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Best Practice

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Issue 69 August 2015

Piles of pills: Prescribing appropriate quantities of medicines

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better medicine

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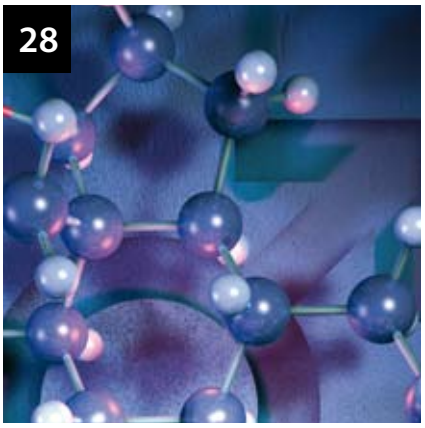

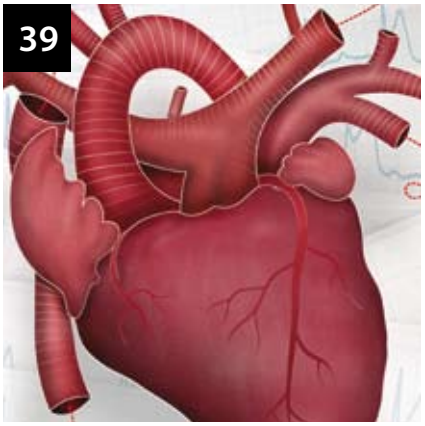

All web links in this journal can be accessed via the online version:
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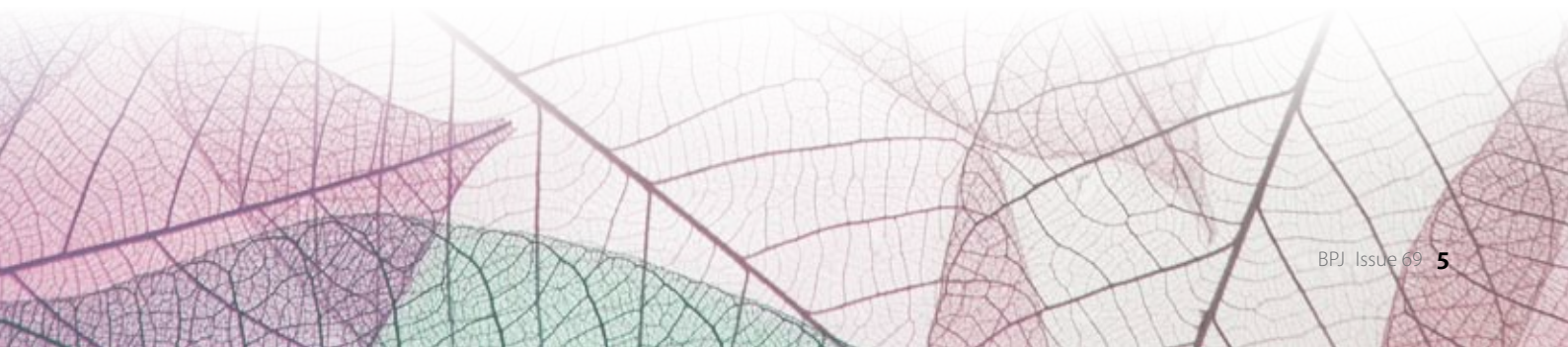
An avoidable death: the importance of **communication** in clinical care

ARTICLE WITHDRAWN

This article has been withdrawn as the case study submitted by ACC is no longer available




OXYCODONE
HYDROCHLORIDE

Nationally Funded Modules available for general practice

BPAC Inc is pleased to be able to offer general practices a suite of clinical decision support modules, free-of-charge. These modules have been nationally funded for healthcare professionals in New Zealand through arrangements with the Ministry of Health, PHARMAC and Medsafe.

These modules act as a both a decision support tool and process guide in each clinical area. Individualised options, questionnaires, standard treatment suggestions and appropriate referral documents are generated in a logical flow. Links to relevant websites for additional information and support are built in to each module. Downloadable patient information and/or links to suitable online patient advice are at your immediate call.

The Nationally Funded modules are accessed via Best Practice decision support, which can be installed free-of-charge at any general practice in New Zealand.

The Nationally Funded suite is made up of the following modules:

- Adverse Reaction Reporting
- Hazardous Substances & Lead Poisoning Notifications
- Childhood Asthma
- Childhood Asthma – Action Plan
- Depression (4 modules)
  - Depression in Adults
  - Depression in Young People
  - Ante/Postnatal Depression
  - Depression in the Elderly
- INR
- Acne Management
- Isotretinoin
- TIA/Stroke – *recently released nationally*
- Chronic kidney disease – *coming soon*

Adverse Reaction Reporting

For the last two decades or more, New Zealand has had one of the highest rates per capita in the world of reporting adverse reactions to medicines. This high rate does not, however, reflect a more serious problem in New Zealand with adverse reactions to medicines; rather that we are more diligent about reporting these events.

To help maintain this trend, this module enables the reporting of suspected adverse drug reactions directly to the National Centre for Adverse Reactions Monitoring (CARM). By "auto-filling" with information already held in the Patient Management System (PMS) the reporting of an adverse reaction is rapid and efficient. A copy of the report is automatically saved on the patients' record.

Hazardous Substances & Lead Poisoning Notifications

General Practitioners are now asked to notify cases of disease and injury caused by hazardous substances seen in primary care to their appropriate Medical Officer of Health. Notification may result in a Public Health Unit investigation of that particular event or a collection of related cases, or may initiate the investigation of a particular substance in a region or nationwide. This module guides the user quickly through the reporting process, supplies the information needed by the Ministry of Health and forwards the notification to the appropriate recipient. A copy of the report is then automatically saved to the patients' record.

Childhood Asthma

New Zealand has one of the highest rates of childhood asthma in the developed world. Between 20 – 30% of the children in your practice are predicted to develop symptoms. Based on current guidelines, this module provides decision support for the diagnosis, control and treatment of childhood asthma using a stepwise approach. This in turn links into the Childhood Asthma Action Plan module.

Childhood Asthma – Action Plan

This module enables you to create an individualised action plan for a child with asthma (Space-to-Breath), illustrating which device they should use and when to use it. A black and white copy can be given to the family at the consultation and a high quality, colour version is automatically generated and posted to the patient's address.

Depression

The World Health Organisation estimates that by the year 2020, depression will be the second most common cause of ill health and premature death worldwide. The depression modules are divided into four key groups of patients: Young People, Adults, Elderly People and Ante/Postnatal depression. The patient's demographic information is used to initiate the appropriate module, with relevant questionnaires and tools.

These modules allow you to step through the appropriate questions as you talk with your patient, giving you more time to listen and engage. This is followed by the guidelines which suggest appropriate treatment and /or referrals. Patient resources, including further questionnaires, information and website links, are included in the modules.

Young People

Every interaction with a young person in primary care should be regarded as an opportunity to assess their psychosocial as well as physical wellbeing. Young people may not be forthcoming with their problems and issues, but sensitive questioning can identify the need for further assessment.

Adolescent depression is similar to depression in adults, with a greater likelihood of mood symptoms at presentation, but these may still be masked by behavioural problems, substance misuse or somatic symptoms. The assessment tools within this module will assist and support you as you work with these young patients.

Adults

People are reluctant to discuss their depression symptoms for a number of reasons. It is estimated that two-thirds of people with depression who see a healthcare provider present with physical symptoms, such as headache, back problems or chronic pain. Use of this module during a routine consultation will help clarify and quantify a diagnosis of depression and subsequent management plan.

Ante/Postnatal

Depression affects up to 10% of pregnant women and up to 15% of women in the postnatal period. This module focuses on the recognition, assessment and management of patients during this important time in their lives.

Elderly people

Many older people are reluctant to "bother" their general practitioner about something other than a physical illness. They seldom mention depression and are more likely to talk about vague symptoms. Although they know they need help, some people have difficulty putting troubled feelings into words. Many older people may also perceive that a low mood is normal. Tools within this module, such as the Geriatric Depression Scale, have been specifically developed for older populations to help address these issues and to give more weight to mood related symptoms.

INR

There are approximately 46,000 people in New Zealand currently taking warfarin. This module utilises a validated formula to assist in ongoing management of a patient's anticoagulant dosing. Included is a review page which prints back to your PMS, graphical display of INR level history, a calculator for average dose rate and a printable calendar for the patient's use which clearly shows their daily dose regimen.

Acne Management

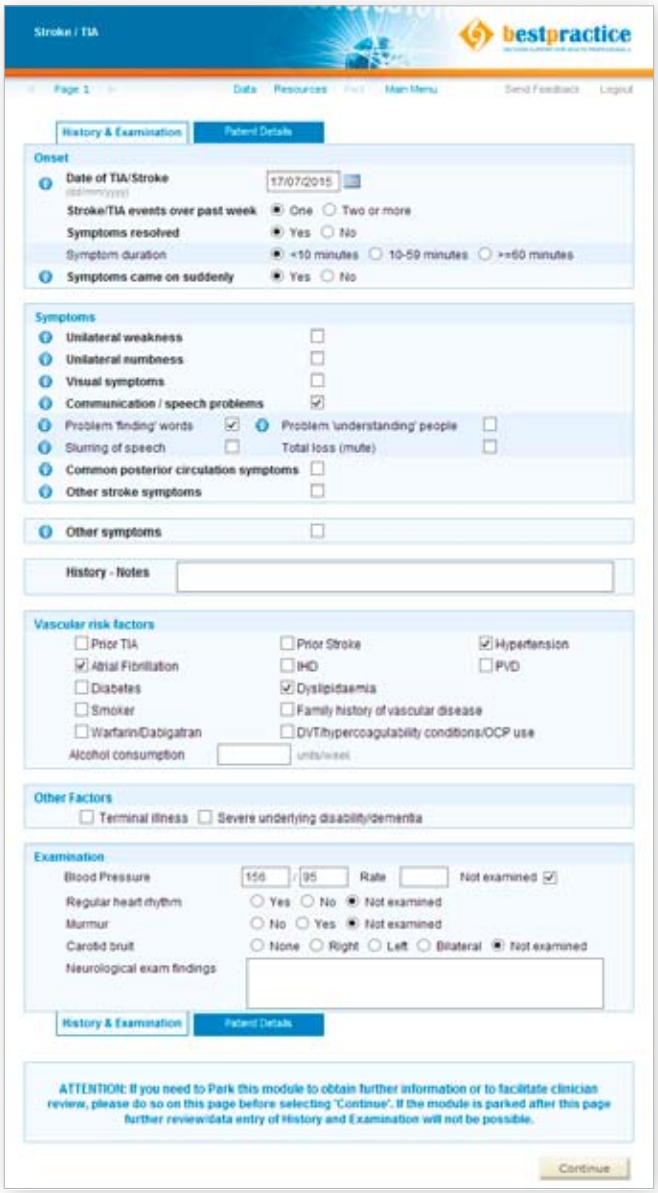
Acne is one of the most common skin conditions, affecting up to 80% of people aged between 15 to 25 years. This module assists you in assessing the severity of acne, and directs you to the most appropriate resources and treatments options for your patient. If isotretinoin is an appropriate treatment, you can progress seamlessly to the isotretinoin module to initiate and manage this.

Isotretinoin

This module can be used either as a stand-alone module or as part of the acne management module; progress through patient consent documents, laboratory request forms, results and writing of the prescription, with quick access to the Special Authority process. This module is designed to meet the PHARMAC recommendation that a support tool be utilised when prescribing isotretinoin. Both patient and prescriber information about the safe use of isotretinoin are included.

New modules: TIA/Stroke and Chronic Kidney Disease

The Ministry of Health has now funded two new Best Practice modules for national release – TIA/Stroke assessment and Chronic Kidney Disease. These modules will be rolled out to practices over the coming months. Further information will be provided in the next update.



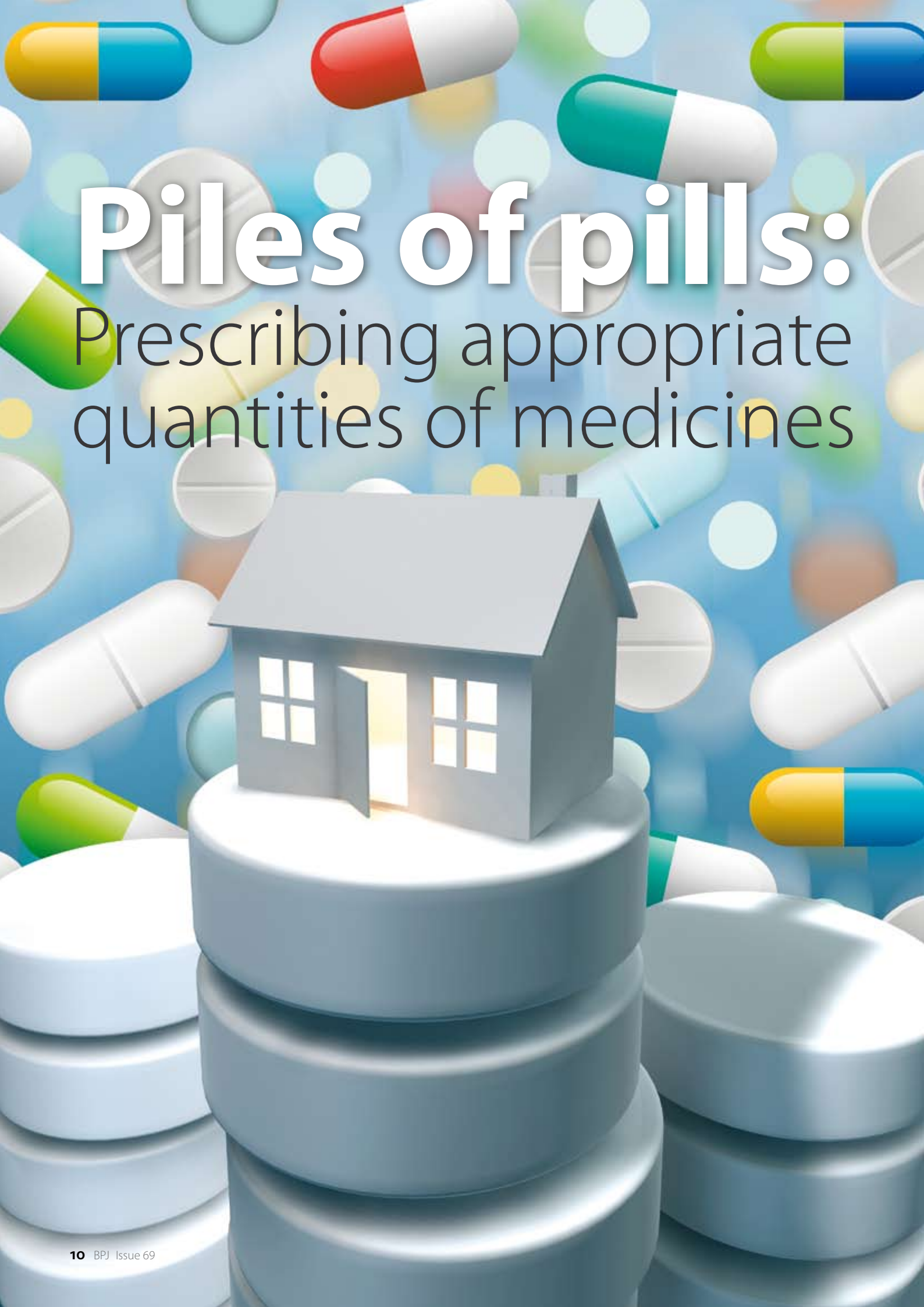
Above: The new TIA/Stroke electronic decision support data entry form showing a sample case.

The product *bestpractice* Decision Support has been developed by BPAC Inc, which is separate from bpac^{nz}. bpac^{nz} bears no responsibility for *bestpractice* Decision Support or any use that is made of it.

For further information about *bestpractice* Decision Support see the website:

www.bestpractice.net.nz

Piles of pills:
Prescribing appropriate quantities of medicines



Medicine wastage is a significant problem in New Zealand, with large quantities of subsidised medicines dispensed, but never used. There are various strategies that can be undertaken by prescribers, pharmacists and patients to reduce medicine wastage and prevent "piles of pills" creating a safety issue in homes. These strategies include regular review of a patient's current medicines, the use of trial periods for new medicines, prescribing appropriate quantities of "as required" medicines, utilisation of the Long Term Condition Service and being aware of "safety medicines." An underlying component of all of these strategies is patient education and support. Gaining an understanding of the Pharmaceutical Schedule rules regarding subsidised community pharmaceuticals can also help clinicians prescribe appropriately.

Every year in New Zealand, it is estimated that hundreds of thousands of subsidised medicines are dispensed to patients and never used. These medicines often end up accumulating in people's homes, where they can cause safety issues such as accidental or intentional overdose, inappropriate sharing of medicines or use of expired medicines which may no longer be effective. If medicines are inappropriately disposed of they can also cause environmental pollution, e.g. if placed in household rubbish or flushed down the toilet.

Medicines are wasted for various reasons, including unintentional oversupply, non-adherence, changes in treatment or dose, allergic reaction or intolerance to the medicine, resolution of the condition or death of the patient. In a New Zealand survey completed by 452 people, 56% reported that they collect all items prescribed by their doctor, and just over 25% collect all medicine repeats, even if the medicine is no longer needed or wanted.[1] Only 13% of respondents reported that they returned unwanted medicines to a pharmacy.[1]

Regular review to check the appropriateness of, and adherence to, long term medicines is not only essential clinically but is one of the most important ways to prevent wastage. There are various other strategies that can also be undertaken by prescribers, pharmacists and patients to reduce medicine wastage and prevent "piles of pills" creating a safety issue in homes, including:

- Prescribing new medicines for trial periods only in case they are not continued due to intolerability or ineffectiveness
- Prescribing appropriate quantities of "as required" medicines
- Encouraging patients to put prescription items on hold at the pharmacy if they are not currently required
- Prescribing smaller quantities of "safety medicines" which may pose a risk to certain patient groups
- Considering if a patient is eligible and likely to benefit from being registered under the Long Term Condition (LTC) scheme managed by community pharmacists

 For further information on each of these strategies, keep reading.

