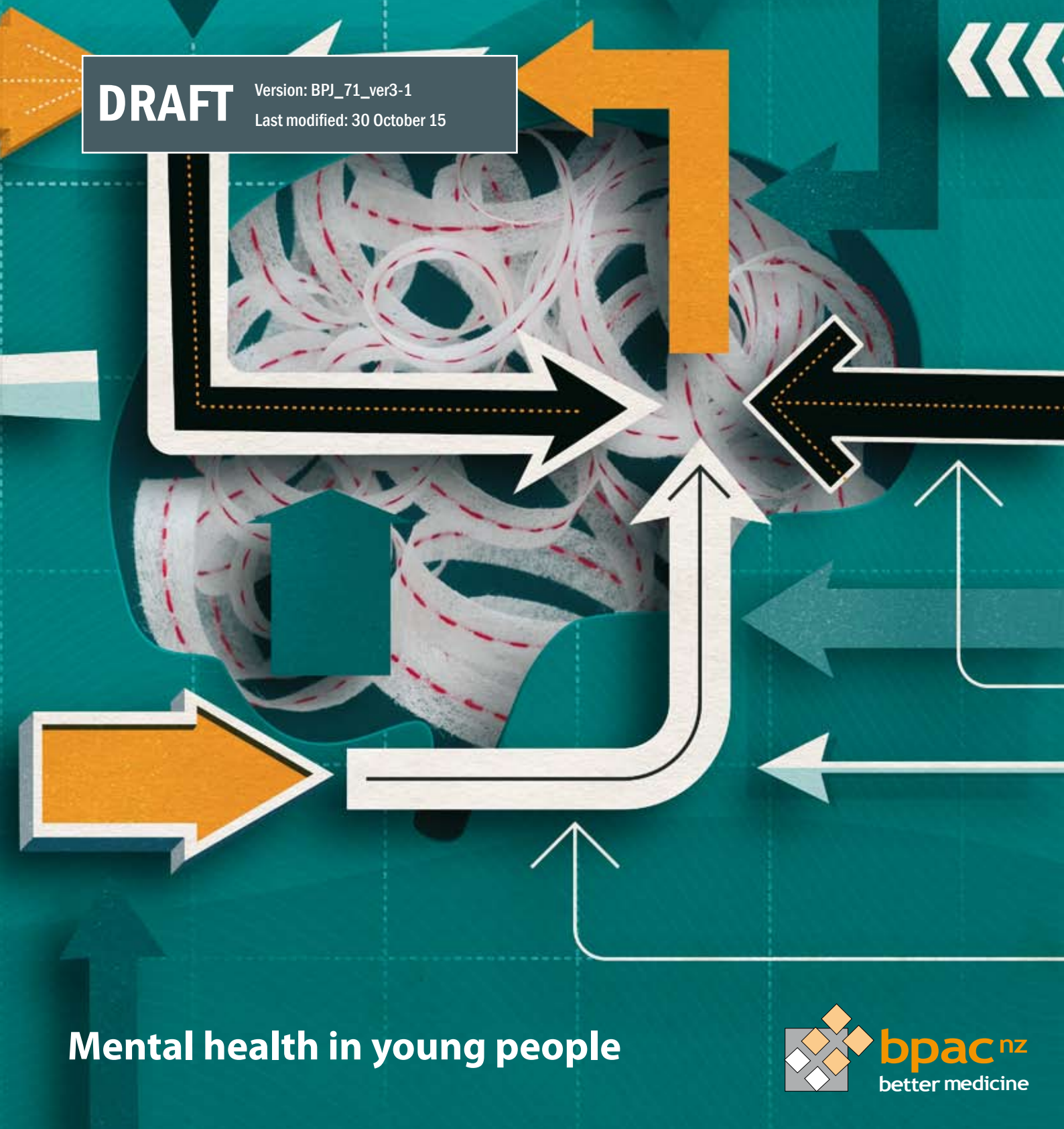
BIOSIMILARS | SMOKING CESSATION | SAFETY WITH CHEMOTHERAPY | HPV UPDATE

Best Practice

www.bpac.org.nz

Issue 71 October 2015

DRAFT Version: BPJ_71_ver3-1
Last modified: 30 October 15



Mental health in young people

bpac nz
better medicine

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

Dr Sue Bagshaw, Christchurch
Dr Alexander Bolotovski, Wellington
Dr Brent Caldwell, Wellington
Dr Theresa Fleming, Auckland
Dr Rebecca Grainger, Wellington
Associate Professor Mark Thomas, Auckland
Rebecca Zonneveld, Wellington

CONTACT US:
Mail: P.O. Box 6032, Dunedin
Email: contact@bpac.org.nz
Phone: 03 477 5418
Free-fax: 0800 27 22 69
www.bpac.org.nz

Best Practice

Issue 71 October 2015

Best Practice Journal (BPJ)
ISSN 1177-5645 (Print)
ISSN 2253-1947 (Online)

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

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

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

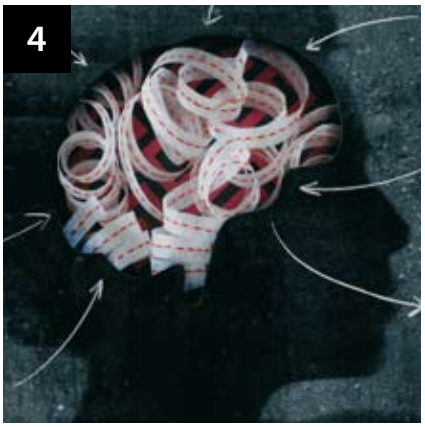
Bpac^{nz} Ltd is currently funded through a contract with PHARMAC.

Bpac^{nz} Ltd has six shareholders: Procare Health, South Link Health, General Practice NZ, the University of Otago, Pegasus and The Royal New Zealand College of General Practitioners

Printed in New Zealand on paper sourced from well-managed sustainable forests using mineral oil free, soy-based vegetable inks

CONTENTS

Issue 71 October 2015



Issue 71 October 2015

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

www.bpac.org.nz

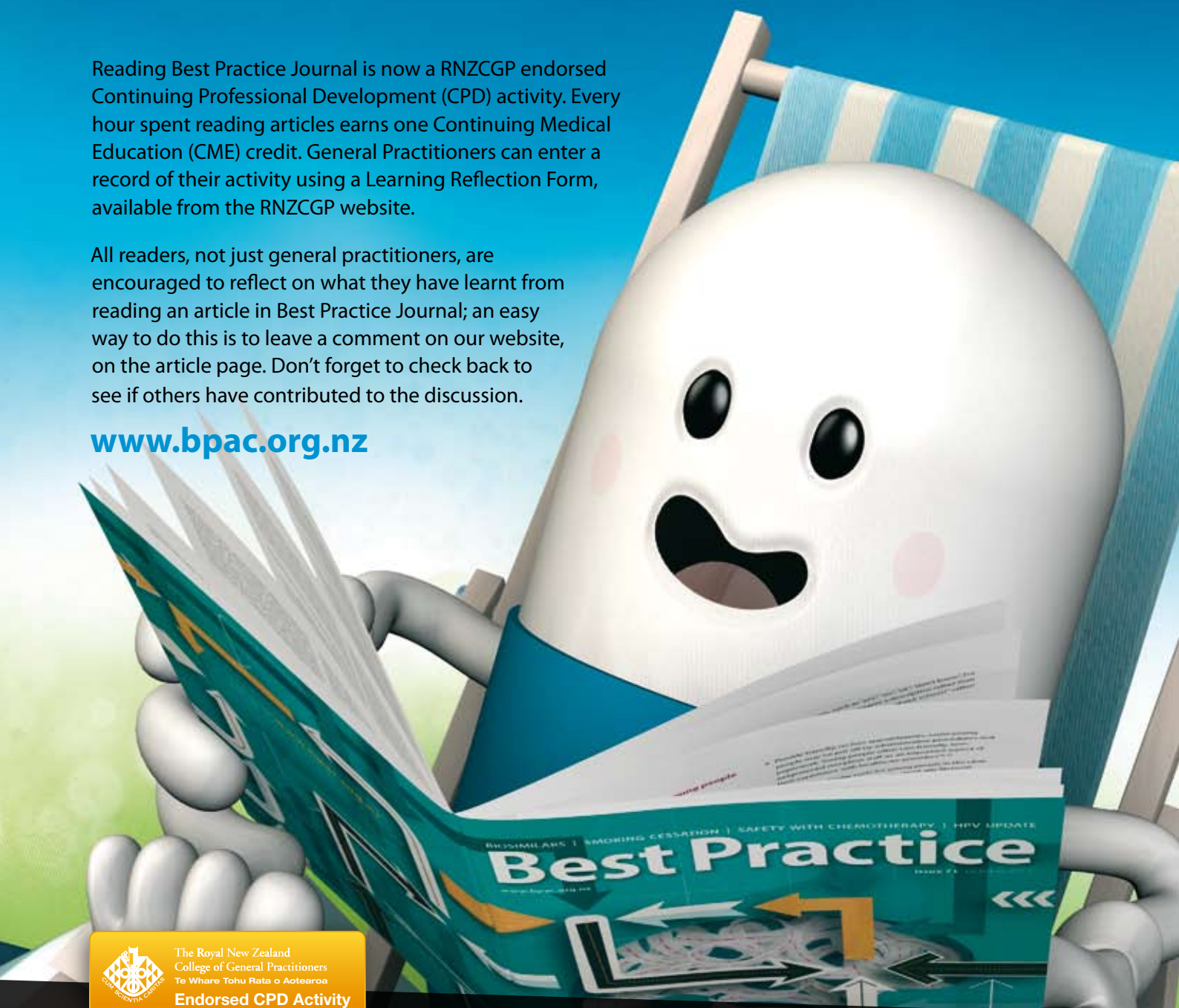
facebook.com/bpacnz

Reading Best Practice Journal just got better!

Reading Best Practice Journal is now a RNZCGP endorsed Continuing Professional Development (CPD) activity. Every hour spent reading articles earns one Continuing Medical Education (CME) credit. General Practitioners can enter a record of their activity using a Learning Reflection Form, available from the RNZCGP website.

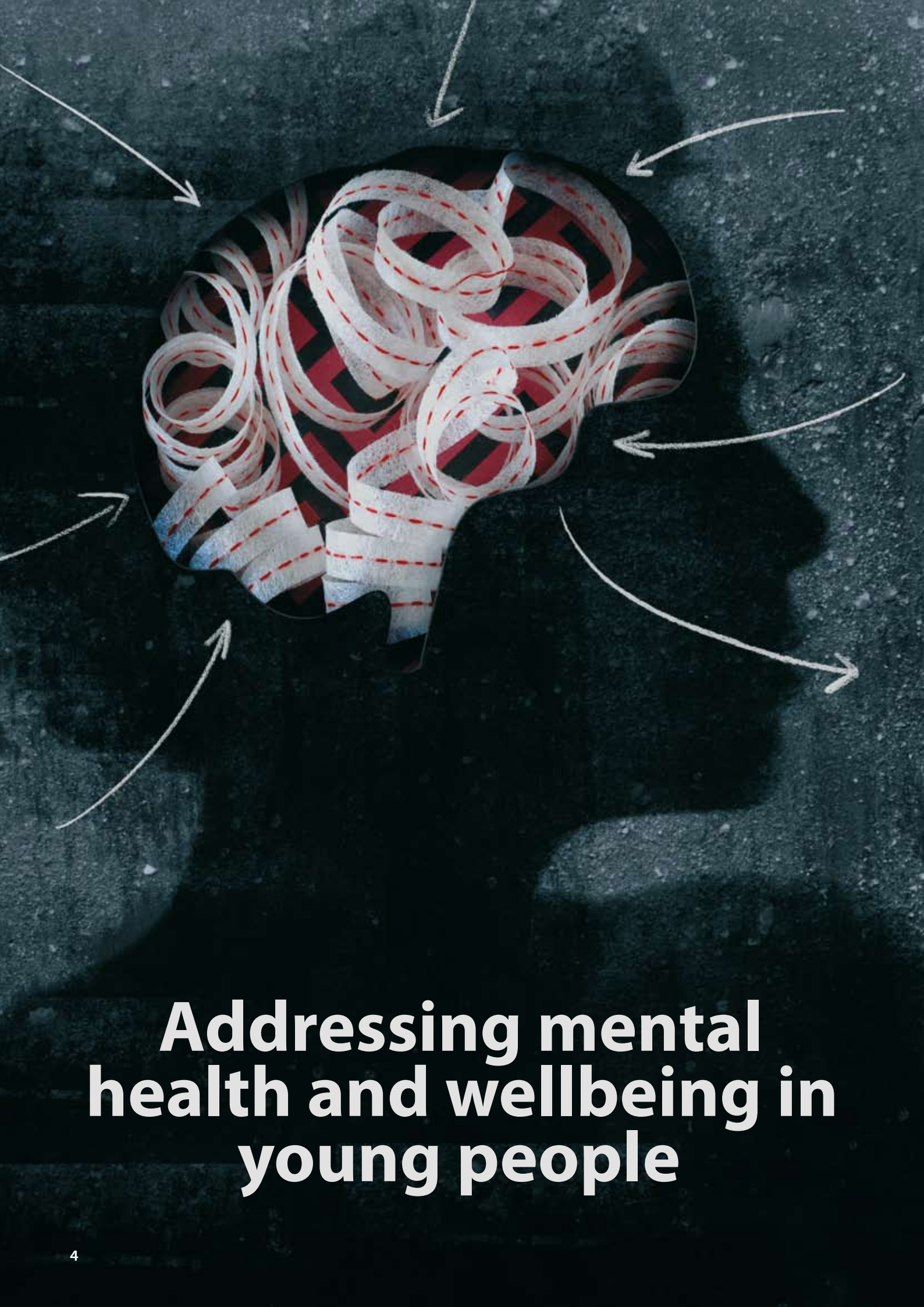
All readers, not just general practitioners, are encouraged to reflect on what they have learnt from reading an article in Best Practice Journal; an easy way to do this is to leave a comment on our website, on the article page. Don't forget to check back to see if others have contributed to the discussion.

www.bpac.org.nz



The Royal New Zealand College of General Practitioners
Te Whare Tohu Rata o Aotearoa
Endorsed CPD Activity

Time spent reading Best Practice Journal (1 credit per hour) has been approved for CME for the Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please visit **www.rnzcgp.org.nz** to download your CPD MOPS Learning Reflection Form. One form per Journal read is required.



Addressing mental health and wellbeing in young people

This is the first of a series of articles which will examine the diverse theme of mental health in young people. Adolescence is a time of physical and psychological maturation, changing social roles and a move away from childhood towards greater independence and responsibility. It may bring increased exposure to risky behaviours involving sex, alcohol, drugs and motor vehicles, as well as worries about body image, relationships, peer pressures and educational achievements. From puberty the incidence of mental health conditions increases, including depression, anxiety, psychosis and suicidal ideation; young people in New Zealand have one of the highest rates of suicide in the developed world. Clinicians in primary care are in a unique position to help young people navigate this transition in life.

Adolescence, the transition from childhood to adulthood, is full of both physical and psychological changes. Young people may change schools, social circles, and face pressures to fit in with peers. In later years they develop greater independence, and with it increased exposure to risky behaviours involving sex, alcohol, drugs and motor vehicles, as well as worries about choosing a future path beyond school. In the course of all this, young people go through internal changes and develop their own sense of identity and views about themselves and the world around them; they may feel a conflict between their growing sense of identity and expectations of them.

Whatever our experiences of adolescence were, young people today face a transition from childhood to adulthood that is in many ways different to our own. Internet and mobile phone technology enables new forms of interaction, ranging from useful, positive developments in education and communication, to cyber-bullying and "sexting". The ease of using the internet and mobile phones can amplify the nature of peer pressure due to their "always on" presence. These technologies have also undermined censorship laws; young people can easily access explicit sexual, violent or drug-related content that was previously subject to age-appropriate restrictions. In addition, the visual nature of internet content can further increase exposure to idealised body types and reinforce body image concerns.

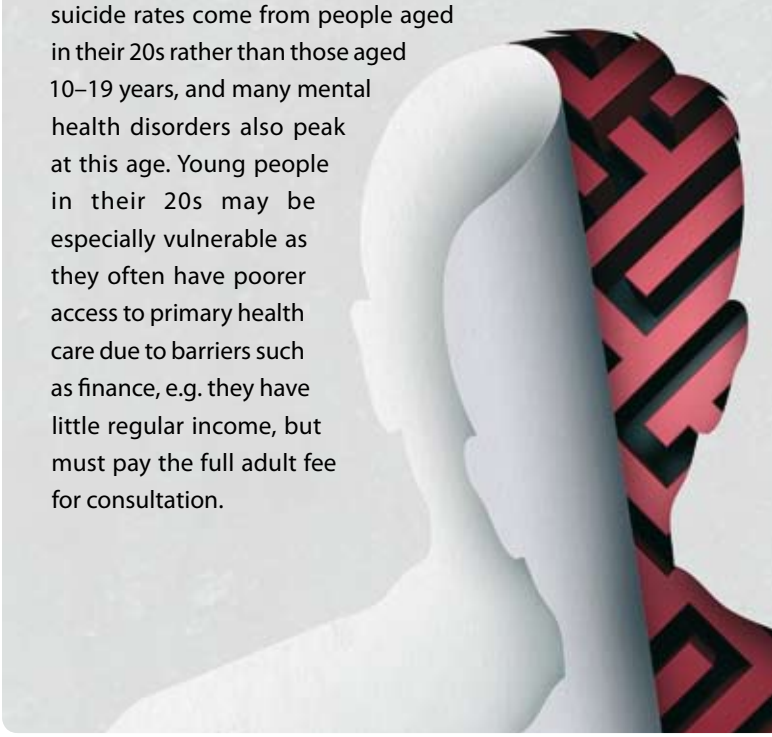
A generation or two ago, it was not unusual for teenagers to leave school early and join the workforce in paid apprenticeships. Educational requirements, the job market, and societal expectations have now changed. Teenagers having problems at school may feel trapped in "the system", and even students who enjoy their school days may feel daunted by the pressure to plan their future when they are still unsure of who they are and wish to be. Others may have a strong desire to get out of the education system and start earning their own

What is a "young person"?

Terms to describe young people are often used interchangeably, and a variety of official definitions exist. The World Health Organisation defines the terminology using the following age groups:

- Adolescent – age 10 – 19 years
- Youth – age 15 – 24 years
- Young people – age 10 – 24 years

It is important to remember when considering the mental health and wellbeing of young people that those aged in their early 20s are often still navigating the same emotional and developmental issues as younger adolescents. Many of the adverse sexual health statistics and high suicide rates come from people aged in their 20s rather than those aged 10–19 years, and many mental health disorders also peak at this age. Young people in their 20s may be especially vulnerable as they often have poorer access to primary health care due to barriers such as finance, e.g. they have little regular income, but must pay the full adult fee for consultation.



money as a means of gaining independence and getting away from problems at home or in their neighbourhood.

It is no wonder that this time in life is associated with an increased risk of mental health issues. Even young people who are otherwise happy and healthy may need help from time to time with issues relating to peers, family, relationships and their place in the world that they find overwhelming to face on their own.

