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Upfront: End-of-life care for patients with chronic disease: have we made a difference?

The year in review: What did we learn in 2014?
In 2014 we published over 60 medical education articles in Best Practice Journal, spanning more than 450 pages. Context is crucial for understanding and accepting why any recommendations are made, but if we take away the “why’s, where’s and how’s”, we are left with a list of key messages to guide the responsible use of medicines in primary care.

The optimal management of patients with COPD

Part 1: The diagnosis
A diagnosis of COPD may be considered in adult patients with long-term exposure to respiratory irritants, e.g. cigarette smoke, or with symptoms typical of COPD, i.e. breathlessness, cough, and/or sputum production. COPD cannot be reliably diagnosed on symptoms alone and requires spirometry to confirm a diagnosis.

Part 2: Stepwise escalation of treatment
The progression of COPD can be slowed by providing support for patients to stop smoking, and encouraging regular exercise and annual influenza vaccination. The pharmacological treatment of COPD needs to be individualised according to the patient’s response; regular follow-up is an important part of this process. Short-and then long-acting bronchodilators are the mainstays of treatment, depending on the patient’s symptom severity.

Essentials for people with COPD
Overuse of benzodiazepines: still an issue?
Benzodiazepines may be considered as a short-term treatment for insomnia and anxiety; zopiclone, a benzodiazepine-like medicine, is indicated for the treatment of insomnia only. Long-term use of these medicines for insomnia or anxiety is discouraged as they are associated with dependency, an increased risk of falls and dementia in elderly people, cognitive difficulties and an increased risk of motor vehicle accidents. Data from New Zealand show that patients are currently being prescribed large volumes of benzodiazepines and zopiclone.

The detection and management of patients with chronic kidney disease in primary care
A New Zealand consensus statement for the management of chronic kidney disease (CKD) in primary care has recently been developed. The statement reinforces the need to view CKD as a significant contributor to cardiovascular risk and recommends that targeted testing for CKD should be linked to routine cardiovascular risk assessments and diabetes testing.

Research Updates:
Shorter courses of oral corticosteroids for the management of exacerbations in patients with COPD
Diet and the risk of COPD

Correspondence:
Milk and bone density
Is phentermine addictive?
In late 2011 we published an article on end-of-life care for patients with respiratory failure, contributed by Professor D. Robin Taylor, who at the time was a Professor of Respiratory Medicine, at the Dunedin School of Medicine, University of Otago. Professor Taylor has since moved on from this role, but continues his research on end-of-life care at the University of Edinburgh. In his article, Professor Taylor called for a paradigm shift in the way that health care organisations and their staff provided care for patients with chronic illnesses, who are dying. Professor Taylor described what measures the service that he worked for were implementing to address these concerns. However, he noted that progress would not be made unless healthcare organisations adopted these tools at a strategic level. Organisations must work cohesively to attain the best outcome possible for the patient who is dying. Where death is an inevitable end-point, the ultimate aim is to achieve “a good death”.

Now, over three years on, we revisit Professor Taylor’s article and question whether this paradigm shift has occurred. The philosophies that Professor Taylor expresses are still highly relevant, however, some aspects have changed, such as the rise and fall from favour of the Liverpool Care Pathway. Things have moved in a positive direction since 2011, and there is much greater interest in advanced care planning across health care organisations, but there is still room for improvement. We invited Dr Syed Hussain, Respiratory Physician and Advanced Care Planning “clinical champion” at Auckland City Hospital, to comment on how far we have come in the provision of end-of-life care, and how much further we need to go.
Part 1: The need for a paradigm shift

Contributed by: Professor D. Robin Taylor

Death comes to all of us, and if we survive into our late 70s or 80s, progressive organ failure, often with multiple co-morbidities, usually characterises the pathway towards the end of life. The care of patients with end-stage cardiac, renal or respiratory failure feature increasingly in the provision of health services, and the costs are immense particularly in the last year of life.\(^1\)

However, it is also increasingly apparent that our current model of care does not provide what is best for patients at end-of-life. No one clinical service is equipped to provide for the patient’s needs at all stages of their illness trajectory. Indeed, the philosophy of care and management priorities often differ between service providers. This leads to discontinuity of care. The emergency department and medical teams are geared to dealing with acute deterioration: the model is predominantly curative or “patch up and mend”. Palliative care and hospice teams focus on “end-of-life” much more readily, but tend to operate in another domain, often separated from acute services not just philosophically but often geographically or by cost-centre. Because each of us operates in our separate silos, moving from a “curative” to an “end-of-life” management approach is difficult. Even where the diagnosis of dying has been embraced, our behaviours are more powerfully governed by the context in which we work. Often the default position is to continue as before, however inappropriate that may be.

A new model is required. Appropriate end-of-life care means less intensive, non-curative, symptom-relieving support in which preparing for death is seen as more important than clinging on to life. This means that “a good death” should be regarded as a quality outcome for all clinical services irrespective of where and by whom they are provided. It means striving to provide continuity of care at the end-of-life. It means that chronic disease management, palliative care, end-of-life care and terminal care are regarded as a continuum to which all health care providers contribute. Whether in rest homes, primary care, emergency departments, medical wards or outpatient clinics, the “diagnosis of dying” should be entertained, sensitively communicated, and allowed to shape subsequent management.

In our own Unit, a very bad death made us realise that there was a significant gap between our intentions and what we actually delivered. Since that incident, we have been attempting to improve end-of-life care in the Respiratory Medicine service in Dunedin Hospital. But we recognise that the obstacles are considerable, not
because of attitudes on the part of individuals, but because “the system” militates against it. We have adopted several practical tools which can be applied to improving end-of-life care, but we realise that these have limited impact unless they are accepted across the wider organisation of a District Health Board. In isolation, progress is almost impossible. As well as specific tools, there is a need for strategic initiatives. The approach has to be “both ... and”.