An underlying component of all of these strategies is patient education and support, i.e. ensuring that the patient understands what medicines they are prescribed, what they are for and how to use each medicine correctly. In 2009 the Nelson Marlborough DHB ran a "Discarding Unwanted Medicines through Pharmacies" (DUMP) campaign, which included a questionnaire for patients on why they were returning unwanted medicines. Several patients commented that they did not take some of their prescribed medicines at all even though they were required (e.g. amoxicillin, bisacodyl and naproxen), because they were afraid of experiencing the adverse effects that they were warned about. In this scenario, non-adherence and medicine wastage was an unintended consequence of providing patients with adverse effect information, but not checking that they understood that it was still important that they took the medicine. This highlights the need to ensure that patients are not only provided with information about their medicines, but that they also comprehend the information that they are given.

Ask patients about their medicines

Whenever medicines are prescribed or dispensed there should be a conversation with the patient about their use of each medicine. Try to ask questions such as those below in an open-ended manner to avoid patients responding with the answer that they "expect" you want. If medicines are no longer required or not being used (and this non-adherence is appropriate), consider "de-prescribing".

Prescribers:

- Ask what medicines* the patient has at home before prescribing more
- Ask if they are using each medicine they have been prescribed
- Ask if they are experiencing any adverse effects or difficulties with taking any of their medicines

* include all options, e.g. pills, inhalers, topical preparations and also over-the-counter products

Pharmacists:

- Ask the patient if they require all of the medicines on their prescription before they are dispensed
- Ask if they know what their medicines are for
- Ask if they have any concerns or questions about the medicines they have been dispensed

Trial periods for new medicines

In surveys of medicine wastage, a common reason for the return of unused medicines is a change in dose or a change to a different medicine. There are several clinical scenarios where initiating pharmacological treatment for a patient is a "trial and error" process, e.g. managing hypertension. This can lead to medicine wastage if a 90-day supply of a new medicine is dispensed, but the medicine dose or type needs to be changed within a week or two.

If it is uncertain if a medicine will be continued, consider prescribing it for a trial period only. It is possible to use the "trial period" dispensing provision of the Pharmaceutical Schedule to allow dispensing of a small portion of the first supply of a new or changed dose of medicine, to check acceptability and tolerability of the medicine for the patient.

If the trial of treatment goes well, the patient can contact their pharmacist so that they can dispense the remainder of the prescribed medicine; this is at no additional cost to the patient provided the medicine is fully subsidised. Ideally the patient should also contact their doctor, particularly if they have had problems while taking the new medicine. If a different dose or medicine is likely to be required, this can be discussed or a consultation can be scheduled. A reminder placed in the patient's notes at the start of the trial period can be used to ensure that the outcome of the trial is documented and to check that the patient has correctly understood the reason for the trial and is continuing on the medicine or has a review in place.

Example of how a trial prescription can be written:

Rx Cilazapril 500 microgram tablets*
Sig 1 tablet daily
Mitte 3 months, **Trial 30 days**

The prescription must be endorsed with the words "Trial period" or "Trial" and the quantity or time for the trial specified.

This can be done when generating a prescription using Medtech by entering a number of days for an initial dispensing period in the provided box. The prescription will then be printed with a specified Trial Period.

* In the Pharmaceutical Schedule, the status of a medicine with regards to its dispensing frequency is indicated with * or ▲ beside the name of the medicine. In the New Zealand Formulary, this information can be found by hovering over the word 'restrictions' beside a medicine's listing, where it will say: "Statim: Three months or six months, as applicable, dispensed all-at-once".

In the scenario given for cilazapril, it is recommended that the patient be seen at the practice during the trial period so their blood pressure can be re-checked. This also provides an opportunity for laboratory assessment if required, e.g. renal function. N.B. When checking for adverse effects during the trial period for a patient taking cilazapril, an ACE related cough may or may not develop within one month.

Appropriate quantities for "as required" medicines

PHARMAC subsidy regulations require pharmacists to dispense 90-day single "stat" supply for many medicines (or 180 days for oral contraceptives); other medicines (often more costly medicines) must be dispensed in monthly quantities. (see: What are the Pharmaceutical Schedule rules regarding the dispensing of medicines in the community?, Page 15)

The 90-day supply requirement also applies to medicines that are prescribed "as required" (also known as p.r.n. – pro re nata). This can lead to unnecessarily large quantities of medicines being dispensed, if the prescriber does not specify an amount to be dispensed on the prescription. Depending on the medicine, this can pose a safety risk to the patient and their family, as well as contributing to medicine wastage.

It is recommended that when a medicine is prescribed "as required", prescribers decide on and specify the appropriate quantity (e.g. of tablets or inhalers) to be dispensed. As well as minimising wastage, this provides clinicians with an opportunity to reassess the patient in a follow up phone call or return consultation, if they require more medicine than expected.

Examples of appropriate quantities for "as required" medicines

Example 1: Laxatives

A patient requires a laxative on an intermittent but ongoing basis and is given the following standard prescription:

Rx Docusate and senna (Laxsol)
Sig 1 – 2 tablets prn, morning and night
Mitte 3 months

The pharmacist dispensing this prescription could dispense a total of 360 tablets (to allow for up to four tablets per day for 90 days). The pharmacist should discuss the amount required by the patient and use their clinical reasoning when deciding on the frequency and quantity on each dispensing, but ideally the prescriber should first consider if this is an appropriate quantity for the patient to be supplied before they are reviewed again.

Suggested alternative prescription:

Rx Docusate and senna (Laxsol)
Sig 1 – 2 tablets prn, morning and night
Mitte 200 tablets

This quantity of tablets will provide the patient with enough to take one tablet twice daily, regularly, with 20 extra tablets for the occasional higher dose.

Example 2: Analgesia

Paracetamol is often prescribed "as required" for analgesia, e.g.:

Rx Paracetamol 500 mg tablets
Sig 1 – 2 tablets q4h prn, up to qid
Mitte 3 months

The pharmacist will dispense a total of 720 tablets if the prescription is written in this way. This is appropriate if the intention of the prescriber is for the patient to take 1 g paracetamol on a regular basis, four times daily, for three months, e.g. for osteoarthritis. However, it is worth considering if this quantity is appropriate for the patient you have in front of you – what is the paracetamol being prescribed for? Is the intention that the paracetamol be used occasionally, when required, and not continuously? Is it safe for this household?

Suggested alternative prescription:

Rx Paracetamol 500 mg tablets
Sig 1 – 2 tablets q4h prn, up to qid
Mitte 180 tablets

This quantity provides the patient with enough supply to take two tablets, twice daily, for a few days a week over a three month period, e.g. for intermittent headaches or pain, or two tablets, four times daily, for approximately three weeks, e.g. for an injury.

Example 3: Asthma inhalers

Asthma reliever inhalers, such as salbutamol, are most often prescribed "as required". Ideally, patients with asthma will be well controlled with preventive medicines and will require reliever medicines infrequently. If a patient is requiring frequent prescriptions for reliever inhalers, this is an indication that they may not be using their preventer inhaler optimally, or at all.

A typical prescription for salbutamol is:

Rx Salbutamol inhaler 100 microgram/puff
Sig 1 – 2 puffs prn, up to qid
Mitte 3 months

In this example prescription the pharmacist would dispense four salbutamol inhalers to cover 56 doses per week (200 doses per inhaler) over three months, most likely as two inhalers in the first month and a further one in the second and third months: 2+1+1 (as salbutamol is not a stat medicine). N.B. The Pharmacy Procedures Manual states that a maximum of six inhalers (1,200 doses) will be subsidised and these should be dispensed according to the patient's needs, e.g. as 2+2+2 or 3+2+1 or 4+1+1.[3] Would it be more appropriate for the patient if they were prescribed only one or two salbutamol inhalers and to monitor requests for additional salbutamol inhalers?

Suggested alternative prescription:

Rx Salbutamol inhaler 100 microgram/puff
Sig 1 – 2 puffs prn, up to qid
Mitte 2 inhalers

The appropriate quantity of inhalers to prescribe is determined by the intended frequency of use, which will differ with the individual requirements of the patient. If their asthma is well controlled with a corticosteroid inhaler you would expect them to only need one salbutamol inhaler every three to six months. However, a patient may require a larger quantity of reliever inhalers to account for more doses during winter months if they contract a respiratory tract infection, or during "hay fever season" if they have concurrent allergic rhinitis, but may require fewer inhalers at other times during the year. Patients may also require an extra inhaler for their car or sports bag, but will not require this extra amount every prescription.

Best Practice Tip: Different types of asthma inhalers vary in the number of doses they contain, e.g. most reliever inhalers contain 200 doses; corticosteroid inhalers, long-acting beta2 agonist inhalers and combined inhalers usually contain 60, 112 or 200 doses, inhalers that require insertion of a capsule containing the dose usually contain 28 or 30 doses. Make sure the number of inhalers (or capsules for inhalers) indicated on a prescription will provide enough quantity to deliver the intended number of doses for the time frame indicated.

Putting prescription items on hold

When a patient presents a prescription at a pharmacy, any item on the prescription can be held at the pharmacy for up to three months, and dispensed at a later date if needed. This is a useful strategy for minimising medicine wastage, if a medicine is prescribed at the time of a consultation, but it is uncertain whether the medicine will be needed by the patient. This might be done to avoid the patient having to return for another consultation. For example, a patient who takes omeprazole on as "as needed" basis rather than daily may have this added to their prescription, but instructed to tell the pharmacist to hold it for them and only dispense it if the patient's existing supply runs out. An alternative strategy is to write the prescription item on a separate page from the other items, and instruct the patient to only have it dispensed if they require it; a prescription is eligible for subsidy if it is presented within three months from the date it was written. Ideally a notification or communication from the pharmacist would allow the prescriber to document whether or not a prescription has been dispensed. This may become more common place as electronic prescribing systems evolve and information is able to be more quickly and easily shared.

It is useful for the pharmacist also to ask patients if they require all of the medicines on their prescription to be dispensed. If a patient repeatedly asks their pharmacy to not dispense a medicine, however, and there is a concern about their adherence with prescribed medicines, the pharmacist should discuss this with the prescriber.

Prescribing safety medicines

Decisions around quantities of medicines prescribed often factor in financial considerations for the patient, i.e. wanting to provide people with an adequate, but not excessive, quantity of medicine for their condition taking into account the cost of the prescription and the visit they have made to the clinician, while minimising unnecessary additional costs. However, the quantities of medicines that will be stored in homes, and may not be used, should also be kept in mind. The "Safety Medicine" provision of the Pharmaceutical Schedule has been designed to minimise dispensing large quantities of high-risk medicines with no financial penalty to the patient.

What are the Pharmaceutical Schedule rules regarding the dispensing of medicines in the community?

The rules relating to how medicines are dispensed are set out in various sections of the Pharmaceutical Schedule. Section A: General Rules sets out the requirements for the subsidy and dispensing of community pharmaceuticals while Section F provides additional information on exemptions to monthly dispensing. The Dispensing Frequency Rule (Part IV under Section A) was introduced in July, 2012 to replace the Close Control Rule and was further amended in June, 2014.

N.B. The prescribing module of your PMS system may not currently contain up to date information stating which medicines are required to be dispensed all-at-once or identification of those medicines listed as "safety medicines".

Pharmaceutical dispensing rules:

- If a prescription item is marked with an asterisk * in the Pharmaceutical Schedule, three months supply of the medicine will be dispensed all-at-once or, in the case of oral contraceptives, six months will be dispensed all-at-once, unless the medicine meets the Dispensing Frequency Rule criteria (see opposite). Items marked with an * will only be subsidised if they are dispensed in a 90 Day Lot.
- A prescription item marked with a triangle ▲ in the Schedule may be dispensed in a three month supply all-at-once if the prescription is endorsed "certified exemption" by the prescriber or the pharmacist, e.g. gabapentin
- Community Pharmaceuticals not marked with an * or a ▲, will be dispensed in monthly lots. These medicines may be dispensed in a 90 Day Lot if the practitioner or pharmacist endorses the prescription with the words "certified exemption" or if the patient qualifies for an Access Exemption due to factors such as poor mobility, distance from the pharmacy, relocation or travel. The prescription must be signed on the back by the patient and the reason identified.
- The Dispensing Frequency Rule defines the medicines or patient groups that are eligible for more frequent dispensing (usually monthly) and outlines the conditions that allow for the pharmacy to claim payment for the additional dispensings. This rule allows more frequent dispensing in the following circumstances:
  - Patients who are eligible for the Long Term Condition (LTC) service
  - Non-LTC (core) patients as determined by the pharmacist if monthly dispensing or with approval by the prescriber if more frequent than monthly
  - People in residential care
  - Trial periods
  - Items identified as "safety medicines" (and co-prescribed items)
  - Pharmaceutical supply management

In practice, these rules mean that if you have been prescribing an item marked in the Schedule with an *, e.g. paracetamol, as "mitte 100 tablets + 2 repeats" it is likely that the patient will have been dispensed 300 tablets at the initial dispensing with no repeats dispensed. However, if the pharmacist has considered that more frequent dispensing is warranted (as outlined above) the patient may have received 100 paracetamol tablets each month. On your electronic prescribing system, there is likely to be a box to tick for "Frequent Dispense" replacing the one that used to be ticked for "close control", which is no longer relevant (N.B. this annotation does not need to be initialled.) This can give an indication to the pharmacist that the prescriber feels more frequent prescribing is required and provided that the patient or the medicine are eligible under the Dispensing Frequency Rule, this will enable the items to be dispensed monthly. For many patients, stat prescribing of prescription items will save them repeated trips to the pharmacy, but for others where there may be safety issues in particular, the prescriber and pharmacist should work together to determine the appropriate prescribing frequency.

Separate rules continue to apply to dispensing of Class B Controlled drugs.

Understanding prescription charges

The current prescription co-payment is $5 per medicine item if the medicine is fully subsidised in the Pharmaceutical Schedule. The $5 co-payment fee is paid by the patient the first time the prescription is dispensed; any medicines on the prescription that require repeat dispensing (e.g. medicines prescribed for more than 30 days) do not have another co-payment payable until the next prescription is written. The maximum number of $5 prescription co-payments for an individual or a family group is 20 per year* provided the same pharmacy has been used or receipts from other pharmacies have been presented to their regular pharmacist; this information is recorded in pharmacies but it is up to the patient to pass the information on if they are using more than one pharmacy to dispense their medicines.

* A year being defined as from 1 February until 31 January in the following year

Manufacturer's surcharges are payable by the patient when the medicine they are prescribed is only partially subsidised or is not listed at all in the Pharmaceutical Schedule. The manufacturer's surcharge is calculated per unit of medicine although this may vary between pharmacies, and is in addition to the $5 prescription co-payment. This reiterates the importance of specifying appropriate quantities of "as required" medicines, to minimise unnecessary costs for patients.

What is a Safety Medicine?

Many medicines on the Pharmaceutical Schedule have a default dispensed quantity of 90 days' supply. However, there are a number of "Safety Medicines" that can be dispensed in smaller than 90-day stat quantities at no extra cost to the patient, if the maximum supply quantity or period of supply is specified by the prescriber on the prescription, or is otherwise communicated to the dispensing pharmacist. This strategy is aimed at limiting the supply quantities of medicines that pose a particular clinical risk to patients who, for example, have difficulty managing their medicines, patients who may be at risk of intentional overdose, or who may be inclined to use the medicines inappropriately or in an unsafe way.

Safety Medicines are identified in the Pharmaceutical Schedule with the words "Safety Medicine" written alongside the medicine's listing; the current Safety Medicines are:

- Antidepressants listed under the "cyclic and related agents" subheading, e.g. amitriptyline, clomipramine, doxepin, imipramine, nortriptyline
- Antipsychotics
- Benzodiazepines*
- Zopiclone
- Class B Controlled Drugs, e.g. methylphenidate, morphine
- Codeine (a class C2 Controlled Drug) including paracetamol 500 mg with codeine 8 mg tablets
- Buprenorphine with naloxone (Suboxone, a class C4 Controlled Drug)

* A previous requirement that benzodiazepines had to be prescribed for a maximum of a 30-day supply per prescription was changed in 2010; benzodiazepines are now Safety Medicines, for which an appropriate dispensing quantity or frequency can be specified by the prescriber.

How do you prescribe a Safety Medicine?

Prescribe the medicine in the usual way and specify a maximum quantity of the medicine to be supplied to the patient on each dispensing (e.g. 90 tablets in total, supplied 30 tablets at a time) or time period of supply (e.g. supply tablets for 90 days in total, 30 days at a time).

Co-prescribed medicines are medicines that are prescribed at the same time as a Safety Medicine, e.g. regular cardiovascular or diabetes medicines; the dispensing pharmacist can choose to dispense these at the same time as the Safety Medicine if they judge that this is safer for the patient's circumstances.

Consider eligibility for the Long Term Condition service

The Long Term Condition (LTC) service was introduced in 2012 as part of a number of changes under the Pharmacy Services Agreement. General practitioners, other health professionals or family members can contact or refer a patient to a pharmacist to assess whether the patient may be eligible for this service. Patients may also self-refer.

A pharmacist will determine if the patient qualifies to be registered as a LTC patient. To be eligible the patient must live in the community and have at least one long term condition that requires medicine as part of its management. The patient then needs to have been either referred for assessment by a general practitioner or have contact with another allied health service, e.g. district nursing, secondary care, or have had concerns about their ability to self-manage their medicines identified by the pharmacist, family or the patient themselves. In addition, there must be evidence that the patient collected less than 80% of their regular medicines over the past six months or that despite collection there are concerns regarding adherence or the patient has had a recent review of their medicine use which has identified that support and monitoring is required.

Once eligibility has been determined and the patient's consent obtained, the pharmacist will undertake a review with the aim of assisting the patient with management of the medicines relating to their LTCs. This is likely to include an assessment of factors that may be affecting adherence, determining an appropriate dispensing frequency and increasing the patient's understanding of their medicines and how to use them.

For further information on the LTC Service see: **www.centraltas.co.nz**

A number of helpful resources can be accessed here under the Community Pharmacy Programme section of the website including the LTC Service Protocol, the LTC Service Eligibility and Assessment tool used by pharmacists and a "Guide to the Community Pharmacy LTC Service".