Mental health in young people in New Zealand

Most young people in New Zealand are relatively happy and healthy. In the Youth '12 survey, which assessed the health and wellbeing of students in a random sample of secondary schools (covering 3% of all secondary school students in 2012), 82% of males and 71% of females reported good emotional wellbeing.[1] However, most classrooms in New Zealand will have students in them with some form of mental health concern (Table 1). In young adults aged 15 to 24 years participating in the 2013/2014 New Zealand Health Survey, 7% reported high levels of psychological distress, with higher rates in females (10%) than males (5%).[2] A sample of 1,388 students across six secondary schools in Auckland found that 37% reported sleep problems lasting longer than one month, with 19% of students reporting depression and 17% reporting anxiety.[3] Rates of mental health conditions are higher in students attending alternative education schools (for students aged 13 to 16 who have become alienated from mainstream education), with 25% of male students and 53% of female students in alternative education reporting being depressed for two weeks or more in the previous year, and 23% reporting that they had seriously thought about suicide in the last year.[4]

Rates of youth suicide in New Zealand are among the highest in the world. Data published in 2012 show that among 32 OECD countries, New Zealand had the highest rate of suicide for males aged 15–19 years, the fourth highest rate for females aged 15–19 years and the third highest rate for males or females aged 20–24 years.[5] In the Youth '12 survey, one in five females and one in ten males had seriously thought about suicide in the last 12 months, with 6% of females and 2% of males having attempted suicide.[1] Suicide accounts for approximately one quarter of all deaths in people aged between 15 and 24 years in New Zealand.[6]

Self-harm is also common among young people in New Zealand. In the Youth '12 survey, 29% of females and 18% of males had deliberately harmed themselves in the previous 12 months.[1] Self-harm behaviours vary, and some types of self-harm behaviour, e.g. cutting or burning the skin in a non-lethal manner, are distinct from self-harm with suicidal intent.[7] A survey of 1,162 students in the Wellington region found that approximately 50% of students reported having tried some form of non-suicidal self-harm at least once, suggesting that experimenting with self-harm could be regarded as characteristic of adolescent behaviour. However, only a minority of young people engage in these behaviours repeatedly: 3.7% of students reported having cut their skin many times and 2.1% having burned themselves with a lighter or cigarette many times.[7] Ongoing self-harming behaviour was associated with other aspects of poor mental health, such as low self-esteem, depression, anxiety or being bullied.[7] Self-harm behaviours can also lead to other psychological issues such as embarrassment, the need to cover the body part affected, and fear of it being discovered.[7]

Risk factors for mental health issues in young people include events early in life, such as childhood trauma or physical or sexual abuse, poverty and social deprivation.[8] In New Zealand, Māori and Pacific peoples are at increased risk: the Youth '12 survey found that Māori were more likely to have attempted suicide (odds ratio 1.97, 95% CI 1.40, 2.76).[9] Recently released provisional suicide statistics for 2014/15 showed the rate amongst Māori was the highest since records began in 2007/08.[10] Young people who identify as LGBTI (lesbian, gay, bisexual, transgender or intersex) are at increased risk of mental health issues. In the Youth '12 survey, LGBTI students were found to have poorer mental health and wellbeing compared to non-transgender, exclusively heterosexual students, such as higher rates of being bullied, having depressive symptoms and attempting suicide.[11, 12]

Table 1: Key mental health statistics for young people in New Zealand, 2008–2012[1, 5]

	Females	Males
Report clinically significant depressive symptoms	16%	9%
Deliberately self-harmed	29%	18%
Seriously thought about suicide in the last 12 months	21%	10%
Attempted suicide in last 12 months	6%	2%
Suicides per 100,000 people in each age band:		
Ages 15 – 19 years	6	23
Ages 20 – 24 years	10	33

Maximising engagement with young people in primary care

Against a backdrop of high rates of mental health issues among young people in New Zealand compared to other OECD countries, it is important to ensure that opportunities to engage in primary care are maximised, and healthcare is provided which is accessible and appropriate to a young person's needs.

Improve awareness:[13–15]

- Reach out to where they are: offering clinics, education sessions or presentations in schools improves awareness and helps break down barriers to access for young people; consider if this is something your practice could offer
- Participate in youth awareness and service delivery workshops*, to help your practice provide an experience of coming to a clinic which is positive and welcoming for young people. Ask for feedback from young people to identify areas where you could improve. Also consult the Youth Health Resource Manual† to identify areas of improvement.
- Let young patients know about dedicated local youth health services‡

* For example, the Goodfellow Unit offers continuing medical educations courses for primary care on youth engagement: www.goodfellowlearning.org.nz/course-search?keys=CEP

† The Youth Health Resource Manual: Enhancing the skills of primary care practitioners in caring for all young New Zealanders (2011) is available from the Collaborative for Research and Training in Youth Health and Development Trust for $31. See: www.collaborative.org.nz/index.php?page=youth-health-resource-manual

‡ For a list of "Youth One Stop Shops", see: www.health.govt.nz/our-work/mental-health-and-addictions/youth-mental-health-project/youth-mental-health-project-initiatives/youth-one-stop-shops

Help young people access and engage with your practice:[13–15]

- Let young people know that they do not need anyone's permission to visit the doctor, e.g. a sign in the waiting room. They can make an appointment themselves by calling or emailing the clinic, and can come along by themselves or with a support person
- Consider increasing appointment availability after 3.30pm and having a late opening night so that there is plenty of appointment time available for young people to attend after school
- Provide friendly, no fuss appointments. Young people often rate friendly, non-judgemental reception staff as an important aspect of their experience with healthcare providers[14, 16]
- Display costs for young people in the clinic or online and ensure they know about any local services or funding which may be available from the PHO. Cost barriers might mean that young people need to tell their parent or caregiver they wish to see a doctor, which can act as a further disincentive to accessing care.
- Consider the clinic environment and whether it would be seen as a welcoming, comfortable space for a young person. Having youth-appropriate magazines, posters and health information in the waiting area can let young people know the clinic has them in mind.
- If possible, offer the choice of seeing a male or female clinician; a young person may feel more comfortable discussing problems with someone of their own sex
- Aim for short wait times. Long wait times, especially if seeking help for mental health issues, may lead to young patients second guessing why they have come to the clinic and contemplate leaving, or may be a disincentive to return for follow-up appointments. Reception staff can indicate the expected wait time.

Building trust: the linchpin to engagement with young people

Privacy concerns may limit honesty and openness with healthcare professionals

Young people may not be aware of the strict professional codes and legislation that govern the confidentiality of the information they share with their general practitioner and primary care team, and may hold back due to fear their parents or school could find out about what they share.

Key practice points include:[13, 14, 17]

- Formally declare the privacy of the patient's health information, but do so in youth-appropriate language, e.g. "everything you say to me will be kept private between us"
- Explain that you might want to share information with other health professionals in order to better help the young person, e.g. a colleague or psychologist, but that you will ask their permission first
- Highlight that the only exceptions to confidentiality would be when they or someone else is at risk of getting hurt, e.g. they're threatening suicide or are being abused. Emphasise that in those cases you would try to work with them to identify who should know and how they should be informed.

Tips for communicating with young people

The key to effective communication with young people is listening to what they say, and ensuring that they feel heard and acknowledged. The important part of this skill is to be able to judge the stage of cognitive development of the young person as it does not always correlate with chronological age.

Consider the following:

- The concept of time develops with age. For example, a two-year-old may not understand what tomorrow means but an older child may be able to tell you how many sleeps it is until their birthday and understand how long this will take. It is important to judge how far the young person's concept of time stretches, as to talk beyond that means it is less relevant to them. For example, a 14-year-old may not be able to relate to a conversation about what they will do after they complete their schooling, but may be worried about a social interaction in the next school holidays.
- Where the young person is on the concrete/abstract thinking spectrum. This is important as to ask abstract questions of a concrete thinker will not usually elicit an answer beyond "dunno".
- The young person's ability to think more complexly. This is important to judge how many choices a young person can cope with at one time.

These developmental aspects are also important when judging capacity to consent, which is based on competency, not age.

Acknowledging the young person as an individual

Reassure young people that their health as an individual is important to you. They may feel that they are seen by clinicians as "the child of their parent/caregiver" rather than as their own person with their own health needs. Only 37% of secondary school students who had seen a healthcare professional in the previous 12 months in the Youth' 12 survey reported having the opportunity to see them in private.[1]

Key practice points include:

- Suggest to the young person and accompanying family members/caregivers that you could start the appointment together and then see the young person in private, or vice versa, and highlight that this is usual clinical practice. This could be raised at the start of an appointment, e.g. "When you are a child we almost always see you with your mum or dad/caregiver and when you are an adult you will usually come by yourself; now you are somewhere in between and we can do something in between"
- Try to build a transition period into consultations, so that the young person becomes more familiar with seeing a doctor on their own and are later able to initiate and attend appointments of their own accord. For example, reinforce that: "I can see you with your parent/caregiver now, and at other times you can make an appointment yourself or come in by yourself when you are ready to do that. This is what most of my patients do as they get older."

Clinicians are likely to be familiar with the potential for parental or caregiver disapproval when discussing sensitive topics with young people, particularly when they are asked to leave the room. Parents or caregivers may need reassurance that the conversation is done with their child's best interests in mind.

The nature of communication is as important as the content

Assessments of young people's attitudes to healthcare and what they value from clinicians highlight that they:[13, 14, 16]

- Value healthcare where they feel like they are heard, listened to and understood
- Want clinicians to give them health information and advice in a straightforward way
- Want clinicians to work in partnership with them to address their health concerns
- Can be discouraged from engaging with clinicians due to fear of being judged, "told off" or lectured to

- May present with a "safe" symptom to begin a consultation before deciding whether the clinician is trustworthy and reveal what is really concerning them

Opportunistic screening for mental health concerns

As young people typically do not engage in health care services as frequently as people in other age groups, any encounter should be considered as an opportunity to discuss their psychological and emotional wellbeing.

Performing a HEADS assessment

HEADS (sometimes referred to with multiple letters, e.g. HEEADDSSS) is a framework for a semi-structured interview conducted during a consultation, which involves asking adolescents about their Home, Education and Employment, Eating and Exercise, Activities and peers, Drugs and Alcohol, Depression and suicide, Sexual health, Safety and Strengths. Questions covering these topics are flexible and intended to guide conversation rather than a rigid set of instructions to follow (Table 2, over page). Raising these issues may help a young person know that their clinician is interested in their psychological and emotional health as well as their medical concerns. Even if a young person has no particular concerns at that time, bringing up issues related to emotional wellbeing can build trust and act as an invitation to discuss these issues in the future.

Clinicians will need to make a judgement based assessment of the psychological development and level of maturity of the young person under their care in order to pitch their line of questioning and approach to the HEADS assessment at an appropriate level. Questions should be framed in a way that avoids simple answers, such as "yes", "no", "ok", "don't know". For example, ask a question that requires a description rather than an opinion, such as: "What do you like about school?" rather than "Do you like school?".

There is no single correct way of performing a HEADS assessment; Table 2 (over page) highlights some of the topics that can be discussed. Questions should be adapted to the circumstances of individual patients, and delivered in a non-judgemental and informal way so that it does not sound like a test. If there is a particular presenting problem, link as many of the questions as possible to this, e.g. exploring issues of sexual health or bullying.

Approaching the HEADS assessment:[19]

- Explain the purpose of the assessment so a young person does not wonder why they are being asked questions unrelated to their visit, e.g. "I ask all the young people I see about how things are going in other areas of their lives, because so many things are important for health, is that okay if we do that now?"
- Reiterate patient confidentiality
- Begin with topics that a young person is likely to find non-threatening: Starting with strengths and activities the young person is good at can help ease into the conversation. Keep in mind that for many young people the order of the questions may begin as non-threatening by starting the discussion with home and education environments before moving onto topics they may be reluctant to discuss such as drug use and sex, but for some young people their home environment may be a source of stress, so flexibility is important
- Asking about the activities of friends or peers can be an entry into sensitive topics such as drug use, i.e. "do any of your friends smoke marijuana?", "do you do it too?"
- Keep in mind that young people with depression may not label their experience as depression, and clinicians should be alert for other signs such as a change in weight, altered behaviour or academic achievement at school, conflict with others at home or other behavioural changes consistent with a diagnosis of depression[20]
- Record potential co-morbidities and the young person's social, educational and family context in their notes [21]

Closing off the HEADS assessment:

- Thank the young person for their answers and their honesty, reinforce their good health behaviours, remind them about the confidentiality of their answers and ask if they have any questions
- Address any immediate safety issues which have been raised
- Reassure the young person – if it is appropriate, normalising their experience can help to place it in context so that they do not feel like they are outliers or in some way unusual, e.g. body image concerns, "fitting in", disagreements with parents or uncertainty about sexuality
- Discuss which items they would like to address now. Acknowledge the emotional content of what they have told you before introducing a logical potential solution; many young people are not yet fully able to use thoughts to control their emotions.
- Make a plan with them for follow-up

N.B. Future articles in the mental health in young people series in Best Practice Journal will cover management strategies for mental health problems identified during HEADS assessment.

Table 2: Examples of HEADS questions (adapted from Wilson *et al*, 2012[18] and Klein *et al*, 2014[19])

Home	Who do you live with? What are your or your family's cultural/spiritual beliefs? Is there someone you can talk with about personal things at home? Do you feel safe at home?
Education and Employment	How are things at school/work? How do you get along with teachers and other students? Have your grades changed recently? Many young people experience bullying at school, have you ever had this?
Eating and exercise	How often do you do some form of physical activity? We all have different body sizes and shapes – do you think about or worry about your weight?
Activities and peers	What do you like to do for fun/ to have a good time? What things do you like to do with friends? Have you sent messages or texts to friends that you later regretted?
Drugs and alcohol	Do any of your friends smoke? What about you? Do any of your friends drink? What about you? What other drugs are people your age using these days? What have you tried?
Depression and suicide	Do you have trouble sleeping? If so, what do you usually think about when awake, is there something that bothers you? Everyone has up days and down days what about you? Do you ever feel overwhelmed or so down you can't cope? Have you ever felt like you want to end it all? Have you ever hurt yourself, i.e. by cutting yourself, to feel better?
Sex	I ask all young people about sexuality because it is an important area of heath, is it okay if I do that? Have you ever been made to do sexual things that you didn't want to do? Have you ever wondered about whether you might be straight or gay? Have you got any questions about sexuality?
Safety	Have you ever been a car where the driver has been drunk or stoned? Is there much violence at your school, in your neighbourhood or at home? Have you ever been in trouble with the police?
Strengths	What is something you're good at, that you like doing? What groups are you part of that you feel you belong in? Does your family spend time together, e.g. eating meals? How would your friends describe you? Do you have a close friend or trusted adult that you can talk to if you're feeling down?

A short video introduction to the HEADS assessment is available at: **www.goodfellowlearning.org.nz/courses/introduction-heeadsss-assessment**

For further information on HEADS assessment, see: **www.bpac.org.nz/BPJ/2012/february/substanceMisuse.aspx**

and

www.werrycentre.org.nz/elearning-courses

Screening for depression, suicide risk and substance use can be incorporated into the HEADS assessment

Depending on the information that is revealed from the HEADS assessment, further exploration of some topics may be warranted, e.g. to examine feelings of depression or suicidal ideation or to assess for alcohol and drug misuse.

There are many different screening tools available for use in this situation; it is recommended that clinicians become familiar with a few in particular that they are most comfortable using. Practices that use the *bestpractice* Decision Support module for depression in young people can access a variety of these tools electronically.

The "depression in young people" module is nationally funded and available for any practice to install, free of charge. For further information, see: **www.bestpractice.net.nz/feat_mod_deprYoung.php**

Research suggests that young people have a high acceptance rate for completing screening questions for psychosocial issues in a self-administered format.[22] Depending on the type of assessment tool being used, consider asking the young person to go through the questions themselves in a private space, with the responses then reviewed by a clinician. Keep in mind that some young people may have literacy issues or speak English as a second language so may require additional help in completing the assessments.

Screening for depression and suicidal ideation

Evidence suggests that directly asking patients about depression and suicide is the best method for detecting and identifying people at risk, rather than relying on patients to volunteer this information themselves.[20]

Examples of quick screening tools which show good sensitivity and specificity in research studies and are suitable for use with young people in primary care include the Patient Health Questionnaire (PHQ-2) and Ask Suicide-Screening Questions (ASQ) tools.

PHQ-2 consists of two questions: "Over the last two weeks, how often have you been bothered by either of the following problems?":[23]

- Little interest or pleasure in doing things
- Feeling down, depressed, or hopeless

Responses can range from not at all (0 points), to several days (1 point), more than half the days (2 points) or nearly every day (3 points). A combined score ≥3 across the two questions has a good sensitivity and specificity for detecting young people with depression compared to more involved and lengthy screening questionnaires.[23]

ASQ involves asking young people:[24]

1. In the past few weeks, have you wished you were dead?
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?
3. In the past week, have you been having thoughts about killing yourself?
4. Have you ever tried to kill yourself?

If the patient answers "yes" to Question 4, they should be asked how they tried to kill themselves and when. A "yes" response to any of the questions would prompt further assessment and referral as appropriate.

Screening for alcohol and drug misuse

The CRAFFT screening tool is a validated method of detecting substance use problems in young people, and can be incorporated into a conversation or used as a self-report questionnaire:[25]

- Have you ever been in **car** driven by someone (including yourself) who was "high" or had been using alcohol or drugs?
- Do you ever use alcohol or drugs to **relax**, feel better about yourself, or fit in?
- Do you ever use alcohol or drugs while you are **alone**?
- Do you ever **forget** things you did while using alcohol or drugs?
- Do your **family or friends** ever tell you that you should cut down on your drinking or drug use?
- Have you ever gotten into **trouble** while you were using alcohol or drugs?

Two or more "yes" answers indicate the need for a more detailed assessment.

The Substances and Choices Scale (SACS) is another tool that can be used to assess for misuse of alcohol and drugs in young people. It can identify specific areas of concern that would prompt more in-depth assessment. As the tool measures behaviour over the last month, it can also be used to monitor progress and outcomes during treatment for alcohol or substance misuse.

The young person can complete the SACS questionnaire themselves (the community version); there is also a more detailed clinician version available. The main difference between the versions is that the community version only asks about alcohol and cannabis use, with spaces to record other drug use. The clinician version names and asks about a wide range of substances. When the clinician is administering the questionnaire, it is also recommended to ask about the use of other substances not included on the list, such as herbal highs, party pills, sedatives and other latest "fad" drugs.

When the questionnaire is completed, the clinician can score the items to indicate whether further assessment or intervention is indicated. When the questionnaire is used to monitor progress, the ticked boxes are connected with lines and the page turned on its side to see the "SACS difficulties mountain range" and whether progress is "smooth" or "rocky".

SACS was developed and validated in a New Zealand population, therefore is preferred to CRAFFT by some clinicians.