### The tools

An Advanced Care Plan provides the opportunity for patients, their family, and health care providers to enter into the territory of “end-of-life”. Importantly, it opens up conversations. In many cases it is liberating – from denial of the reality that a patient is experiencing and from fear of what might lie ahead. The New Zealand Advanced Care Planning (ACP) Co-operative has been established through the Ministry of Health. Excellent guidelines on the principles and application of ACP have just been published.\(^2\,^3\) Advanced Care Planning is not the prerogative of a single professional group - specialists, General Practitioners or palliative care physicians.

In Dunedin, we have started a Respiratory Failure Supportive Care Clinic which includes, among other things, the opportunity to introduce the concept of ACP. The qualification for referral to the Clinic is the so-called “surprise question”, i.e. would we be surprised if the patient were to die within the next year? Areas for discussion include the medical prognosis, the patient’s hopes and fears for the future, palliative treatments that are currently needed, as well as ACP, i.e. treatments that would be acceptable and those that would be excessive or futile in the event of acute deterioration. A generic ACP needs to be modified for specific disease groups such as patients with respiratory failure, and we have recently done so.

Resources, including generic templates, are available from the Advanced Care Planning Co-operative website: [www.advancecareplanning.org.nz/resources/](http://www.advancecareplanning.org.nz/resources/)

Try as everyone might, there are still occasions when acute-on-chronic deterioration is too distressing to be managed at home and patients present to hospital. The context of deterioration needs to be urgently considered (is this an end-of-life or terminal event?). The concept of Ceiling of Care is relevant in this setting, and derives from the ACP. The aim is to provide guidance to admitting staff who do not know the patient, so that there is continuity with the patient’s previously expressed wishes, and/or limitations to their treatment are clear. We are currently working to have Ceiling of Care information electronically tagged to the patient’s NHI, so that on admission, along with adverse drug reactions, the information is readily available. Of course patients may change their minds about how much intervention is desirable or appropriate – the approach cannot be rigid. But in our experience having the Ceiling of Care defined at the time of admission provides direction and security, particularly to nursing staff, as to how the patient is to be managed.
There is also immense scope for improving end-of-life care in the patient’s home and in rest homes, and many in the primary care sector are working to this end. The introduction of ACP in rest homes is an obvious need. But the tool cannot be applied in isolation. Developing the palliative care skills of community and practice nurses as well as rest home carers is an obvious area where resources need to be allocated.

**The strategies**

Perhaps the most powerful incentive to improve end-of-life care is that this is what patients want, and it is something that we would want for ourselves. Attitudes to death and dying from cancer have been powerfully and positively influenced by the hospice movement. But the philosophy of care which has been nurtured in that particular setting now needs to be extended and integrated into institutions where “cure and mend” has historically been the over-riding objective. The time has come for “both … and” rather than “either … or”.

Patients at the end of life do not always want, and do not necessarily need, vigorous interventions, but quality supportive care. Quality improvement for such patients will be achieved not by straining indefinitely to extend life via acute medical services, nor by abandoning them when these fail. Adjusting what we do in light of the diagnosis of dying, and managing the approach to death positively and meaningfully needs to be integrated into all clinical services, not just a few, so that a “good death” is included in what we mean by quality of life.

**References**

Part 2: The distance we have travelled
Contributed by: Dr Syed Hussain

Most of us find it difficult to talk about death and subsequently delay making decisions primarily due to fear of the unknown. Discussion and planning improves the care and assistance that the patient and their whānau/families receive at the end of life. There have been positive changes in the past few years in the way the Auckland Region delivers care to our chronic condition patients during their final years of life, by implementation of Advanced Care Planning (ACP).

In the last few years there has been training of healthcare staff in our region through the ACP Collaborative, and since mid-2012 there has been ongoing integration of ACP into the routine clinical work of each service within DHBs. There are now “champions” in many institutions and departments who lead the ACP for their own chronic disease patients, which is helping patients make informed choices for their future healthcare.

It is quite important that a discussion of ACP does not start at the time of the patient’s diagnosis or by someone who has never been involved in the patient’s care. We need to remind ourselves that it is all about the patient, not about us. The patient has to make their own informed, competent decision and has to write down their own Advanced Care Plan.

The first steps in identifying patients suitable for starting a conversation about ACP are to consider the following questions:

- Is the person seriously ill?
- Is their condition deteriorating or unlikely to improve
- Will their condition worsen or cause death?
- What is your response to the “surprise question”, i.e. “Would I be surprised if this patient died in the next 12 months?”
For patients with chronic respiratory conditions, the main identifying points that they are ready for a conversation about ACP are as follows:

- Severe airflow obstruction (FEV₁ < 30%)
- Meets criteria for long-term oxygen therapy
- Breathless at rest or on minimal exertion, or housebound
- Falling BMI
- More than three hospital admissions in one calendar year or any admission with respiratory failure requiring non-invasive ventilation

More details are available at: [www.advancecareplanning.org.nz](http://www.advancecareplanning.org.nz)

More structured ACP will in most cases take away the burden of trying to set the ceiling of care by unfamiliar staff in consultation with family members during an acute admission, and allow implementation of a patient’s expressed choice of health care when they are no longer capable of that expression. At present the ACP is filed as a clinical alert in the Concerto electronic record and therefore visible to all secondary care staff. There is continuing work to make the ACP a living electronic document visible on the system for primary care.

The Liverpool Care Pathway, which was introduced to improve care in the terminal phase of illness, has been under a considerable amount of criticism in the United Kingdom after the Government commissioned review headed by Lady Neuberger. However, the fault was not with the pathway itself but was due to “wrong interpretation by inadequately trained staff members” which led to the “misuse and misunderstanding” of the pathway. In Auckland DHB we now use the Last Days of Life Care Plan Pathway (LDL CP). As with any pathway this supports, but does not replace, clinical judgment and good communication between all involved, which is the key to successful planning for end of life care.