References

1. Braund R, Peake B, Shieffelbien L. Disposal practices for unused medications in New Zealand. Environ Int 2009;35:952–5.
2. Tong A, Peake B, Braund R. Disposal practices for unused medications in New Zealand community pharmacies. J Prim Health Care 2011;3:197–203.
3. Community Pharmacy Services. Pharmacy Procedures manual – a guide to payment and claiming. Version 7.0. 2015. Available from: www.centraltas.co.nz (Accessed Aug, 2015).

How to appropriately dispose of unwanted medicines

Patients should be advised to take their unwanted medicines (both prescribed and self-purchased) to a pharmacy for safe disposal. In most areas, DHBs fund the collection and disposal of unwanted medicines with pharmacies acting as the depot and sorting area; pharmacies should ensure that they are familiar with local protocols and adherent with correct disposal guidelines. In a New Zealand survey completed by 265 community pharmacists, 80% said that they disposed of returned tablets and capsules via third party contractors (i.e. the DHB-funded disposal service) and 61% said they disposed of ointments and creams in the same way.[2] However, 45% reported that they pour returned liquid preparations down the sink and 7% flush liquid preparations down the toilet.[2]

"Discarding Unwanted Medicines through Pharmacies" (DUMP) campaigns are periodically run by DHBs in conjunction with community pharmacies, using media and other publicity about medicines safety to raise community awareness.

Returned medicines (e.g. to pharmacies or general practice clinics) cannot be reused or donated if the storage conditions and integrity of the medicine cannot be guaranteed. N.B. Some practices may participate in schemes for forwarding a variety of unused medicines to developing countries. Medicines should be of original quality, stored correctly and not expired; ideally medicines should have a remaining shelf-life of at least 12 months. For example, see: **www.maa.org.nz**

For further information, see: "Waste not want not: reducing wastage", BPJ 23 (Sep, 2009).

Melatonin

is it worth losing any sleep over?

Modified-release melatonin is an unsubsidised medicine that is approved for, and moderately effective at, improving sleep quality in adults with insomnia; other formulations of melatonin are unapproved. Shift-workers or people concerned about jet lag may wish to discuss the "off-label" benefits of melatonin treatment. Melatonin also may be used in specialist situations, such as in children or adolescents with neurodevelopmental disorders and sleep disturbances. Prescribers should be mindful that melatonin must be dosed at the correct time in order to be effective for assisting sleep. Due to a lack of studies on the potential adverse effects of the long-term use of melatonin, prescribing for prolonged periods should be approached with caution, particularly in children and adolescents.

Key messages

- Non-pharmacological interventions remain the first-line treatment for patients with insomnia
- There is only one approved formulation of melatonin in New Zealand (not subsidised), which is indicated for treating adults aged over 55 years with insomnia
- Melatonin may be useful "off-label" for treating sleep disturbances in children with neurodevelopmental disorders, for preventing or reducing jet lag and improving sleep in shift-workers
- There is a lack of studies on the potential adverse effects of prolonged melatonin use, particularly in children and adolescents

Melatonin: "Nature's most versatile biological signal"

Melatonin is regarded as a hormone which regulates the circadian rhythm of sleep. It is synthesised from the amino acid tryptophan and then released from the pineal gland; the process is controlled by a biological clock in the suprachiasmatic nucleus located within the hypothalamus.[1] An adult produces 20 – 60 micrograms of melatonin every 24 hours.[1]

The release of melatonin from the pineal gland is suppressed by ocular light at the retina.[1] In a person with a normal sleep-wake cycle melatonin is released at night, typically beginning 14 hours after spontaneous awakening, i.e. at 9 pm in a person who wakes up at 7 am.[2] Melatonin release therefore provides time-of-day information, i.e. onset of darkness, to various organs and tissues throughout the body. During a normal circadian cycle, melatonin reaches a peak concentration at approximately 2 – 3 am.[1] Melatonin secretion then decreases and due to its relatively short biological half-life of 15 – 30 minutes is undetectable in the bloodstream by approximately 7 am.[1, 3]

People who work night-shifts have a delayed peak in melatonin secretion, the degree of which is influenced by their level of night-light exposure and number of nights worked.[4] In people who live in extreme northern or southern latitudes the duration of melatonin secretion is increased during the longer winter nights.[1] As children enter puberty the rhythm of melatonin release is delayed resulting in later onset of sleepiness and a later natural wake time.[5] The secretion of melatonin decreases in later adulthood and by the age of 70 years it is reported that a person's nocturnal melatonin concentration may be less than a quarter of what it was when they were younger.[6]

Melatonin is reported to have a range of actions in the human body, other than just regulating sleep (see: "Melatonin does more than regulate sleep", Page 21).

Melatonin as a medicine

The majority of the evidence relating to the therapeutic use of melatonin involves treating people with insomnia. This is because the nightly melatonin peak may be altered in people who report problems with the quality or quantity of their sleep.[10] When given as a treatment for insomnia melatonin is referred to as a chronobiotic, i.e. it alters the timing of sleep, as opposed to hypnotic medicines, e.g. zopiclone, which act to rapidly initiate and prolong sleep.[1]

There is evidence that melatonin can be effective in treating people with other forms of circadian disturbances, such as sleep disturbances in children or adolescents with neurodevelopmental disorders, the reduction or prevention of jet lag (when taken at the right time) and for sleep disturbances in people with vision abnormalities (Page 24).

Modified-release and immediate-release melatonin

Melatonin is available in modified and immediate-release formulations. Modified-release melatonin causes the blood concentration over time to more closely mimic a naturally occurring melatonin profile (Figure 1). Immediate-release melatonin results in a relatively rapid increase in melatonin levels.[2] Although large head-to-head trials are lacking, there is limited evidence that the initial rise in melatonin levels provided by either formulation may be sufficient to induce sleep, and in addition the length of sleep may also be improved by modified-release melatonin.[2]

Melatonin in New Zealand

In New Zealand melatonin is a prescription only, unsubsidised medicine. A 2 mg modified-release formulation of melatonin is approved for the treatment of primary insomnia in adults aged over 55 years (Page 23); all other formulations of melatonin are unapproved* and all other uses for melatonin are "off-label".[11] This means that modified-release melatonin is the only formulation of melatonin in New Zealand that has undergone Medsafe's regulatory approval process. Therefore if prescribers are considering initiating melatonin treatment, modified-release melatonin is the only formulation that Medsafe has assessed as being safe, under the conditions set out in the Medicine Data Sheet.

* Section 29 of the Medicines Act specifies that a person or company who supplies this medicine must notify the Director-General of Health (via Medsafe) of the supply and record the name of the prescribing practitioner

Generally, modified-release melatonin taken one to two hours before sleep onset is desired is a reasonable dosing regimen. It is recommended that modified-release melatonin be taken with, or just after, food.[11] Patients should be advised to avoid drinking alcohol before bedtime as this may increase the speed of melatonin release into the blood stream, effectively turning the modified-release formulation into an immediate-release medicine.[12] Patients should not drive or operate machinery for the rest of the evening once they have taken melatonin.

Note that crushing or halving of tablets is not recommended by the manufacturer, as this alters the release profile of the medicine. However, if immediate-release melatonin is required, crushing of the approved modified-release formulation may be appropriate, e.g. for the treatment of jet lag off-label (Page 26). If the patient is unable to swallow tablets, modified-release

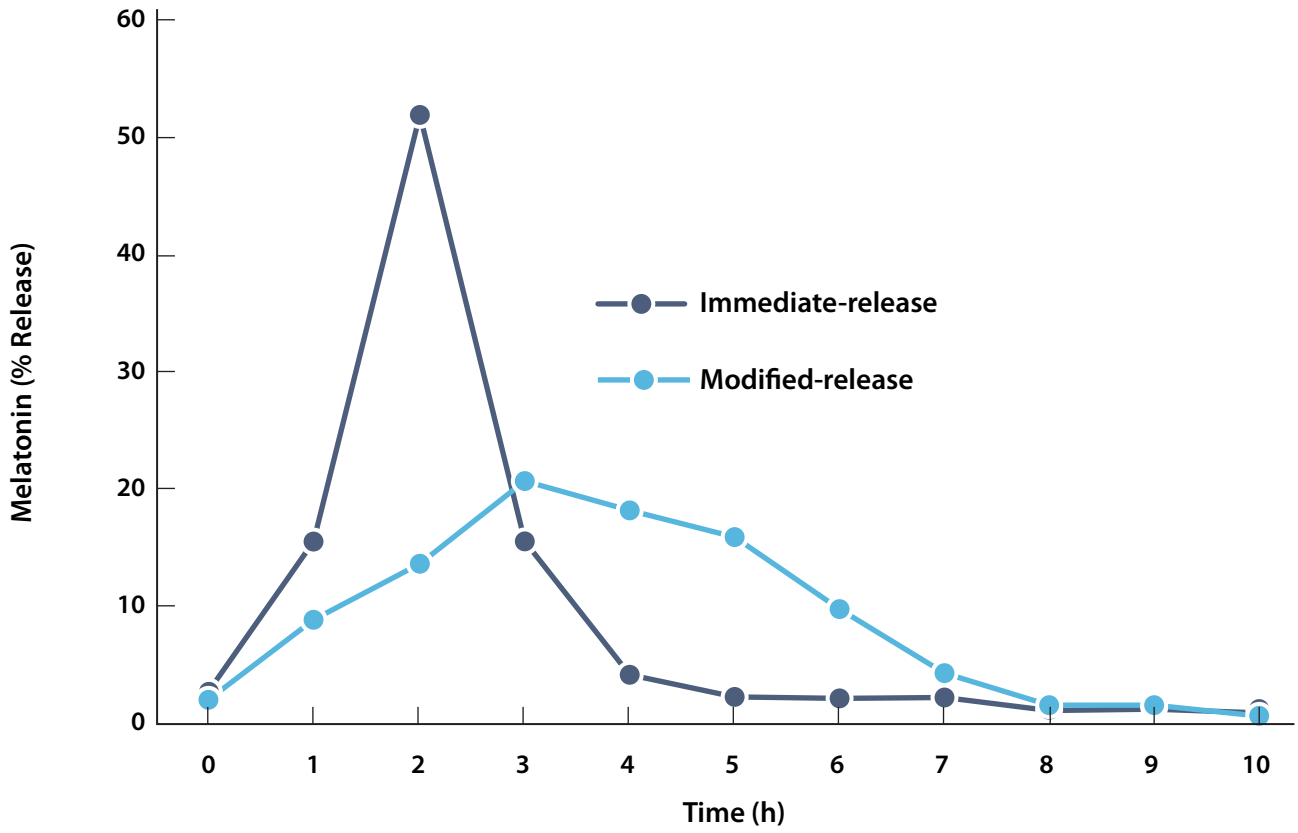


Figure 1: Pharmacokinetics of immediate-release melatonin and modified-release melatonin. Adapted from Zisapel, 2010[2]

melatonin tablets may need to be crushed or halved; careful halving of tablets may retain some of the delayed release profile.[13] Crushed melatonin tablets should not be stored, but can be mixed with cold food or drinks to aid digestion.[13]

If a patient taking immediate-release melatonin would like to switch to modified-release melatonin, it is reasonable to take the same dose of modified-release melatonin one to two hours earlier than they had been taking the immediate-release formulation.

The adverse effects of melatonin treatment

The timing of melatonin administration is important when treating people with circadian disorders as delays in sleep onset may be experienced if melatonin is taken between six and 15 hours after a person's endogenous levels of melatonin begin to rise (usually around 9pm in a person who wakes at 7am).[14]

The adverse effects associated with melatonin use are diverse but relatively uncommon. The rate of adverse events in patients taking short courses of modified-release melatonin are reported to be similar compared with placebo, and include: asthenia (weakness), headache, respiratory infections and back pain.[15] It is recommended that melatonin be avoided in patients with hepatic impairment.[11]

Interactions with other medicines

Melatonin is mainly metabolised by CYP1A enzymes therefore if it is taken concurrently with other substances that interact with this class of enzyme its metabolism may be affected.[12] Examples of medicines that may increase the plasma concentration of melatonin include: citalopram, cimetidine and quinolones (e.g. norfloxacin, ciprofloxacin).[12] Carbamazepine and rifampicin may cause plasma concentrations of melatonin to be reduced.[12]

It should also be noted that children may have reduced CYP1A2 levels compared to adults, which in addition to the above potential drug interactions, may expose children to higher concentrations of melatonin than anticipated.[16]

Whether or not medicines that affect the endogenous production of melatonin interact with melatonin taken orally is unknown.[12] There is some evidence that beta blockers may reduce melatonin levels.

Melatonin compared with hypnotics

Melatonin may be preferable to zopiclone and benzodiazepines for the short-term treatment of insomnia because

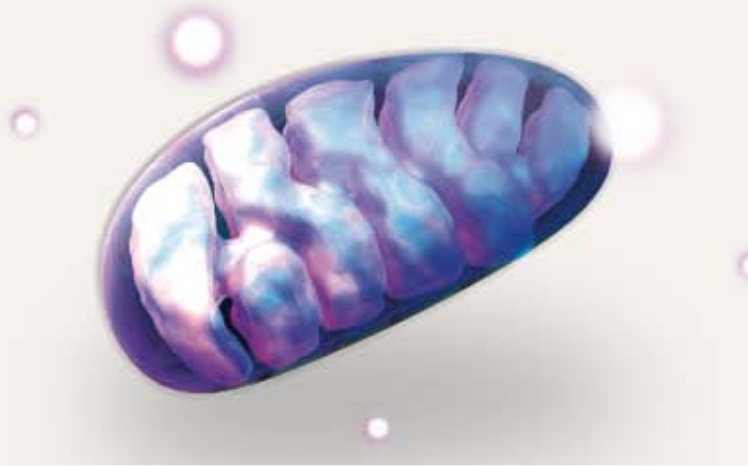
Melatonin does more than regulate sleep

Due to its diverse range of biological functions melatonin is sometimes referred to as "Nature's most versatile biological signal".[7] As well as being present in the nervous system, melatonin receptors are distributed throughout the human body. Melatonin receptors in arteries are known to be involved in thermoregulation.[8] The coronary arteries, aorta and left ventricle have melatonin receptors and depending on which subset of receptor is present activation can lead to vasodilation or vasoconstriction.[8] Melatonin can also regulate haematopoiesis via receptors on bone marrow cells.[8] The body's immune function is influenced by melatonin, which is able to stimulate production of the cytokine interleukin-2 and its receptor, which in turn regulates leukocyte activity.[8] Melatonin has been demonstrated to have an inhibitory effect on carcinomas *in vitro* and *in vivo*.[9]

Melatonin is a powerful antioxidant

Melatonin is an "old" molecule in an evolutionary sense and is produced in a variety of different organisms; as well as being a hormone it is a free radical scavenger, due to its antioxidant properties, and is produced by single cell organisms.[7] Melatonin readily penetrates cellular membranes and can therefore provide antioxidant protection to mitochondria and DNA.[7] Studies have shown that melatonin may have a protective effect against the development of skin cancer, both by eliminating free radicals produced by ultraviolet radiation and promoting DNA repair.[7]

Novel derivatives of melatonin are being synthesised and there is interest in their potential role in treating or preventing a diverse range of diseases involving oxidative stress including Alzheimer's disease, rheumatoid arthritis and cancer.[3]



it does not cause adverse effects such as excessive daytime sleepiness, vertigo and muscle weakness.[15] There is no evidence that modified-release melatonin causes tolerance, dependence, withdrawal or rebound insomnia.[15] There has been no reported increased risk of cognitive impairment or falls, fractures or motor vehicle accidents associated with the use of melatonin in older patients.[15]

More studies on the long-term safety of melatonin are needed

The safety of long-term melatonin use has not been widely studied and there are concerns that the long-term use of melatonin may have unforeseen consequences.[1]

The major safety concern with melatonin is what is not known about its long-term use, particularly among children and adolescents. In animals that are seasonal breeders variations in melatonin production causes seasonally-appropriate changes,[17] e.g. oestrus in females and increasing testosterone production in males. A formulation of melatonin is used in some countries to enhance fertility in sheep.[1] It is uncertain if melatonin taken as a medicine may have adverse effects on human reproductive physiology. However, precocious puberty has been associated with abnormalities in melatonin rhythms and the possibility has been raised that the long-term use of melatonin in children may postpone the onset of puberty.[17] This concern has been partially allayed by a relatively small study which found no detectable disruption to pubertal development and mental health in 51 children aged between six and 12 years who had taken doses ranging from 0.3 mg of melatonin daily to 10 mg melatonin daily, for 1 – 4.6 years.[17] The New Zealand Formulary for Children recommends that melatonin should be initiated and supervised by a specialist and reviewed every six months.[18]

Table 1: Causes of insomnia[10, 11]

Environmental	Medicines/substances	Conditions	Psychological
■ Change in sleeping environment, e.g. living in a new house ■ Jet lag ■ Daylight saving ■ "Sunday night" insomnia after an active weekend ■ Noise ■ Temperature or humidity ■ Discomfort ■ A disruptive partner or family member	■ Alcohol ■ Stimulants, e.g. caffeine ■ β-agonists ■ Bupropion ■ Ciprofloxacin ■ Corticosteroids ■ Decongestants ■ Diuretics ■ Stimulants, e.g. modafinil ■ Thyroid hormones ■ Selective serotonin reuptake inhibitors	■ Cough ■ Dyspnoea due to lung disease or heart failure ■ Gastro-oesophageal reflux disease ■ Menopause ■ Nasal congestion ■ Nocturia ■ Pain, e.g. dental problems, chronic back pain	■ Anxiety ■ Conditioned insomnia ■ Depression ■ Grief ■ Mania ■ Stress

The role of melatonin in sleep disorders

Most people will report sleep problems at some stage in their life

Dissatisfaction with sleep quality or distress from not sleeping will be experienced by most people at various times in their lives.[10] Sleep disturbances are reported to affect 10–50% of patients presenting to primary care clinics in New Zealand, depending on the definition that is applied.[19] People should expect some small changes in the amount of sleep they have as they get older, even in the absence of sleep problems. Studies show that total sleep duration decreases by approximately ten minutes per decade of age, and cohorts of adults aged 55 years and older consistently report sleeping an average of seven hours per night.[20, 21]

Diagnosing primary insomnia

Primary insomnia can be diagnosed if a person has a significant sleep disturbance, occurring at least three nights per week, lasting for longer than one month, and there are no other contributing health conditions or sleep disorder diagnoses.[19] Primary insomnia is therefore a diagnosis of exclusion once other causes of sleep disturbance have been ruled-out, e.g. restless leg syndrome, depression, anxiety and stress, sleep apnoea and long-term alcohol use.[10]

Patients with primary insomnia have long-term insomnia and one or more of the following symptoms:[10]

- Difficulty falling asleep at bedtime
- Waking frequently or having a restless sleep
- Waking during the night with difficulty getting back to sleep
- Early waking with an inability to get back to sleep

Due to age-related hormonal changes, insomnia is increasingly reported by people aged over 55 years.