For an electronic version of SACS and a guide for administering and scoring the tool, see: **www.sacsinfo.com**

For further information on additional screening tools for mental health issues in young people, see: **www.bpac.org.nz/BPJ/2010/January/assessment.aspx**

Final thoughts

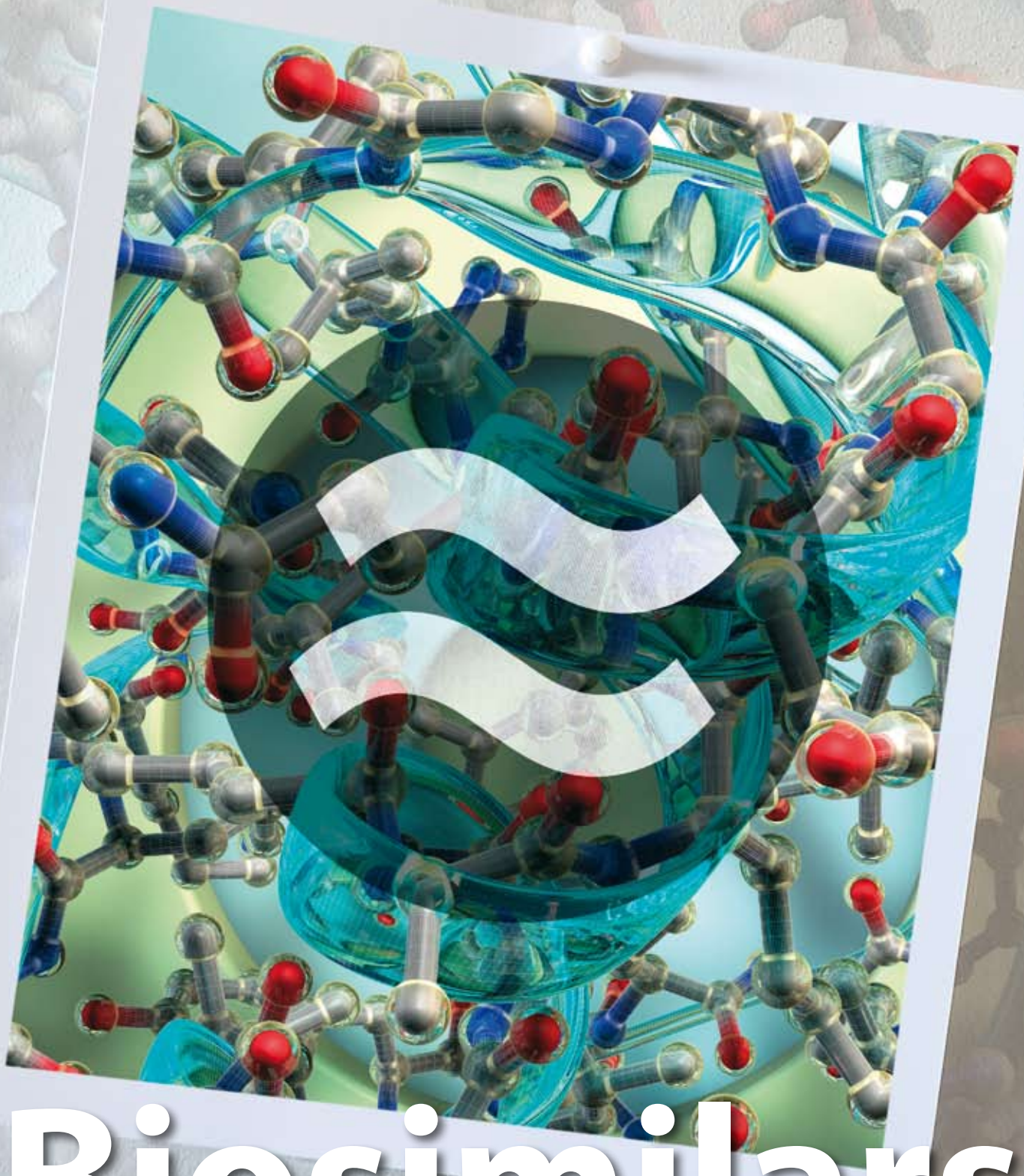
Young people face many hurdles as they navigate the transition from childhood to adulthood, increasing their susceptibility to emotional and psychological distress. General practitioners are in a unique position to screen for problems, as well as offer support and help for young people and their families. While working with young people can be challenging at times, it is richly rewarding supporting them through this period as they mature, develop resilience and overcome their obstacles.

Acknowledgement: Thank you to **Dr Sue Bagshaw**, Senior Medical Officer Youth Health, Director of the Collaborative for Research and Training in Youth Health and Development Trust, Senior Lecturer, Paediatrics, University of Otago, Christchurch, **Dr Theresa Fleming**, Senior Lecturer, Psychological Medicine and Paediatrics, Chair of the Adolescent Health Research Group, School of Medicine, University of Auckland and **Rebecca Zonneveld**, Nurse Practitioner, Evolve Wellington Youth Service, Lecturer, Graduate School of Nursing, Midwifery and Health, Victoria University for expert review of this article.

References:

1. Clark T, Fleming T, Bullen P, et al. Youth'12 Overview: The health and wellbeing of New Zealand secondary school students in 2012. Auckland, N.Z.: The University of Auckland 2013.
2. Statistics New Zealand. NZ social indicators. Prevalence of psychological distress. 2014. Available from: www.stats.govt.nz (Accessed Oct, 2015).
3. Fernando AT, Samaranayake CB, Blank CJ, et al. Sleep disorders among high school students in New Zealand. J Prim Health Care 2013;5:276–82.
4. Clark T, Smith J, Raphael D, et al. Youth '09: the health and wellbeing of young people in alternative education. Auckland, NZ: University of Auckland 2010. Available from: www.fmhs.auckland.ac.nz (Accessed Oct, 2015).
5. Patton GC, Coffey C, Cappa C, et al. Health of the world's adolescents: a synthesis of internationally comparable data. Lancet 2012;379:1665–75.
6. Office of the Prime Minister's Science Advisory Committee. Improving the transition. Reducing social and psychological morbidity during adolescence. Auckland, N.Z.: Office of the Prime Minister's Science Advisory Committee 2011. Available from: www.pmcsa.org.nz (Accessed Oct, 2015).
7. Garisch JA, Wilson MS. Prevalence, correlates, and prospective predictors of non-suicidal self-injury among New Zealand adolescents: cross-sectional and longitudinal survey data. Child Adolesc Psychiatry Ment Health 2015;9:28.
8. Patel V, Flisher AJ, Hetrick S, et al. Mental health of young people: a global public-health challenge. Lancet 2007;369:1302–13.
9. Crengle S, Clark T, Robinson E, et al. The health and wellbeing of Māori New Zealand secondary school students in 2012. Te Ara Whakapiki Taitamariki, Youth'12. 2013. Available from: https://cdn.auckland.ac.nz/assets/fmhs/faculty/ahrg/docs/youth12-Māori-report.pdf (Accessed Oct, 2015).
10. Coroners Court. Provisional Suicide Statistics. Available from: www.justice.govt.nz (Accessed Oct, 2015).
11. Clark TC, Lucassen MFG, Bullen P, et al. The health and well-being of transgender high school students: results from the New Zealand adolescent health survey (Youth'12). Journal of Adolescent Health 2014;55:93–9.
12. Lucassen MF, Clark TC, Denny SJ, et al. What has changed from 2001 to 2012 for sexual minority youth in New Zealand? J Paediatr Child Health 2015;51:410–8.

13. World Health Organisation. Adolescent friendly health services: an agenda for change. Geneva: World Health Organisation 2002. Available from: www.who.int (Accessed Oct, 2015).
14. Kang M, New South Wales. Centre for the Advancement of Adolescent Health, New South Wales, et al. Better practice in youth health: final report on research study Access to health care among young people in New South Wales, phase 2. [Sydney]: NSW Centre for the Advancement of Adolescent Health 2005.
15. Royal College of Paediatrics and Child Health. Bridging the gaps: health care for adolescents. London: Royal College of Paediatrics and Child Health 2003. Available from: www.rcpch.ac.uk (Accessed Oct, 2015).
16. McPherson A. Adolescents in primary care. BMJ 2005;330:465–7.
17. Tylee A, Haller DM, Graham T, et al. Youth-friendly primary-care services: how are we doing and what more needs to be done? Lancet 2007;369:1565–73.
18. Wilson H, Bostock N, Phillip N, et al. Opportunistic adolescent health screening of surgical inpatients. Arch Dis Child 2012;97:919–21.
19. Klein D, Goldenring J, Adelman W. HEEADSSS 3.0: The psychosocial interview for adolescents updated for a new century fueled by media. Contemporary Pediatrics 2014. Available from: www.modernmedicine.com/tag/heeadsss-30-and-sshadess (Accessed Oct, 2015).
20. Zuckerbrot RA, Cheung AH, Jensen PS, et al. Guidelines for Adolescent Depression in Primary Care (GLAD-PC): I. Identification, assessment, and initial management. Pediatrics 2007;120:e1299–312.
21. Hopkins K, Crosland P, Elliott N, et al. Diagnosis and management of depression in children and young people: summary of updated NICE guidance. BMJ 2015;350:h824–h824.
22. Bradford S, Rickwood D. Psychosocial assessments for young people: a systematic review examining acceptability, disclosure and engagement, and predictive utility. Adolesc Health Med Ther 2012;3:111–25.
23. Richardson LP, Rockhill C, Russo JE, et al. Evaluation of the PHQ-2 as a brief screen for detecting major depression among adolescents. Pediatrics 2010;125:e1097–103.
24. Horowitz LM, Bridge JA, Teach SJ, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. Arch Pediatr Adolesc Med 2012;166:1170–6.
25. Dhalla S, Zumbo BD, Poole G. A review of the psychometric properties of the CRAFFT instrument: 1999-2010. Curr Drug Abuse Rev 2011;4:57–64.



Biosimilars

– what does a primary care clinician need to know?

"Biosimilars" is likely to become an increasingly familiar term for clinicians in New Zealand and worldwide. Medicines produced from biological sources (biologics) have come to play a large role in clinical practice over the last few decades, including human hormones (e.g. human insulins) and monoclonal antibodies (e.g. adalimumab [Humira] and trastuzumab [Herceptin]) made with recombinant DNA technologies. Biosimilars are comparable versions of an existing biological medicine and can receive marketing approval once patent protection has expired for the innovator (original) biological medicine. Biologics and biosimilars are most likely to be initiated in secondary care, but primary care clinicians may find it useful to have some background knowledge of biosimilars in order to provide optimal care for patients using these medicines.

Biological medicines (also known as "biologics") are produced from living sources such as yeast, bacteria or animals, usually by genetic engineering; as opposed to pharmaceutical medicines which are chemically synthesised (including those initially derived from a plant source). The manufacture of biologics such as human insulin and erythropoietin only became possible when recombinant DNA technologies were introduced in the 1970–80s; these proteins are too complex to be manufactured by purely chemical processes.[1] The chemical composition of a biological medicine varies and includes products made of sugars, proteins or nucleic acids (DNA or RNA segments) alone or in combination.[2]

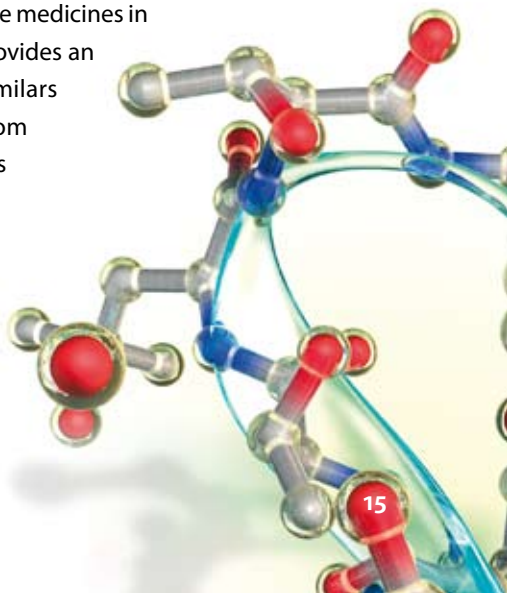
Most biologics currently in use are either monoclonal antibodies or proteins manufactured using genetically engineered bacteria or yeast cells, including:

- A variety of recombinant human hormones, cytokines and growth factors, e.g. erythropoietin, insulin, granulocyte colony-stimulating factor (G-CSF), human growth hormone
- Monoclonal antibodies designed to target specific proteins in the human body (the "mabs"), such as trastuzumab (Herceptin) which binds to the HER2 receptor, and adalimumab (Humira) which inhibits tumour necrosis factor alpha (TNFα)
- Fusion proteins such as etanercept, where the extracellular domain of a TNFα receptor is fused to part of a human IgG protein
- Antibody + drug combinations such as trastuzumab + emtansine (Kadcyla) in which the trastuzumab antibody is bound to a cytotoxic small molecule to deliver the drug to target cells

Biologics have become particularly important for the treatment of diseases characterised by inflammatory and immune changes, such as rheumatoid arthritis, Crohn's disease and multiple sclerosis, as well as treatments for patients with cancer. The high cost and increasing use of biological medicines means that they have become one of the largest and fastest growing areas of pharmaceutical expenditure in many countries, including New Zealand.[3]

Biosimilars are biological medicines that are designed to be comparable to an existing, approved, reference biological medicine once patent protection has expired on the original product; in much the same way as generics are off-patent versions of an existing chemically synthesised medicine.

The majority of biologics in use in New Zealand require prescription and Special Authority applications to be made by a relevant clinician in secondary care and this will remain the case in the near future. Therefore, general practitioners are unlikely to initiate the use of biological or biosimilar medicines. However, since more patients in New Zealand are likely to be using these medicines in the future, this article provides an overview of what biosimilars are, how they differ from generic pharmaceuticals and discusses areas of clinical certainty or uncertainty that are useful for the primary care team to be aware of.



Biosimilars: the new generics, but different

Biologics are typically larger and more structurally complex than chemically synthesised medicines; e.g. a monoclonal antibody can be approximately 800 times the size of an aspirin molecule.[4]

The production of biological medicines is different to the manufacture of a chemically synthesised medicine. For example, the production of a human hormone as a biological medicine requires:[1]

1. Genetic modification of a cell line so that it possesses the human hormone gene sequence
2. Cell culture, allowing cells to transcribe the DNA sequence, translate it into an amino acid sequence, and fold the amino acid chain into a three-dimensional protein
3. After protein translation, other modifications may include glycosylation of amino acids or cleaving of a portion of the amino acid sequence so that a prohormone is processed into an active hormone
4. Manufacturing steps to separate the hormone from the cells which produced it, and purify and concentrate the hormone for packaging into a formulation suitable for patient administration; currently almost all biologics in use worldwide are administered via injection

Generics can be made to have the exact same active ingredient, biosimilars cannot

Generic pharmaceutical medicines can usually be chemically synthesised to have the exact same molecular structure as the original patented pharmaceutical.[5] This is not the case for biosimilar medicines. The processes used to manufacture innovator biologics or biosimilars use living systems and are inherently variable. These medicines exhibit what is known as "microheterogeneity", where small differences in the protein or antibody may be detectable between batches of the same biologic produced by one manufacturer.[1] For example, a protein could have the same amino acid sequence but have differences in glycosylation patterns.[1] In addition, once an original biological medicine has come off patent, it is unlikely that a competing manufacturer will be able to exactly replicate the full manufacturing and production process of the innovator, especially as some aspects of the process may not be available in the public domain.

As a result of this complexity, no two batches of an original biologic medicine are identical, and similarly alternative versions of a biologic medicine **cannot be identical to the original; hence the name "biosimilars".**[1, 5] These medicines are also referred to as subsequent entry biologics, follow-on biologics, or similar biotherapeutic products.

Evaluating and approving biosimilars: a new challenge in medicine requires a new approach

The regulatory approval of generically equivalent medicines is dependent on demonstrating that the generic has an identical chemical structure and pharmacokinetic bioequivalence via the same route of administration in healthy volunteers as the original patented medicine.[5] Clinical trials to demonstrate that the generic medicine has equivalent clinical efficacy and safety as the innovator medicine are not required.

Due to variability in biosimilars, criteria for regulating generic medicines are insufficient to ensure that a biosimilar has the same clinical efficacy and safety as a previously patented biologic medicine.[5] In addition, since biologics can be large and structurally complex, it is difficult to analyse whether they have the same physical and chemical structure as the innovator biologic.[1]

This leads to the key questions which regulatory authorities face regarding the evaluation and approval of biosimilars:

- How much change can there be in a biosimilar, relative to the original biologic, before clinical efficacy and safety are affected?
- What is the best way to ascertain potential differences and evaluate the efficacy and safety of biosimilars?

Biosimilars are a relatively new area of medical science, and new regulatory frameworks for how to best answer these questions have been required and come into use over the last decade. In 2015, new guidelines on the approval of biosimilars from the Europe Medicines Agency and guidance from the Food and Drug Administration (FDA) to manufacturers in the United States have been released.[6–8] Increased market competition from off-patent biologic medicines has the potential to reduce costs and widen access so more patients can use them, which could be a desirable outcome; the challenge is to ensure that this can happen without compromising patient safety or reducing efficacy.

To address the question of how much difference there can be between a biosimilar and the originator biologic before clinical efficacy and safety are affected, many regulatory agencies around the world have devised processes for evaluating and approving biosimilars. In New Zealand, Medsafe has adopted the guidelines of the European Medicines Agency

for the approval of biosimilars.[9] These guidelines require the manufacturer of a biosimilar product to demonstrate that the biosimilar:[10]

A. Is similar to the reference medicine in terms of chemical and physical properties (the already approved, "original" biological medicine)

This is assessed by a range of laboratory experiments, such as antigen binding tests for antibodies. In general, there is no "gold standard" to quantify chemical and physical similarity; the purpose of these tests is to identify any differences between the biosimilar and the original biologic.

B. Does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy

This is assessed by a variety of tests including pharmacodynamic and pharmacokinetic studies, as well as clinical trials of efficacy compared to the reference biologic. These tests must demonstrate that any detected differences in chemical or physical properties do not have a meaningful impact on clinical efficacy and safety.[6] For example, biosimilar versions of epoetins are known to have different glycosylation profiles, but have been demonstrated to have the same clinical efficacy and safety, so are approved for use.[1] In the assessment of a biosimilar version of recombinant human follicle stimulating hormone (Ovaleap), the European Medicines Agency noted minor chemical differences are present compared to the innovator biologic (Gonal-f), but approved the biosimilar on the basis of clinical evidence of similar efficacy and safety.[11]

The European Medicines Agency has additional specific criteria depending on the type of biologic medicine under consideration, e.g. chemical and clinical efficacy criteria for biosimilar insulins, epoetins and filgrastims.[12, 13]

Are there any safety or efficacy issues with biosimilar medicines?

Multiple indications

A biological medicine may be used to treat patients with different conditions and be approved for multiple indications. The question which then arises is whether a biosimilar needs to be assessed in clinical trials for every indication of the original biologic, or could it be approved for all of the indications held by the original biologic medicine once similar efficacy and safety is shown for a subset of those indications?

When a biosimilar is approved for an indication which has not been directly assessed in clinical trials, regulatory agencies refer to these as "extrapolated indications". Authorities, including the World Health Organisation (WHO) and European Medicines Agency, have provided guidance on the scenarios that would form a sound scientific basis for approving a biosimilar for extrapolated indications, such as when a medicine is believed to have similar mechanisms of action in different conditions and is used in similar doses or durations.[7, 14] However, the interpretation of evidence can differ between regulatory authorities, e.g. a biosimilar version of Remicade (infliximab) is approved for a more limited range of indications in Canada than in most other countries.[15]

Extrapolated indications are likely to be an area of ongoing debate where there may be disagreements between regulatory authorities or clinicians depending on the biosimilar and indications in question.[14] Ultimately, for any medicine, safety and efficacy can only be demonstrated through the accumulated evidence of appropriate clinical trials and real world data on rates of clinical response and adverse effects.

Immunogenicity and tolerance

One of the key concerns with biologics and biosimilars is the potential for unforeseen adverse effects resulting from variability, especially immune reactions. The immunogenicity of biological products is likely to arise from their biological complexity but predicting whether a biological product will produce an immune reaction is difficult.[1, 7] The potential clinical impact of an immune reaction can also be highly variable; consequences can range from little clinical impact, to influencing the achieved dose and efficacy of the medicine or leading to the development of antibodies which cause autoimmune reactions.[14] As is the case with any new medicine, long-term data on the safety of biosimilars in large numbers of patients will not be available until these have been in clinical use for some time.

The lesson from Eprex

An example of an unforeseen adverse effect from a biological medicine comes from changes in the manufacture and use of the innovator biologic Eprex (epoetin alfa, a recombinant erythropoietin). Until the late 1990s bovine serum albumin (sourced from cows) was used as a vehicle in Eprex production. Due to concerns about the potential development of Creutzfeldt–Jakob disease, bovine serum albumin was swapped for another compound, polysorbate-80. Adverse reaction monitoring detected an increased occurrence of a rare condition in patients treated with Eprex: pure red-cell aplasia due to the presence of anti-erythropoietin antibodies. Subsequent investigation implicated the change

in vehicle as a cause of increased immunogenicity leading to the development of anti-erythropoietin antibodies in some patients. Other factors also implicated in the increased occurrence of pure red-cell aplasia included a change in clinical practice with increasing subcutaneous instead of intravenous administration, variable storage conditions and possible leaching of compounds from rubber stoppers in syringes.[16, 17]

This case involved a change in manufacturing process and administration of the original patented medicine, rather than the introduction of a biosimilar. However, it highlights that small alterations in the preparation of biologics could have important clinical effects, and this has informed current approaches to the safety of biologics and biosimilars. Firstly, changes in the manufacturing process of approved biologics are now more tightly regulated.[16] Secondly, it is recognised that biosimilars could have important differences in clinical effect even if they have little difference in terms of composition to the original biologic; thus, clinical tests of efficacy and immunogenicity in sensitive populations are included in current approval guidelines around the world.