**A conversation that counts**

Conversations that Count Day on the 16th April, 2015, is an event to raise awareness about advance care planning, so that people start thinking, talking and planning for their future and end-of-life care.

For further information, see: [www.conversationsthatcount.org.nz](http://www.conversationsthatcount.org.nz)
**Have your say**

What aspects of these commentaries most resonated with you?

In terms of the provision of end-of-life care in your organisation/DHB/geographical region, what aspects are being done well and what could be improved?

Do you find it difficult to know when or how to raise the subject of end-of-life planning, e.g. with a patient with COPD?

How do patients usually respond to initial conversations about end-of-life planning?

Do you use an advanced care plan or ceiling of care document with your patients? What aspects of these plans work the best? Are there any aspects which do not work so well?

Visit [www.bpac.org.nz/BPJ/2015/February/end-of-life.aspx](http://www.bpac.org.nz/BPJ/2015/February/end-of-life.aspx) to answer any of these questions or make your own comment. We encourage you to interact with your peers and share experiences and opinions.
The Year in Review

What did we learn in 2014?
In 2014 we published over 60 medical education articles in Best Practice Journal, spanning more than 450 pages. Context is crucial for understanding and accepting why any recommendations are made, but if we take away the “why’s, where’s and how’s”, we are left with a list of key messages to guide the responsible use of medicines in primary care.

Of these key messages, we consider the following to be the most essential learning points covered last year:

1. **Think twice before you prescribe oxycodone**

   There is a significant problem in New Zealand with oxycodone misuse and addiction. General practice is leading the way in reducing unnecessary use of this medicine, but there is still room for improvement. Oxycodone is a strong opioid, approximately twice as potent as morphine (oral preparations), and there is little indication for prescribing it in a community setting to manage non-malignant pain. If a strong opioid is necessary, morphine is the first-line choice, used at the lowest effective dose for the shortest possible time. READ MORE

2. **Consider whether you can manage a patient with chronic non-malignant pain without opioids**

   The problem with chronic pain is that patients just want you to fix it…now. It is tempting for both the patient and doctor to see an opioid as being a fast solution to this problem. However, pain is more complex than just a physical sensation, and the psychological and social factors that influence pain can also be used as a way to manage pain. For many patients, learning to understand their pain and accepting that “fixing it” may not be a realistic outcome will help them to cope. Exercise, cognitive behavioural therapy, non-opioid analgesics such as paracetamol and NSAIDs, and adjuvant medicines such as tricyclic antidepressants, are all options for managing chronic non-malignant pain. Current opinion is that opioids have a very limited role in the management of patients with chronic non-malignant pain. READ MORE

3. **Practice the principles of antimicrobial stewardship**

   New Zealand has one of the highest levels of antibiotic use per capita in the Western world, resulting in increasing rates of antibiotic resistance and less effective treatment for infectious diseases. Antimicrobial stewardship is about taking responsibility for the use of
antibiotics and following a guiding set of principles to ensure we get the most out of what antibiotics we have left. It’s about using the right antibiotic (matching sensitivity, avoiding broad spectrum antibiotics where possible), at the right time (correct duration of treatment, avoid repeated or prolonged courses) and for the right patient (is an antibiotic indicated for the condition being treated? Will it resolve without treatment?). READ MORE

4. **Topical antibiotics should be used for very few indications only; predominantly localised areas of impetigo**

Topical antibiotics are often used excessively, however, there are very few reasons that they should be prescribed. Fusidic acid can be considered for treating localised areas of impetigo caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or other related streptococci. Fusidic acid is occasionally used as part of a decolonisation regimen in patients with recurrent *S. aureus* abscesses. Mupirocin is used if the isolate is found to be resistant to fusidic acid (and sensitive to mupirocin). Good skin hygiene (e.g. managing skin conditions, treating dry skin) and general infection control measures (e.g. avoiding sharing personal care items) is essential for reducing skin infections. READ MORE

5. **Optimise prescribing in older people; consider treatment goals and benefits vs. risks when changing a patient’s medicine regimen**

Polypharmacy can be appropriate and beneficial for patients, however, it also increases the risk of problematic prescribing and adverse health outcomes. Older people are especially vulnerable to the adverse effects of taking multiple medicines. Review the patient’s medicine regimen regularly and consider whether each medicine is still needed and if the goals of treatment are still being met; consider involving a pharmacist in this review. Check that the patient is taking their medicines as prescribed. Also enquire about medicines/supplements the patient is taking that have not been prescribed by you. If the benefit of a medicine is considered marginal or the risks may exceed the benefit, agree on a trial treatment period, followed by a review. READ MORE

6. **Review patients who have been prescribed PPIs long-term with a view to reducing their dose and/or switching to “as needed” treatment**

Proton pump inhibitors (PPIs) are one of the most widely used medicines in New Zealand; omeprazole was the third most commonly prescribed medicine in 2014. It is likely that there are a significant number of patients who have been taking PPIs for prolonged periods, often at doses that are not necessary. PPIs should not be prescribed indefinitely, without review. After initial symptom control as been achieved, down titration of PPIs (both in dose and frequency, e.g. alternate day dosing) is often possible. Rebound acid secretion can occur when PPIs are withdrawn but this can usually be managed with antacids, and levels generally return to normal within two weeks. READ MORE
Finally, an essential practice point that will lead on to prescribing decisions:

**ABPI is a non-invasive, low cost way to detect peripheral artery disease in the lower limbs in a primary care setting.**