Patients who report severe insomnia or who have insomnia that is not responding to treatment are likely to benefit from referral to a sleep specialist.

Establishing the cause of insomnia

When consulting with patients who report sleep problems, a detailed history is essential to establish patterns of insomnia, associated symptoms, as well as any underlying causal factors.[10] Insomnia is different to sleep deprivation caused by a lack of opportunity to sleep. People who experience insomnia are unable to sleep despite having sufficient time and desire to sleep. In some people this desire to go to sleep produces a paradoxical alertness and arousal that counteracts somnolence.[10]

Insomnia may be due to one or a combination of four causes: external factors, medicines or substances, medical conditions and psychological disturbances (Table 1).[10] A New Zealand survey of over 1500 patients in the waiting rooms of three general practices found that mental health issues, e.g. depression and anxiety, and physical issues, e.g. pain or breathing problems, caused the majority of sleep disturbances.[19]

Non-pharmacological treatment of insomnia is first-line

The first-line treatment for insomnia should always be the elimination of any underlying causes of sleep disturbance before pharmacological treatment is considered. A tailored approach is likely to be required, depending on the patient's circumstances and lifestyle. Sleep hygiene, stimulus control and sleep restriction treatment can be effective for people who are experiencing insomnia.

Simple changes can make a big difference

Sleep hygiene refers to adopting behaviours and modifying environmental factors to increase the likelihood of sleep. Examples of sleep hygiene include ensuring light and temperature are conducive to sleep, avoiding heavy meals close to bedtime, limiting caffeine intake, restricting alcohol intake, avoiding smoking close to bedtime, avoiding napping during the day and avoiding vigorous exercise close to bedtime.[22]

The objective of stimulus control is to retrain the patient to associate their bed and bedroom as a place of sleep and thereby establish a normal sleep-wake cycle. This involves:[22]

- Only going to bed when sleepy
- Restricting the use of the bedroom to sleep and sexual activity
- Leaving the bedroom if unable to fall asleep for longer than 20 minutes, and then returning only when sleepy
- Sticking to a fixed time for getting up every morning

Sleep restriction treatment involves the clinician calculating how many hours the patient spends in bed at night and then

how many of these hours they are actually asleep. This is usually done with the use of a sleep diary. The patient then restricts their time in bed to their calculated average sleep time, with a minimum time in bed of five hours.[23]

There is some evidence that bright light in the morning can be used to treat patients with insomnia with delayed sleep-onset, and bright light in the evening may be effective in treating insomnia associated with early morning waking.[24]

For further information see: "Managing insomnia", BPJ 14 (Jun, 2008).

The approved use of melatonin

Modified-release, 2 mg melatonin tablets, once daily, one to two hours before bedtime is indicated for the treatment of primary insomnia in people aged over 55 years, for up to 13 weeks.[11] The use of melatonin in younger patients is not currently approved as the clinical trials that showed modified-release melatonin was moderately effective at treating insomnia only included patients who were aged 55 years or over.[6]

It is important that patients who are prescribed melatonin take the medicine as directed. If melatonin dosing occurs at times of the day other than when treatment is recommended sleep patterns could be disrupted even further.

How much improvement in sleep can patients expect?
In patients aged over 55 years it is reported that melatonin produces meaningful improvements in both quality of sleep and morning alertness in 32% of patients.[15] However, there is likely to be a significant placebo effect involved in treatment success as 19% of patients treated with placebo also experienced meaningful improvements in sleep.[15] In two clinical trials patients treated with modified-release melatonin had a time to sleep onset of approximately ten minutes compared to approximately twenty minutes for patients taking placebo.[6] There were no reported increases in sleep duration following melatonin treatment.[6]

Off-label uses of melatonin

Patients may often enquire about the suitability of melatonin treatment for indications other than insomnia, e.g. for preventing jet lag or for managing sleep in shift work; or parents may enquire about melatonin treatment for their child. Melatonin should not be prescribed in primary care to children with sleep disturbances who are otherwise healthy. In general, melatonin treatment is only appropriate for children with neurodevelopmental disorders and sleep disturbances (see below).

Patients who are prescribed melatonin for "off-label" purposes should be told that there is limited data available concerning the safety or efficacy of the medicine for this use and that the details of the prescription will be recorded on a database as requirement of the Medicines Act.[25] As in many cases of off-label medicine use, there is no established dosing regimen for melatonin; an appropriate protocol may be derived from clinical studies. In some situations it is not clear whether modified-release or immediate-release is the most effective treatment option as some studies do not specify which formulation of the medicine was used. Discussing the patient with a sleep specialist may be beneficial before prescribing "off-label" melatonin long-term, although this will not always be practical.

For further information see: "Upfront: Unapproved medicines and unapproved uses of medicines: keeping prescribers and patients safe", BPJ 51 (Mar, 2013)

Melatonin in children with developmental disorders

Sleep disturbances are common in children with developmental disorders, e.g. autism and attention deficit hyperactivity disorder (ADHD), and complex neurodevelopmental disorders, e.g. visual impairment, epilepsy, cerebral palsy. These sleep disturbances are often long-term and harder to treat than in their age-matched peers.[26] Sleep disturbances in these children may be exacerbated by the use of stimulants, e.g. methylphenidate for ADHD. Melatonin treatment for children with neurodevelopmental disorders and sleep disturbances is initiated by a specialist, e.g. a paediatrician or a psychiatrist.

A study that included 263 children aged three to fifteen years with a history of impaired sleeping and a diagnosed neurodevelopmental disorder investigated whether immediate-release melatonin was beneficial in improving total sleep time and sleep onset. Children were initiated on 0.5 mg of immediate-release melatonin daily, or placebo, and this was titrated to effect through 2 mg, 6 mg and 12 mg during the first four weeks of treatment.[26] It was found that on average children treated with immediate-release melatonin went to sleep 45 minutes earlier, compared with placebo treatment, which was considered to be clinically significant.[26] Total time slept was increased on average by 23 minutes, compared to placebo, but this was not considered to be clinically significant.[26] It is not known if modified-release melatonin increases total sleep time in children with neurodevelopmental disorders as head-

to-head trials with immediate-release melatonin have not been conducted.

The recommended dose of melatonin for the treatment of sleep onset insomnia and delayed sleep phase disorder in children aged one month to 18 years is 2 – 3 mg daily, before bedtime*.[18] While this can theoretically be increased to 4 – 6 mg after one to two weeks, to a maximum of 10 mg daily, due to differences in CYP1A2 activity and weight-based dosing in children, higher doses should be used with caution. In addition, given that lower doses of melatonin have been reported to be effective in other populations, e.g. 0.5 mg of melatonin for people with vision disturbances,[27] a lower dose may be effective and safer in children. Many experts would commence treatment with a 1 mg dose.

* Modified-release melatonin tablets can be given one to two hours before bedtime, or if the child is unable to swallow tablets then modified-release tablets can be crushed and mixed with a drink immediately before bedtime (or administered via a gastrostomy/nasogastric tube).

Children with autism may have abnormal melatonin production

Children with autism often secrete lower levels of melatonin compared with children in the general population.[28] Modified-release melatonin treatment does appear to be effective for children with autism with sleep disturbances in the short-term, and the effectiveness of treatment appears to be substantially increased when melatonin is combined with cognitive behavioural therapy.

A study including 134 children aged between four and ten years, with a confirmed diagnosis of autistic disorder, compared the effectiveness of 3 mg, daily, modified-release melatonin treatment with cognitive behavioural therapy, or with both treatments combined.[29] Children with an average reported duration of insomnia of 2.4 years were given 3 mg of modified-release melatonin at approximately 9 pm for 12 weeks.[29] The combined treatment approach was superior to melatonin or cognitive behavioural therapy alone and resulted in 85% of children either sleeping within 30 minutes of bedtime or reducing sleep onset by 50%.[29] In contrast, 40% of children treated with melatonin alone meet this criteria compared with 10% of the children who received cognitive behavioural therapy alone.[29]

Adolescents often do not get enough sleep

Insufficient sleep and poor sleep hygiene are the most frequent reasons for sleep disturbances in teenagers.[5] Melatonin use in adolescents should be reserved for those diagnosed with a specific circadian disturbance, e.g. delayed sleep phase disorder (see below).

Adolescents naturally go to bed later and sleep later due to changes in lifestyle and changes in the timing of melatonin release.[5] Teenagers will also often have a more variable sleep pattern across the week as they go into sleep deficit during the week, while attending school, and then recover this debt over the weekend by sleeping for longer.[30] These changes in sleeping patterns make it difficult to assess the prevalence of insomnia in teenagers. However, 21 studies across a range of countries found that 20–26% of teenagers regularly experienced difficulty falling asleep within 30 minutes.[30] In general, it appears that teenagers do not get enough sleep. Studies have shown that teenagers typically need at least 9 hours sleep a night, but often only manage 7.5 to 8.5 hours a night.[5]

Melatonin is appropriate for patients with delayed sleep phase disorder

Delayed sleep phase disorder is a clinical term applied to people who may also be described as extreme "night owls".[10] Delayed sleep phase disorder occurs when a person's natural sleep time is mismatched with expectations of what is normal.[10] This disorder is estimated to have a prevalence of 2% in patients attending general practice in New Zealand.[19] Delayed sleep phase disorder is associated with attention-deficit/hyperactivity disorder (ADHD), increased rates of smoking, alcohol use, caffeine use and depression.[10] Delayed sleep phase syndrome is estimated to occur in 5–10% of adolescents.[5]

A meta-analysis of five trials found that melatonin could advance mean sleep onset by 40 minutes in patients with delayed sleep phase disorder.[14] It appears that melatonin is most effective for this patient group when given five to six hours before physiological levels of melatonin would begin to rise in a normal person, i.e. in the early to mid-afternoon.[14] The optimal dose for treating patients with delayed sleep phase disorder is unknown; studies have used nightly doses of melatonin ranging from 0.5 to 5 mg.[14] A small study involving 13 patients found that 0.3 mg of melatonin and 3 mg of melatonin daily were both equally effective in advancing sleep onset.[31] Another small study of 21 teenagers, aged 14 to 19 years, who reported being unable to sleep until 1 am on at least two weekdays per week with substantial daytime sleepiness found that 1 mg of melatonin taken in the late afternoon reduced sleep onset by approximately one hour and increased duration of sleep by the same length.[32]

Melatonin may reduce or prevent jet lag

Most people experience jet lag when they travel across multiple time zones. Jet lag is a collection of symptoms that usually includes daytime fatigue and sleep disturbance, but may also involve reduced cognitive function, dizziness, weakness and irritability.[33] These symptoms occur when a person's circadian rhythm becomes desynchronised with the day-night cycle of their travel destination and it may take four to six days for synchronisation to occur.[33]

There is evidence that immediate-release melatonin is effective in reducing or preventing jet lag and the benefit is greater the more time zones that are crossed.[33] This effect seems to be strongest for people travelling across five or more time zones, particularly in an easterly direction, e.g. New Zealand to New York.[33] Modified-release tablets are thought to be less effective at preventing jet lag than immediate-release melatonin. Patients who want to take the approved form of melatonin may wish to crush modified-release melatonin tablets before taking them.

The optimal timing of melatonin dosing for the prevention or reduction of jet lag is important and people should take melatonin in the late afternoon or early evening at their destination.[33] Doses may be repeated for several days after arrival. Exposure to bright light in the morning also assists in adjusting to the new time zone.[34] Taking melatonin prior to departure at a time corresponding to night-time at the destination, i.e. to anticipate the change in time zone, is not recommended.[33]

A Cochrane review found that in eight of ten trials where melatonin was taken close to bedtime at the destination (10 pm to midnight) there was a reduction in jet lag for travellers crossing five or more time zones.[33] People appeared to fall asleep faster with 5 mg melatonin compared to 0.5 mg melatonin, but otherwise the effectiveness of doses between these ranges was the same and doses above 5 mg were found to be no more effective.[33] The only study that included modified-release melatonin found that immediate-release was more effective, suggesting that a short peak in melatonin concentration is more effective at entraining the sleep-wake cycle in people with jet lag in a new time zone.[33]

N.B. Patients can be advised that in countries where melatonin is available without prescription the quality and purity of the product may not meet the standards of pharmaceutical preparations. If melatonin is brought back into New Zealand it should be declared at customs where it will be held until a New Zealand prescription is obtained for it.

Melatonin may increase sleep length for people doing shift-work

People who do shift-work may experience sleep disturbances resulting in sleepiness when working at night and reduced sleep duration and quality during the day. In patients with extreme symptoms this is termed shift-work sleep disorder.[35] The use of melatonin may increase the time shift-workers are able to sleep, but there is no evidence that it will reduce the time taken to fall asleep.

A 2014 Cochrane review assessed the effectiveness of melatonin for improving sleep in shift-workers and found low quality evidence from nine studies that melatonin use improved sleep duration during the day by approximately 25 minutes, and sleep length the next night that they were off shift-work by approximately 15 minutes.[35] In seven of the nine trials melatonin was administered in the morning, after the night shift had finished, and before the day time sleep period.[35] The doses used in the meta-analysis ranged from 1 mg to 10 mg, but there was no additional benefit observed at doses higher than 5 mg.[35]

Melatonin is useful for treating sleeping problems in people with vision loss

People who are blind report an increased prevalence of sleeping problems compared to the general population; estimates vary, but approximately 50% report problems.[36] This is because the transmission of ocular light from the retina to the circadian clock is impaired and desynchronisation of the circadian clock and the external day/night cycle can occur.[27] In people who are totally blind this may result in a lifelong sensation of jet lag which can be improved by treatment with melatonin if it is given at the appropriate time relative to the patient's circadian clock.[27]

Melatonin at a daily dose of 0.5 mg has been shown to be effective at synchronising abnormal circadian rhythms in people who are either partially sighted or totally blind.[27] As treatment with melatonin may be lifelong for people who are blind the lowest effective dose of melatonin is preferable. One small study found that treatment with 0.3 mg of melatonin was sufficient to synchronise circadian rhythms in ten totally blind subjects.[37] To achieve synchronisation of abnormal circadian rhythms it is important that melatonin dosing occurs at the appropriate time for the individual. Therefore, assessment of the circadian phase of the individual patient is helpful to guide treatment before melatonin is initiated.[27] The degree of circadian misalignment can be determined with a combination of sleep diary and actigraphy (sleep/activity monitoring) at one of four or five sleep clinics across New Zealand.

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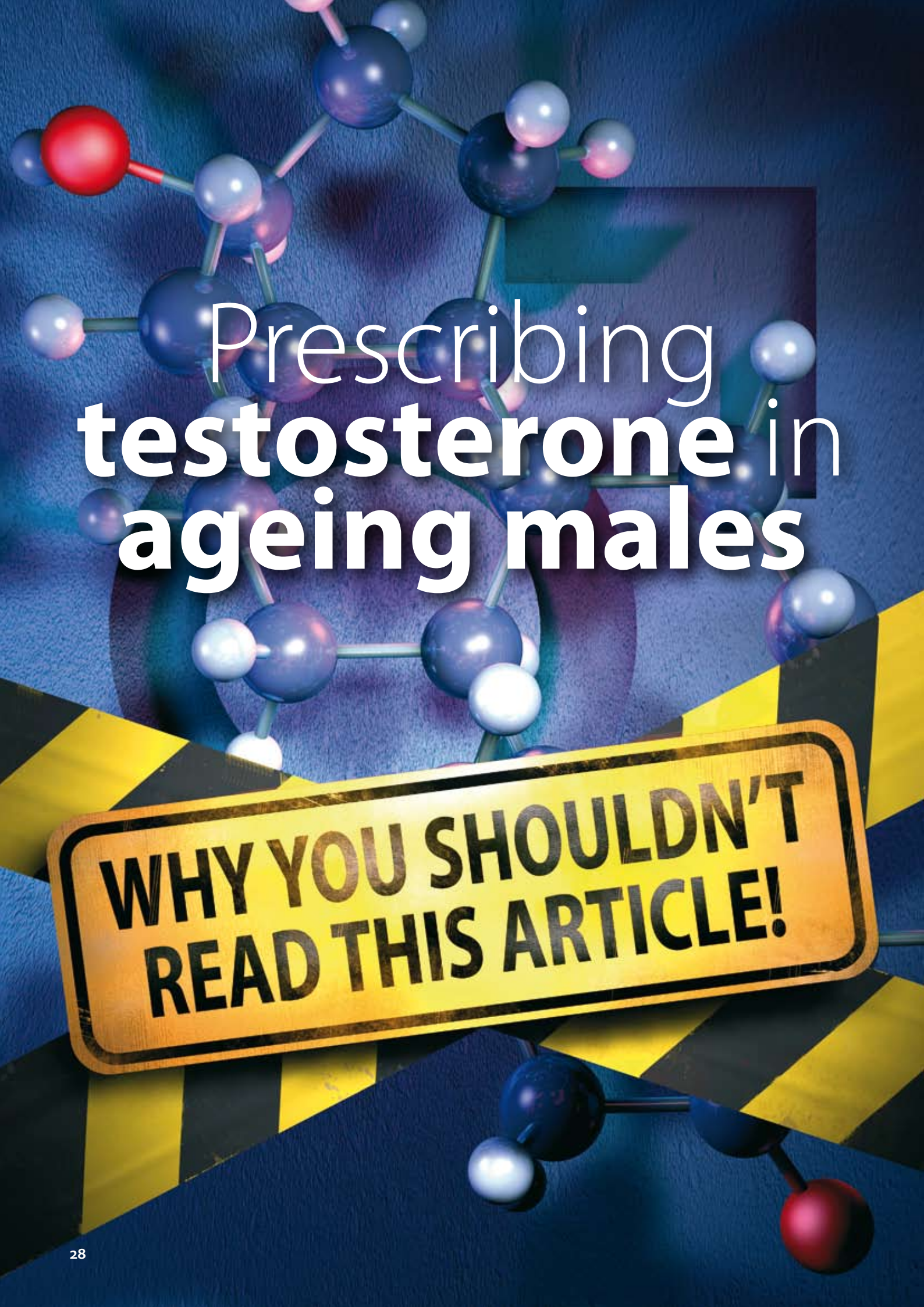
References