Immunogenicity in European guidelines

The approval process for biosimilars in Europe requires that a manufacturer demonstrates comparable (or lower) immunogenicity to the reference product. For any medicines which are used long-term, the European Medicines Agency has stated that immunogenicity data for one year of use will normally be required for approval.[7] One of the concerns with extrapolated indications is that use in different patient populations (such as people with different autoimmune conditions) could influence immunogenicity.[14] The FDA and WHO recommend that immunogenicity tests performed to support an approval application are conducted in patients with the greatest expected risk of developing adverse immune reactions, so that any extrapolated indications are for uses and patient populations where a lower risk would be expected, e.g. due to lower doses or shorter durations of use.[8, 14] As is the case with any medicine, including innovator biologics and biosimilars, regulatory authorities can request post-marketing surveillance studies to collect additional data on safety during routine clinical use, and some biosimilars have been approved in Europe with post-marketing surveillance requirements in place.

Assessing biosimilar safety in New Zealand

In New Zealand, manufacturers of all biological medicines (either original innovator medicines or biosimilars) are required to submit Periodic Benefit Risk Evaluation Reports, which compile new and emerging evidence about the risks and benefits of a medicine for approved indications.[18]

Quick-fire questions about biosimilar medicines

Are biosimilars just generic versions of a biological medicine?

No. Although they are alternative versions of a medicine developed after the patent has expired on the original product, they differ from generic medicines in that:

- Generic medicines have an identical chemical structure to a patented pharmaceutical; biosimilars are highly similar to an existing biological medicine, but not identical
- Since biological medicines are often large, complex structures it can be difficult to measure the physical and chemical similarity of a biosimilar version of a medicine compared to the innovator product due to analytical limitations

As a result, the approval process for biosimilars is more rigorous than the approval process for generic versions of a chemically synthesised medicine, and requires clinical tests of efficacy and safety.

Will patients have the same degree of clinical benefit if they take a biosimilar instead of the original biological medicine?

The approval process for biosimilars requires that the manufacturer demonstrate comparable clinical quality, efficacy and safety to a pre-existing, approved, reference medicine (usually, the original branded version of the biological medicine). When biosimilars are used for treating patients with conditions which have been directly studied in clinical trials there will be clinical evidence of comparable efficacy. When biosimilars are used for "extrapolated indications", which have not been directly assessed in clinical trials, the level of evidence that they will produce the same degree of clinical benefit is lower. However, in these cases there is an expectation that they will produce the same degree of clinical benefit on the basis of factors such as the chemical and physical similarity of the medicines, evidence from clinical studies showing similar pharmacodynamics and pharmacokinetics, and consideration of the mechanism of action of the original biologic in that indication.

Will the original biologics that the biosimilars are designed to replicate still be subsidised by PHARMAC?

This will vary on a case by case basis and will depend on the outcome of the competitive pricing process run by PHARMAC. Currently, two biosimilar medicines are funded in New Zealand, Zarzio (filgrastim) and Omnitrope (somatropin); the innovator versions of these medicines are no longer funded.

What do I do if a patient has adverse effects with a biosimilar or feels that it is not as effective?

If a patient has an adverse drug reaction to any pharmaceutical, a report should be submitted to the Centre for Adverse Reactions Monitoring (CARM). This is particularly important for newer medicines and can be done using the adverse reaction reporting tool via your practice management system, electronic forms via the New Zealand Pharmacovigilance Centre website (**https://nzphvc.otago.ac.nz/**), email (**carmnz@otago.ac.nz**) or using the pre-printed CARM adverse drug reaction report card.

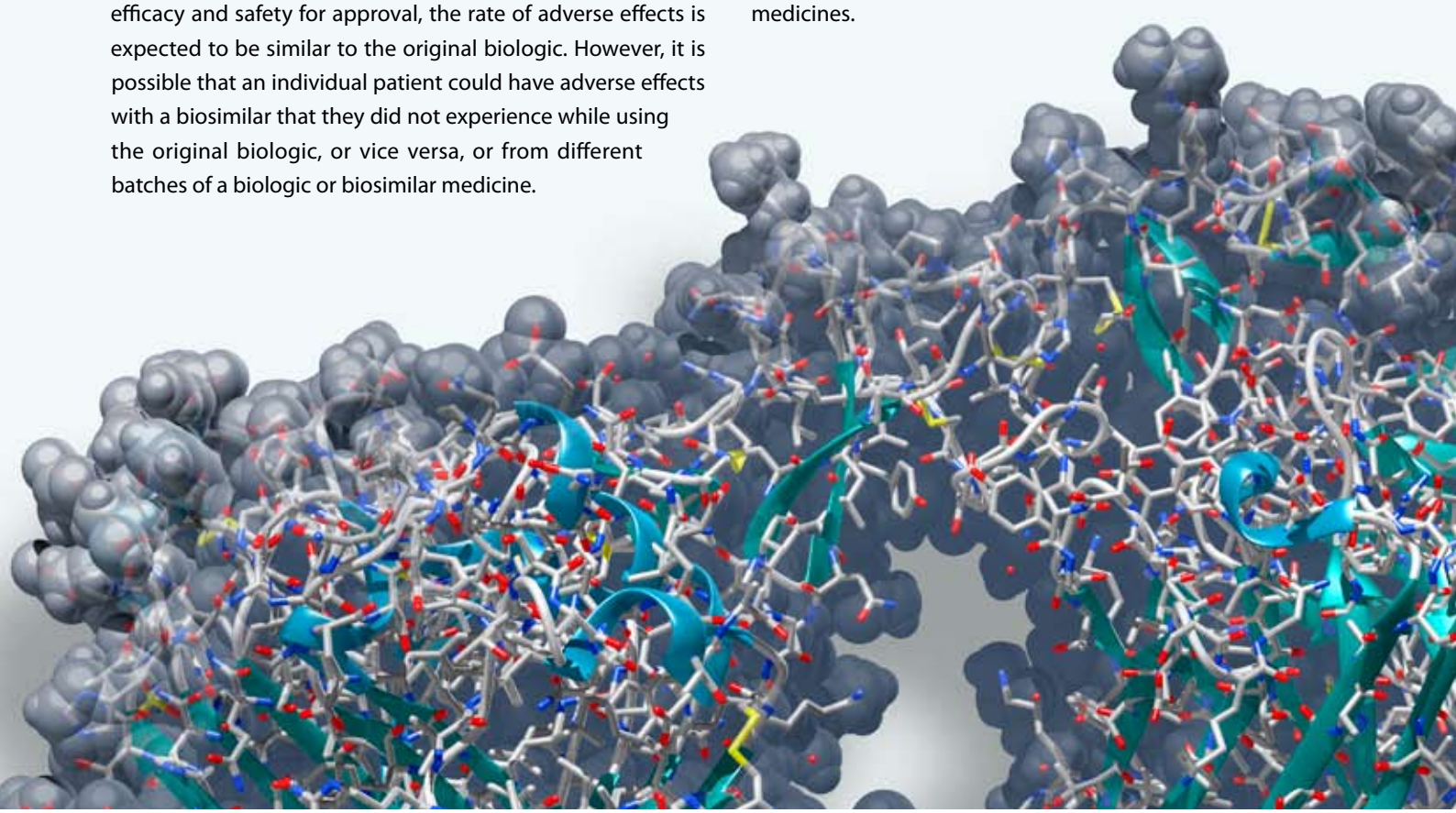
For further information on reporting adverse effects, see: "Adverse drug reactions" in the New Zealand Formulary: **www.nzf.org.nz/nzf_107**

As biosimilars are required to demonstrate comparable quality, efficacy and safety for approval, the rate of adverse effects is expected to be similar to the original biologic. However, it is possible that an individual patient could have adverse effects with a biosimilar that they did not experience while using the original biologic, or vice versa, or from different batches of a biologic or biosimilar medicine.

How do I switch a patient from a biologic to a biosimilar?

Most biologics currently in use require prescription and/or application for Special Authority approval to be completed by a specialist in an appropriate field, e.g. rheumatology, oncology. Hence decisions regarding switching a patient from using a biologic to a biosimilar will likely be managed in secondary care. General practitioners may be involved in follow-up and monitoring for adverse effects. Patients should be made aware that they are taking a different brand of biological medicine, and the patient, general practitioner and clinician who initiated the biosimilar should all be alert to the development of adverse effects or changes in clinical efficacy.

In many cases funding arrangements and cost to a patient are likely to dictate whether the original biologic or biosimilar are initially prescribed, similar to the case with brand name or generic medicines. The most likely cases where patients may switch from using a biologic to a biosimilar would be due to a funding change or if a clinician and patient decide to trial a biosimilar after a poor response or intolerance to the original biologic or vice versa; in these cases the alternative medicine may not be routinely subsidised and a Named Patient Pharmaceutical Assessment application for funding may be necessary. PHARMAC regularly seeks clinical input and consultation before changing funding arrangements for medicines.



Biosimilars currently subsidised in New Zealand

At present two biosimilar medicines are subsidised for use in New Zealand: a filgrastim biosimilar (Zarzio; recombinant human G-CSF) and a biosimilar version of somatropin (Omnitrope; recombinant human growth hormone). As with the original biologic medicines, both of these biosimilars require Special Authority approval with applications from a relevant specialist.

Zarzio is indicated for the treatment of neutropenia of various causes.[19] Zarzio has been compared with the original biologic Neupogen in studies in healthy males and females, and in females with neutropenia undergoing chemotherapy for the treatment of breast cancer.[20] At the time that PHARMAC announced it intended to subsidise Zarzio, it was estimated that it had been used by approximately 80,000 patients overseas without any safety concerns raised compared to the original biologic.[21] Zarzio is also approved for use in other regions, including Europe and the United States.

After approval and funding of Zarzio in New Zealand, PHARMAC estimated cost savings to be approximately $5 million per annum, despite an increase in usage of filgrastim of approximately 25%.[3] It is likely that similar trends will be seen with other biosimilars, and that the introduction of biosimilar versions of patented biologics may enable wider access to these medicines and improved health outcomes at a reduced overall cost.

Omnitrope is used for the treatment of short stature due to a variety of conditions: growth hormone deficiency, Prader-Willi syndrome, Turner syndrome, chronic kidney disease in children and adolescents and short stature without growth hormone deficiency.[19] It has been assessed in clinical trials in children with growth hormone deficiency, and its use in other indications is by extrapolation; the indications subsidised with Special Authority approval in New Zealand are similar to the approved uses of Omnitrope in Europe.[22] Omnitrope is also in use in other countries and has been approved for use in Europe and the United States.

Many other biologics will lose their patent protection soon

Given their relatively recent introduction to clinical practice, many biologics in use in New Zealand are still under patent. The biosimilars that have been approved for use in New Zealand are available due to patent protection expiring on the original biological medicine here. In other cases, the expiry of patent protection on biologics has led to price negotiations with manufacturers via a competitive tender process, with the result that the innovator biologic has continued to be funded at a lower cost , such as the sole supply funding decision for Remicade (infliximab).[23] A number of biologics will lose their patent protection within the next five years or so, which may lead to lower pricing through biosimilar competition, including:[24]

- Adalimumab (Humira)
- Bevacizumab (Avastin)
- Etanercept (Enbrel)
- Insulin detemir (Levemir)
- Insulin glargine (Lantus)
- Insulin glulisine (Apidra)
- Natalizumab (Tysabri)
- Pegfilgrastim (Neulastim)
- Rituximab (Mabthera)
- Teriparatide (Forteo)
- Trastuzumab (Herceptin)

Acknowledgement: Thank you to **Dr Alexander Bolotovski**, Senior Medical Advisor, Clinical Risk Management, Medsafe, Ministry of Health, Wellington and **Dr Rebecca Grainger**, Rheumatologist, Wellington Regional Rheumatology Unit, Hutt Valley DHB and Senior Lecturer, Department of Medicine, University of Otago, Wellington for expert review of this article.

References:

1. Ahmed I, Kaspar B, Sharma U. Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. Clin Ther 2012;34:400–19.
2. U.S. Food and Drug Administration (FDA). Information for healthcare professionals (Biosimilars). FDA 2015. Available from: http://www.fda.gov/ (Accessed Oct, 2015).
3. PHARMAC. Pharmaceutical management agency annual review December 2014. Wellington, New Zealand: PHARMAC 2014. Available from: http://www.pharmac.health.nz (Accessed Oct, 2015).
4. Kozlowski S, Woodcock J, Midthun K, et al. Developing the nation's biosimilars program. N Engl J Med 2011;365:385–8.
5. de Mora F. Biosimilar: what it is not. Br J Clin Pharmacol 2015; [Epub ahead of print].
6. European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as

active substance: quality issues. WC500167838. London: EMA 2014. Available from: http://www.ema.europa.eu (Accessed Oct, 2015).

7. European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. WC500180219. London: EMA 2014. Available from: http://www.ema.europa.eu (Accessed Oct, 2015).
8. U.S. Food and Drug Administration (FDA). Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. FDA 2015. Available from: http://www.fda.gov (Accessed Oct, 2015).
9. Medsafe. Biosimilars. 2014. Available from: http://www.medsafe.govt.nz/ (Accessed Oct, 2015).
10. European Medicines Agency (EMA). Questions and answers on biosimilar medicines. WC500020062. London: EMA 2012. Available from: http://www.ema.europa.eu (Accessed Oct, 2015).
11. European Medicines Agency (EMA). Ovaleap. Follitropin alfa. Public assessment report. WC500152908. London: EMA 2013. Available from: http://www.ema.europa.eu (Accessed Oct, 2015).
12. Heinemann L, Khatami H, McKinnon R, et al. An overview of current regulatory requirements for approval of biosimilar insulins. Diabetes Technol Ther 2015;17:510–26.
13. Bennett CL, Chen B, Hermanson T, et al. Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncol 2014;15:e594–605.
14. World Health Organisation (WHO). Guidelines on evaluation of similar biotherapeutic products (SBPs), Annex 2, Technical Report Series No. 977. Geneva: WHO 2009. Available from: http://www.who.int (Accessed Oct, 2015).
15. Health Canada. Summary basis of decision (SBD): Inflectra. 2014. Available from: http://www.hc-sc.gc.ca (Accessed Oct, 2015).
16. Bennett CL, Luminari S, Nissenson AR, et al. Pure red-cell aplasia and epoetin therapy. N Engl J Med 2004;351:1403–8.
17. Ebbers HC, Crow SA, Vulto AG, et al. Interchangeability, immunogenicity and biosimilars. Nat Biotechnol 2012;30:1186–90.
18. Medsafe. Guideline on the regulation of therapeutic products in New Zealand. Part 8: pharmacovigilance. Wellington, New Zealand: Medsafe 2015. Available from: http://www.medsafe.govt.nz (Accessed Oct, 2015).
19. New Zealand Formulary (NZF). NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
20. Gascon P, Fuhr U, Sörgel F, et al. Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol 2010;21:1419–29.
21. PHARMAC. Consultation: proposal for sole supply of, and wider funded access to, filgrastim. 2012. Available from: http://www.pharmac.health.nz (Accessed Oct, 2015).
22. European Medicines Agency (EMA). Omnitrope: EPAR product information. London: EMA 2015. Available from: http://www.ema.europa.eu/ (Accessed Oct, 2015).
23. PHARMAC. Decision to award sole supply to Remicade (infliximab). 2014. Available from: http://www.pharmac.health.nz (Accessed Oct, 2015).
24. Chandra A, Vanderpuye-Orgle J. Competition in the age of biosimilars. JAMA 2015;314:225–6.

Improving the safety of community-based **chemotherapy**

Chemotherapy is predominantly managed in secondary care, but many prescriptions for oral medicines are dispensed and taken in the community. Chemotherapy medicines are cytotoxic, and their regimens are often complicated; prescribers and pharmacists need to take added care as errors can result in severe harm to patients. Defined processes when prescribing or dispensing, combined with good communication between prescribers, patients and pharmacists, improves the safety of community-based chemotherapy.

Cancer treatment in the community is increasing

As the average age of the population increases and detection techniques improve, the number of people diagnosed with cancer continues to grow. In 1950 there were 3605 new cancer diagnoses registered in New Zealand; in 2010 this number had increased to more than 21 000.[1] Improved treatments mean that people diagnosed with cancer are living longer. Chemotherapy is increasingly available in oral formulations that the patient takes at home, rather than in a hospital setting. In 2014, oral chemotherapy and immunosuppressant medicines were dispensed more than 345 000 times from community pharmacies in New Zealand to over 52 000 people.[2]

Chemotherapy has a narrow therapeutic window

Systemic chemotherapy targets malignant cells but also adversely affects normal cells. Oncologists optimise the patient's treatment plan to maximise the toxicity to cancer cells while minimising the adverse effects on the rest of the body. There is a narrow threshold between the therapeutic window and the development of serious complications. Due to this fine balance even small irregularities in prescribing or dispensing can result in serious adverse effects. If a patient receives a dose that is too low, this may allow proliferation of neoplastic cells. Over-treatment can result in complications ranging from vomiting to neurotoxicity, renal and liver dysfunction, bone marrow suppression or death.[3]

Chemotherapy regimens are often complicated

The complex and cyclical nature of some chemotherapy treatment regimens increases the potential for error during prescribing or dispensing. Doses of chemotherapy medicines may be fixed or they may be continually adjusted depending on the patient's body weight, body surface area, neutrophil count, renal or hepatic function or response to treatment. Chemotherapy dosing may be altered if other medicines are taken concurrently.

How common are errors in chemotherapy?

A study from the United States found an overall error rate of 1.4% for outpatient chemotherapy.[4] This was higher than the 0.8% overall rate of errors for patients taking non-chemotherapy medicines.[4] Paediatric patients appear to be particularly vulnerable to community-based chemotherapy treatment errors. At one paediatric cancer clinic 77% of medicine errors involved medicines taken at home.[4]

For further information, see: "The medicine errors most often associated with oral chemotherapy", Page 24.

Practice points to improve the safety of chemotherapy regimens

The Health Quality and Safety Commission (HQSC) and the Clinical Oncology Society of Australia have recommended practice points to improve the safety of chemotherapy. The theme across many of these recommendations is the need for clear, and where possible documented, communication between patients, oncologists, general practitioners and pharmacists.

Communication between prescribers, patients and pharmacists improves safety

Chemotherapy is safer when there is good communication between prescribers, patients and pharmacists. Before a patient begins treatment it is a good idea to discuss all the medicines they are currently taking including any over-the-counter (OTC) or complementary and alternative medicines (CAM). A number of CAMs have the potential to interact with chemotherapy medicines, including: gingko biloba, echinacea, ginseng, St. John's Wort and kava.[8] Discussions between prescribers and pharmacists about the chemotherapy regimen reduce the risk of errors, particularly before a patient begins chemotherapy and whenever the treatment regimen is changed.

The medicine errors most often associated with oral chemotherapy

The oral chemotherapy medicines that were most frequently involved in errors in a review conducted in the United States were:[5]

- Capecitabine – indications for cancer treatment include: breast, colon and oesophago-gastric cancers
- Imatinib – indications for cancer treatment include: leukaemia, gastrointestinal stromal tumours and dermatofibrosarcoma protuberans
- Temozolomide – indicated for: glioblastoma multiforme, recurrent high grade glioma, advanced metastatic melanoma
- Methotrexate – indications for cancer treatment include: general antineoplastic chemotherapy
- Hydroxyurea – indications for cancer treatment include: chronic myeloid leukaemia, cancer of the cervix, head or neck
- Vinorelbine – indicated for: non-small cell lung cancer and advanced breast cancer

Capecitabine is reported to be particularly prone to dispensing errors due to the number of different indications it is used for and because it has a variety of dosing algorithms;[5] it is available in 150 mg and 500 mg tablets.

The common errors associated with oral chemotherapy

The most frequent types of errors involving oral medicines prescribed for chemotherapy reported by the same study from the United States are shown in Figure 1.