Peripheral artery disease (PAD) increases the risk of cardiovascular mortality by three to four times, however, the majority of general practitioners are unable to accurately assess the extent of PAD as they do not have the necessary equipment to do so. The ankle brachial pressure index (ABPI) can be measured in a general practice setting, using a hand-held Doppler device and probe. This gives an indication of the patient’s atherosclerotic burden, which is the most frequent cause of PAD. Measurement of ABPI is recommended for all patients who present with signs and symptoms of PAD and in patients who are at an increased risk of developing PAD, e.g. older patients, smokers and those with diabetes and hypertension. READ MORE

**Other main messages covered in 2014 included:**

- NSAIDs are considered the most effective analgesic for initial management of pain in people with renal or biliary colic READ MORE and READ MORE

- If migraine symptoms do not resolve with paracetamol or an NSAID, change to (or add) a triptan; choose the triptan formulation most preferred by the patient READ MORE

- Azithromycin use in New Zealand has grown considerably since subsidised access was widened. It is important that azithromycin is preserved as a treatment for pertussis in children, chlamydia and acute non-specific urethritis, and is not used to treat other conditions. READ MORE

- Encourage women who are pregnant to be vaccinated against pertussis to protect their newborn infant; the highest risk period for infants is the first six months of their life READ MORE

- Treatment of irritable bowel syndrome should focus on the most troublesome symptom: diarrhoea, constipation or pain READ MORE

- Assess all patients with diabetes for peripheral neuropathy; it is one of the most common long-term complications READ MORE

- Patients taking statins do not require routine laboratory monitoring for adverse effects, unless symptomatic READ MORE

- Detect and treat glaucoma early; ideally all patients aged over 45 years (or earlier for those with risk factors) should be encouraged to have an eye examination, including an assessment of their optic nerve READ MORE
Detect and treat Parkinson’s disease early; combination levodopa medicines should be initiated in patients aged over 40 years as soon as they display significant symptoms. The role of the general practitioner is to ensure that patients are referred for diagnosis and assessment early. READ MORE

Dry skin can be a significant burden to older people; it is a cause of dermatitis, chronic wounds and infection. Assess skin health periodically, and encourage regular use of emollients to reduce these risks. READ MORE

“Watch this space” Headlines

- Intranasal fentanyl is increasingly being used in children for the management of acute moderate to severe pain; could this be something for the general practice cupboard? READ MORE

- Rotavirus has been added to the National Immunisation schedule for infants from age six weeks. Uptake and impact will be monitored over the next few years. READ MORE

- There is increasing focus on managing obesity and encouraging physical activity to underpin all health targets READ MORE

- Effective communication with patients enhances care and increases self-efficacy, therefore improving health outcomes READ MORE

- Faecal antigen test has been identified as the “best test” for investigating H. pylori; ensure patients are not taking PPIs when requesting this test READ MORE

Make your own quick reference guide to 2014 by building your own journal of key messages: “Build My bpac” – available to My bpac subscribers, sign up for your free account at: www.bpac.org.nz
The optimal management of patients with COPD

Part 1: The diagnosis
Chronic obstructive pulmonary disease (COPD) affects approximately one in seven New Zealanders aged over 40 years, and is the fourth leading cause of premature death, illness or impairment in this country behind heart disease, anxiety/depression and stroke. A diagnosis of COPD may be considered in adult patients with long-term exposure to respiratory irritants, e.g. cigarette smoke, or with symptoms typical of COPD, i.e. breathlessness, cough, and/or sputum production. COPD cannot be reliably diagnosed on symptoms alone and requires spirometry to confirm a diagnosis. However, in some patients it can be challenging to differentiate between COPD and asthma with chronic airflow limitation. Spirometry can be reliably performed in primary care with the appropriate training.

COPD is a significant cause of morbidity and mortality in New Zealand

COPD is almost an entirely preventable disease as more than 85% of cases are caused by tobacco smoking. Approximately 15% of people who smoke long-term will develop COPD, although individual susceptibility to the damaging effects of cigarette smoke varies greatly. The major risk factors for COPD include:

- Tobacco smoking – especially smoking 20 cigarettes per day for 20 or more years
- Long-term cannabis smoking
- Air pollution
- Airway infection
- Occupational exposure, e.g. exposure to cadmium, silica, asbestos or dusts
- Genetic predisposition, including alpha1-antitrypsin deficiency
- Bronchial hyper-responsiveness
- Childhood asthma may also be a risk factor

Māori are more severely affected by COPD

The burden of COPD among Māori and Pacific peoples represents one of the most significant healthcare disparities in New Zealand. This is primarily due to the higher rates of smoking in Māori and Pacific peoples, compared to the rest of the New Zealand population. The prevalence of COPD among Māori is more than twice that of non-Māori and the burden of the disease is greater. Māori males aged 50 – 64 years are almost five times more likely to be hospitalised due to COPD and more than four and a half times more likely to die due to COPD than non-Māori males. Māori females aged 50 – 64 years are more than six and a half
times more likely to be hospitalised due to COPD and more than five times likely to die due to COPD. Māori are also affected by COPD up to 20 years earlier than non-Māori.

For further information see: “Diagnosis and management of COPD in Māori and Pacific peoples”, BPJ 43, 2012.

Forming a diagnosis of COPD

A clinical diagnosis of COPD can be considered in anyone aged over 35 years who has had long-term exposure to cigarette smoke, occupational exposure to dust, fumes or gas, or who has typical symptoms of COPD, i.e. breathlessness, cough and/or sputum production. Symptoms such as chest tightness, wheezing, and airway irritability are also common, although wheezing is not an indication of disease severity.