1. Kennaway DJ. Potential safety issues in the use of the hormone melatonin in paediatrics. J Paediatr Child Health 2015;51:584–9.
2. Zisapel N. Melatonin and sleep. Open Neuroendocrinol J 2010;3:85–95.
3. Suzen S. Melatonin and synthetic analogs as antioxidants. Curr Drug Deliv 2013;10:71–5.
4. Papantoniou K, Pozo OJ, Espinosa A, et al. Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes. Cancer Epidemiol Biomarkers Prev 2014;23:1176–86.
5. Moore M, Meltzer LJ. The sleepy adolescent: causes and consequences of sleepiness in teens. Paediatr Respir Rev 2008;9:114–20.
6. Therapeutic Goods Administration. Australian public assessement report for melatonin. 2009. Available from: www.tga.gov.au/file/850/download (Accessed Jul, 2015).
7. Fischer TW, Slominski A, Zmijewski MA, et al. Melatonin as a major skin protectant: from free radical scavenging to DNA damage repair. Experimental Dermatology 2008;17:713–30.
8. Pandi-Perumal SR, Trakht I, Srinivasan V, et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol 2008;85:335–53.
9. Cutando A, López-Valverde A, Arias-Santiago S, et al. Role of melatonin in cancer treatment. Anticancer Res 2012;32:2747–53.
10. Sutton EL. Insomnia. Med Clin North Am 2014;98:565–81.
11. New Zealand Formulary (NZF). NZF v37. 2015. Available from: www.nzf.org.nz (Accessed Jul, 2015).
12. Pharmacy Retailing. Circadin. Medicine Data Sheet. 2011. Available from: www.medsafe.govt.nz/profs/datasheet/c/circadintab.pdf (Accessed Jul, 2015).
13. South West London and St George's Mental health NHS Trust. Shared Care Guideline: Prescribing Agreement Melatonin (Circadin®) for persistent sleep disorders in school age children with neurodevelopmental disabilities. 2013. Available from: www.swlstg-tr.nhs.uk (Accessed Jul, 2015).
14. van Geijlswijk IM, Korzilius HPLM, Smits MG. The use of exogenous melatonin in delayed sleep phase disorder: a meta-analysis. Sleep 2010;33:1605–14.
15. NPS RADAR. Melatonin prolonged-release tablets (Circadin) for primary insomnia in older people. 2010. Available from: www.nps.org.au (Accessed Jul, 2015).
16. Sonnier M, Cresteil T. Delayed ontogenesis of CYP1A2 in the human liver. Eur J Biochem 1998;251:893–8.
17. van Geijlswijk IM, Mol RH, Egberts TCG, et al. Evaluation of sleep, puberty and mental health in children with long-term melatonin treatment for chronic idiopathic childhood sleep onset insomnia. Psychopharmacology 2011;216:111–20.
18. New Zealand Formulary for Children. NZFC. 2015. Available from: www.nzfchildren.org.nz (Accessed Jul, 2015).
19. Arroll B, Fernando A, Falloon K, et al. Prevalence of causes of insomnia in primary care: a cross-sectional study. Br J Gen Pract 2012;62:e99–103.
20. Dashti HS, Follis JL, Smith CE, et al. Habitual sleep duration is associated with BMI and macronutrient intake and may be modified by CLOCK genetic variants. Am J Clin Nutr 2015;101:135–43.
21. Ohayon MM, Carskadon MA, Guilleminault C, et al. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. Sleep 2004;27:1255–73.
22. Siebern AT, Suh S, Nowakowski S. Non-pharmacological treatment of insomnia. Neurotherapeutics 2012;9:717–27.
23. Fernando A, Arroll B, Falloon K. A double-blind randomised controlled study of a brief intervention of bedtime restriction for adult patients with primary insomnia. J Prim Health Care 2013;5:5–10.
24. Lovato N, Lack L. The role of bright light therapy in managing insomnia. Sleep Medicine Clinics 2013;8:351–9.
25. MEDSAFE. Compliance: use of unapproved medicines and unapproved use of medicines. 2014. Available from: www.medsafe.govt.nz/profs/RIss/unapp.asp (Accessed Jul, 2015).
26. Appleton RE, Jones AP, Gamble C, et al. The use of melatonin in children with neurodevelopmental disorders and impaired sleep: a randomised, double-blind, placebo-controlled, parallel study (MENDS). Health Technol Assess 2012;16:i – 239.
27. Skene DJ, Arendt J. Circadian rhythm sleep disorders in the blind and their treatment with melatonin. Sleep Med 2007;8:651–5.
28. Tordjman S, Davlantis KS, Georgieff N, et al. Autism as a disorder of biological and behavioral rhythms: toward new therapeutic perspectives. Front Pediatr 2015;3:1.
29. Cortesi F, Giannotti F, Sebastiani T, et al. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. J Sleep Res 2012;21:700–9.
30. Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta-analysis of age, region, and sleep. Sleep Med 2011;12:110–8.
31. Mundey K, Benloucif S, Harsanyi K, et al. Phase-dependent treatment of delayed sleep phase syndrome with melatonin. Sleep 2005;28:1271–8.
32. Eckerberg B, Lowden A, Nagai R, et al. Melatonin treatment effects on adolescent students' sleep timing and sleepiness in a placebo-controlled crossover study. Chronobiol Int 2012;29:1239–48.
33. Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2002;2:CD001520.
34. Burke TM, Markwald RR, Chinoy ED, et al. Combination of light and melatonin time cues for phase advancing the human circadian clock. Sleep 2013;36:1617–24.
35. Liira J, Verbeek JH, Costa G, et al. Pharmacological interventions for sleepiness and sleep disturbances caused by shift work. Cochrane Database Syst Rev 2014;8:CD009776.
36. Warman GR, Pawley MDM, Bolton C, et al. Circadian-related sleep disorders and sleep medication use in the New Zealand blind population: an observational prevalence survey. PLoS ONE 2011;6:e22073.
37. Lewy AJ, Emens JS, Lefler BJ, et al. Melatonin entrains free-running blind people according to a physiological dose-response curve. Chronobiol Int 2005;22:1093–106.



Prescribing **testosterone** in **ageing males**

Testosterone supplementation may be an appropriate treatment for males with clinical features of androgen deficiency and early morning serum total testosterone levels consistently below the accepted threshold of normal. Testosterone supplementation is not, however, appropriate for ageing males with non-specific symptoms and signs and slowly declining testosterone levels; the risks and benefits of treatment are uncertain for these patients. A mildly subnormal testosterone level may improve with changes in lifestyle, such as reducing alcohol intake, weight loss in those who are overweight or obese or improving sleep patterns. A significant rise in prescriptions for testosterone in older males has been observed in New Zealand, as it has in other countries such as the United States, United Kingdom and Australia. If you have never had cause to prescribe testosterone in an ageing male with non-specific symptoms and signs and slowly declining testosterone levels, continue this practice and read no further…

Key concepts

- As seen in other countries, testosterone use in New Zealand is increasing and it is possible that some of this use may be inappropriate
- Although testosterone levels decline with age, the risks and benefits of testosterone supplementation in older males is unclear as appropriate randomised controlled trials have not been conducted
- The diagnosis of hypogonadism should be based on multiple signs and symptoms and consistently low testosterone levels
- Lifestyle factors, co-morbidities and the use of some medicines can influence a patient's reproductive hormone levels and should be assessed and altered where possible to first exclude modifiable reasons for altered gonadal function
- For males with hypogonadism, prescribing testosterone may be appropriate if there are no contraindications and the uncertain risks, along with the monitoring and testing requirements, are discussed with the patient

The role of testosterone in adult males

Testosterone in males is responsible for the development and maintenance of typical secondary sex characteristics, such as increased facial and body hair, increased muscle growth, increased bone mass, and effects on libido.[1] It also has effects on energy and stamina, and psychological influences, e.g. on mood and drive.

In adult males, approximately 95% of testosterone is produced in the testes, with the remainder produced by the adrenal gland.[1] The effects of testosterone in the body can derive from testosterone itself, from conversion to its active metabolite dihydrotestosterone (DHT) and conversion to oestrogen by aromatase enzymes.[2]

Production of testosterone is regulated by the hypothalamic-pituitary-gonadal reproductive axis (HPG axis). The hypothalamus secretes gonadotropin-releasing hormone (GnRH), which in turn causes the anterior pituitary to release luteinising hormone (LH) and follicle stimulating hormone (FSH). LH stimulates Leydig cells in the testes to produce testosterone. Most of the testosterone in the body (total testosterone) is bound to sex hormone binding globulin (SHBG) or weakly bound to albumin; approximately 1 – 3% of total testosterone is non-bound (free testosterone).[3] While free testosterone is the fraction available for uptake and binding to androgen receptors in the tissues, measurement of free testosterone (by measuring SHBG) is not usually necessary. Total testosterone measurement is the key laboratory test for assessing gonadal function in males.

Hypogonadism can have an early or late onset, and can result from a low or absent testicular production of testosterone despite increased stimulation from the pituitary (primary hypogonadism), a failure of the appropriate output from the hypothalamus and pituitary (secondary hypogonadism) or a combination of the two.

Testosterone levels generally decline with age

Unlike the relatively abrupt fall in oestrogen levels in women during menopause, in most population studies testosterone production declines very slowly with age in males. The diurnal rhythm of peak levels in the morning and lowest levels in the

afternoon and evening also becomes less pronounced.[3] In addition, the concentration of SHBG increases in males with age, therefore resulting in declining levels of free testosterone.[3] In cohorts of males aged 40 years and older, total testosterone levels have been observed to fall by 1 – 2% per year.[4] However, the rate of decline varies between individuals and is influenced by factors such as obesity, co-morbid conditions and some medicines. Changes in reproductive hormone levels with age are not inevitable or universal and some studies of healthy active older males suggest they retain reproductive hormone levels comparable with younger males.[5] Age-related testosterone decline results from dysfunction in both testicular and hypothalamic-pituitary function, and therefore can have aspects of both primary and secondary hypogonadism.[5]

Are we "disease mongering"?

There has been considerable concern in the international literature that the clinical significance of testosterone decline in ageing males has been overstated (largely by pharmaceutical companies who manufacture testosterone products), and that testosterone supplementation in males with low levels due to ageing is not justified based on current evidence.[6–8] An increase in prescriptions for testosterone has been observed in many countries over the past decade, in the absence of any research findings or changes in clinical guidance to prompt a change in prescribing. For example, in the United States the number of patients prescribed testosterone increased by 76% between 2010 (1,299,846) and 2013 (2,291,266), with approximately 0.7% of the population being prescribed testosterone.[7, 9] Furthermore, a sample of 250,000 males prescribed testosterone found that only 72% had evidence of undergoing a testosterone measurement prior to initiating use, so that approximately one-quarter of patients had apparently not been diagnosed using a standard appropriate to best clinical care.[7] Similar trends of increasing testosterone use have been observed in the United Kingdom and Australia.[6, 8]

Testosterone dispensing in New Zealand

Testosterone use in New Zealand is lower overall than in the United States, with approximately 0.2% of the male population being dispensed testosterone in 2013.[10, 11] However, data from New Zealand indicate that use has increased over the last few years, from 3,129 males dispensed testosterone preparations in 2011 to 4,415 in 2014; a 41% increase.[11] While the largest group of males dispensed testosterone are those aged 50 years and older, increases in dispensing rates during this time have occurred across all age groups (Figure 1). This increase in the number of people using testosterone could be due to population rise, an increasing clinical recognition and detection of hypogonadism, inappropriate prescribing or any combination of these factors; dispensing data do not allow an assessment of the underlying reasons for prescription. However, given the international experience, it is worthwhile considering the clinical indications and current guidelines for prescribing testosterone.

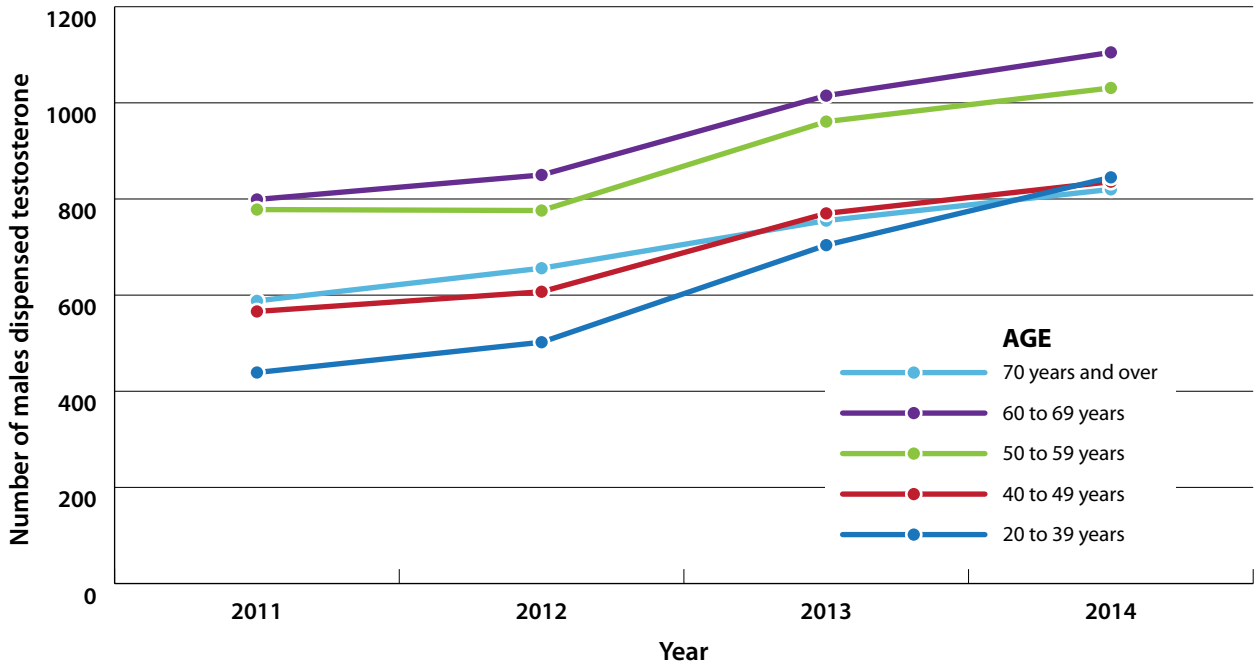


Figure 1: Number of males dispensed testosterone (all formulations) by age group in New Zealand from 2011 to 2014.

Recent research into testosterone use in older males spells a note of caution

Three recent studies investigating the use of testosterone in older males have generated media coverage and controversy in medical journals regarding whether testosterone use increases cardiovascular risk in these men.[13–15] These recent studies have recognised weaknesses in study design and it would be inappropriate to base treatment decisions on these studies alone, but their results do raise concern.

Reaction from regulatory and clinical bodies

Organisations and committees such as the United States' Food and Drug Administration (FDA), American Urological Association and New Zealand's Medicines Adverse Reaction Committee have all met to discuss these findings. Their conclusions are not entirely congruent, which reflects the varying interpretations possible from the current evidence and highlights the current uncertainty surrounding the risks and benefits of prescribing testosterone in older males:

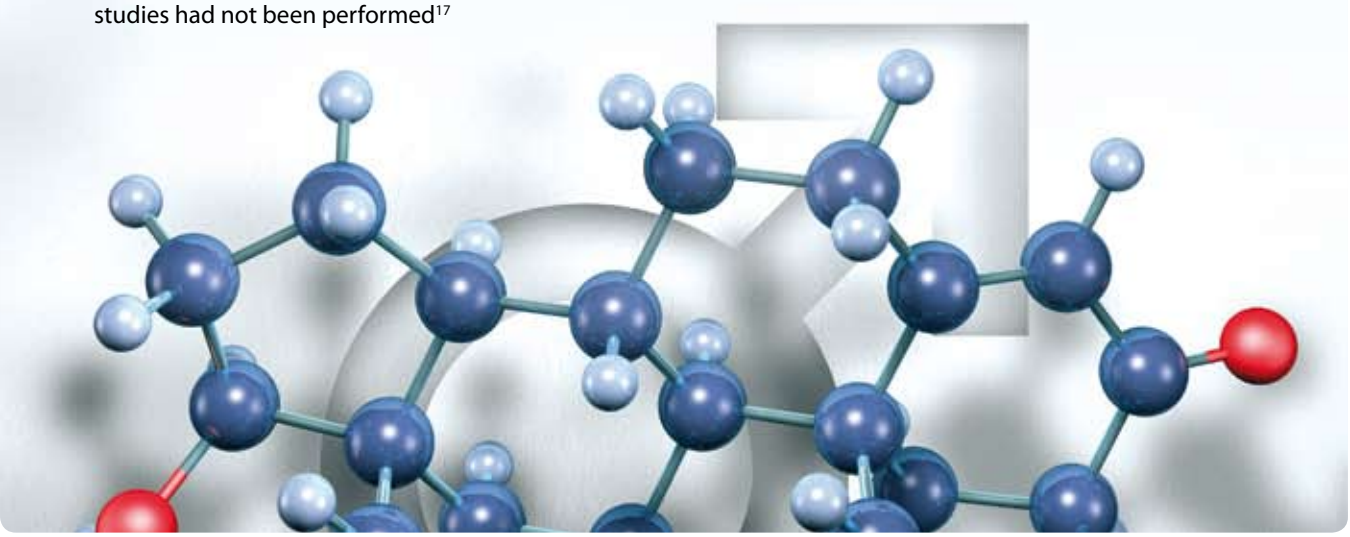
- The FDA recommended on the basis of these studies that information labels for testosterone products include that there may be an increased risk of cardiovascular disease[12]
- The New Zealand Medicines Adverse Reactions Committee concluded that there was no statistical evidence to support an association between testosterone replacement (as opposed to misuse) and myocardial infarction, venous thromboembolism or stroke[16]
- The American Urological Association concluded that evidence was contradictory and that definitive studies had not been performed[17]

Lessons from the Women's Health Initiative: randomised controlled trials are necessary to evaluate risks and benefits

The reality of medical practice is that medicines are prescribed on the basis of the safety information at hand, and with further time and research additional adverse effects can come to light which alter the balance of risks and benefits for any medicine. The current situation of testosterone use in older males is clearly reminiscent of the practice of prescribing reproductive hormones to peri- and postmenopausal females to alleviate the symptoms of menopause. In that case, the Women's Health Initiative study produced a sudden change in medical practice as the risks of hormone treatment from randomised controlled trial data were greatly different from previous data available from case control studies. There is obvious concern that a similar situation could arise for the prescription of testosterone in older males, where this practice could become widespread only to be later shown in appropriately controlled trials to carry substantial risks.