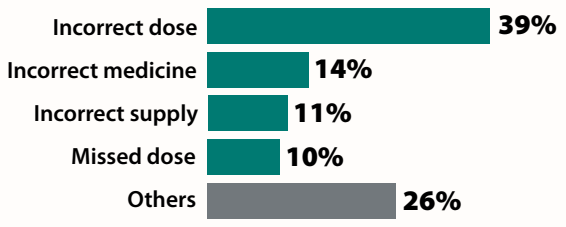


Figure 1: Types of oral chemotherapy errors[5]

The majority of errors involved "near misses" where the error was identified before any harm was caused to the patient.[5] Errors involving chemotherapy medicines were intercepted by a pharmacist before serious harm was done to patient in 38% of cases.[5]

Incorrect doses cause patient harm

Incorrect dosing resulted in patient harm in approximately 40% of reported cases.[5] Problems with prescribers writing prescriptions accounted for almost 60% of these errors.[5] For example, a patient died after a doctor prescribed a ten-fold overdose of temozolomide;[5] this can easily occur when medicines have formulations with many different strengths.

Medicine administration errors accounted for 27% of dosing errors.[5] These errors included patients taking medicines daily instead of weekly, or not stopping medicines when intended.

Dispensing errors accounted for 3% of dosing errors.[5] In one case a pharmacist misinterpreted a prescription for mercaptopurine 50 mg, twice daily, as 300 mg, daily; the patient experienced serious bleeding.[5] Mercaptopurine indications include acute leukaemias and chronic myeloid leukaemia.[6]

Multiple formulations of medicines can cause errors

Different formulations of oral chemotherapy medicines can cause confusion when patients need to take multiple tablets of different strengths to make up a dose. For example, temozolomide is available in four different subsidised strength capsules and patients may need to take multiple strengths to achieve the correct dose.[6]

Supplying the incorrect number of days treatment

Chemotherapy medicines that are taken on specific days, rather than daily, may be supplied in the wrong quantity if the prescription is not processed correctly. For example, lomustine is indicated for patients with brain tumours, Hodgkin's lymphoma and small cell lung carcinoma and is taken as a single dose, once every six weeks.[7] A patient taking lomustine died of complications of bone marrow suppression after they were dispensed, and took, 190 mg of lomustine, daily, rather than every six weeks.[5]

It is important that patients understand why they need to take chemotherapy medicines as prescribed. Treatment non-adherence is a frequent finding in studies of patients taking chemotherapy in the community, sometimes because prescriptions are not collected from the pharmacy. One study found that approximately one in four women with early-stage breast cancer who were prescribed anastrozole did not have sufficient supply to take the medicine for at least 80% of the days they were prescribed it.[9] Chemotherapy regimens usually need to be taken at the full, or near-full, dose to maximally benefit patients. An early study of postoperative breast cancer treatment with cyclophosphamide, methotrexate and fluorouracil (CMF) found that patients given ≥ 85% of the planned dose had a five-year relapse-free survival of 77%.[10] This compared with a five-year relapse-free survival of 48% for patients who received less than 65% of the planned dose due to reasons such as toxicity, the patient's age or their preference.[10] The equivalent survival rate in patients treated by surgery alone was 45%.[10]

Practice points for general practitioners

General practitioners involved in the care of patients with cancer should be provided with a copy of the patient's treatment plan from the clinician who is managing their care.[3] The treatment plan should include the name of the chemotherapy protocol and all medicines the patient is taking, as well as how to manage any adverse effects.

General practitioners are recommended to discuss the treatment plan with the patient. Patients who recognise the medicine and formulation they are taking can help to detect any prescribing or dispensing errors before they cause harm. Asking the patient what they know about a medicine and how frequently they should take it is one way of assessing their understanding and uncovering any misinformation. Patients need clear instructions, including how to identify different strengths of a medicine and when medicines should be taken. When chemotherapy medicines are prescribed the information that is discussed with the patient should be documented.

Prescribers are recommended to include the start date and duration of treatment on chemotherapy prescriptions.[11] It is recommended that only one cycle of chemotherapy be prescribed at a time, e.g:[11]

- Fludarabine 30 milligrams, daily, for three days (days 1 – 3)
- Cyclophosphamide 200 milligrams, daily, for five days (days 1 – 5)
- Day 1 is 1st October, 2015

The patient's height, weight and body surface area should be included on the prescription along with the name of the chemotherapy treatment protocol, e.g. "FC protocol for chronic lymphocytic leukaemia".[11] All units should be recorded in full to prevent quantities such as microgram and milligram amounts being confused.[12] Abbreviations should also be avoided when specifying how frequently medicines should be taken.[12] The term "as directed" should never be used when prescribing chemotherapy medicines.[3] Prescribers should avoid hand writing prescriptions for chemotherapy medicines. Patients should be given advice on how to manage missed doses and what to do if they vomit shortly after taking a chemotherapy medicine.

Managing the adverse effects of chemotherapy

Patients may take oral chemotherapy medicines at home for weeks without direct clinical supervision. The clinician who is responsible for the patient's care will generally manage any adverse effects. However, general practitioners may treat mild symptoms and need to be alert to the possibility of serious adverse effects requiring urgent referral to secondary care.

Nausea and vomiting is expected to occur in 70–80% of patients and may be experienced before chemotherapy, i.e. anticipatory, or up to 72 hours later.[8] Prophylactic lorazepam, metoclopramide or prochlorperazine are often prescribed when the patient has low to moderate risk of chemotherapy-induced nausea.[8] Serotonin antagonists, e.g. ondansetron, are appropriate for more severe chemotherapy-induced nausea; these are highly effective and have minimal adverse effects.[8] Antiemetics are taken between 30 and 90 minutes before the administration of oral chemotherapy, unless the protocol specifies otherwise.[12]

Diarrhoea can be caused by variety of mechanisms in patients undergoing chemotherapy, depending on the treatment regimen. A stool sample is generally recommended to exclude the possibility of an infective organism.[8] Antibiotics may be appropriate if the stool sample is positive for bacteria, otherwise treatment with loperamide may be considered.[8]

Infection can be life-threatening in patients undergoing chemotherapy. Patients who present with an elevated temperature should be carefully assessed, particularly if they are at risk of neutropenia, as clinical signs may be reduced. The risk of serious complications due to infection is proportional to the severity of any finding of neutropenia on full blood count.[8] Clinicians should have a low threshold for requesting further investigations and contacting the clinician managing the patient's care if a patient undergoing chemotherapy presents with signs of infection.

Rarer but serious adverse effects of chemotherapy that require immediate referral to secondary care include: tumour lysis syndrome, superior vena cava syndrome and spinal cord compression.[8]

Be aware of clinically significant interactions

There are a number of clinically significant interactions that can occur between chemotherapy medicines and medicines commonly prescribed in primary care. For example, the toxicity of methotrexate can be increased in patients taking analgesic doses of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) for arthritis or gout. N.B. this risk is much less when methotrexate is used in lower doses for rheumatoid arthritis.[3] Capecitabine significantly reduces the metabolism of warfarin and increases its anticoagulant effect;[3] the increased risk of bleeding should be discussed with patients taking warfarin who are being treated with capecitabine, and warfarin doses and INR frequency may need to be adjusted.

The New Zealand Formulary has a medicine interaction checker available from: **www.nzf.org.nz/nzf_1**

Practice points for pharmacists dispensing chemotherapy medicines

Pharmacists need to recognise when they receive a prescription for medicines as part of a chemotherapy protocol and have additional safety procedures in place for checking, handling and dispensing cytotoxic medicines. This includes confirming that:[11]

- The medicines dispensed match those on the treatment protocol and none have been confused with another medicine of a similar name
- Any calculations involving the patient's body surface area are still accurate
- The dose and formulation of the medicine are correct
- The patient understands the treatment regimen

The NZF has a body surface area calculator available from: **www.nzf.org.nz/nzf/resource/body%20surface%20Area%20Calculator.htm**

Patients undergoing cyclical chemotherapy are usually clinically reassessed between treatment cycles, therefore only enough medicine for one cycle is recommended per dispensing.[11] Dispensing more medicine than is required may create confusion and increase the risk of a dosing error.

When dispensing chemotherapy medicines ensure that patients understand all the information that is on the medicine label; medicine information should also be printed if it has not already been supplied to the patient by the clinician managing their care.

If a medicine is not to be taken every day patients need to be told this; it should be clearly stated what the interval between each dose should be and that a dose should not be repeated until that interval has passed. Particular care should be taken when consulting with patients with English as a second language and all information should be appropriate to the patient's stage of health literacy.

To ensure the pharmacokinetics of the treatment is not altered patients taking oral chemotherapy should never crush or chew tablets, unless advised to do so.

Pharmacists who are aware which patients are taking chemotherapy medicines can contact prescribers if prescriptions are not being collected.

Provide the patient with "trusted" sources of information

People with cancer and their families may search the internet for information about their condition or the medicines that they are prescribed. It is important that patients make treatment decisions based on evidence-based information from reliable sources.

The Cancer Society of New Zealand has patient-centred cancer treatment information, for further information see: **www.cancernz.org.nz** keyword search = chemotherapy

The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) have safety information available for chemotherapy medicines, e.g.:

www.medsafe.govt.nz/consumers/cmi/m/methotrexatesandoz.pdf

Other reliable international sources of cancer-related information for patients include:

www.nhs.uk/conditions/chemotherapy/pages/definition.aspx

www.cdc.gov/cancer/index.htm

A case of mistaken medicine identity

The office of the Health and Disability Commissioner recently released findings from an investigation as to whether a pharmacist provided a patient with an appropriate standard of care when they were mistakenly dispensed a chemotherapy medicine instead of an immunosuppressant. Although this example does not involve a patient intentionally on a chemotherapy regimen, it shows how care needs to be taken when processing prescriptions for medicines with similar names that are not routinely dispensed.

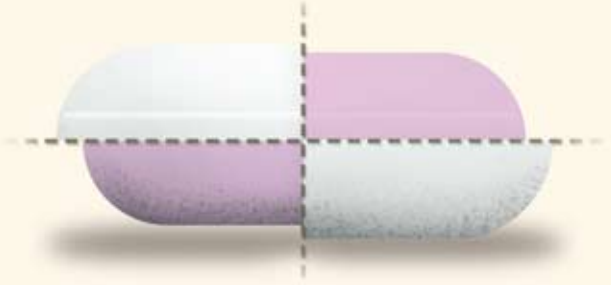
The incident occurred when a patient who had previously had an organ transplant presented at a pharmacy to collect a repeat of their medicines, which included cyclosporin 50 mg (also referred to as ciclosporin and cyclosporine). Cyclosporin is an immunosuppressant with a range of indications and was prescribed to the patient to prevent organ transplant rejection.[13]

A pharmacy technician processed the prescription and selected cyclophosphamide 50 mg capsules, instead of cyclosporine 50 mg capsules.[13] Cyclophosphamide is a chemotherapy medicine indicated to treat patients with leukaemia, lymphomas, some solid tumours and rheumatoid arthritis.[6] Cyclophosphamide tablets are smaller than cyclosporin capsules, pink, and dispensed "loose" in a bottle. Cyclosporin capsules are white, sealed in foil, and dispensed in a cardboard box.

The processed prescription was checked and signed as correct by the attending pharmacist who then supplied this to the patient.[13]

Approximately six weeks later, when the patient presented at the pharmacy again, the same pharmacist was asked why the tablets were different from their regular cyclosporin capsules; an investigation was triggered which uncovered the error.[13] The patient did not appear to have experienced any long-term harm despite taking cyclophosphamide for approximately three weeks.

This is an example of a "mix-up" between medicines with similar names that were both in 50 mg tablets. The pharmacist was found to be in breach of the Code of Health and Disability Services Consumer's Rights for making a serious dispensing error.[13] An adverse comment was also made about the technician's error in selecting the incorrect medicine.[13] The pharmacy has reviewed its standard procedures for dispensing and reporting incidents.[13]



References

1. Ministry of Health (MoH). Cancer: Historical summary 1948-2011. MoH, 2014. Available from: www.health.govt.nz/publication/cancer-historical-summary-1948-2011 (Accessed Oct, 2015).
2. Ministry of Health. Pharmaceutical Claims Collection. 2015.
3. Carrington C. Safe use of oral cytotoxic medicines. Aust Prescr 2013;36:9–12.
4. Walsh KE, Dodd KS, Seetharaman K, et al. Medication errors among adults and children with cancer in the outpatient setting. J Clin Oncol 2009;27:891–6.
5. Weingart SN, Toro J, Spencer J, et al. Medication errors involving oral chemotherapy. Cancer 2010;116:2455–64.
6. New Zealand Formulary (NZF). NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
7. Bristol-Myers Squibb (NZ) Limited. Data sheet. 2013. Available from: www.medsafe.govt.nz/profs/datasheet/c/ceenucap.pdf (Accessed Oct, 2015).
8. Smith GF, Toonen TR. The role of the primary care physician during the active treatment phase. Prim Care 2009;36:685–702.
9. Partridge AH, LaFountain A, Mayer E, et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. J Clin Oncol 2008;26:556–62.
10. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. N Engl J Med 1981;304:10–5.
11. Health Quality & Safety Commission New Zealand (HQSC). Medication safety watch 2015;13:3.
12. Clinical Oncological Society of Australia (COSA). Guidelines for the safe prescribing, dispensing and adminsitration of cancer chemotherapy. COSA, 2008. Available from: www.cosa.org.au/media/1093/cosa_guidelines_safeprescribingchemo2008.pdf (Accessed Oct, 2015).
13. Pharmacist, Mr C: A report by the Deputy Health and Disability Commissioner (Case 14HDC00439). 2015. Available from: www.hdc.org.nz/media/291762/14hdc00439.pdf (Accessed Oct, 2015).

SMOKING CESSATION

Helping patients stick with it, until they quit

Key practice points:

- Always offer both pharmacological and behavioural support to people who want to quit smoking
- Combination nicotine replacement therapy (NRT), e.g. patches and gum or lozenges, is usually the first-line pharmacological treatment for people who want to quit
- NRT can also be offered to people who are not yet ready to stop smoking to help them "cut down" before quitting
- If a person experiences a lapse in their quit attempt, behavioural support and the continued use of NRT increases their chances of stopping long-term
- Buproprion, nortriptyline and varenicline are other pharmacological options for smoking cessation. Varenicline is the most effective of these treatments, and is approximately as effective as combination NRT. It is subsidised for patients who have previously tried to quit with other smoking cessation medicines.

Part 1: Providing behavioural support for patients

Nicotine addiction is a disorder that should be considered at every patient contact. All patients who smoke should be encouraged to stop and provided with cessation support. Patients who are not yet ready to quit smoking can be encouraged to reduce the amount they smoke and provided with support in the same way as people who have committed to complete abstinence from tobacco. Patients trying to quit who view a lapse in smoking abstinence as a hurdle, rather than a failure, are more likely to become permanently smokefree.

Treating the deadly habit

Half of people who take up tobacco smoking long-term, die from this cause.[1] Approximately 5 000 people in New Zealand die each year due to smoking related causes; 350 of these deaths are caused by second-hand smoke.[2] People who smoke cigarettes die ten years younger than non-smokers on average,[1] an effect on mortality similar to that of morbid obesity.[3]

The harm smoking causes can be undone

People who smoke can reverse the long-term effects of smoking if they stop early enough. Quitting smoking before age 40 years results in approximately nine more years of life expectancy compared to those who continue to smoke.[1] Each year of smoking beyond this age reportedly results in three months loss of life.[3]

Are we on track for a smokefree New Zealand?

In 2011, the New Zealand government committed to achieving a smokefree New Zealand by 2025. The aim is to reduce the prevalence of smoking to less than 5% across all groups of people.[4]

The rate of smoking has been declining over New Zealand in the last decade. Current smoking (defined as smoking at least once a month), was reported by 17% of the population sampled in 2013/14, a decrease from 20% in 2006/07.[5] Encouragingly, the rate of current smoking in people aged 15 – 17 years has dropped by half since 2006/07 and was 8% in 2013/14.[5] However, 41% of Māori aged 18 years or over reported current smoking in 2013/14, unchanged from 2006/07.[5] The growing up in New Zealand study found that nearly 11% of pregnant women overall and over one-third of Māori women, smoke during pregnancy.[6] Adults living in the most deprived communities in New Zealand are 3.5 times more likely to smoke than adults living in the least deprived areas once adjustments for age, ethnicity and sex have been made.[5]

Offer cessation support to every patient who smokes, at every contact

Nicotine addiction should be managed like other long-term health issues and be addressed at every patient contact, unless it is inappropriate to do so.[3] This can be challenging as patients may find it irritating if clinicians continually point out the need to stop smoking. However, the majority of people who smoke

wish that they did not. The 2009 New Zealand Tobacco Use Survey found that 80% of current smokers aged 15–64 years would not smoke if they had their life over again.[7] Initiating discussions about smoking cessation in different ways is one approach to reducing repetition. For example, smoking cessation conversations could begin by mentioning:

- Stoptober, a 31 day smokefree challenge that is run every October
- The idea of making the family home smokefree, starting from Christmas day
- The possibility of starting the new year with a quit attempt
- How quitting smoking improves cardiovascular risk

Tailor the ABC pathway to the individual patient

The risks of continued smoking and the benefits of quitting should be tailored to the individual in a non-judgemental way. For example, the financial cost of smoking may be emphasised to some patients whereas others may find health reasons more of a motivation. The revised ABC pathway for smoking cessation is:[2]

Ask about and document the smoking status of every patient.

Give **Brief advice** to stop to every patient who smokes.

Strongly encourage every person who smokes to use **Cessation support** and offer help accessing this. A combination of behavioural support and smoking cessation medicine works best.

The offer of cessation support is particularly important in the ABC model. The authors of a systematic review estimated that if all smokers were given advice to stop smoking, 25% would attempt to stop within six months of the consultation, but this could be increased to 35% if advice was followed with an offer of cessation support.[8] Without cessation support half of all quit attempts fail within the first week.[3]

When cessation support is offered this is an opportunity to acknowledge and explore the barriers people have to being smokefree. Health professionals who understand the day-to-day difficulties faced by people who smoke can point out ways behavioural and pharmacological support helps people overcome their barriers to a healthier life.

What to do if a patient declines an offer of support

Document when a patient declines an offer of smoking cessation support and advise them that they will be offered cessation support again at the next consultation.[2] A New Ministry of Health target requires all patients who smoke to have documented evidence of an offer of cessation support in the last 15 months (see: "Primary care achieves health targets as new targets are announced", Page 32). This new target encourages more frequent use of the ABC model. Varying the ways the pathway is implemented and discussed with patients may be necessary to maintain a fresh approach.

 For further information see: "Smoking cessation beyond the ABC: Tailoring strategies to high-risk groups", BPJ 64 (Oct, 2014).

Cessation support can reduce smoking before a patient quits

People who smoke who are not yet ready to commit to a quit date are more likely to stop smoking if they are offered cessation support.[9] NRT can be prescribed to people who want to reduce the amount they smoke before they quit (see: "A focus on pharmacological support", Page 33).[2] There is evidence that quitting smoking by reduction is as effective as quitting abruptly.[10]

A pragmatic approach would be to acknowledge the challenge the patient faces in becoming smokefree, offer them treatment and encourage them to reduce their cigarette consumption by half. A follow-up consultation could review the patient's progress and offer referral to a support provider. Smoking cessation providers can contact people who are ambivalent about quitting smoking to discuss their options.[2]

Behavioural support options available

Smoking cessation interventions can be divided into behavioural and pharmacological support. The benefits of these two forms appears to be additive and behavioural support improves adherence to pharmacological treatment.[3] The two approaches are used in combination where possible. It is not known which is the most effective form of behavioural support and each probably has a small additive effect; some patients may find different forms more effective than others.[3] Interventions with some evidence of improving smoking cessation treatment adherence include: education, positive feedback from a health professional, reminders, psychological support and counselling.[11]

What appears to be common across successful methods is that they hold the "quitter" accountable and engender some form of loyalty towards the person who is supporting the quit attempt.[3]

Table 1: Examples of smoking cessation support services available in New Zealand

Support provider	Services available	How to access
Quitline	Telephone counselling, text and online support. The smoking cessation support service most often used in New Zealand. Once a person has been referred by the primary care team they will be contacted by the service in one to three days.[2]	Phone 0800 778 778 or register at **www.quit.org.nz**
Aukati KaiPaipa	Face-to-face coaching in individual and group settings. A smoking cessation service based on a Māori health framework, operating from more than 30 sites throughout New Zealand.	For further information, see: **www.aukatikaipaipa.co.nz/contact**
Pacific Quit Smoking Service	Face-to-face coaching, telephone and text support	Email: **pacificquit@adhb.govt.nz**
Comprehensive care	Mobile quit bus in Auckland area, face-to-face and telephone support. Interpreters may be available who speak Samoan, Chinese (Mandarin and Cantonese), Korean, Hindi and Gujarati, Czech and Slovak	For further information, see: **www.comprehensivecare.co.nz**
Innov8 smokefree	Home visits in the Christchurch area for women who are pregnant, telephone and text support and biochemical confirmation of abstinence	For further information, see: **www.innov8smokefree.co.nz**

Refer all patients who want to quit to a cessation support provider

All patients who accept an offer of cessation support should be referred to a support provider, or be supported in primary care.[2] There are a number of different free smoking cessation support services available depending on the needs of the patient. Quitline and Aukati KaiPaipa are national smoking cessation support providers. Some areas may have specialised services depending on the demographics of the local population (Table 1). The primary care team should be familiar with the local services available and can find out more information by contacting their local DHB.