Take a focused history

Many patients will be aware that they have increasing breathlessness, increasing frequency or duration of “colds” and limitations in their physical ability. However, they may not have attributed these symptoms to a respiratory illness and instead consider them to be due to old age, a lack of fitness or merely “a smoker’s cough”. Patients can often note periods where they have had significant worsening of symptoms without recognising these as exacerbations.

For patients suspected of having COPD take a focused history to identify risk factors and symptoms. A focused history includes:

- Exposure to COPD risk factors, i.e. cigarette smoke, occupational or environmental compounds
- Previous respiratory conditions including asthma, allergies, sinusitis, nasal polyps, respiratory infections during childhood
- Pattern of symptom onset, e.g. age, gradual versus acute, triggers
- Exacerbation history or prior hospitalisations for respiratory symptoms
- Co-morbidities such as heart disease, osteoporosis and musculoskeletal disorders which may further limit the patient’s ability to remain active
- The impact the patient’s symptoms are having on their life, e.g. physical activity, ability to work or fulfil family duties, depression or anxiety, sexual activity
- The amount of family and social support the patient is able to access
- Opportunities that the patient has to reduce exposure to risk factors or triggers, e.g. smoking cessation
The Modified Medical Research Council Dyspnoea Scale (Table 1) is a useful tool that allows patients to communicate their level of breathlessness to health professionals.8

### Table 1: Modified Medical Research Council Dyspnoea Scale, adapted from Abramson et al, (2014)8

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>“I only get breathless with strenuous exercise”</td>
</tr>
<tr>
<td>1</td>
<td>“I get short of breath when hurrying on the level or walking up a slight hill”</td>
</tr>
<tr>
<td>2</td>
<td>“I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level”</td>
</tr>
<tr>
<td>3</td>
<td>“I stop for breath after walking 100 metres or after a few minutes on the level”</td>
</tr>
<tr>
<td>4</td>
<td>“I am too breathless to leave the house” or “I am breathless when dressing”</td>
</tr>
</tbody>
</table>

### The differential diagnosis of COPD

The differential diagnosis of respiratory disorders is influenced by the age of the patient. Asthma is the most likely chronic airway disease in children and young adults, once infectious disease has been excluded. COPD becomes increasingly more likely from the age of 35 years.

Table 2 provides features that are helpful for distinguishing between COPD and asthma, however, this can be complicated by the fact that some patients may have features of both conditions. Post-bronchodilator spirometry (see below) can be useful in differentiating asthma from COPD, but is less helpful in differentiating between asthma with fixed airflow limitation and COPD.10

### Asthma-COPD overlap syndrome (ACOS)

Asthma and COPD are relatively common conditions, therefore they may be present concurrently in some patients. Patients with features of both COPD and asthma have more frequent exacerbations, reduced quality of life and more rapidly declining lung function than patients with COPD alone.10 The increased severity of outcomes in these patients has led to the identification of asthma-COPD overlap syndrome (ACOS) that is thought to account for approximately 15 – 25% of all obstructive airway diseases.11 Features associated with ACOS are shown in Table 2. Currently this syndrome lacks a clinical definition and no defining features have been identified. This is in part because the way that clinical trials are designed makes ACOS hard to study; patients with asthma are generally excluded from studies involving COPD and patients with COPD are often excluded from trials investigating asthma.
**Table 2:** Typical features of COPD, asthma and asthma-COPD overlap syndrome (ACOS), adapted from GINA, 2014<sup>10</sup>

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>COPD</th>
<th>Asthma</th>
<th>ACOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>Usually older, e.g. &gt; age 35 years</td>
<td>Usually during childhood but can be at any age</td>
<td>Usually older, but may have had symptoms earlier in life</td>
</tr>
<tr>
<td>Pattern of symptoms</td>
<td>Long-term symptoms which are often continuous and particularly noticeable with exercise. Some days may be better than others.</td>
<td>Symptoms may vary from day-to-day or over longer periods. Often triggered by exercise, emotions, including laughter, dust or allergies. Will often limit the patient’s activity.</td>
<td>Exertional dyspnoea and other respiratory symptoms may be persistent but there may be noticeable variability</td>
</tr>
<tr>
<td>Lung function</td>
<td>FEV₁ may be improved by treatment but post-bronchodilator FEV₁/FVC &lt; 0.7 generally persists</td>
<td>Variable airflow limitation, e.g. post-bronchodilatory reversibility, airway hyper-responsiveness</td>
<td>Airflow limitation not fully reversible but displays current or historical variability</td>
</tr>
<tr>
<td>Lung function when symptoms absent</td>
<td>Airflow limitation persists</td>
<td>May be normal</td>
<td>Airflow limitation persists</td>
</tr>
<tr>
<td>History</td>
<td>History of exposure to noxious particles or gases, e.g. cigarette smoke</td>
<td>Many patients display atopy and have allergies and personal history of asthma in childhood, and/or family history of asthma</td>
<td>Often has previously had a diagnosis of asthma, allergies, a family history of asthma, and a history of noxious exposure</td>
</tr>
<tr>
<td>Time course</td>
<td>Generally a slow progression of symptoms despite treatment</td>
<td>Will often improve spontaneously or with treatment, but can develop into a fixed airflow limitation</td>
<td>Symptoms are partially, but significantly, relieved by treatment. Progressive, with high treatment needs.</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Severe hyperinflation with other changes visible</td>
<td>Usually normal</td>
<td>As for COPD</td>
</tr>
</tbody>
</table>

ACOS – Asthma COPD Overlap Syndrome
Having three or more of the features for either COPD or asthma, without any features of the other condition, and the absence of an alternative diagnosis provides a degree of diagnostic certainty. However, the absence of any of these features does not have a strong predictive value and does not rule out either asthma or COPD. If a patient has a similar number of features for COPD and asthma then a diagnosis of ACOS is more likely.

Referral to a respiratory physician is recommended for patients suspected of having ACOS.

