyline may not be well tolerated in some patients, e.g. anticholinergic effects (dry mouth, blurred vision) and sedation/drowsiness. The action of nortriptyline in helping people to stop smoking is independent of its antidepressant effects, therefore it is not restricted to people with a history of depressive symptoms during smoking cessation.

Nortriptyline dosing

Nortripyline should be commenced while the patient is smoking, with a quit date set for ten to 28 days later. The initial dose is 25 mg/day, increased gradually to 75–100 mg/day over ten days to five weeks. The maximum dose can be continued for eight to 12 weeks and tapered down at the end to avoid withdrawal symptoms that may occur if it is stopped abruptly. There is limited evidence of any benefit of extending treatment past three months.

Practice points for nortriptyline use [4]

- There is insufficient evidence to recommend combining norptriptyline with any other smoking cessation medication
- People with cardiovascular disease should use nortriptyline with caution, as cardiac conductivity can be affected. Tricyclic antidepressants are contraindicated in the immediate recovery period after myocardial infarction (MI) and in arrthymias (particularly heart block).
- There is insufficient evidence to recommend the use of nortriptyline by pregnant women or young people aged under 18 years who smoke
- There is insufficient evidence to recommend using nortriptyline to prevent smoking relapse, i.e. long-term use is not recommended

Varenicline

Varenicline is now funded with Special Authority, with the following criteria:

- The patient has not used varenicline in the past 12 months AND:
- The patient has had two or more unsuccessful quit attempts using NRT, at least one of which involved comprehensive advice about the use of NRT