Supporting patients who are attempting to become smokefree

Throughout a person's quit attempt support from the primary care team is beneficial. This may involve education and correcting mistaken beliefs that make it more difficult for people to stop smoking.

"Smoking does not reduce stress – in fact it creates it." Many smokers claim that smoking improves their mental health by alleviating emotional problems, stabilising mood and reducing stress, depression and anxiety.[12] This belief originates from their experience with nicotine. People who smoke often have withdrawal symptoms which they relieve by smoking the next cigarette. Each cigarette that is smoked therefore contributes to the addiction and reinforces the misbelief that cigarettes reduce stress, when in fact they cause it. People who believe that smoking is a coping mechanism for stress often find it harder to quit smoking than people who smoke predominately for pleasure. A study of over 2 000 people using a smoking treatment service in England found that the one-year quit rate was 20% for people who smoked mainly for pleasure, but 11% for people who smoked mainly as a coping strategy.[13]

Primary care achieves health targets as new targets are announced

In the final quarter of 2014/15, primary care, for the first time, achieved documented evidence that more than 90% of patients in New Zealand who smoke and were seen by a health practitioner were given brief advice and support to quit smoking.[17] Across all DHBs, 90.5% of people who smoked were offered brief advice and support to quit smoking; a 1.4% increase from the previous quarter.[17] The Southern DHB and MidCentral DHB still have some way to go to achieving the target with 74% and 82% respectively of patients having documented evidence of the ABC model being used.[17] Northland, Hawke's Bay, Hutt Valley, Capital and Coast, Taranaki, Canterbury and Wairarapa DHBs are slightly below the 90% threshold.[17]

The Ministry of Health has now released a new target for primary care. This is for 90% of PHO-enrolled patients who smoke to have been offered help to stop smoking in the last 15 months, even if they have not attended a primary care clinic.[18] Patients who smoke who do not regularly attend general practice may need to be contacted and followed-up by phone calls or letters to achieve the new target.

For further information see: **www.health.govt.nz/new-zealand-health-system/health-targets/about-health-targets/health-targets-better-help-smokers-quit**

"The withdrawal symptoms will pass – hang in there" People who are struggling with nicotine withdrawal can be reassured that the symptoms largely pass after a few weeks.[2] Sleep disturbances can be expected to last for one week, poor concentration and urges to smoke due to nicotine withdrawal may last for two weeks.[2] Irritability, depression and restlessness are likely to resolve within four weeks.[2] An increased appetite may last for more than ten weeks.[2] Patients may report an increase in cough and sputum production, although this is uncommon.[14] Patients who express concern about an increase in productive respiratory symptoms after quitting can be reassured of the health benefits of being smokefree and that any increase in cough is likely to be transitory.

"You may put on a bit of weight – but you'll be fitter and enjoy exercise more" Quitting smoking is associated with an increase in bodyweight of 4 – 5 kg after 12 months of abstinence.[15] However, this increase varies and approximately 16% of people who quit smoking lose weight.[15] The majority of weight gain occurs within three months of quitting;[15] reassure patients that weight gain is unlikely to continue. The negative consequences of any weight gain can be balanced against the reduced risk of smoking–related illnesses and increased cardiovascular fitness.

Behavioural support can increase treatment adherence and prevent smoking relapses

Smoking relapses, i.e. a return to regular smoking, are characterised by many intermittent lapses in abstinence over days or weeks.[16] How the person responds emotionally to these lapses is thought to determine whether they fully relapse to smoking or if they are able to re-establish abstinence.[16] Smoking relapse is thought to be more likely, if following a lapse, a person blames themselves, feels excessive guilt and experiences a loss of self-efficacy; collectively referred to as an abstinence violation effect.[16] In other words, if a person interprets a lapse in smoking as a lack in will-power they are more likely to lapse multiple times and start regular smoking again; perhaps because abstinence is viewed as being pointless and smoking inevitable.[16]

If a person who is trying to quit reports a lapse the primary care team can help by attempting to maintain the patient's morale and improve their self-efficacy, i.e. their belief in their ability to quit smoking.[16] This may include focusing on the length of time that they have been able to stay smokefree and explaining that the odd lapse is normal. The reasons for the lapse can be discussed as a learning opportunity and framed as a positive in the sense that a trigger for smoking can be avoided in the future.

Part two: A focus on pharmacological support

All patients who want to quit smoking should be offered pharmacological cessation support. Nicotine replacement therapy (NRT) is often the first smoking cessation medicine people try and is also recommended for use by people who want to reduce the amount that they smoke. Most people trying to quit smoking do not use enough NRT and the use of multiple forms, e.g. patches and gum or lozenges, is highly effective relative to other treatments. Bupropion and nortriptyline are fully subsidised smoking cessation medicines that have approximately the same efficacy as treatment with one form of NRT. Varenicline is subsidised with Special Authority approval for people who have been unsuccessful in quitting with other cessation medicines; it has approximately the same efficacy as treatment with combination NRT.

Addiction and nicotine replacement therapy: fighting fire with fire

Smoking is the most reinforcing and dependence-producing form of nicotine administration.[19] Nicotine reaches the brain 10–20 seconds after an inhalation of tobacco smoke; faster than could occur with intravenous administration.[19] The speed with which nicotine from tobacco smoke enters the blood stream and crosses the blood brain barrier allows smokers to titrate their levels of nicotine by altering the number of inhalations, the volume of each inhalation and the length of time they hold the smoke in their lungs.[19]

Pharmacological support reduces the urge to smoke when people are experiencing nicotine withdrawal. It also enables the person to unlearn the perceived association between smoking and reward over several months, after the withdrawal symptoms have abated.[3]

Nicotine replacement therapy is often the first cessation medicine used

The patient's preferences, likely adherence to treatment as well as their previous experience of smoking cessation aids and the possibility of adverse effects are all important considerations when recommending smoking cessation medicines. Nicotine, as replacement therapy, is usually the first-line smoking cessation medicine recommended. Using NRT approximately doubles a person's chances of quitting smoking.[20] The different forms of NRT are thought to be equally effective.[20] If a person is not ready to quit, NRT can be used to reduce the amount that they smoke before they stop.[2]

Multiple forms of NRT are recommended

Combination NRT is recommended for people who smoke more than ten cigarettes a day or who smoke within one hour of waking;[21] combination NRT may be as effective as varenicline.[20]

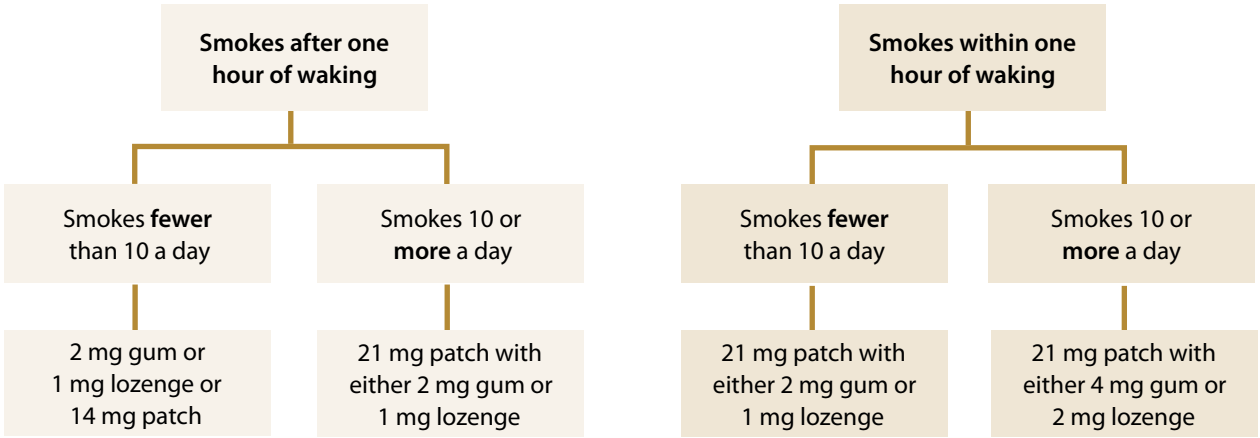


Figure 1: Nicotine dependence assessment algorithm for determining an appropriate NRT treatment regimen, adapted from Ministry of Health, 2014[21]

Nicotine from NRT is absorbed more slowly than from tobacco smoke; nicotine from patches takes one hour to be detected in the blood.[19] New Zealand guidelines recommend the concurrent use of both long-acting NRT, e.g. patches, and short-acting NRT, e.g. gum or lozenges, to enable sustained slow-release nicotine delivery and more rapid delivery of nicotine when people are experiencing a craving, e.g. when friends are smoking.[2] Combination NRT treatment is more effective than NRT monotherapy, i.e. patches and gum are more effective than patches alone.[20] Nicotine mouth spray (1 mg nicotine per spray) is licensed for use in New Zealand, but is not currently subsidised on the Pharmaceutical Schedule.[21] Because people using NRT that is not inhaled do not get the same "rush" from nicotine as when they are smoking, NRT is considered to have a low potential for misuse.[19] Dependence on nicotine gum is estimated to occur in 2% of users.[22]

How much NRT should be prescribed?

Most people who are trying to quit smoking do not use enough NRT.[21] To determine an appropriate regimen the time until first cigarette after waking is combined with the total number of cigarettes a person smokes each day (Figure 1). People who are severely dependent on nicotine may benefit from wearing two nicotine patches.

NRT is typically prescribed for 8 – 12 weeks but people may take it for longer to prevent a relapse in smoking.[21] The strength of nicotine patches can be slowly reduced over the patient's course of treatment (see NZF for details).[23]

Managing the adverse effects of NRT treatment

All forms of NRT may cause palpitations.[23] Oral NRT can cause irritation of the throat, dry mouth or increased salivation, and gastrointestinal symptoms are common although these are most likely due to swallowed nicotine.[23] Mild skin reactions often occur with the use of nicotine patches.[21] Nicotine patches can be removed overnight if sleep is disturbed.[21] If a patient reports feeling nauseous with the use of NRT, reduce the dose. Data on the safety of the long-term use of NRT is scarce. *In vitro* studies provide limited evidence that nicotine could theoretically accelerate cancer formation in people who used to smoke.[24] However, it is broadly accepted that if a person is at a high risk of relapse the long-term use of NRT should be encouraged rather than risk a return to smoking.[21, 24]

Preventing relapses in patients taking nicotine replacement therapy (NRT)

Patients who report a smoking lapse while taking NRT should be urged to continue treatment. A study of over 300 people who had smoked at least 15 cigarettes, daily, for a minimum of five years randomised participants wanting to quit smoking to placebo or nicotine patches.[16] Overall, patients using NRT had smokefree periods between smoking lapses that were nearly twice as long as patients using placebo patches, and were significantly less likely to relapse to regular smoking.[16] The protective effect of NRT against smoking relapse diminished with the number of lapses and there appeared to be little benefit in NRT treatment after eight lapses.[16]

Other smoking cessation medicines

Bupropion and nortriptyline are medicines used to aid smoking cessation which may be appropriate for people who have previously tried to quit smoking with NRT or who prefer to quit using a medicine that does not contain nicotine.

Bupropion has a similar efficacy to NRT

Bupropion is an atypical antidepressant that reduces the desire to smoke by increasing the levels of dopamine and noradrenaline in the brain as well as being a nicotinic acetylcholine receptor antagonist.[20] It is thought that bupropion blocks the effects of nicotine and elevates mood in people who are experiencing nicotine withdrawal.[20]

A Cochrane review found that NRT monotherapy and bupropion were equally effective as smoking cessation interventions.[20] No head-to-head studies comparing combination NRT with bupropion were identified,[20] although it is likely that combination NRT is more effective as a smoking cessation aid than bupropion as it has a similar efficacy to varenicline. A review of 27 trials found insufficient evidence that adding bupropion to NRT provided any long-term benefit over treatment with bupropion alone.[25] If bupropion is taken in combination with NRT weekly monitoring of blood pressure is recommended.[26]

Treatment with bupropion begins one to two weeks before the patient's quit date.[23] Initially, 150 mg bupropion, daily, for three days, then 150 mg bupropion, twice daily (a maximum single dose of 150 mg, a maximum daily dose of 300 mg and a minimum of eight hours between doses), usually for seven weeks.[23] The maximum daily dose for bupropion for patients with risk factors for seizures and patients who are elderly is 150 mg.[23]

Bupropion is contraindicated in patients during acute alcohol or benzodiazepine withdrawal, or in patients with severe hepatic cirrhosis, central nervous system tumour, a history of seizures, eating disorders, bipolar disorder or in patients who have used monoamine oxidase inhibitors within the last 14

days.[23] Patients using bupropion with any of the following medicines may be at increased risk of seizures: antipsychotics, antidepressants, antimalarials, tramadol, theophylline, systemic corticosteroids, quinolones and sedating antihistamines.[23]

The most common adverse effects associated with bupropion are insomnia in 30 – 40% of patients, dry mouth in 10% of patients and nausea.[25] Approximately one in 1 000 patients taking bupropion will experience a seizure.[20]

Nortriptyline is as effective as bupropion

Nortriptyline is a tricyclic antidepressant that increases the levels of noradrenaline in the brain. It has a more complicated dosing regimen than bupropion.

A Cochrane review of six trials found nortriptyline was twice as effective as placebo as a smoking cessation medicine and equally as effective as bupropion.[25] There are no head-to-head comparisons of nortriptyline with NRT or varenicline.[25] There was insufficient evidence that adding nortriptyline to NRT provided any long-term benefit.[25]

Nortriptyline is started ten to 28 days before a person attempts to quit smoking.[23] Initially, nortriptyline 25 mg, daily, increased gradually over ten days to five weeks to 75 – 100 mg, daily, for up to six months.[23] The dose should be slowly tapered when the medicine is stopped.[23]

Common adverse effects of nortriptyline include dry mouth, drowsiness, light-headedness and constipation.[25]

Varenicline is subsidised as a second-line smoking cessation medicine

Varenicline is a partial nicotinic agonist which stimulates and blocks nicotinic acetylcholine receptors in the brain.[3] This reduces nicotine reward and causes a moderate and sustained release of dopamine in the brain,[20] but not the substantial increases associated with smoking tobacco.

Special Authority approval is required for subsidised treatment

Varenicline is fully subsidised with Special Authority approval for a maximum of three months use as a smoking cessation treatment. To qualify for subsidised treatment a patient must:

- Be enrolled in, or about to enrol in, a smoking cessation programme which includes prescriber or nurse monitoring
- Have previously tried to quit smoking at least twice with NRT, with at least one of these attempts involving comprehensive advice on the use of NRT, or the patient must have tried previously to quit smoking with bupropion or nortriptyline
- Not have used varenicline in the previous 12 months
- Have agreed that varenicline is not to be used in combination with other pharmacological smoking cessation treatments, including NRT

How effective is varenicline as a smoking cessation medicine?

Varenicline is the most effective single formulation smoking cessation medicine subsidised in New Zealand.[2] A Cochrane review found that varenicline is more effective as a smoking cessation aid than any single NRT product or bupropion.[20] However, varenicline has a similar efficacy to combination NRT treatment.[20]

Initiating varenicline treatment

Varenicline treatment usually begins one to two weeks before the patient's quit date with a two week "starter-pack" followed by a ten week maintenance regimen:[23]

- Initially, varenicline 500 micrograms, once daily, for three days
- Increase to, varenicline 500 micrograms, twice daily, for four days
- Then, varenicline 1 mg, twice daily, for seven days until the starter pack is finished. During this period the patient should stop smoking.
- Maintenance treatment of varenicline 1 mg, twice daily, for ten weeks

In patients with an estimated glomerular filtration rate (eGFR) < 30 mL/minute/1.73m^2 the maintenance dose of varenicline is 1 mg, once daily.[23] Varenicline should be avoided by women who are pregnant or breast-feeding.[23]

When initiating treatment for varenicline consider offering the patient a quick follow-up consultation or phone call from a practice nurse around the time of their quit date. This enables confirmation that the patient has successfully completed the "starter pack" and to remind them to begin the maintenance treatment.

An additional 12 weeks of varenicline treatment increases the rates of continuous biochemically validated abstinence from tobacco at 24 weeks by 1.42 times and at 52 weeks by 1.19 times.[27] Treatment beyond 12 weeks with varenicline is not subsidised in New Zealand.

Varenicline in combination with NRT – unsubsidised but effective

A clinical trial that randomised 446 people trying to quit smoking with varenicline to either a nicotine patch or a placebo patch found that varenicline in combination with NRT was more effective than varenicline with placebo.[34] After 12 weeks of treatment, 55% of patients treated with varenicline and NRT were biochemically confirmed to be abstinent from tobacco, compared to 41% of patients treated with varenicline and a placebo patch; statistically significant differences persisted between these groups at 24 weeks and six months.[34] There was no difference in adherence rates with approximately 80% of patients in each group completing the treatment regimen.[34]

Patients who were treated with varenicline in combination with NRT were more likely to experience skin reactions, nausea, sleep disturbances, constipation and depression, although only the increased rate of skin reactions was statistically significant (14% versus 8%).[34] The group treated with varenicline alone reported more abnormal dreams and headaches.[34]

Varenicline is not subsidised if it is co-prescribed with NRT although some patients who want to maximise their chances of quitting smoking may be prepared to pay for this combination treatment.

Prescribe the "starter pack" and the maintenance treatment together

To ensure that patients receive the entire 12 week course of subsidised varenicline the prescription items for both the starter and maintenance treatment can be included on the same form. Pharmacists will supply patients with the "starter pack" and up to four weeks of initial maintenance treatment if a prescription for both items is presented. Patients will need to return to the pharmacy to collect the remainder of their maintenance treatment. In 2014, almost 32 000 people in New Zealand were dispensed varenicline from a community pharmacy, of whom over 2 200 were not dispensed the "starter pack" and maintenance treatment on the same day, i.e. they may not have received a full course of treatment.[28] If a patient is prescribed a "starter pack" without maintenance treatment they should be contacted before this is finished and offered another prescription for maintenance treatment.

Prepare patients for the adverse effects of varenicline treatment

To help patients taking varenicline complete the course of treatment they should be prepared for the possibility of adverse effects before they begin. The "starter pack" allows the dose of varenicline to be increased slowly to reduce the likelihood of adverse effects. In general, advise patients to contact the practice if they are considering stopping treatment as many of the symptoms associated with treatment are manageable.