The bottom line – for now

At present, there are concerns that testosterone use could cause adverse cardiovascular effects in older males but there is also a clear acknowledgement that additional randomised controlled trials specifically designed to provide safety information in this patient group are necessary.



So, is testosterone an appropriate treatment for ageing males?

In March 2015, the United States Food and Drug Administration cautioned against the use of testosterone treatment in older males with low testosterone levels for no apparent reason other than ageing.[12] There is a lack of randomised controlled trials assessing benefits and risks of testosterone supplementation to guide evidence-based management of older males who experience symptoms of hypogonadism and have low levels of testosterone. Therefore, testosterone treatment in older males should only be considered in those with clinically established hypogonadism, with symptoms and signs that significantly impact their quality of life, after reversible causes have been eliminated, other treatments had been trialled, and discussion about the lack of conclusive evidence of both benefit and adverse effects.

For further discussion of the evidence on cardiovascular safety of testosterone, see: "Recent research into testosterone use in older males spells a note of caution".

Table 1: Symptoms and signs of testosterone deficiency in males (features are not individually diagnostic of hypogonadism)[5]

More specific	
■ Decreased or absent early morning/spontaneous erection	■ Testicular atrophy
■ Reduced libido and sexual activity (often an early symptom of deficiency)	■ Infertility, low sperm count (usually only if long-term deficiency)
■ Erectile dysfunction	■ Height loss, low velocity fractures, low bone mineral density
■ Breast discomfort, gynaecomastia (more common with primary hypogonadism)	■ Hot flushes, sweats (usually only if severe deficiency or rapid decrease)
■ Loss of facial, axillary and pubic hair (usually only if long-term deficiency)	

Less specific	
■ Decreased energy, motivation and confidence	■ Mild anaemia (normochromic)
■ Depressed mood (often an early symptom of deficiency)	■ Reduced muscle bulk and strength (usually only if long-term deficiency)
■ Poor concentration and memory	■ Increased body mass index and body fat
■ Sleep disturbance and increased sleepiness	■ Decreased physical performance

Assessing older males with potentially low testosterone levels

1. Patient history: does the patient report specific symptoms of hypogonadism, or could non-specific symptoms be explained by other causes, including expected age-related changes?
2. Clinical examination: are there any features that support a diagnosis of hypogonadism or suggest a possible cause?
3. Investigation: does the patient have specific features of hypogonadism present, that are impacting the quality of their life, and therefore investigation of testosterone levels is warranted?

Symptoms, signs and risk factors for hypogonadism

Many of the symptoms and signs of hypogonadism are non-specific, present in other conditions and are also associated with ageing, making diagnosis challenging. In addition, patients may experience symptoms of hypogonadism at variable testosterone levels.[2] Therefore a diagnosis of hypogonadism is more certain in patients with multiple, more specific features consistent with low testosterone, rather than isolated symptoms.[5]

Symptoms and signs of hypogonadism are given in Table 1; these features are not individually diagnostic of hypogonadism. A study of over 3,000 males aged 40 to 79 years found that a combination of three sexual symptoms was highly predictive of low testosterone levels and the presence of these three features might suggest that investigation of testosterone levels is warranted: [18]

- Decreased frequency of morning erections
- Erectile dysfunction (inability to achieve or maintain penile erection for satisfactory sexual performance)
- Decreased frequency of sexual thoughts (low sexual desire)

A number of medical conditions can influence the function of the HPG axis and are associated with hypogonadism. Patients with these conditions do not necessarily need to be investigated for hypogonadism, but the presence of the co-morbidity, along with symptoms and signs of testosterone deficiency, would increase suspicion of the diagnosis. Conditions associated with hypogonadism include:[2, 3, 19]

- End-stage renal disease
- Osteoporosis
- Moderate to severe COPD
- Severe obstructive sleep apnoea
- Type 2 diabetes (see note below)
- Pituitary tumour
- HIV
- Testicular cancer
- Haemochromatosis
- Chronic inflammatory disease, e.g. arthritis
- Eating disorders (malnutrition)

N.B. Testosterone levels are approximately 3 nmol/L lower in males with type 2 diabetes. However, these patients should only be prescribed testosterone if they meet diagnostic requirements for hypogonadism. Evidence does not support the use of testosterone to improve diabetes control.[20]

The use of some medicines is also associated with hypogonadism, including:[2, 3, 19]

- Opioids
- High dose systemic corticosteroids
- Anabolic steroids
- Oestrogens and progesterones
- Chemotherapy medicines
- GnRH antagonist, e.g. prostate cancer treatment
- Phenothiazines

Lifestyle factors associated with hypogonadism include:[19]

- Obesity
- Chronic excess alcohol intake (recent alcohol intake can also cause transient decreases in total testosterone levels)
- Vigorous exercise
- Significant stress
- Sleep deprivation
- Illicit drug use, including misuse of anabolic steroids

Clinical examination should focus on assessing the patient's body hair distribution and testicular size, and assessing for gynaecomastia. If pituitary disease is suspected, evidence of deficiency of other endocrine axes (e.g. secondary hypothyroidism, hypoadrenalism) and assessment of visual fields should be considered.

Investigate testosterone levels if significant features of hypogonadism are present

The diagnosis of hypogonadism in males should be based on the presence of consistent symptoms and signs of hypogonadism in combination with a finding of a low testosterone level.[5] Therefore, measuring testosterone is not

necessary unless patients show symptoms and signs related to altered function of the HPG axis. When considering the timing of testing, control for factors that may cause a transitory drop in testosterone levels such as acute illness, recent alcohol intake or excessive exercise.[19]

Investigation of testosterone levels should be carried out before the patient begins any testosterone replacement treatment. Evaluation of the HPG axis becomes very difficult in patients who are already taking, or have been recently taking, testosterone replacement in any form, as endogenous testosterone production can be suppressed. These influences can persist for weeks or even months after stopping such preparations.

The recommended initial laboratory investigation for hypogonadism is an **early morning serum total testosterone** when the patient is well. The suggested protocol is as follows:[19]

1. Request a total testosterone test between 7 am – 10 am (unless the patient is a long-term shift worker; shift workers who sleep during the day have highest levels in the afternoon)
2. If the level is within the reference range, no further testing is required
3. If the level is below the reference range, repeat the test at least once to confirm a consistently low result; 30% of males with an initial low testosterone level will have a normal level on re-testing
4. Request a LH test with the subsequent testosterone test to help distinguish between primary and secondary hypogonadism
5. Consider testing SHBG and free testosterone only if there is reason to suspect that SHBG levels may be abnormal (e.g. marked obesity, thyroid disease, treatment with some medicines such as anticonvulsants); some males with total testosterone levels in the lower normal range may exhibit hypogonadism due to elevated SHBG levels and low free testosterone

Reference intervals for testosterone differ depending on the assay used; consult your local laboratory. A general reference interval for total testosterone in adult males is 11–40 nmol/L.[19] The testosterone level at which signs and symptoms of deficiency become apparent varies between individuals and the likelihood of symptoms increases at testosterone levels near the lower limit of the reference range for healthy young males.[2,5] However, it is generally agreed that

Erectile dysfunction is a common reason for men to request testosterone investigation

A common reason for an older male to ask their general practitioner to investigate their testosterone level is because they are experiencing a sexual problem such as erectile dysfunction.

If erectile dysfunction is their only symptom of hypogonadism, investigation of testosterone levels is not warranted; erectile dysfunction is only rarely caused by low testosterone levels and is more likely to be caused by neurological or vascular disease, medicines or psychological factors. A PDE-5 inhibitor such as sildenafil is first-line treatment, after modifiable causes have been addressed.

If the patient has erectile dysfunction, along with other symptoms of hypogonadism, such as decreased frequency of morning erections and low libido (sexual thoughts), it is reasonable to request a serum total testosterone level. If the level is below the reference range, the test should be repeated to confirm consistently low testosterone levels (see above).

If a testosterone deficiency is established, testosterone replacement treatment can be discussed as an option to improve some sexual dysfunction symptoms. Improvements in libido and sexual function in general have been reported in males taking testosterone replacement. However, testosterone treatment is not thought to significantly improve erectile dysfunction when compared to the use of sildenafil (Page 35).

For further information, see: "Selected topics in men's health: erectile dysfunction", Best Tests (Sep, 2010).

if the level is consistently below 8 nmol/L, this is diagnostic of hypogonadism, in conjunction with relevant symptoms and signs.[2, 18]

It is recommended that patients with consistently low testosterone levels are discussed with an endocrinologist to guide further investigations. Primary hypogonadism is characterised by low testosterone levels along with elevated LH levels. If seminiferous tubule function and spermatogenesis is also affected, then FSH may also be elevated. Secondary hypogonadism is most commonly associated with low LH or inappropriately normal levels of LH in a patient with low testosterone levels.[3] A prolactin test may be indicated if a pituitary tumour is suspected as a cause of secondary hypogonadism.[19]

Managing older males with established testosterone deficiency

1. Manage modifiable factors: does the patient have co-morbidities (including the effect of medicines) or lifestyle factors that can be optimally managed to improve symptoms?
2. Consider testosterone treatment as an option: Does the patient have specific features for which improvement with testosterone treatment can be measured/assessed? Does the patient have any contraindications or risk factors for treatment? Have you explained the risks and benefits of testosterone treatment and monitoring requirements to the patient?
3. Second opinion: have you discussed the management strategy and possible treatment options with an endocrinologist?
4. Monitoring testosterone treatment if prescribed: has testosterone treatment resulted in an improvement of symptoms? Are there any adverse effects of treatment?

Address reversible causes of hypogonadism

If a patient is confirmed to have hypogonadism, any co-morbidities or lifestyle factors that may be contributing to their symptoms and signs should be optimally managed before considering testosterone replacement treatment. This may involve recommending increased physical activity, weight loss and smoking cessation and reviewing treatment for COPD, sleep disorders (e.g. obstructive sleep apnoea), diabetes or any other long-term conditions.

Discuss the pros and cons of testosterone treatment

Testosterone replacement is a treatment option for older males with established hypogonadism; it is more likely to be worthwhile for those with specific symptoms for which improvements can be evaluated. The decision whether to initiate testosterone should take place after a discussion with the patient on the benefits and risks of treatment, which to some extent are both uncertain as detailed data on long-term health benefits and risks in large randomised controlled trials is currently lacking.[5] In addition, patients should be made aware of the testing requirements both prior to initiating treatment (e.g. for the possibility of undetected prostate cancer), and during treatment to assess response and safety (e.g. haemotocrit levels).

The benefits of testosterone treatment can include a reduction in depressive symptoms and improvements in mood and cognitive functioning, an overall feeling of energy and well-being and reported improvements in libido and sexual function.[2, 5] For males with erectile dysfunction and low testosterone levels, however, a large randomised controlled trial investigating the effect of testosterone replacement in addition to sildenafil found that the combination of treatment was not superior to sildenafil plus placebo in improving erectile function.[21] Effects which can be ascertained by the clinician include changes in body composition, such as an increase in muscle mass and a decrease in abdominal fat, and changes in surrogate markers of cardiovascular risk; testosterone treatment may improve a patient's glycaemic control and lipid profile, depending on their initial state of health.[2]

Potential adverse effects of testosterone treatment

Secondary polycythaemia is one of the main adverse effects of testosterone treatment, detected by an elevation in haematocrit levels (also referred to as packed cell volume – PCV). It is caused when levels of testosterone rise above the normal physiological range, and is more likely to occur with injectable preparations where the treatment regimen causes fluctuating testosterone levels.[5] Polycythaemia can lead to cardiovascular and thrombotic complications due to the increased viscosity of the blood and thrombosis. In men already at relatively high cardiovascular risk, testosterone treatment has been associated with an increase in cardiovascular events, and should be used with caution.[22]

For further discussion of the evidence on c**ardiovascular safety** of testosterone, see: "Recent research into testosterone use in older males spells a note of caution", Page 31.

Table 2: Testosterone formulations subsidised in New Zealand[2, 23]

	Amount of active ingredient*	Initial dosing interval*	Notes
Intramuscular injections:			
Testosterone esters†	250 mg in 1 mL injection	250 mg, every three weeks	Fluctuations in testosterone levels occur across injection cycle with higher levels following injections, tapering off over time. Patients may experience fluctuations in symptoms of hypogonadism. Risk of elevated haematocrit is greater with injections due to periods of elevation of testosterone above physiological range. To be given by deep IM injection, e.g. gluteal muscle
Depo-testosterone (testosterone cipionate)†	1000 mg in 10 mL injection	50 – 400 mg, every two to four weeks	
Testosterone undecanoate (undecylate)†	1000 mg in 4 mL injection	1000 mg, every 10 – 14 weeks	
Oral capsules:			
Testosterone undecanoate (undecylate)†	40 mg	120–160 mg, daily, in two divided doses initially, reduced to 40 – 120 mg, daily, in two divided doses	Recommended to be taken with or immediately after food. Absorption is dependent on fat intake, adequate absorption is, however, usually achieved as long as patients are not fasting or taking with low-fat meals.[26]
Transdermal applications:			
Transdermal patch	2.5 mg delivered over 24 hours, recommended to be applied at 10 pm daily to mimic normal circadian rhythm	2.5 – 7.5 mg, daily	Frequently causes skin reactions – including blistering and burning. More than one patch will be required, and applied at the same time, for doses above 2.5 mg daily. To be applied to intact, non-scrotal skin (e.g. back, abdomen, thighs, upper arms) and pressed firmly in place, especially around the edges; the area of application should be changed to give an interval of seven days between applications to the same site

* Due to differences in testosterone salts used in injections and bioavailability, the amount of testosterone administered is not directly comparable across formulations. Dosing amount and interval should be adjusted according to response to achieve a physiological testosterone level.

† These formulations are "retail pharmacy – Specialist" which means that specialist prescription or endorsement is required for subsidy; all listed formulations are fully subsidised.

Growth of a prostate cancer may be accelerated with testosterone treatment. Meta-analyses have not shown that testosterone treatment causes the initiation of prostate cancer, but rather may increase the rate of growth of pre-existing androgen-dependent prostate cancer cells.[2]

Sperm production reduces with testosterone supplementation. Therefore it is not an appropriate treatment for men who wish to retain their fertility. Depending on the underlying cause, suppressed spermatogenesis due to testosterone treatment can potentially be reinitiated by hCG treatment under specialist fertility clinic care.

Other adverse effects experienced by males taking testosterone include acne, oily skin and worsening of male pattern baldness. There is weak evidence that testosterone treatment may induce or worsen obstructive sleep apnoea.[5] Oral formulations of testosterone have been rarely associated with hyperbilirubinaemia and liver toxicity.[5]

Testosterone treatment is contraindicated in males with:[5, 23]

- Metastatic prostate cancer
- Breast cancer
- Primary liver tumours
- Hypercalcaemia
- Nephrotic syndrome

Testosterone treatment is not recommended in males with:[5]

- A palpable prostate nodule or induration
- PSA > 4.0 ng/mL or 3.0 ng/mL if they have a family history of prostate cancer
- Severe lower urinary tract symptoms associated with benign prostatic hyperplasia
- Haematocrit (PCV) > 50%
- Severe untreated obstructive sleep apnoea
- Uncontrolled or poorly controlled congestive heart failure
- Requirement for fertility
- Previous testosterone misuse

Initiating and monitoring testosterone treatment

If the decision is made that testosterone treatment is appropriate and the patient wishes to proceed, it is recommended that this is discussed with an endocrinologist. In most cases, an initial trial of testosterone treatment is recommended for three to six months, to evaluate improvement in symptoms and tolerability. If symptoms do not improve within six months, treatment should be discontinued.[24] If testosterone treatment is found to be beneficial and therefore continued, it is likely to be required long-term.