Other respiratory conditions to consider
Bronchiectasis is frequently present in patients with moderate-to-severe COPD and is associated with increased exacerbation frequency, bacterial colonisation and mortality rate. Bronchiectasis is suggested in patients with large volumes of purulent sputum and wheeze that does not respond to treatment, and is often associated with bacterial infections. COPD is not treated any differently in patients with bronchiectasis, although some patients may need more aggressive and longer duration of treatment with antibiotics.

For further information see: “Bronchiectasis: rates still increasing among Pacific peoples”, BPJ 46 (Sep, 2012).

Additional differential diagnoses to consider, especially if the patient does not have a history of smoking or has borderline respiratory results, include: respiratory infection, alpha1-antitrypsin deficiency and tuberculosis.

Spirometry confirms a diagnosis of COPD
COPD cannot be diagnosed based on the presence of symptoms alone. Spirometry is required to confirm a diagnosis, however, the results of spirometry are not disease specific. For example, it may not be possible to differentiate between COPD, chronic bronchitis or asthma as the cause of a patient’s low FEV1.

Spirometry can be performed in primary care
Spirometry can be reliably performed in a general practice setting, although training is required in both the technique and the maintenance of the equipment.

When performing spirometry:
- Patients should be clinically stable and free of respiratory infection
- Patients should not have inhaled a short-acting bronchodilator in the previous six hours, or a long-acting beta2-agonist (LABA) in the previous 12 hours
An FEV₁ < 80% predicted and a FEV₁/FVC ratio < 0.7 indicates an airflow limitation

Over-diagnosis of COPD is more likely in older patients who have decreased lung function and under-diagnosis of COPD is more likely in younger patients, especially when the FEV₁/FVC is close to 0.7.¹³

For information on spirometry training courses see: www.asthmafoundation.org.nz/education/for-health-professionals/spirometry-courses-in-nz/

Patients with suspected COPD should be referred to a respiratory service if reliable spirometry is unable to be performed in primary care, or there is uncertainty surrounding a test result, or if the patient has difficulty performing spirometry.

If there will be a delay in accessing spirometry testing there are clinical questionnaires that can be used to determine the likelihood of a patient having COPD. These can be downloaded and completed by the patient and clinician in a few minutes. However, patients suspected of having COPD should still undergo spirometry testing early during their management to confirm a diagnosis.

The Clinical COPD Questionnaire is available from: http://ccq.nl

Spirometry is not recommended to “screen” for COPD

Spirometry testing should be reserved for patients who are suspected of having COPD. There is no evidence that spirometry screening improves management or outcomes in patients with COPD before they develop significant symptoms.⁹

The terminology of spirometry¹²,¹³

**Forced vital capacity (FVC)** is the maximum volume of air exhaled forcefully after a maximal inspiration. For a healthy adult this should last at least six seconds, although patients with COPD may take considerably longer than this to exhale.

**Forced expiratory volume in one second (FEV₁)** is the volume of air exhaled during the first second of the forced expiratory manoeuvre. The ratio of FEV₁ to FVC expressed as a percentage is used to assess obstructive lung disorders.
Assessing COPD severity with spirometry

The results of spirometry are used to assess the severity of COPD, in combination with the clinical signs and symptoms of hypoxaemia, hypercapnia, pulmonary hypertension, heart failure and polycythaemia. Table 3 provides a tool for assessing COPD severity, although symptom descriptions may not always match spirometry levels.

**Table 3:** COPD severity assessment guide, adapted from Abramson *et al* (2014)\(^8\)

<table>
<thead>
<tr>
<th>COPD severity</th>
<th>FEV(_1) (% predicted)</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>60 – 80</td>
<td>- Breathlessness on moderate exertion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Recurrent chest infections</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Little or no impact on daily activity</td>
</tr>
<tr>
<td>Moderate</td>
<td>40 – 59</td>
<td>- Increasing dyspnoea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Breathlessness walking on level ground</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Increasing limitation of daily activities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Cough and sputum production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Exacerbations require corticosteroids and/or antibiotics</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 40</td>
<td>- Dyspnoea following minimal exertion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Daily activity severely limited</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Chronic cough</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Regular sputum production</td>
</tr>
</tbody>
</table>

Frequency of exacerbations is likely to increase with severity. Other long-term conditions are likely to be present in patients with varying degrees of COPD severity. Conditions may include: cardiovascular disease, peripheral vascular disease, chronic kidney disease, lung cancer, sleep apnoea, muscle dysfunction, osteoporosis, obesity, type 2 diabetes, anxiety and depression. Treatment will also be guided by the results of routine investigations used to manage these long-term conditions.

The role of post-bronchodilator spirometry

COPD guidelines recommend that patients with a diagnosis of COPD have a post-bronchodilator spirometry test documented in their clinical record.\(^8\) A post-bronchodilator FEV\(_1\)/FVC < 0.7 confirms the presence of persistent airflow limitation limitation, and is therefore consistent with a diagnosis of COPD.\(^9\) Post-bronchodilator testing is appropriate for all patients with suspected COPD who display a complete reversal of baseline airflow limitation, once treatment with a bronchodilator is initiated, to exclude the possibility of asthma.
To assess the patient’s post-bronchodilator response once a baseline spirometry measurement has been taken:

1. Give a bronchodilator, e.g. salbutamol 200 – 400 micrograms (two to four puffs of a standard 100 micrograms per puff inhaler), via a metered dose inhaler (MDI) and spacer using correct inhalation technique
2. Repeat spirometry 15 – 30 minutes after the bronchodilator has been given
   - An increase in FEV₁ of ≥ 12% and ≥ 200 mL is regarded as indicating reversibility