Nausea is the most common adverse effect of varenicline treatment

Nausea can be expected in 17% of patients taking varenicline and is generally mild, although in up to 8% of patients it may be severe enough to cause discontinuation of treatment.[20] If a patient taking varenicline reports nausea emphasise the health benefits of quitting smoking and encourage them to continue with treatment. Patients may experience less nausea if they take varenicline with food and a glass of water. Foods containing easily digested carbohydrates, e.g. bananas or white rice, may be effective at reducing varenicline-induced nausea. An antiemetic, e.g. prochlorperazine or metoclopramide, may be appropriate for patients experiencing moderate to severe varenicline-induced nausea, assuming there are no interactions with any other medicines. The nausea associated with varenicline appears to be dose-dependent and reducing the dose decreases its severity, although this also reduces the effectiveness of varenicline.[20] A reduced dose, e.g. varenicline 500 micrograms, twice daily, results in quit rates comparable with that achieved with NRT alone or bupropion, and is preferable to the patient stopping treatment.[27]

Patients may experience sleep disturbances or headaches

Insomnia, abnormal dreams and headaches are associated with varenicline treatment.[27] Patients who experience mild to moderate adverse effects can be encouraged to finish the course of treatment as these relatively short-term effects are likely to be outweighed by the long-term benefits of smoking cessation. Unlike the other adverse effects associated with

varenicline, headache does not appear to be dose-dependent and reducing the dose may not reduce this symptom.

Serious adverse psychological effects are rare

Varenicline treatment has been linked with serious psychological adverse effects. The evidence supporting an association, however, is relatively weak and studies are confounded by the increased rate of suicide in people who smoke compared to the general population.[27] Patients taking varenicline should stop treatment and contact a health professional if they notice negative changes in behaviour or thinking, mood swings, anxiety, depression or suicidal ideation.

In 2015, the United States Federal Drug Administration (FDA) found no association linking the use of varenicline with neuropsychiatric disturbances, although it noted the low quality of the evidence prevented reliable conclusions from being made.[29] A recent study of over 51 000 patients in England who had taken varenicline found that it was actually associated with a significantly reduced risk of depression and self-harm compared to treatment with NRT.[30] From April, 2007 to March, 2008, 3 415 patients in New Zealand were dispensed prescriptions for varenicline, 1 394 of whom were surveyed about neuropsychiatric disturbances.[31] Sleep disorders were reported by 4% of patients and 3% of patients reported depression (24 new-onset cases and 14 cases of worsening of existing depression).[31] One case of suicide, two cases of suicidal ideation and three cases of psychotic reaction were reported;[31] it is not known what the prevalence of these conditions are in people quitting smoking in New Zealand with other smoking cessation medicines or among people who smoke in general.

Varenicline may reduce tolerance to alcohol

The FDA recently advised that varenicline may change the way people react to alcohol, including decreased tolerance to alcohol, unusual or aggressive behaviour when drinking and memory loss.[29] It is recommended that until patients know how varenicline affects the way they react they should reduce their consumption of alcohol.[29] Reducing alcohol consumption will reduce the likelihood of smoking lapses in some people trying to quit.

Varenicline does not increase cardiovascular risk compared to NRT

There is limited evidence that the use of varenicline may be associated with a small increase in cardiovascular risk. However, the authors of the recent study from England concluded that the use of varenicline was not associated with an increased cardiovascular risk; compared to NRT it was associated with a significantly reduced risk of ischaemic heart disease, cerebral infarction and heart failure.[30]

Preventing relapses in patients taking varenicline

The first two weeks of a quit attempt is a crucial time for patients taking varenicline. Patients who remain completely smokefree during this time are significantly more likely to be adherent to treatment and achieve long-term abstinence from smoking.[32] A study of almost 700 people taking varenicline found that patients who were abstinent from tobacco two weeks after quitting were 2.7 times more likely to be adherent to varenicline treatment than those who were not completely smokefree at this point.[33] This two week window is the best time to deliver behavioural support.

Patients taking antipsychotic medicines who quit smoking may need dose reductions

The cytochrome P450 enzyme CYP1A2 which metabolises some antipsychotics is induced by the hydrocarbons and tar-like compounds in tobacco smoke.[35] Patients who are taking certain antipsychotics, e.g. clozapine, olanzapine, chlorpromazine and haloperidol, may have increased serum levels of these medicines following smoking cessation and therefore will require dose reductions.[35] There have been reports in the literature of serious adverse effects following abrupt smoking cessation in people taking clozapine.[36] Some smoking cessation medicines may not be appropriate for patients with a history of mental disorders.

For further information see: "Smoking cessation beyond the ABC: Tailoring strategies to high-risk groups", BPJ 64 (Oct, 2014).

Acknowledgement: Thank you to **Dr Brent Caldwell**, Senior Research Fellow, Wellington Asthma Research Group, Department of Medicine, University of Otago, Wellington for expert review of this article.

References

1. Doll R, Peto R, Boreham J, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 2004;328:1519.
2. Ministry of Health. The New Zealand guidelines for helping people to stop smoking. 2014. Available from: www.health.govt.nz/system/files/documents/publications/nz-guidelines-helping-people-stop-smoking-jun14.pdf (Accessed Oct, 2015).
3. Aveyard P, Raw M. Improving smoking cessation approaches at the individual level. Tob Control 2012;21:252–7.
4. Smokefree Aotearoa New Zealand 2025. Smokefree 2025. Available from: http://smokefree.org.nz/smokefree-2025 (Accessed Oct, 2015).
5. Ministry of Health (MoH). New Zealand Health Survey: Annual update of key findings 2012/13. MoH, 2013. Available from: www.health.govt.nz/publication/new-zealand-health-survey-annual-update-key-findings-2012-13 (Accessed Oct, 2015).
6. Morton S, Atatoa C, Bandara D, et al. Growing up in New Zealand: A longitudinal study of New Zealand children and their families. Report 1: Before we are born. 2010. Available from: http://researchspace.auckland.ac.nz/handle/2292/6120 (Accessed Oct, 2015).
7. Ministry of Health (MoH). Tobacco use in New Zealand: Key findings from the 2009 New Zealand tobacco use survey. MoH, 2010.
8. Aveyard P, Begh R, Parsons A, et al. Brief opportunistic smoking cessation interventions: a systematic review and meta-analysis to compare advice to quit and offer of assistance. Addiction 2012;107:1066–73.
9. Wu L, Sun S, He Y, et al. Effect of smoking reduction therapy on smoking cessation for smokers without an intention to quit: An updated systematic review and meta-analysis of randomized controlled trials. Int J Environ Res Public Health 2015;12:10235–53.
10. Lindson-Hawley N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. Cochrane Database Syst Rev 2012;11:CD008033.
11. Hollands GJ, McDermott MS, et al. Interventions to increase adherence to medications for tobacco dependence. Cochrane Database Syst Rev 2015;2:CD009164.
12. Taylor G, McNeill A, Girling A, et al. Change in mental health after smoking cessation: systematic review and meta-analysis. BMJ 2014;348:g1151.
13. Ferguson J, Bauld L, Chesterman J, et al. The English smoking treatment services: one-year outcomes. Addiction 2005;100 Suppl 2:59–69.
14. Warner DO, Colligan RC, Hurt RD, et al. Cough following initiation of smoking abstinence. Nicotine Tob Res 2007;9:1207–12.
15. Aubin H-J, Farley A, Lycett D, et al. Weight gain in smokers after quitting cigarettes: meta-analysis. BMJ 2012;345:e4439.
16. Kirchner TR, Shiffman S, Wileyto EP. Relapse dynamics during smoking cessation: recurrent abstinence violation effects and lapse-relapse progression. J Abnorm Psychol 2012;121:187–97.
17. Ministry of Health (MoH). Health targets - 2014/15 quarter 4 - results summary. MoH, 2015. Available from: www.health.govt.nz/new-zealand-health-system/health-targets/how-my-dhb-performing (Accessed Oct, 2015).
18. Ministry of Health (MoH). Health targets: better help for smokers to quit. MoH, 2015. Available from: www.health.govt.nz/new-zealand-health-system/health-targets/about-health-targets/health-targets-better-help-smokers-quit (Accessed Oct, 2015).
19. Benowitz N, Hukkanen J, Jacob P, editors. Nicotine chemistry, metabolism, kinetics and biomarkers. Handb Exp Pharmacol 2009;192:29–60.
20. Cahill K, Stevens S, Perera R, et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329.
21. Ministry of Health (MoH). Guide to prescribing nicotine replacement therapy. MoH, 2014. Available from: www.health.govt.nz/system/files/documents/publications/guide-to-prescribing-nicotine-replacement-therapy-nrtv2.pdf (Accessed Oct, 2015).
22. Hughes JR, Pillitteri JL, Callas PW, et al. Misuse of and dependence on over-the-counter nicotine gum in a volunteer sample. Nicotine Tob Res 2004;6:79–84.
23. New Zealand Formulary (NZF). NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
24. Shields PG. Long-term nicotine replacement therapy: cancer risk in context. Cancer Prev Res 2011;4:1719–23.
25. Hughes JR, Stead LF, Hartmann-Boyce J, et al. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2014;1:CD000031.
26. GlaxoSmithKline NZ Limited. New Zealand data sheet: ZYBAN tablets. 2015. Available from: www.medsafe.govt.nz/profs/datasheet/z/zybantab.pdf (Accessed Oct, 2015).
27. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2012;4:CD006103.
28. Ministry of Health. Pharmaceutical claims collection. 2015.
29. U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA updates label for stop smoking drug Chantix (varenicline) to include potential alcohol interaction, rare risk of seizures, and studies of side effects on mood, behavior, or thinking. FDA, 2015. Available from: www.fda.gov/Drugs/DrugSafety/ucm436494.htm (Accessed Oct, 2015).
30. Kotz D, Viechtbauer W, Simpson C, et al. Cardiovascular and neuropsychiatric risks of varenicline: a retrospective cohort study. Lancet Respir Med 2015;3(10):761-8.
31. Harrison-Woolrych M, Ashton J. Psychiatric adverse events associated with varenicline: an intensive postmarketing prospective cohort study in New Zealand. Drug Saf 2011;34:763–72.
32. Liberman JN, Lichtenfeld MJ, Galaznik A, et al. Adherence to varenicline and associated smoking cessation in a community-based patient setting. J Manag Care Pharm 2013;19:125–31.
33. Hays JT, Leischow SJ, Lawrence D, et al. Adherence to treatment for tobacco dependence: association with smoking abstinence and predictors of adherence. Nicotine Tob Res 2010;12:574–81.
34. Koegelenberg CFN, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. JAMA 2014;312:155–61.
35. Ministry of Health (MoH). New Zealand smoking cessation guidelines. MoH, 2007. Available from: http://nihi.auckland.ac.nz/sites/nihi.auckland.ac.nz/files/pdf/addictions/nz-smoking-cessation-guidelines-v2-aug07.pdf (Accessed Oct, 2015).
36. van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics 2003;13:169–72.

An HPV update: vaccination coverage needs to be improved

Vaccination against human papillomaviruses (HPV) is fully subsidised for girls and young women to reduce their risk of cervical cancer and genital warts. Vaccination for boys and young men also provides protection against genital warts, as well as anal and penile cancer, and indirectly provides protection against cervical cancer for any future female partners. However, immunisation rates for females in New Zealand are below target and an action plan has been published to improve vaccination coverage. Recent research suggests that HPV vaccination may provide additional benefits to women during gestation and childbirth.

The benefits of HPV vaccination

Human papillomaviruses (HPV) are small DNA viruses; more than 40 types are reported to be able to infect the anogenital tract.[1] HPV infection is considered to be necessary for the development of cervical cancer;[2] it is associated with over 99% of cervical cancers.[1] Infection with HPV is also associated with approximately 95% of anal, 65% of vaginal, 60% of oropharyngeal and 35% of penile cancers.[1]

Human papillomaviruses are classified according to their ability to increase cancer risk.

- High-risk types include serotypes: 16, 18, 31, 33, 45, 52 and 58; types 16 and 18 are most frequently associated with cervical cancer[1]
- Low-risk HPV serotypes are predominantly associated with warts but can also cause recurrent respiratory papillomatosis; types 6 and 11 are frequently associated with genital warts[1]

HPV infection is common and often occurs shortly after a person becomes sexually active; there is a lifetime risk of infection of more than 80%.[1] Infection by HPV occurs following skin-to-skin contact which allows the virus to penetrate small lesions in the epithelium.[1] From here, the virus infects basal epithelial cells, causing them to produce proteins that slow cellular maturation.[1] Most HPV infections are transient and asymptomatic with no clinical signs.[2] It is reported that more than 90% of HPV infections, of any serotype, clear or become undetectable within two years; this generally occurs in the first six months following infection.[2] In some patients, repeated division of infected cells in combination with viral replication results in the development of warts.[1] The majority of females who are infected with a high-risk serotype do not develop cancer, but in some, cancer will develop decades after the infection.[1] There were 164 women newly registered with cervical cancer in New Zealand in 2013,[3] and approximately 50 women die due to cervical cancer each year.[1] People who use condoms can still become infected with HPV.[1]

The HPV vaccination programme in New Zealand

The HPV vaccination was added to the New Zealand Immunisation Schedule in 2008. It is free for girls and young women until their 20th birthday, as well as for women with HIV infection who are aged under 26 years and for people who have undergone an organ transplant.[1] The funded vaccine, Gardasil, is effective against the high-risk HPV types 16 and 18 as well the low-risk types 6 and 11.[1] The vaccine is not "live" as it is made of virus-like-particles that contain immunogenic protein produced by genetically engineered yeast.[1]

To substantially reduce the incidence of cervical cancer, models predict vaccination coverage needs to be over 70% for females aged 10 – 13 years.[4] The Ministry of Health has set a immunisation target of 75% coverage for all 12-year old girls by December, 2017.[5] Overall the HPV vaccination rate for females born between 1996 and 2000 is 54%, although vaccination rates are higher for Pacific (73%) and Māori females (62%) of the same age.[6]

The optimal age to administer the vaccine to females is before they become sexually active, e.g. 11–13 years.[1] All girls in New Zealand schools are offered HPV vaccination in Year Eight as

HPV vaccination may protect against complications of pregnancy

A recent New Zealand study suggests that HPV infection can adversely affect pregnancies. Therefore HPV vaccination may have additional benefit beyond cancer and genital wart prevention.

Placental HPV infection was analysed in 339 women involved in the Otago Placenta Study who gave birth between 2009-2014; placenta were studied from 232 women with pregnancy complications and 107 women with uncomplicated pregnancies.[7] The cohort included: 305 women of European descent, 13 Māori and Pacific women, five women of Chinese descent and 16 women who identified as mixed ethnicity.[7] Women who had smoked more than ten cigarettes per day were excluded.[7] The group were from a diverse range of socioeconomic backgrounds and had not been vaccinated against HPV.[7] There was no statistically significant difference in the mean maternal age or body mass index (BMI) between the groups of women who were HPV positive and those who were HPV negative.[7] The study was deliberately biased towards pregnancy complications and included: 88 cases of prematurity, 72 cases of idiopathic fetal growth restriction, 44 pregnancies with diabetes and 20 cases of pre-eclampsia.[7]

Evidence of HPV infection was found in the placenta of 100% of women with pre-eclampsia, 95% of women who had diabetes, 92% of women with acute chorioamnionitis, 84% of women who had pre-term births, 81% of women who had intrauterine deaths and 76% of women with fetal growth restriction.[7] Women with uncomplicated pregnancies had an HPV placenta infection rate of 57%; suggesting that HPV infection during pregnancy is not always pathogenic.[7]

Overall, women who had HPV identified in their placenta had babies with lower gestational age at birth compared to women who tested negative for HPV.[7] All of the women who developed pre-eclampsia had placenta that were infected with a high-risk form of HPV.[7] The authors concluded that previous assumptions that HPV infection does not cause adverse outcomes during pregnancy may be incorrect.[7] This study suggests that HPV vaccination may reduce the prevalence of pregnancy complications such as pre-eclampsia, although further work is needed to confirm this. The major limitation of this study was that it was biased towards selection of women with pregnancy complications and is not representative of the community as a whole.

part of a school-based programme or by a general practitioner.[1] The vaccine is given as three doses, ideally at zero, two and six months.[1] There does not appear to be a reduction in vaccine efficacy if the intervals between doses are longer.[1]

Vaccination against HPV is recommended, but not funded, for boys and young men under 20 years, people who are immunocompromised and men who have sex with men.[1]

For further information see: "The HPV vaccination programme: addressing low uptake", BPJ 43 (Apr, 2012)

Recommendations for primary care to improve vaccination rates

In August, 2014, the Ministry of Health held a workshop to discuss strategies to increase HPV vaccination coverage. The agreed outcomes of this workshop were recently published as an action plan. Nurses running school-based vaccination programmes are reminded to liaise with primary care teams to ensure that all girls who have not received all three doses of the HPV vaccination are offered them in their 14th year.[5] It is recommended that as of October, 2015, general practices begin recalling all 14-year old girls who are not fully immunised against HPV.[5] General practices should also have recalls in place for any 12-year old girls who chose to have their HPV vaccination administered by the primary care team.

For further information see: **www.health.govt.nz/system/files/documents/publications/hpv-revitalisation-final.pdf**

References

1. Ministry of Health (MoH). Immunisation handbook. MoH, 2014. Available from: www.health.govt.nz (Accessed Oct, 2015).
2. Hariri S, Dunne E, Saraiya M, et al. Chapter 5: Human papillomavirus (HPV). In: Vaccines and immunizations. Centres for Disease Control and Prevention: Atlanta 2014. Available from: www.cdc.gov (Accessed Oct, 2015).
3. Ministry of Health (MoH). Selected cancers 2011, 2012 & 2013 (Provisional). 2014. Available from: www.health.govt.nz (Accessed Oct, 2015).
4. World Health Organisation. Human papillomavirus vaccines WHO position paper. Wkly Epidemiol Rec 2009;84:117–32.
5. Ministry of Health (MoH). Revitalising the National HPV Immunisation Programme with Agreed Outcomes from the August 2014 Workshop. MoH, 2015. Available from: www.health.govt.nz (Accessed Oct, 2015).
6. Ministry of Health. HPV immunisation programme. MoH, 2015. Available from: www.health.govt.nz (Accessed Oct, 2015).
7. Slatter TL, Hung NG, Clow WM, et al. A clinicopathological study of episomal papillomavirus infection of the human placenta and pregnancy complications. Mod Pathol 2015;[Epub ahead of print].

An update on the use of **nitrofurantoin** in patients with **renal impairment**

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) have updated their guidance to allow nitrofurantoin to be prescribed to patients with reduced renal function. This change was influenced by increasing resistance to trimethoprim and amoxicillin in the UK; meaning that there is an increased need to prescribe nitrofurantoin to patients with acute cystitis.[1] The Medicines Adverse Reactions Committee (MARC) recently discussed whether a similar change in guidance was appropriate for New Zealand.

It was concluded by MARC that **the contraindication of creatinine clearance of < 60 mL/min for the use of nitrofurantoin**, as listed on the New Zealand medicine datasheet, **should remain**.[2, 3] The recent Best Tests article on treating urinary tract infections (UTIs) in older people (July, 2015) reported guidance on the use of nitrofurantoin in patients with reduced renal function consistent with the UK position, i.e. avoid in patients with estimated glomerular filtration rate [eGFR] < 45 mL/min/1.73m^2; this advice has now been updated in the online version of this article to account for the recent decision by MARC.

For further information, see: "A pragmatic guide to asymptomatic bacteriuria and testing for urinary tract infections (UTIs) in people aged over 65 years", Best Tests (Jul, 2015).

The role of nitrofurantoin in the treatment of acute cystitis

Nitrofurantoin or trimethoprim are suitable first-line treatment options for non-pregnant females and males with acute cystitis.[4–7]

Use of nitrofurantoin can be problematic for patients with renal dysfunction. Reduced renal function may lead to toxicity due to an increase in nitrofurantoin serum levels.[1] Impaired renal function also decreases the efficacy of nitrofurantoin as an antibacterial medicine in the urinary tract.[1]

Serious pulmonary reactions, both acute and chronic, and which can be fatal, have been reported secondary to treatment with nitrofurantoin.[8] The incidence of acute pulmonary reactions in patients taking nitrofurantoin is estimated to be less than 1% and it most often affects females aged 40 – 50 years.[8] Acute pulmonary reactions are reported to occur more frequently after repeated courses of nitrofurantoin treatment.[8]

Trimethoprim is generally considered to be better tolerated than nitrofurantoin and the dosing regimen is simpler as it is taken once daily, at night. However, antibiotic resistance levels for *Escherichia coli*, the most frequent cause of cystitis, are reported to be higher for trimethoprim compared with nitrofurantoin. In 2013, the percentage of urinary *E. coli* reported as resistant to nitrofurantoin from hospital and community laboratories was 1.3% (from almost 100 000 isolates tested).[9] During the same period the percentage of urinary *E. coli* reported as resistant to trimethoprim was 26.2% (from approximately 98 000 isolates tested).[9]

Deciding whether to prescribe trimethoprim or nitrofurantoin

The patient's renal function, tolerance, the complexity of the dosing regimens and local bacterial susceptibility are relevant considerations when prescribing antibiotics for acute cystitis.