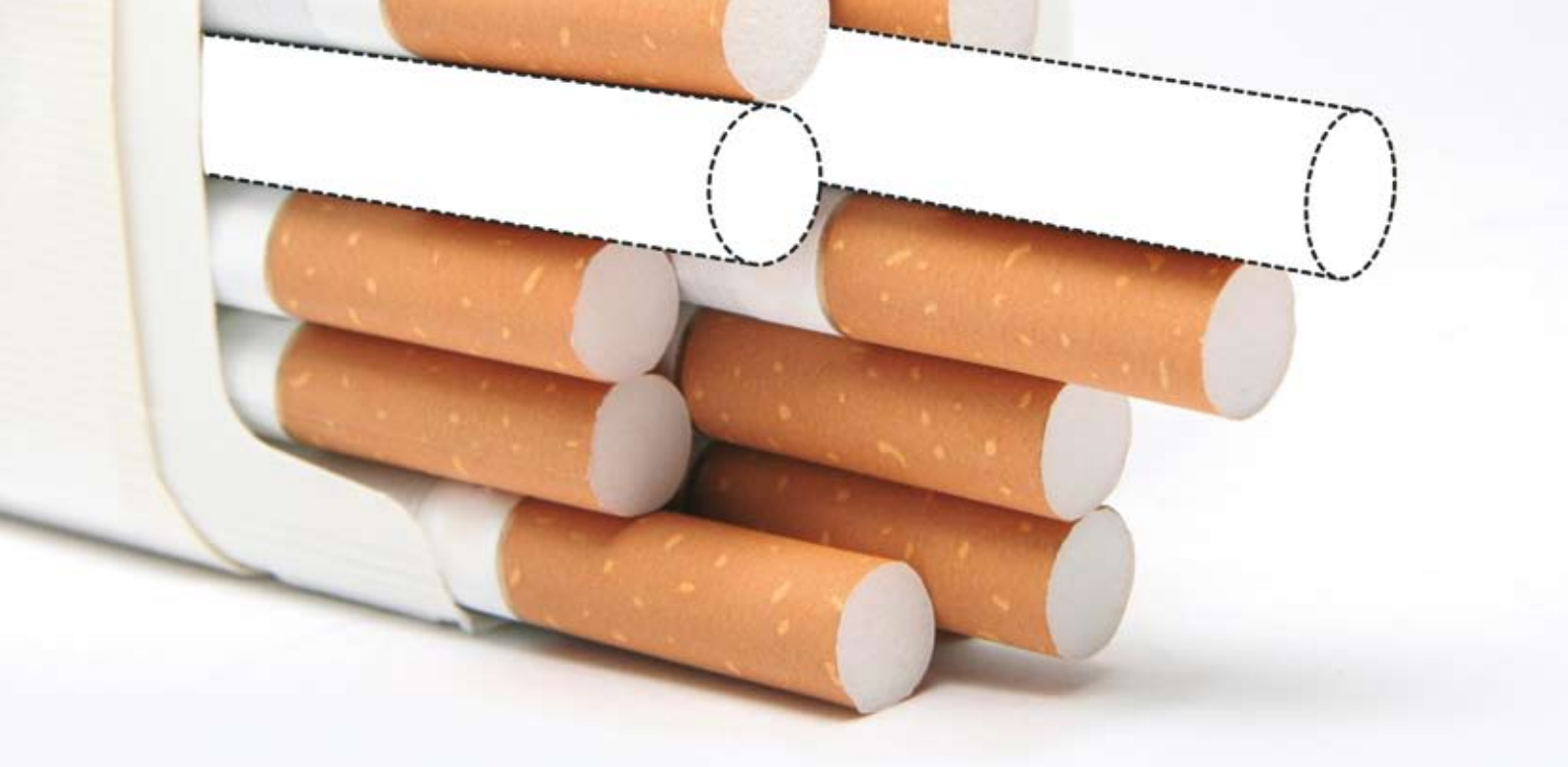
OR

- The patient has had an unsuccessful quit attempt using bupropion or nortripyline

Special Authority is also subject to the patient enrolling in a support and counselling programme for smoking cessation, including monitoring.

Unsubsidised use of varenicline for a 12-week course costs approximately $700.

Varenicline (Champix) works by binding to nicotine receptors in the brain to reduce the severity of tobacco withdrawal symptoms, while simultaneously reducing the rewarding effects of nicotine. It approximately doubles to triples the chances of long-term abstinence (up to 12 months).[4]



The most commonly reported adverse event is nausea (experienced by approximately 30% of people). In the majority of cases, nausea occurs early in the treatment period, is mild to moderate in severity, lessens over time and seldom results in discontinuation of the medication. Varenicline can also cause temporary sleep disturbance and constipation.[4]

Varenicline has been associated with adverse psychiatric effects. Patients and their families should be advised to monitor for neuropsychiatric symptoms including changes in behaviour or thinking, anxiety, psychosis, mood swings, agitation, aggression, depressed mood, suicidal ideation and suicidal behaviour or worsening of pre-existing psychiatric illness. If any of these symptoms occur, varenicline should be ceased immediately.[8]

The safety and efficacy of varenicline in people with serious psychiatric illness such as schizophrenia, bipolar disorder and major depressive disorder has not been established.[8]

Varenicline dosing

Varenicline is commenced while the patient is still smoking, with a quit date set for one to two weeks later.

- Days 1–3: 0.5 mg, once daily
- Days 4–7: 0.5 mg, twice daily
- Day 8 to end of treatment (12 weeks): 1 mg, twice daily

Patients who cannot tolerate the adverse effects of varenicline may have the dose lowered temporarily or permanently to 0.5 mg, twice daily.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline at 1 mg twice daily may be considered. N.B. this additional treatment would not be funded (unless 12 months had elapsed since starting the first 12-week course).

Practice points for varenicline use

- There is insufficient evidence to recommend combining varenicline with any other smoking cessation medication
- Varenicline is contraindicated in young people aged under 18 years and in women who are pregnant or breastfeeding
- Dose adjustment is not required for older people or people with mild to moderate renal or hepatic impairment. In people with severe renal impairment, the dose can be reduced to a maximum of 1 mg daily.
- Varenicline has no known clinically meaningful drug interactions

Further reading: Best Practice Journal, available from: **www.bpac.org.nz** keyword: smoking cessation

Patient resources:
Quitline: Ph: 0800 778 778 Website: **www.quit.org.nz**

Aukati Kai Paipa: Ph: (09) 638 5800 Website: **www.tehotumanawa.org.nz**

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Risk of hyponatraemia with antidepressants

Dear bpac,

I note on reading the article "Pharmacological management of depression in adults" (BPJ Special Edition, July 2009), that there is no mention of hyponatraemia. It is of enough concern in those over 65, or those medically ill, to warrant routine electrolytes after a week or two of treatment on SSRIs, venlafaxine and TCAs.

Dr Peter Miller, Psychiatrist
Christchurch

There has been increasing awareness of the risk of hyponatraemia after starting antidepressants.[1] Many guidelines in primary and secondary care are now being updated to include monitoring advice.

Risk factors for antidepressant-induced hyponatraemia include older age, low body weight, female gender, previous history of hyponatraemia, reduced renal function and concurrent intake of other hyponatraemic medicines, such as diuretics. Most reports have been linked to SSRIs but hyponatraemia can occur with any antidepressant including TCAs and newer agents such as venlafaxine and mirtazapine.