It is important if post-bronchodilator spirometry testing is performed that the results are not used to predict the patient’s response to future treatments. Patients with COPD may experience symptomatic and functional benefits from the use of bronchodilators, without any change in spirometry, due to a reduction in hyperinflation. Furthermore, any acute response to a bronchodilator that a patient displays may not predict a subsequent response to long-acting beta agonists. Whenever post-bronchodilator spirometry is considered it is important to remember that even in patients who have never smoked, poorly controlled asthma can lead to a chronic and irreversible narrowing of the airways.⁸

Acknowledgement: Thank you to Professor John Kolbe, Respiratory Medicine Physician, University of Auckland and Auckland DHB for expert review of this article.
References


The optimal management of patients with COPD

Part 2: Stepwise escalation of treatment
The progression of COPD can be slowed by providing support for patients to stop smoking, and encouraging regular exercise and annual influenza vaccination. The pharmacological treatment of COPD needs to be individualised according to the patient’s response; regular follow-up is an important part of this process. Short- and then long-acting bronchodilators are the mainstays of treatment, depending on the patient’s symptom severity. Reducing the risk of exacerbations and ensuring acute exacerbations are promptly and appropriately treated with oral corticosteroids and antibiotics (if indicated) are important roles undertaken in primary care.

**The pharmacological treatment** of COPD has two aims:

1. To provide symptom control
2. To reduce the risk of exacerbations which are associated with increased mortality

Medicines should be introduced in a step-wise approach, according to the severity and progression of the patient’s condition (Table 1).

**Non-pharmacological interventions** are an important aspect of the management of patients with COPD, including:

- Smoking cessation
- Physical activity, including pulmonary rehabilitation
- Maintenance of normal weight

**Stepwise pharmacological treatment**

There is currently no high-quality evidence that any medicine is able to modify the long-term decline of lung function in patients with COPD. Medicines are given to manage symptoms and reduce the risk of exacerbations. The relationship between symptom severity, airflow limitation and exacerbation frequency varies between patients, therefore treatment needs to be individualised.

As there are a large number of inhaled medicines indicated for the treatment of COPD it is important to ensure that medicine classes are not duplicated whenever changes are made to the patient’s treatment regimen.

**Step 1: For all patients with symptomatic COPD**

Prescribe an inhaled short-acting beta2-agonist (SABA, e.g. salbutamol or terbutaline) or a short-acting muscarinic antagonist (SAMA, e.g. ipratropium). Short-acting bronchodilators are likely to be beneficial when used by patients during periods of acute breathlessness.
Table 1: The stepwise escalation of pharmacological treatment for COPD, based on severity, adapted from Abramson et al, 2014¹

<table>
<thead>
<tr>
<th>Severity</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Few symptoms</td>
<td>Increasing dyspnoea</td>
<td>Dyspnoea on minimal exertion</td>
<td></td>
</tr>
<tr>
<td>Breathless on moderate exertion</td>
<td>Breathless walking on level ground</td>
<td>Daily activities severely restricted</td>
<td></td>
</tr>
<tr>
<td>Recurrent chest infections</td>
<td>Increasing limitation of daily activities</td>
<td>Experiencing regular sputum production</td>
<td></td>
</tr>
<tr>
<td>Little or no effect on daily activities</td>
<td>Cough and sputum production</td>
<td>Chronic cough</td>
<td></td>
</tr>
<tr>
<td>FEV₁ ≈ 60–80% predicted</td>
<td>Infections requiring corticosteroids</td>
<td>FEV₁ &lt; 40% predicted</td>
<td></td>
</tr>
</tbody>
</table>

**Medicines management**

| CHECK DEVICE USAGE TECHNIQUE AND ADHERENCE AT EACH VISIT – Up to 90% of patients do not use devices correctly |
| FOR ALL PATIENTS: Inhaled short-acting reliever, e.g. salbutamol, terbutaline or ipratropium |

**SYMPTOM RELIEF IF PERSISTENT TROUBLESOME DYSPNOEA:** Add a long-acting beta agonist (LABA, e.g. salmeterol, indacaterol or formoterol) OR a long-acting muscarinic antagonist (LAMA, e.g. tiotropium* or glycopyrronium*).

*This may also help to prevent exacerbations.*

* Special Authority criteria apply; must have tried ipratropium first, see NZF for details

**EXACERBATION PREVENTION IF TWO OR MORE EXACERBATIONS IN LAST 12 MONTHS AND FEV₁ < 50% PREDICTED:** CHANGE TO inhaled corticosteroid (ICS)/LABA combination treatment (fluticasone/salmeterol OR budesonide/formoterol*); ADD a LAMA (e.g. tiotropium* or glycopyrronium*) if the patient continues to experience frequent exacerbations.

N.B. When considering the use of inhaled corticosteroids in patients with COPD it is important to consider the risk of adverse effects, particularly pneumonia

* Special Authority criteria apply; must have tried ipratropium first, see NZF for details
Ensure that patients are able to use inhaler devices correctly.

Patients should be educated in the correct use of inhalers and spacers before treatment with an inhaled medicine is initiated, and before stepping up treatment. Patients require sufficient dexterity and breath control to use inhaler devices and must also be able to use them when they are acutely unwell. As few as 10% of patients with COPD may use their inhalation device correctly; the patient’s ability to use an inhaler may dictate the choice of the available medicines. If patients are using a metered dose inhaler (MDI) confirm that they are using a spacer as this overcomes coordination problems, improves lower airway deposition of medicines and increases the clinical benefit of the medicine. Placebo inhaler devices are available for demonstrating correct inhaler technique.

Step 2: For patients with COPD and persistent troublesome dyspnoea

Consider the addition of a long-acting beta2-agonist (LABA, e.g. salmeterol, indacaterol or formoterol) or a long-acting muscarinic receptor antagonist (LAMA, e.g. tiotropium or glycopyrronium under Special Authority if the patient was taking ipratropium at Step 1 and has not responded adequately).