Comment from Associate Professor Mark Thomas, Infectious Diseases Specialist, University of Auckland:

> *I would recommend nitrofurantoin, 50 mg, four times daily, for five days in females and seven days in males, as the first-line treatment for uncomplicated acute cystitis in patients with creatinine clearance > 60 mL/min (avoid*

in women who are 36+ weeks pregnant). In patients with renal impairment or known intolerance or allergy to nitrofurantoin, use trimethoprim 300 mg, once daily for three days in females (avoid during the first trimester of pregnancy) and seven days in males. If there is a known high rate of resistance (> 15%) to trimethoprim in E. coli *in the local area, consider taking a urine sample and adjust treatment based on the susceptibility results of the organism isolated.*

While norfloxacin is an alternative antibiotic for the treatment of cystitis, it should be strictly reserved for isolates resistant to trimethoprim or nitrofurantoin.[7] Norfloxacin should be avoided in pregnant women or in patients who have severe renal impairment (refer to the New Zealand Formulary for details).[6]

For further information about the use of norfloxacin see: "Quinolone antibiotics – limit use", BPJ 35 (Apr, 2011).

References

1. Medicines and Healthcare product Regulatory Agency (MHRA). Nitrofurantoin now contraindicated in most patients with an estimated glomerular filtration rate (eGFR) of less than 45 ml/min/1.73m^2. MHRA, 2014. Available from: www.gov.uk/drug-safety-update (Accessed Oct, 2015).
2. New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Minutes of the 163rd medicines adverse reactions committee meeting – 10 September 2015. Medsafe, 2015. Available from: www.medsafe.govt.nz (Accessed Oct, 2015).
3. W. M. Bamford & Company Limited. Nifuran. Medicine Datasheet, 2004. Available from: www.medsafe.govt.nz (Accessed Oct, 2015).
4. Scottish Intercollegiate Guidelines Network (SIGN). Management of suspected bacterial urinary infection in adults. Edinburgh: SIGN, 2012. Available from: www.sign.ac.uk (Accessed Oct, 2015).
5. Auckland District Health Board (ADHB). Adult empirical antimicrobial treatment guidelines. ADHB, 2014. Available from: www.adhb.govt.nz (Accessed Oct, 2015).
6. New Zealand Formulary (NZF). NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
7. bpacnz. Antibiotics: choices for common infections. Available from: www.bpac.org.nz (Accessed Oct, 2015).
8. Kanji Z, Su VCH, Mainra R. Nitrofurantoin-induced pulmonary reaction involving respiratory symptoms: case report. Can J Hosp Pharm 2011;64:362–5.
9. The Institute of Environemental Science and Research Ltd (ESR). Antimicrobial resistance data from hospital and community laboratories. ESR, 2013. Available from: https://surv.esr.cri.nz/PDF_surveillance/Antimicrobial/AR/National_AR_2013.pdf (Accessed Oct, 2015).

CORRESPONDENCE

Should antibiotics be continued for a sore throat if GAS negative?

Dear Editor,
There are occasional exceptions to every rule, including Mark Thomas' generally good advice to stop antibiotics if a throat culture fails to confirm GAS. Throat cultures, if properly taken, are 90-95% sensitive for GAS, not 100%, and that is only if they are properly taken from the tonsils and the posterior pharynx. If a child has a classic appearance with fever, tachycardia, dusky red moist tonsils, tonsillar pillars and pharynx, quite large neck nodes, a bit of a scarlatiniform rash, and the complete absence of nasal or chest symptoms, I would want that child to complete ten days of antibiotics regardless of the swab result.

Dr Ronald Baker [Online comment]

Dear Editor,
Mark Thomas might spare a thought for the mountains of unused antibiotics that might appear in vulnerable households from those who stop a ten day course early. Surely this is a greater risk than one unnecessary but properly completed course. While awaiting swab results a more practical option might be to prescribe a five day course with one repeat available at no extra charge if the swab returns positive.

Is near-patient testing for GAS likely to become a practical option in New Zealand? And how did the UK manage to eliminate rheumatic fever from its morbidity profile?

Dr David Smith, *General Practitioner*
Pahiatua
(Personal view only)

Response from Associate Professor Mark Thomas:

I recently strongly advised that antibiotic treatment should be promptly discontinued in a person at high risk of rheumatic fever, with a sore throat, who has a negative swab for *Streptococcus pyogenes* ["*Should antibiotics be continued for a sore throat if GAS negative?", Correspondence, BPJ 69 (Aug, 2015)*].

Dr Baker suggests that because culture of a throat swab is *only* 90–95% sensitive, he would advise patients with many clinical features associated with streptococcal pharyngitis to complete a ten day course of treatment. However, such clinical findings are not more reliable than culture as evidence that pharyngitis is due to *S. pyogenes*. Clinical prediction rules can help to indicate which children with a sore throat are most likely to have *S. pyogenes* isolated from a throat swab. However, none of these clinical prediction rules is either very sensitive or very specific. A recent study of the most effective clinical prediction rule[1] in children in Brazil, found that *S. pyogenes* was present in only 41% of children with the highest test scores.[2] Use of this and other clinical prediction rules is not much better than a coin toss, and certainly very much less reliable than laboratory culture results!

Dr Smith suggests that "mountains of unused antibiotics" might accumulate in the households of people at high risk of rheumatic fever, and these unused antibiotics might pose a greater risk to the family members than consuming five or ten days of an antibiotic course, prescribed for an infection that is not present. A simple solution to this problem is to advise patients not to have the antibiotic prescription dispensed unless informed by the practice that the throat swab is positive. To suggest that a patient who does not have *S. pyogenes* infection should be the disposal unit for an unnecessary course of antibiotics seems surprising to me. While putting the unneeded antibiotics in the rubbish or down the lavatory will make a small contribution to contamination of a landfill or of the waterways, surely that is better than advising the patient to consume the antibiotic when there is no expectation of any benefit for the patient and only the risk of an adverse event, such as diarrhoea or rash, and disruption of their normal microbiome?[3, 4]

Dr Smith also asks whether near patient testing, using a rapid antigen detection test is likely to become a practical option in New Zealand. A recent study of one such test found that of 61 school children with *S. pyogenes* cultured from a throat swab only 22 had a positive rapid test (sensitivity 36%), and of 237 school children who did not have *S. pyogenes* cultured from a throat swab 37 had a false positive rapid test (specificity 84%). This particular test was considered insufficiently robust for routine use in school based clinics.[5]

Associate Professor Mark Thomas
Department of Molecular Medicine and Pathology
Faculty of Medical and Health Sciences
University of Auckland

References:

1. Le Marechal F, et al. Streptococcal pharyngitis in children: a meta-analysis of clinical decision rules and their clinical variables. BMJ Open 2013;3:e001482.
2. Joachim L, et al. Pragmatic scoring system for pharyngitis in low-resource settings. Pediatrics 2010;126:e608-e614.
3. Saari A, et al. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics 2015;135:617-26.
4. Gough EK, et al. The impact of antibiotics on growth in low and middle income countries: systematic review and meta-analysis of randomised controlled trials. BMJ 2014;348:g2267:1-13.
5. Upton A, et al. Disappointing performance of rapid antigen detection tests for group A streptococcus in the Auckland school-based sore throat programme. N Z Med J 2014;127:1389; 103-5.

Comment from bpac^{nz} editorial team:

In his letter, Dr Smith was also making reference to another article which appeared in the same edition of BPJ – "Piles of pills: prescribing appropriate quantities of medicines", BPJ 69 (Aug, 2015). If a medicine is no longer required, patients can take their additional supply to a pharmacy for safe disposal. Disposal of medicines in the household rubbish or by flushing down the toilet is not advised.

In regards to the final question Dr Smith asked, there are many and varied factors as to why rheumatic fever has been largely eliminated from the United Kingdom. It essentially comes down to improved standards of living and better access to healthcare. Rheumatic fever is now most prevalent in developing countries that lack good health infrastructure and where there is overcrowding and poor sanitation. It also affects indigenous communities in countries such as Australia and New Zealand. Rheumatic fever still persists in

low socioeconomic communities in the Northern and Central North Island, and in some parts of the Wellington region, and almost exclusively affects Māori and Pacific peoples in New Zealand.

Is co-trimoxazole an appropriate treatment for cellulitis?

Dear Editor,
Is there a place for using co-trimoxazole in view of increasing resistance to flucloxacillin, as it appears to be equally effective for patients with cellulitis?

Online comment

This question was initially published online in response to a peer group discussion topic based on the article "Cellulitis: skin deep and spreading across New Zealand", BPJ 68 (Aug, 2015).

Response from bpac^{nz} editorial team:
Flucloxacillin has traditionally been the first-line oral antibiotic for patients with cellulitis. Flucloxacillin is a narrow spectrum antibiotic that penetrates skin and soft tissue well. All *Strepococcus pyogene*s and other related streptococci are susceptible to treatment with flucloxacillin, as are approximately 90% of strains of *Staphylococcus aureus* (i.e. all *S. aureus* except for MRSA).[1,2] Co-trimoxazole (trimethoprim + sulfamethoxazole) has poor streptococcal coverage, therefore it is not usually recommended for the empiric treatment of skin infections.[3] Second-line antibiotics for patients with cellulitis include cephalexin, erythromycin and roxithromycin.

Trimethoprim + sulfamethoxazole is best reserved for patients where MRSA is present or suspected, or when antibiotic sensitivities indicate it is an appropriate choice There is a limited choice of oral antibiotics available for the treatment of infections due to MRSA and trimethoprim + sulfamethoxazole should be reserved for this purpose.

There are a number of risks associated with the use of trimethoprim + sulfamethoxazole. It is associated with rare but serious adverse effects, notably blood dyscrasias and Stevens-Johnson syndrome.[4] Trimethoprim + sulfamethoxazole has also been associated with an increased risk of sudden death in older patients also taking spironolactone;[5] this is thought to be due to both medicines causing hyperkalaemia. Trimethoprim + sulfamethoxazole and spironolactone taken concurrently can also result in hyponatraemia. Patients prescribed trimethoprim + sulfamethoxazole are at risk of hyperkalaemia if taking ACE-inhibitors, and at risk of hypoglycaemia if taking sulphonylureas.[4]

In summary, trimethoprim + sulfamethoxazole is not an appropriate first-line empirical treatment for cellulitis in New Zealand, as it has poor streptococcal coverage. It should be reserved for patients with proven antimicrobial sensitivity to trimethoprim + sulfamethoxazole, or for patients with proven or suspected MRSA.

References

1. Clinical Resource Efficiency Support Team (CREST). Guidelines on the management of cellulitis in adults. CREST, 2005. Available from: www.acutemed.co.uk (Accessed Oct, 2015).
2. Thomas MG, Smith AJ, Tilyard M. Rising antimicrobial resistance: a strong reason to reduce excessive antimicrobial consumption in New Zealand. N Z Med J 2014;127(1394):72-84.
3. Bartlett JG. Cellulitis. Johns Hopkins Antibiotic Guide, 2013. Available from: www.hopkinsguides.com (Accessed Oct, 2015).
4. New Zealand Formulary. NZF v40. 2015. Available from: www.nzf.org.nz (Accessed Oct, 2015).
5. Antoniou T, Hollands S, Macdonald EM et al. Trimethoprim-sulfamethoxazole and risk of sudden death among patients taking spironolactone. CMAJ, 2015;187(4):E138-43.

Melatonin in practice

Dear Editor,
In my view the article on Melatonin [Melatonin: Is it worth losing any sleep over? BPJ 69, Aug, 2015] underestimates the true value of this useful agent and I think its importance in human health warrants further discussion. Sleep quality has rightly been described as a central pillar of health.

Assessing the effectiveness of an endogenous biological substance in a randomised controlled trial as if it was a pharmacological agent will always provide a limited perspective simply because its utility probably only relates to deficiency states, and therefore its use is best appreciated when individualised.[1] In short, giving it to patients who do not need it will have little useful effect, and indeed it is often not tolerated. Conversely patients who have difficulty producing melatonin, for whatever reason, are usually

exceedingly grateful for it. Patients who may be struggling to produce sufficient melatonin can usually be identified by giving some consideration to the biosynthesis and physiology of melatonin, and the many extraneous factors that impinge upon it.[2] The key question that assists in identifying the patients that respond has got little to do with how long it took them to fall asleep, but rather by asking them how they felt when they woke up in the morning.

Melatonin is produced by the acetylation and then methylation of 5-hydroxytryptamine (serotonin).[3] Anything that impinges on the biosynthesis of serotonin can potentially find a way to disrupt melatonin biosynthesis. This will include deficiency of substrates and co-factors (such as zinc, magnesium and B6) as well as the regulatory mechanisms that control tryptophan hydroxylase. Add to this anything that disrupts the methylation cycle, also including the availability of its substrates, co-factors, and a number of common gene polymorphisms that alter the activity of enzymes that are rate limiting. A number of single nucleotide polymorphisms influence the function of the melatonin receptors, and these are in turn associated with several disparate disease entities,[2] and are subject to functional deterioration in the context of neurodegenerative disease. Further to this the production of melatonin is subject to two quite pervasive inhibitory factors- light and cortisol!

A corollary of the above in mental health is that a patient with a mood disorder that has responded especially well to an SSRI but still struggles with poor sleep quality, is usually a good candidate for a trial of melatonin, whereas a patient who has not responded well to SSRIs is more likely to dislike its effects.

Melatonin has pleiotropic effects that should cause us to think first of its application to sleep disorders in certain clinical settings, and to consider that melatonin deficiency or receptor dysfunction may have consequences "which go far beyond sleep difficulties." [2] Melatonin has been widely researched in the context of cancer (there are 1897 papers currently referenced in PubMed),[4, 5] and there are now five known mechanisms for its potential supportive role in cancer treatment, the most widely known being its ability to up-regulate Natural Killer Cell activity.

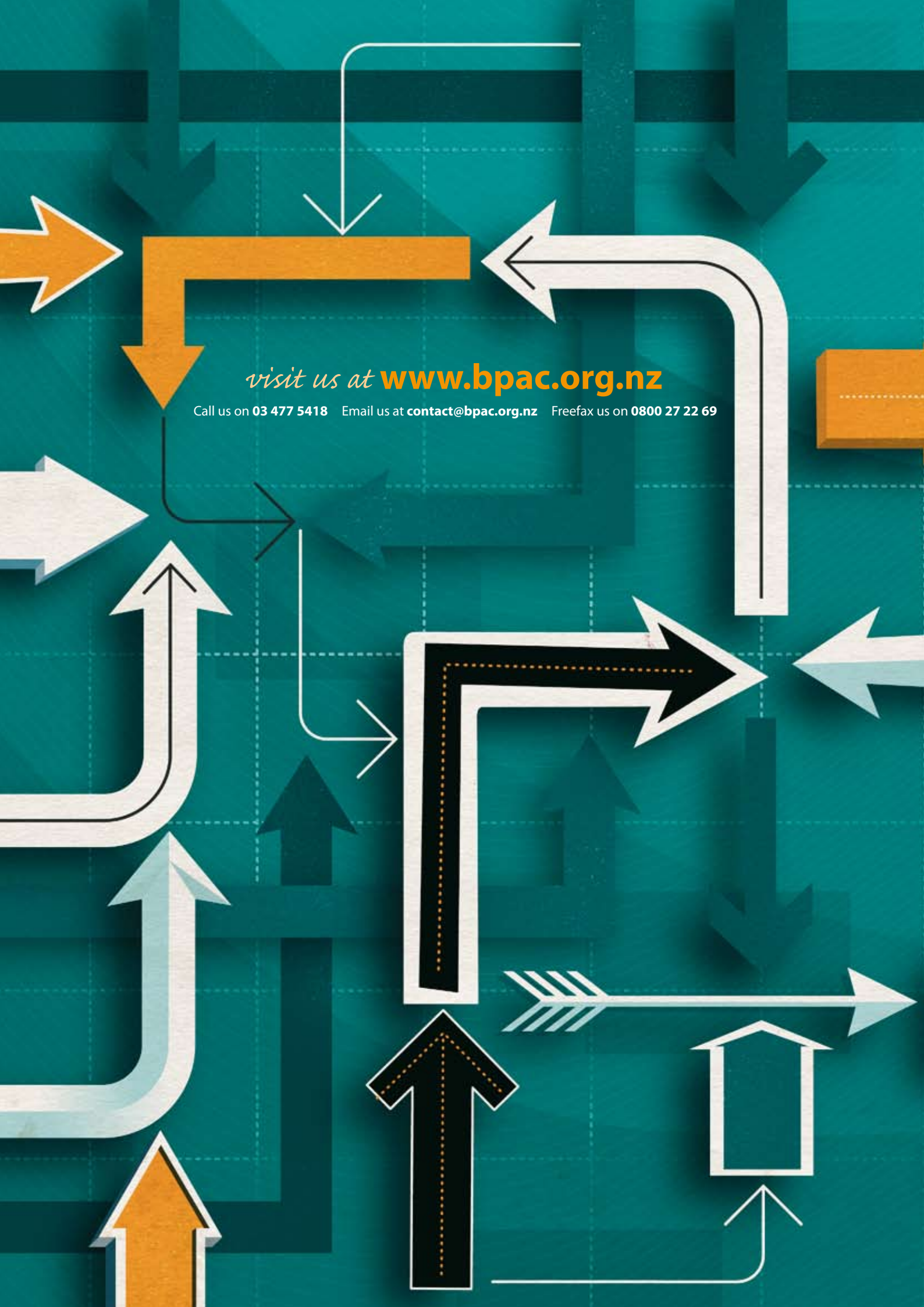
Its reputation as the most powerful anti-oxidant capable of passing the blood-brain barrier suggests a role for it in sleep disorders in the context of neurodegenerative diseases of the ageing brain. Age-related decline in melatonin production is of course a striking feature of its physiology. Melatonin is especially clever in its antioxidant capacity as it achieves this not by actually being an antioxidant itself, but by up regulating endogenous cellular antioxidant defences (the same way that broccoli does!), by activating the ARE-NrF2 transcription complex.[6–9] A recent discovery has been the efficacy of melatonin in restoring normal night time "dipping" of blood pressure in hypertensive patients, who are at especially high risk of end organ damage when the dysregulation of blood pressure has this attribute.[10–15] A protective role in metabolic syndrome has also recently been explored.[16] Sleep disorders in the context of chronic inflammation are also candidates for a trial of melatonin, as certain inflammatory cytokines will upregulate the enzyme IDO, shifting tryptophan metabolism away from the production of serotonin/melatonin, and instead diverting it to an alternate biochemical pathway that can further exacerbate neural inflammation.[17] Sleep problems associated with neurodevelopmental disorders such as autism is another area in which melatonin has demonstrated well established benefits.[18,19]

Whilst there are rightly concerns about the lack of long-term studies on the effects of melatonin , it can at least be said that there are no patients who suffer from benzodiazepine (or other hypnotic drug) deficiency. The benzodiazepines (and probably related drugs) cause down regulation of the GABA receptor, their long term use is linked with cognitive deficits that are not fully recoverable with discontinuation of the drug, and they are associated with an increased incidence of dementia and even mortality.[20–23] They are truly substances of last resort, yet continue to be widely used. That is something to lose sleep over!

Dr William Ferguson, *General Practitioner*
Kumeu

Reference list available from: **www.bpac.org.nz/BPJ/2015/October/correspondence.aspx**

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



visit us at **www.bpac.org.nz**

Call us on **03 477 5418** Email us at **contact@bpac.org.nz** Freefax us on **0800 27 22 69**