Hyponatraemia due to antidepressants or thiazide diuretics usually occurs in the first four weeks of treatment. All patients taking antidepressants should be observed for signs of hyponatraemia (dizziness, nausea, lethargy, confusion cramps and seizures). Monitoring recommendations vary slightly but a general consensus (especially for high risk patients) is as follows:

- Check baseline sodium level before starting the antidepressant
- Check sodium after two weeks, four weeks and again after three months
- Consider checking sodium after a dose increase of the antidepressant or addition of any other hyponatraemic medicine, e.g. a diuretic
- If possible, avoid the combination of a diuretic and an antidepressant (particularly an SSRI) in people already at higher risk of hyponatraemia. Close monitoring is especially important in such patients.

Prescribers should also be aware of other factors that may exacerbate or promote hyponatraemia in a person already taking an antidepressant and/or a diuretic. For example, fluid replacement (during acute gastrointestinal disturbance) with plain water instead of electrolyte solution may acutely aggravate hyponatraemia to dangerous levels.[2]

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Medicine-induced dystonic reactions

Dear bpac

I recently came across two situations where practical information and guidance was rather sparse:

1. *A patient with a known dystonic reaction to metoclopramide required an alternative option for sea sickness - we are trying cyclizine*

2. *A patient developed trismus, most likely due to citalopram and also got very jittery on a tiny dose of quetiapine - all resolved nicely with a small dose of a benzodiazepine*

Often people who experience a dystonic reaction to one medicine need an alternative, e.g. for travel sickness,

and are very scared about having another reaction. Can you offer any guidance on these issues and the treatment of drug-induced dystonias in general?

Dr Margaret Goodey, GP
Auckland

Dystonic reactions are relatively common, occurring in approximately 1% of people receiving metoclopramide or prochlorperazine[1] and in up to one-third of people with acute psychosis who are treated with a typical antipsychotic, such as haloperidol or chlorpromazine. Children, young adults and elderly people seem to be at increased risk. A family history of dystonia and recent alcohol or cocaine use also appear to be risk factors.[2]

Most medicine-induced dystonias are caused by oral or injectable antiemetics or antipsychotics with dopamine blocking activity. A number of other medicines have also been implicated including antidepressants, antihistamines and calcium channel blockers. The mechanism is not always clear and some medicines used to treat dystonic reactions, e.g. antihistamines, have also been reported to cause reactions.

Examples of medicines that can cause dystonic reactions:[1]

- Antiemetics or antipsychotics with dopamine blocking activity, e.g.metoclopramide, prochloperazine, chlorpromazine, haloperidol
- Antihistamines, e.g. promethazine,cyclizine
- Antidepressants – especially SSRIs
- H2 antagonists
- Calcium channel blockers – rare but reported with most medicines in this class

N.B. Although atypical antipsychotics are less commonly associated with dystonic reactions, such reactions still sometimes occur, especially when higher doses are used.

Clinical presentation

Dystonic reactions usually appear soon after the causative medicine is initiated. Approximately 50% of reactions occur within 48 hours and 90% within five days of initiation. Reactions can also occur within minutes of taking a single dose or when the dose is increased. They are characterised by intermittent or sustained involuntary contractions of the muscles in the face, neck, trunk, pelvis or limbs.[2] The typical manifestations can occur alone or in combination. Dystonic reactions are not usually life threatening but can be very distressing for patients and carers. Treatment is usually effective within minutes without long-term consequences.

Manifestations of acute dystonia:[1]

Oculogyric crisis	Spasm of the extraorbital muscles, causing upwards and outwards deviation of the eyes Blepharospasm (twitching of eyelid)
Torticollis	Head held turned on one side
Opisthotonus	Painful forced extension of the neck. When severe the back is involved and the patient arches.
Macroglossia	Tongue does not swell, but protrudes and feels swollen
Buccolingual crisis	May be accompanied by trismus, risus sardonicus (spasm of facial muscles causing grinning appearance), dysarthria and grimacing
Laryngospasm	Uncommon but life-threatening
Spasticity	Trunk muscles and limbs can be affected

Differential diagnosis

The presenting features and a recent history of medicine intake usually give a reliable key to diagnosis. Differential

diagnoses include; tetanus, strychnine poisoning, primary neurological causes such as Wilson's Disease, hypocalcaemia and hypomagnesaemia.[1]

Treatment

The underlying mechanism for most dystonic reactions is thought to involve an imbalance between centrally available dopamine and acetylcholine. Medicines that block dopamine receptors produce a relative excess of acetylcholine which leads to the extrapyramidal-like symptoms. Medicines with anticholinergic properties are effective in controlling most reactions.