Prior to commencing treatment:

1. Measure PSA in males aged 40 years or over; patients with PSA > 0.6 ng/mL should undergo a prostate examination[5]
2. Measure haemoglobin and haematocrit levels (full blood count)

Selecting a preparation:

Fully subsidised testosterone treatment is available in New Zealand in oral, injectable and transdermal preparations (Table 2). Most of these require an initial diagnosis and prescription from a specialist. General practitioners, however, may be involved in the follow-up care and monitoring of these patients and subsequent prescription repeats. The choice of testosterone formulation is largely based on patient preference.[5] There is some evidence from a study of patients taking testosterone in the United States and United Kingdom that short-acting injections carry a higher risk of adverse cardiovascular effects than daily applications such as transdermal patches or gels (available overseas); this study did not include patients using three-monthly testosterone undecanoate injections, which is an alternative injection preparation available in New Zealand.[25] The use of preparations taken on a daily basis (e.g. oral tablets or patches) may be preferable during initial use to allow for withdrawal if adverse effects develop.[2]

Therapeutic range:

The aim of testosterone supplementation in males should be to provide circulating levels within the normal range for their age group. In younger males, aim for a level within the mid-range of the reference interval, and in older males, aim for the lower range of the interval.[5] Testosterone levels should be assessed within three to six months of initiating treatment and then at least annually thereafter.[2, 5]

The ideal time for monitoring testosterone levels depends on the preparation being used:[5]

- Injectable formulations: measure testosterone levels midway between the planned injection interval
- Oral undecanoate capsules: measure levels within three to five hours of dosing
- Transdermal patches: measure levels in the morning if the patch has been applied the previous evening

Monitoring for adverse effects:

PSA should be measured, and digital rectal examination performed, at three, six and 12 months after initiating treatment, then according to local screening guidelines for all males.[2, 5] Due to the effects of testosterone on the prostate small increases in PSA are likely: a systematic review of testosterone

supplementation in hypogonadal males found an average PSA increase of 0.3 ng/mL in younger males and 0.44 ng/mL in older males, but large increases were rare.[5] Discuss with a urologist if PSA increases by > 1.4 ng/mL within 12 months, if PSA velocity is > 0.4 ng/mL/year (if testosterone is taken for more than two years), if prostatic symptoms develop or if a prostatic abnormality is detected.[5, 24]

A full blood count should be requested at three, six and 12 months after initiating treatment, then annually thereafter.[2, 5] If haematocrit rises above 54%, or 48% in patients with a history of thrombosis, stop testosterone treatment until haematocrit levels return to normal. Testosterone may then be reinitiated at a lower dose or in a different formulation.[5] Manifestations of polycythaemia include digital ischaemia, neurological symptoms, hypertension, hypoxaemia and cor pulmonale.

There is no specific requirement to monitor cardiovascular health, however, most older males will already be receiving regular cardiovascular risk assessment.

Discontinue treatment if intolerable or serious adverse effects occur or if no benefit is derived within six months.[24]

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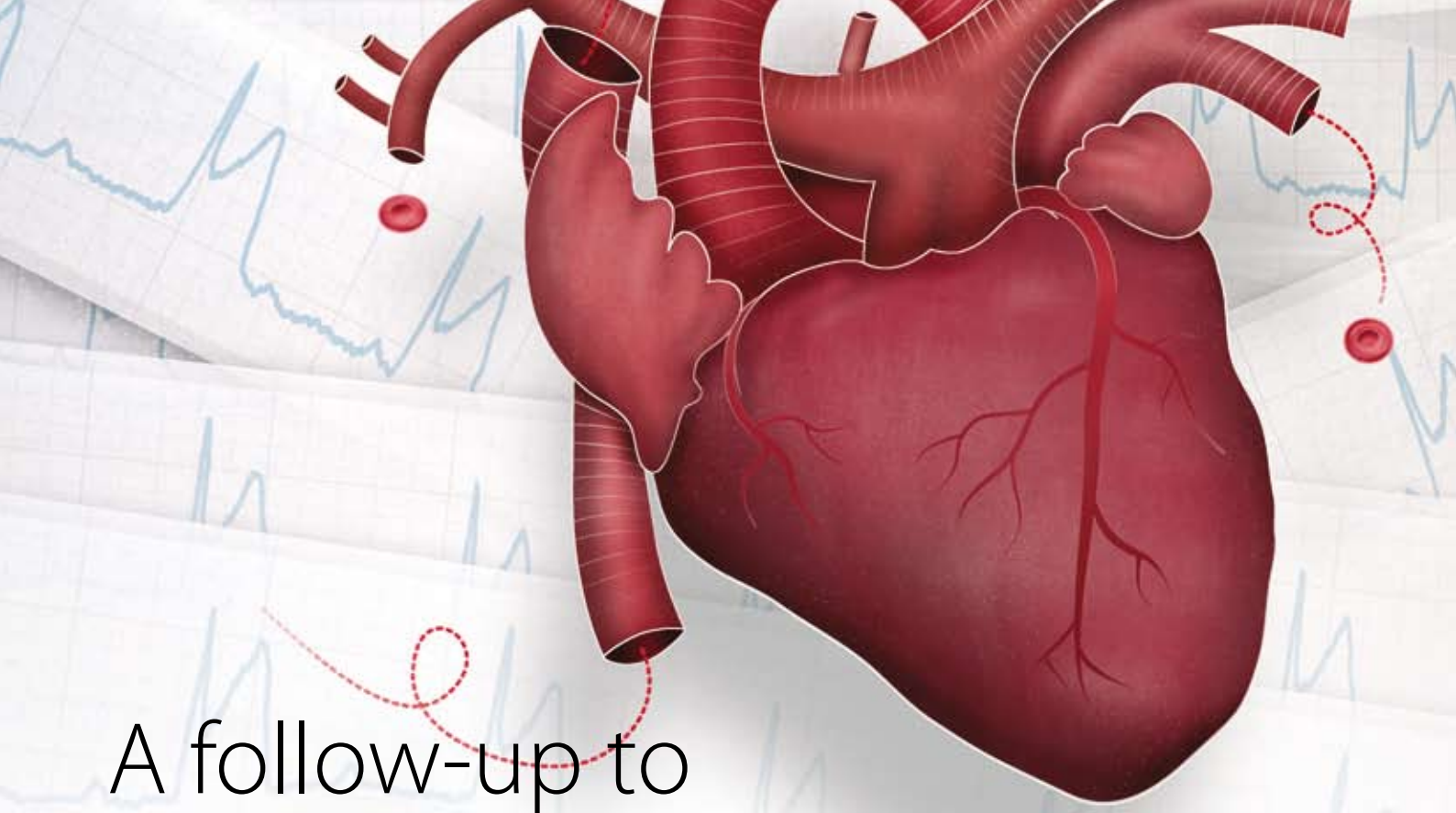
References

1. Ferlin A, Selice R, Carraro U, et al. Testicular function and bone metabolism—beyond testosterone. Nat Rev Endocrinol 2013;9:548–54.
2. Dohle GR, Arver S, Bettocchi C, et al. Guidelines on male hypogonadism. European Association of Urology, 2012. Available from: www.uroweb.org/gls/pdf/18%20Male%20Hypogonadism_LR.pdf (Accessed Jul, 2015).
3. Perry-Keene D. Low testosterone in men. Aust Prescr 2014;37:196–200.
4. Araujo AB, Wittert GA. Endocrinology of the aging male. Best Pract Res Clin Endocrinol Metab 2011;25:303–19.
5. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536–59.
6. Handelsman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992–2010. Med J Aust 2012;196:642–5.
7. Garnick MB. Testosterone replacement therapy faces FDA scrutiny. JAMA 2015;313:563–4.
8. Gan EH, Pattman S, H S Pearce S, et al. A UK epidemic of testosterone prescribing, 2001-2010. Clin Endocrinol (Oxf) 2013;79:564–70.
9. U. S. Census Bureau. Monthly population estimates for the United States: April 1, 2010 to December 1, 2014. Available from: http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk (Accessed Jul, 2015).
10. Statistics New Zealand. Census QuickStats about national highlights. Wellington, New Zealand: Statistics New Zealand, 2013. Available from: www.stats.govt.nz (Accessed Jul, 2015).
11. Ministry of Health. Pharmaceutical Collection. (Accessed Jul, 2015).
12. Office of the Commissioner. FDA cautions about using testosterone products for low testosterone due to aging; requires labelling change to inform of possible increased risk of heart attack and stroke. 2015. Available from: www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm436280.htm (Accessed Jul, 2015).
13. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–22.
14. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829–36.
15. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS ONE 2014;9:e85805.
16. Medicines Adverse Reactions Committee. MARC Minutes 159th Meeting, 11 September 2014. MARC, 2014. Available from: www.medsafe.govt.nz/profs/adverse/Minutes159.htm (Accessed Jul, 2015).
17. American Urological Association. AUA position statement on testosterone therapy. AUA, 2014. Available from: www.auanet.org/about/testosterone-therapy.cfm (Accessed Jul, 2015).
18. Wu FCW, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–35.
19. Kyle C (Ed). Pathology handbook: a guide to the interpretation of pathology tests. New South Wales: Sonic Healthcare, 2014.
20. Grossmann M, Hoermann R, Wittert G, et al. Effects of testosterone treatment on glucose metabolism and symptoms in men with type 2 diabetes and the metabolic syndrome: a systematic review and meta-analysis of randomized controlled clinical trials. Clin Endocrinol 2014;[Epub ahead of print].
21. Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. Ann Intern Med 2012;157:681–91.
22. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–22.
23. New Zealand Formulary (NZF). NZF v37. 2015. Available from: www.nzf.org.nz (Accessed Jul, 2015).
24. Wylie K, Rees M, Hackett G, et al. Guidelines on the management of sexual problems in men: the role of androgens. British Society for Sexual Medicine, 2010. Available from: www.endocrinology.org/policy/docs/10-12-01_UK%20Guidelines%20Androgens%20Male.pdf (Accessed Jul, 2015).
25. Layton J, Meier CR, Sharpless JL, et al. Comparative safety of testosterone dosage forms. JAMA Intern Med 2015;175:1187–96.
26. Schnabel PG, Bagchus W, Lass H, et al. The effect of food composition on serum testosterone levels after oral administration of Andriol Testocaps. Clin Endocrinol 2007;66:579–85.



A follow-up to **acute coronary syndromes**

The article: "The immediate management of acute coronary syndromes in primary care" attracted some interest from emergency care clinicians around the country. In the interests of clarity we provide supplementary material on some of the more contentious issues.

For the full article, see: "The immediate management of acute coronary syndromes in primary care", BPJ 67 (Apr, 2015).

Refer all patients with suspected coronary syndromes to hospital

A 12-lead ECG should be performed on all patients presenting to primary care with chest pain that may be due to a cardiac cause. The results of the ECG may confirm a ST segment elevation myocardial infarction, but more commonly a lack of acute ECG changes will be found which may be consistent with a non-ST segment elevation acute coronary syndrome. It is also possible that there will be delayed cardiac changes that may not be detectable on ECG when the patient is initially triaged. A fourth possibility, which is more likely in older patients or in patients with an underlying cardiac condition, is that the ECG is inconclusive. Immediate transfer to hospital is therefore recommended for all patients with symptoms suggestive of an acute coronary syndrome, where a cardiac cause cannot be reasonably excluded, regardless of the results of their ECG, i.e. a normal ECG does not exclude the possibility of a cardiac cause.

In the original article in BPJ 67 it was stated that: "If the patient's ECG is otherwise abnormal, and suspicion remains of a cardiac cause, then assume that the patient has an acute coronary syndrome and refer them to hospital." We did not intend to imply that, in a patient in whom a cardiac cause for their symptoms is suspected, the finding of a normal ECG would preclude referral to hospital.

Glyceryl trinitrate dosing during an acute coronary syndrome in a primary care setting

Glyceryl trinitrate (GTN) is an important medicine for patients with symptomatic angina. GTN exerts its therapeutic action by relaxing vascular smooth muscle, therefore producing both arterial and venous vasodilation. This results in an improvement in myocardial perfusion and a reduction in cardiac work load. However, GTN can also cause hypotension and it is important that patients with angina do not exceed the recommended dose. GTN should also be avoided by patients with significant pre-existing hypotension or hypovolaemia (both acutely and long-term), or by patients who are concurrently using PDE-5 inhibitors, e.g. sildenafil.[1]

The National Heart Foundation "Angina Action Plan" provides instructions for patients on how to administer GTN during an attack of angina. In summary, patients are advised to take one puff (or tablet) of GTN under their tongue, if symptoms remain the patient is advised to repeat the dose after five minutes, if

after another five minutes the patient's symptoms have not resolved then they are advised to assume they are having a heart attack, call an ambulance and chew an aspirin.

In contrast to the "Angina Action Plan" for patients, we have provided GTN dosing instructions that are appropriate when the patient is under the supervision of a primary care clinician. These include up to three doses of GTN, of one to two sprays, administered to the patient at five minute intervals. This is consistent with the Scottish Intercollegiate Guidelines Network (SIGN) for acute coronary syndromes (2013), the American Heart Association Guidelines for acute coronary syndromes (2010) and the New Zealand medicine datasheet for GTN.[2, 3, 4]

We believe that primary care clinicians will exercise clinical judgement when assessing the risk versus benefit of additional GTN doses when managing patients with suspected acute coronary syndromes. While the patient is awaiting ambulance transfer they may be given GTN and additional analgesia, and will be closely monitored for complications, e.g. cardiac arrest, and adverse effects of treatment, e.g. hypotension caused by GTN. If there is a delay in transfer, it is possible that three doses of GTN may be required in some situations.

Which is the best antiplatelet in combination with aspirin for patients with acute coronary syndromes?

The need to give aspirin to all patients with acute coronary syndromes is universally acknowledged. However, the issue of whether or not to provide an additional antiplatelet medicine, e.g. clopidogrel or ticagrelor, to these patients is more complex and depends on geographical location and clinical context. Given that general practitioners operate in very different situations across New Zealand it is difficult to provide one-size-fits-all guidance.

Neither clopidogrel nor ticagrelor are available on Practitioner's Supply Orders (PSO), therefore it is unlikely that many general practices will have ready access to either of these medicines at short notice. Furthermore, in most urban areas there should not be significant delays in transporting patients by ambulance to hospital and therefore the decision regarding administration of an additional antiplatelet medicine will be left to secondary care. Administering an additional antiplatelet medicine in primary care in this situation is also unlikely to improve the patient's outcome. The "Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery" (ATLANTIC) study found that earlier treatment with ticagrelor did not improve coronary reperfusion prior to percutaneous coronary intervention (PCI).[5] Patients receiving ticagrelor in the ambulance received the medicine at a median time of 31 minutes earlier than patients in hospital.[5] However, in remote communities where there are often significant delays in transporting patients to secondary care, it may be necessary for general practitioners to initiate dual antiplatelet treatment and to thrombolyse patients with acute coronary syndromes.

In the original article in BPJ 67 it was recommended that clopidogrel be given to patients with an acute coronary syndrome if there was evidence of ischaemia on ECG or elevated troponin levels. This was based on SIGN guidelines recommending that all such patients should be treated immediately with both 300 mg of aspirin and 300 mg of clopidogrel.[2] However, in New Zealand, the trend among cardiologists now appears to be a preference for ticagrelor in combination with aspirin over clopidogrel in combination with aspirin.

A meta-analysis of four trials with over 31 000 patients with non ST segment elevation acute coronary syndrome compared the efficacy of ticagrelor or prasugrel with clopidogrel in preventing major cardiovascular events. It was found that ticagrelor or prasugrel, in combination with aspirin, significantly reduced major cardiovascular events in patients with non ST segment elevation acute coronary syndrome, compared with clopidogrel and aspirin.[6] However, there was also an increased risk of major bleeding associated with both ticagrelor and prasugrel, compared with clopidogrel for some patients.[6] For every 1000 patients treated with ticagrelor and aspirin there would be 16 fewer major cardiovascular events and six more major bleeds, compared to patients treated with clopidogrel and aspirin.[6] The issue of antiplatelet treatment in patients with acute coronary syndromes is therefore further complicated by the risk of bleeding associated with subsequent surgical interventions, e.g. stenting, and primary care clinicians will not always be certain of which interventions the patient will undergo later.

The bottom line is that if a patient with recent chest pain has a positive troponin test and/or new ECG changes, and there will be a significant delay in delivering them to secondary or tertiary care, then it is reasonable that either ticagrelor or clopidogrel be administered; in this situation giving either of these medicines is preferable to withholding treatment due to clinical uncertainty.

Administering fibrinolysis in primary care

If a patient has a ST segment elevation myocardial infarction they are likely to gain the greatest benefit from fibrinolytic treatment in the early phase of their condition.[2] Fibrinolytic treatment is recommended for all patients with a ST segment elevation myocardial infarction, who do not have

contraindications, if a percutaneous coronary intervention cannot be performed within two hours of first medical contact.[7] Primary care clinicians working in urban centres are unlikely to need to administer fibrinolytic treatment to patients with ST segment elevation myocardial infarction as transport to hospital can be expected to be relatively rapid. However, in rural settings this practice is more common.

When deciding whether or not to initiate fibrinolytic treatment to a patient with a ST segment elevation myocardial infarction, assuming that intravenous tenecteplase and enoxaparin are available, clinicians should consider the total time that passes from first contact with the patient until the time that a specialist coronary care unit can be expected to perform an intervention. This includes not only the transportation time, as highlighted in our article, but also the time taken to triage the patient and the time the patient must wait until the ambulance arrives. If this total time is estimated to be more than two hours then fibrinolytic treatment should be initiated in primary care, where possible.

N.B. In the printed version of the article there was a "typo" in the sentence discussing enoxaparin, which read: "Patients aged over 75 years are recommended not to receive the IV bolus of tenecteplase, due to the increased risk of bleeding." It should instead read: "Patients aged over 75 years are recommended not to receive the IV bolus of **enoxaparin**, due to the increased risk of bleeding." This has been corrected in the online version of the article.

Acknowledgement: In developing the answers to these issues, we consulted with **Associate Professor Stewart Mann**, Cardiovascular Medicine, University of Otago, Wellington and **Dr Belinda Green**, Cardiologist, Southern DHB.

References

1. Berkhan L. Interpretation of an elevated serum ferritin. N Z Fam Pract 2002;29:45–8.
2. Scottish Intercollegiate Guidelines Network (SIGN). Acute coronary syndromes: a national clinical guideline. SIGN, 2013. Available from: www.sign.ac.uk/pdf/sign93.pdf (Accessed Jul, 2015).
3. O'Connor RE, Brady W, Brooks SC, et al. Part 10: Acute coronary syndromes: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010;122:S787–817.
4. AFT Pharmaceuticals Ltd. Glytrin spray. 2013. Available from: www.medsafe.govt.nz/profs/datasheet/g/Glytrinspr.pdf (Accessed Jul, 2015).
5. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016–27.
6. Bavishi C, Panwar S, Messerli FH, et al. Meta-analysis of comparison of the newer oral P2Y12 inhibitors (prasugrel or ticagrelor) to clopidogrel in patients with non-ST-elevation acute coronary syndrome. Am J Cardiol 2015;[ePub ahead of print].
7. ST-Elevation Myocardial Infarction Guidelines Group, New Zealand Branch of Cardiac Society of Australia and New Zealand. ST-elevation myocardial infarction: New Zealand Management Guidelines, 2013. N Z Med J 2013;126:127–64.