The recommended first choice treatment is an injectable anticholinergic agent such as benztropine. However, benztropine is unlikely to be carried or immediately available to most GPs. Promethazine (an antihistamine with anticholinergic properties) or diazepam are suitable alternatives.[1]

Benztropine
1- 2 mg by slow IV injection

Promethazine
25 – 50 mg IV or IM

Diazepam
5 – 10 mg IV

Oral benztropine (1–2 mg daily) can be continued for two to three days after the initial reaction.

There is very little information on cross reactions between medicines that cause dystonic reactions. The precipitating medicine should be avoided in the future and if required, careful use of a medicine from a different class is recommended. For example, if the reaction was caused by metoclopramide, an antihistamine with antiemetic properties, e.g. promethazine or cyclizine, can be tried. If a reaction occurs with an antidepressant such as citalopram, the same principle applies, that is, a careful trial of an antidepressant from a different therapeutic class such as a tricyclic antidepressant.

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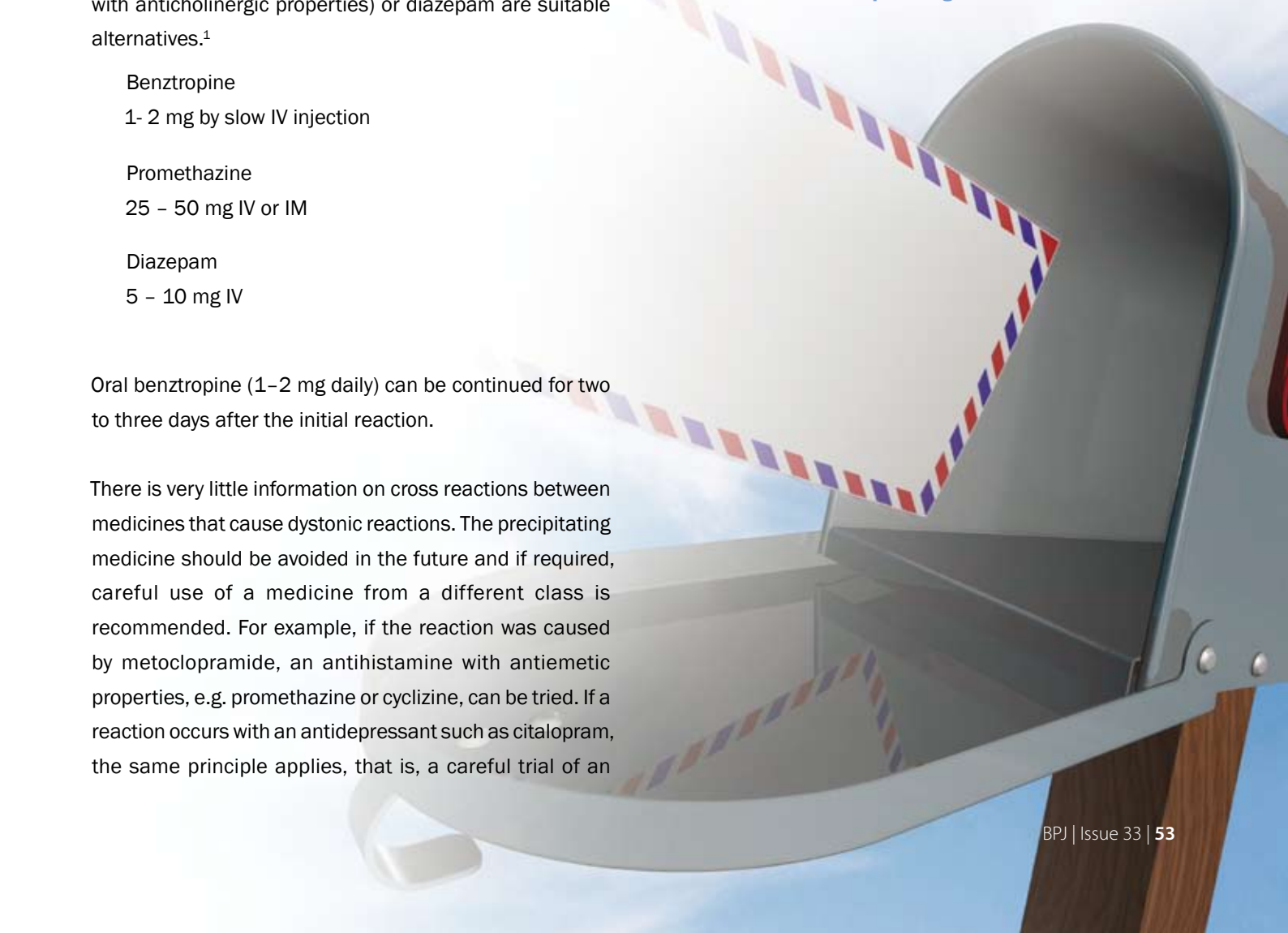

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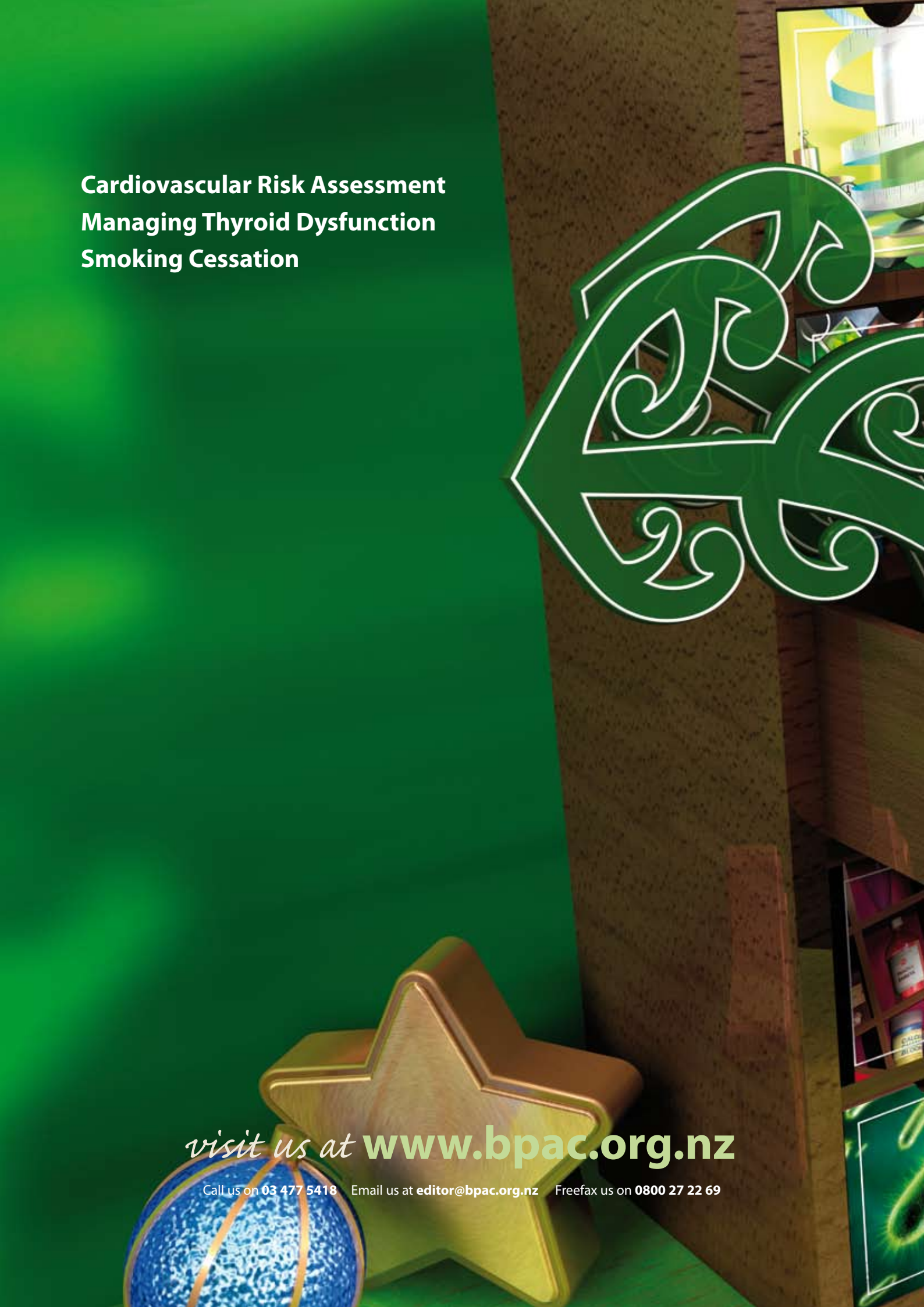

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