"Steady as she goes": helping older people Stay Independent

This month we release a range of resources aimed at falls prevention within the community, developed in partnership with the Health Quality & Safety Commission. The resources are based on the STEADI falls campaign developed by the United States Centers for Disease Control and Prevention (CDC), and have been adapted for use in New Zealand.

Improving awareness and education

Approximately one in every three people aged over 65 years will fall each year, which for many represents a major loss of independence.[1] It is common for older adults to see falls as unavoidable or chance events, and to not recognise that there are things they can do to reduce their risk of falling.[2] Improving awareness and education about the risk factors for falls has the potential to reduce the likelihood of fall-related injuries and loss of independence for older people. Older adults who fall are less likely to have discussed falls, and falls prevention, with their healthcare providers.[3]

As part of the Health Quality & Safety Commission's Standing up to Falls campaign, and following on from April Falls month, a range of resources, developed in partnership with bpac^{nz}, have been released to increase the awareness of falls within the community. The *Stay Independen*t clinician toolkit aims to assist health professionals to highlight the specific factors which may increase a patient's risk of falling by introducing assessments, exercises and referral pathways to local programmes which can help reduce this risk. Evidence suggests that multi-factorial assessments and interventions reduce the rate of falls in older people living in the community.[4] With the growing elderly population, reducing the likelihood of falls is an important step towards reducing health care costs and maintaining independence and quality of life for older people throughout the country.

"Stay Independent" toolkit

The *Stay Independent* toolkit includes both patient and clinician specific information and assessment tools. These resources have been developed to accompany the Health Quality & Safety Commission's national programme Reducing Harm from Falls and the Ask, assess, act resources which are currently available throughout the country.

Patient resources

A poster and accompanying brochure (both titled *Stay independent*) are intended for use in primary care waiting rooms and receptions. The poster encourages patients to complete a checklist (contained within the brochure), and provides background information on falls and preventative steps that can be taken to reduce risk. The brochure is intended to be used by patients before, or during, consultations with the checklist providing ten questions to help identify any risks. Explanations are provided on why each question is important, and local falls prevention programmes can be noted on the back of the brochure for the patient to seek further support.

Clinician resources

The clinician toolkit contains a range of information to assist health professionals in determining if an older patient is at risk of falling. Based around an algorithm which helps guide the assessment of risk factors, the toolkit provides information on falls and falls prevention, assessments which can help clinicians to identify risk factors in older patients, and information on changing patient behaviour and attitudes towards falls.

Clinicians can use the checklist in the brochure as a conversation starter with older patients to discuss falls risk and any concerns the patient has about staying independent. If further investigation is warranted, assessments that can be conducted within a consultation include the Timed Up and Go (TUG) Test, the 30-Second Chair Stand Test and the Four Stage Balance Test, as well as assessing for postural hypotension. A combination of two or more of these tests is recommended to help to identify an older patient who is at risk for falling.[5]

If the patient has risk factors present, or would benefit from active preventative steps, the toolkit contains a sheet for recording local falls prevention programmes, and also instructions for a chair stand exercise that a patient can undertake at home. For patients with multiple risk factors, the toolkit contains a checklist for an in depth assessment, and referral form for specialist services.

Accessing resources

A copy of the *Stay Independent* toolkit has been provided with this month's edition of Best Practice Journal. The Health Quality & Safety Commission is planning a mail-out of posters and brochures to practices. The toolkit and downloadable versions of each resource, including the poster and brochure, can also be accessed online at either the Health Quality & Safety Commission or bpac^{nz} websites:

www.hqsc.govt.nz/our-programmes/reducing-harm-from-falls/projects/primary-and-community-care/

www.bpac.org.nz/falls

For further information on the Health Quality & Safety Commission's Standing up to falls campaign, including many other free resources available for primary care practitioners, patients and their families/whānau, see: **www.hqsc.govt.nz/our-programmes/reducing-harm-from-falls**

A message from the Health Quality & Safety Commission

Health Quality & Safety Commission clinical leads Dr Paul Cooper (GP and Clinical Lead-Primary Care) and Sandy Blake (Director of Nursing and Patient Safety at Whanganui DHB and Clinical Lead – Reducing Harm from Falls Programme) share some thoughts on how to make best use of this new resource: Stay Independent.

Let's talk about falls

Let's talk about falls and how we can raise the awareness of the risk of falling with our patients. Falling is not an unusual event. We need to be asking the right questions, looking and listening for what is not being said.

Some key facts may be surprising:

- Falls are the leading cause of injury to older people
- After three falls with minor injury a person has a 240% increased risk of a fall with major injury
- Approximately one-third of people aged over 65 years fall each year and the likelihood of falling increases with advancing age (each year one in every two people aged over 80 years will fall).

How can we reduce harm from falls in older people?

We need to "normalise" talking about the risk of falls and encourage all elderly people to stay as active as possible, minimising their risk of falling, maintaining their independence and improving their overall quality of life. Falls prevention requires a partnership approach between the older person, their family and their health care team.

The Ask, assess, act process is a guide to remind us to have the conversation, listen to what we are being told, reflect on it and take action. The conversation needs to involve the older person, their family/whānau and other carers, in the identification of falls-related problems and risks that are real for the older person, and lead to shared decisions about actions which will be most helpful and manageable.

Starting the conversation:

ASK the older person three simple screening questions:

1. Have you slipped, tripped or fallen in the last year?
2. Can you get out of a chair without using your hands?
3. Have you avoided some activities because you are afraid you might lose your balance?

Asking yourself: "Is this older person at risk of falling?" and "what is contributing to this risk?", often highlights the number and type of medicines the older person is taking.

What does the patient see as problems and risks associated with falls? Explore with the patient and their family/whānau what has changed for them?

ASSESS the older person to identify their particular falls risk factors:

- Observe as the patient enters the room or rises from the chair. Assess falls risk factors related to physical activity, underlying conditions and home safety. Gather some objective information using the tests in the *Stay Independent* toolkit.
- You might suggest that the patient sees the practice nurse "to do some strength and balance tests and see how we can maintain your mobility".

ACT by putting in place individualised interventions and supports to address the older person's risks:

- Set a partnership plan in motion with the patient in control of their own care. Address the risks identified, discuss and agree specific actions, consider who else cares for this person and how they can assist.
- Consider ways the older person could enhance balance and strength, e.g. through home-based or community-based exercise programmes.
- Refer the older person to the ACC home-safety checklist. What things can the patient do in their everyday life to keep mobile/active?
- Social connection is also very important; consider how the older person can connect with their community.
- Consider what monitoring, investigation or clinical referral might be needed.
- Consider adding the falls questions in your regular "older persons health review". Add a falls question to the medicines template in your practice management system, e.g. Medtech.

Remember that medicines (e.g. medicine class, number of medicines, interactions) are one of the major contributors of falls in older people. Medicines are easy to start and more difficult to stop and as people age we need to accurately seek out the risk of prescribed medicines. Consider: Is this a necessary and useful medicine, do the benefits outweigh the risks?

Clinical pathways for "falls, frailty, and older people" are in development around the country; the *Stay Independent* toolkit provides some tests, checklists and context which might be useful to incorporate in these pathways.

If you have any feedback or questions about the *Stay Independent* toolkit or the Health Quality and Safety Commission's falls programme, please contact Bridgette Connor, Project Manager – Reducing Harm from Falls. Email: **Bridgette.Connor@hqsc.govt.nz**

References

1. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: A review of the literature. Maturitas 2013;75(1):51–61.
2. Stevens JA, Noonan RK, Rubenstein LZ. Older adult fall prevention: Perceptions, beliefs, and behaviors. Am J Lifestyle Med, 2010;4(1):16–20.
3. Lee D, Day L, Hill K, et al. What factors influence older adults to discuss falls with their health-care providers? Health Expectations, 2013.
4. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database Syst Rev 2012;(9):CD007146.
5. Barry E, Galvin R, Keogh C, et al. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis. BMC Geriatrics 2014;14(1):14.

ask assess act

Pertussis vaccine
now subsidised for all pregnant women

Changes to the funding criteria for diphtheria, tetanus and pertussis (Tdap) vaccine (Boostrix) came into effect on 1 August, 2015. The new criteria mean that all pregnant women between 28 and 38 weeks' gestation are now eligible for subsidised vaccination, whereas previously this was only the case during a pertussis epidemic.[1] Pertussis vaccination is also included in the National Immunisation Schedule at age six weeks, three months and five months.

New Zealand has undergone three pertussis epidemics in the last 15 years. In the most recent, from 2011 to 2014, there were on average 102 cases of pertussis per 100,000 population, with the primary burden of disease in infants aged six months or less at a rate of 801 per 100,000.[2] Vaccine coverage for infants from August 2011 to December 2013 was 75% in six month-olds, highlighting a gap in vaccination rates in infants even during an epidemic.[2] The lowest rates of pertussis vaccine coverage were seen in Northland and Waikato DHBs.[2] Vaccination rates were lowest, and pertussis rates highest, for Māori and Pacific children and children in lower socioeconomic circumstances.[2]

The case for maternal vaccination during pregnancy

The Tdap vaccine was subsidised in New Zealand from 1 January, 2013 for use in pregnancy during a pertussis epidemic. Currently, maternal immunisation rates in New Zealand are reported to be poor, and have been identified as a target area for improvement prior to the next pertussis epidemic.[2]

Many cases of pertussis occur in infants too young to have gained immunity from the present national immunisation schedule. Maternal vaccination offers benefit to the infant as maternal antibodies cross the placenta and provide protection prior to the first infant vaccination at age six weeks, as well as boosting maternal immunity to provide indirect protection and "cocoon" the infant.[2, 3] In October 2012, the Advisory Committee on Immunization Practices (ACIP) in the United States recommended that all pregnant females should receive Tdap vaccination during pregnancy.[3] This advice was echoed by the Global Pertussis Initiative in 2015, which now recommends maternal vaccination during pregnancy as the primary prevention strategy for reducing pertussis hospitalisation and mortality in infants.[4]

Maternal Tdap vaccination is highly effective at providing pertussis protection to infants too young to receive vaccination

An assessment of pertussis incidence during an outbreak in England, where vaccination rates reached 60% in pregnant mothers by the end of the outbreak, suggests a vaccine efficacy of 90% for infants aged under two months when vaccination occurs at least seven days before birth.[5] Similar analyses from the United States show a vaccine efficacy of 91% for infants aged two months or under.[4] Protection is lower if the vaccine is given within seven days of birth.[5]

Tdap vaccine safety during pregnancy

Some expectant mothers may be hesitant to take up Tdap vaccination during pregnancy due to fears of adverse effects. Mothers can be reassured that real-world data from tens of thousands of women who have been vaccinated against pertussis during pregnancy report that rates of adverse birth outcomes are similar between vaccinated and unvaccinated

mothers.[4] Infant growth and development up to age 13 months has been assessed in one randomised controlled trial of maternal pertussis vaccination, and found not to differ between infants born to vaccinated or unvaccinated mothers.[6]

Surveillance data from the United Kingdom including 20,074 pregnant females who received pertussis vaccination reported no increased risk of a range of adverse pregnancy outcomes, including: stillbirth, maternal or neonatal death, pre-eclampsia or eclampsia, haemorrhage, fetal distress, uterine rupture, placenta or vasa praevia, caesarean delivery, low birth weight, or neonatal renal failure.[7] In the United States, surveillance data from 123,494 pregnant females, 21% of whom received Tdap, reported no differences in rates of preterm delivery, small for gestational age babies, or hypertensive disorders between vaccinated and unvaccinated mothers.[8] A small difference in rates of chorioamnionitis was noted in this study - subsequent assessment of this study, however, and other data by the Centers for Disease Control (CDC) and Global Pertussis Initiative, suggest that there is unlikely to be a causal association between pertussis vaccination and chorioamnionitis.[4, 9]

As pertussis vaccination during pregnancy has only been recommended and taken up recently, there is little data available regarding long-term health outcomes for children. However, parents can be assured that maternal vaccination offers immediate protection to infants in the neonatal period and a reduced risk of the serious consequences of pertussis infection.

Offering Tdap vaccination to pregnant women

Key practice points:

- Clinicians should offer the Tdap vaccine to all pregnant mothers and for each pregnancy
- Vaccination should preferably occur at least seven days before birth, and is subsidised for women between 28 and 38 weeks' gestation

Vaccination between 28 and 38 weeks' gestation may provide the greatest benefit by allowing transfer of maternal antibodies close to birth.[3] The maximal antibody response develops after two weeks, and evidence indicates the greatest vaccine efficacy occurs when vaccination is given at least seven days prior to birth.[3, 4]

Clinicians can inform patients that they should expect local injection site pain and irritation, and may develop short-term systemic symptoms. Adverse effects following Tdap administration include typical vaccine-associated symptoms, such as local irritation, injection site pain, and possible systemic symptoms, such as headache, fever, and muscle pain.[3, 6]

For mothers who decline vaccination during pregnancy, an alternative strategy for the prevention of infant pertussis is to "cocoon" the infant by providing booster vaccinations for close family members immediately after birth.[4] Vaccination of adult family members against pertussis is not subsidised, but if children aged under 18 years are unvaccinated or have not completed the recommended pertussis vaccination schedule, they can receive funded catch up vaccinations under the Immunisation Schedule.[10]

For further information on pertussis vaccination during pregnancy, see: **www.bpac.org.nz/BPJ/2014/April/pertussis.aspx**

References:

1. PHARMAC. Decisions to list and amend restrictions on various pharmaceuticals. 2015. Available from: www.pharmac.health.nz/news/notification-2015-07-17-various-pharmaceuticals/ (Accessed Jul, 2015).
2. Kiedrzynski T, Bissielo A, Suryaprakash M, et al. Whooping cough—where are we now? A review. N Z Med J 2015;128:21–7.
3. Centers for Disease Control and Prevention (CDC). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women-Advisory Committee on Immunization Practices (ACIP), 2012. Morb Mortal Wkly Rep 2013;62:131–5.
4. Forsyth K, Plotkin S, Tan T, et al. Strategies to decrease pertussis transmission to infants. Pediatrics 2015;135:e1475–82.
5. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet 2014;384:1521–8.
6. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. JAMA 2014;311:1760–9.
7. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. BMJ 2014;349:g4219.
8. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. JAMA 2014;312:1897–904.
9. Datwani H, Moro PL, Harrington T, et al. Chorioamnionitis following vaccination in the Vaccine Adverse Event Reporting System. Vaccine 2015;33:3110–3.
10. Ministry of Health. Immunisation Handbook, 2014. Available from: www.health.govt.nz/publication/immunisation-handbook-2014 (Accessed Jul, 2015).

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

Dear Editor,

As a primary care clinician working with a population at higher risk for developing rheumatic fever, I have a comment and a question for the experts. In a situation of high prevalence of Group A Streptococcus (GAS) and where all "sore throats" are swabbed, some clinicians are mandating that it is preferable/more convenient/safer to treat all children with antibiotics, even when the swab is negative, and not to inform parents/patients of the negative swab result. Weighing up the issue of antibiotic overuse and resistance, my question is simply: Is there any justification to treat children with GAS negative throat swabs, and with no current household members who are GAS positive or have rheumatic fever, with ten day courses of antibiotics, or should we advise them to stop the antibiotics when the swab result is negative?

The risk is that many children would receive several courses of antibiotics per year for viral infections (as they already do with many primary care/ED practitioners still prescribing amoxicillin +/- steroids for every URTI/bronchiolitis). If that risk is outweighed by the benefit of treating, I am happy to change practice but as far as I know, the current published guidelines say "stop the antibiotic" if GAS negative.

I look forward to your response.

Anonymous

We asked Professor Mark Thomas, Infectious Diseases Physician, Auckland DHB to respond to this question.

This letter about treatment of sore throats in people with a high risk of rheumatic fever draws attention to a probably well-intentioned, but ultimately harmful, approach to the prevention of rheumatic fever. If a patient has been given empiric antibiotics for a sore throat, but the subsequent throat swab result is negative for GAS, the antibiotics should not be continued. This is emphasised in the most recent New Zealand Heart Foundation guidelines* for management of sore throat, which very clearly state that antimicrobial treatment should promptly be stopped in people at high risk of rheumatic fever, who present with a sore throat and who do not have GAS (*Streptococcus pyogenes*) isolated from a throat swab. To advise such patients to continue with their antibiotic treatment is not consistent either with the widely accepted New Zealand guidelines or with guidelines from other international authorities.

The advice to continue "treatment" of people who do not have GAS infection, with an antibiotic intended to eradicate GAS infection, risks undermining confidence in the rational basis of the rheumatic fever prevention strategy. If clinicians are advised to "treat" patients for an infection, that they have documented not to be present by the gold standard test, then they may justifiably ask whether they are being encouraged to leave behind the practice of evidence-based medicine and return to practices based on good intentions. Patients and their caregivers are also likely to lose confidence in the wisdom of their health professionals and question why, if the results of the throat swab are to be ignored, the test was performed in the first place?

Adherence to treatment for proven GAS infection is widely acknowledged to be problematic. If clinicians are encouraged to "treat" non-existent infections, and patients and their families are encouraged to persist with "treatment" of non-existent infections then the programme risks losing credibility, which will then increase the risk of patients and their caregivers not persisting with treatment in those high risk patients who do have documented GAS infection.

The adverse effects of antibiotic treatment, whether immediate and minor, such as rash or gastrointestinal upset, or immediate and severe, such as anaphylaxis, or more prolonged, such as selection of antibiotic resistant bacteria or increased risk of obesity, occur regardless of whether the antibiotic was prescribed correctly or incorrectly. However, those risks are very much less acceptable when the antibiotic prescription had no possibility of producing positive effects!

The writer of this letter, and those faced with similar situations, should ask those giving them incorrect advice about the management of sore throats, to carefully read the New Zealand Heart Foundation guidelines.

Associate Professor Mark Thomas
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* available from: www.heartfoundation.org.nz/uploads/sore_throat_guideline_14_10_06_FINAL-revised.pdf

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