There is good evidence that both LABA and LAMA improve lung function and symptom severity and reduce exacerbation frequency.

A combined LABA/LAMA inhaler can be used if treatment with a single medicine is ineffective, however, there are currently no subsidised options available.

Step 3: For patients with an FEV₁ < 50% of predicted and two or more exacerbations in a 12-month period

Consider prescribing a fixed-dose inhaled corticosteroid, in combination with a LABA, e.g. fluticasone + salmeterol or budesonide + formoterol under Special Authority.

If the patient begins combination treatment remember to withdraw any LABA monotherapy.

Patients who continue to experience frequent exacerbations may also benefit from the addition of a LAMA to a combination corticosteroid and LABA inhaler.

When considering the use of inhaled corticosteroids in patients with COPD it is important to balance the risks versus benefits of inhaled corticosteroid treatment.

The long-term use of inhaled corticosteroids (ICS) has been shown to reduce the rate of exacerbations and slow the decline in quality of life in people with COPD. However, the role of ICS in the treatment of COPD is an evolving area of research and it is now accepted...
that their use can cause significant harm to patients with COPD; in particular, an increased risk of pneumonia and other respiratory co-morbidities.

ICS should only be considered for a patient with COPD once their condition has progressed to the point where the reduced risk of exacerbations and increased quality of life outweigh the increased risk of pneumonia and other adverse effects. The current trend among respiratory physicians in New Zealand is to tend to withdraw treatment of ICS, rather than initiate them; it is suggested that general practitioners consult a respiratory physician if they are considering initiating long-term ICS treatment in a patient with COPD.

A Cochrane systematic review of 55 studies with over 16 000 patients with stable COPD found that the use of ICS for more than six months was associated with 0.26 fewer exacerbations per patient per year. However, analysis of long-term studies (> six months) found an increased risk of pneumonia* (odds ratio [OR] 1.56), oropharyngeal candidiasis (OR 2.65) and hoarseness (OR 1.95). The review also found that the benefits of treatment were not matched with statistically significantly reduced rates of decline in FEV\textsubscript{1} or mortality.

An analysis of 25 trials, including over 22 000 patients, found that patients with COPD taking an ICS were more than twice as likely to develop tuberculosis than patients with COPD who were not taking an ICS.

Treatment with ICS in patients with COPD has also been linked in a dose-dependent manner to an increased risk of non-tuberculous mycobacterial (NTM) pulmonary disease.

Prophylactic or continuous use of antibiotics is not currently recommended to prevent exacerbations in patients with COPD on the balance of adverse effects versus benefits. The use of antibiotics in patients with COPD should be reserved for treating infectious exacerbations and other bacterial infections.

Mucolytics, e.g. bromhexine hydrochloride, have a limited role in exacerbation prevention and there are currently no fully subsidised mucolytic medicines in New Zealand for the treatment of patients with COPD.

**Theophylline is now rarely used in the treatment of COPD.**

See Table 2 for information on subsidised medicines for COPD available in New Zealand

* An estimated incidence rate of pneumonia in patients with COPD is 2.4 cases per 100 people per year. A study of 163 514 patients with COPD found that over a period of 5.4 years, 20 344 patients had a serious pneumonia event. Reference: Suissa S, Patenaude V, Lapi F, et al. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax 2013;68:1029–36.
Table 2: Subsidised inhaled medicines for the treatment of patients with stable COPD in New Zealand

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dose</th>
<th>Frequency</th>
<th>Maximum dose</th>
<th>Subsidised device</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bronchodilators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beta2-agonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salbutamol (short-acting)</td>
<td>100 – 200 micrograms (1 to 2 puffs of 100 micrograms)</td>
<td>As needed, up to four times daily</td>
<td>200 micrograms, four times daily</td>
<td>Metered dose inhaler (MDI)</td>
</tr>
<tr>
<td>Terbutaline (short-acting)</td>
<td>250 – 500 micrograms (1 to 2 puffs of 250 micrograms)</td>
<td>As needed</td>
<td>Maximum single dose 1.5 micrograms, maximum daily dose 6 micrograms</td>
<td>Dry powder inhaler (DPI), breath-activated device (Turbuhaler®)</td>
</tr>
<tr>
<td>Salmeterol (long-acting)</td>
<td>25 – 50 micrograms (1 to 2 puffs of 25 micrograms)</td>
<td>Twice daily</td>
<td>50 micrograms, twice daily</td>
<td>DPI, breath-activated device with each dose contained in a disc of eight doses (Accuhaler®) and standard MDI</td>
</tr>
<tr>
<td>Indacaterol* (long-acting)</td>
<td>150 – 300 micrograms (one capsule, 150 or 300 microgram strength)</td>
<td>Once daily</td>
<td>300 micrograms daily</td>
<td>DPI, breath-activated device with each dose contained in a capsule (Breezhaler®)</td>
</tr>
<tr>
<td>Formoterol (long-acting, partially subsidised)</td>
<td>12 micrograms</td>
<td>Once or twice daily</td>
<td>Up to 24 micrograms, twice daily</td>
<td>DPI, breath-activated device</td>
</tr>
<tr>
<td><strong>Anticholinergics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium (short-acting)</td>
<td>40 micrograms</td>
<td>Four times daily</td>
<td>Maximum single dose 80 micrograms, maximum daily dose 240 micrograms</td>
<td>MDI</td>
</tr>
</tbody>
</table>
### Anticholinergic continued

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
<th>Subsidy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tiotropium (long-acting)</strong></td>
<td>18 micrograms</td>
<td>Once daily</td>
<td>18 micrograms daily DPI, breath-activated device with each dose contained in a capsule (HandiHaler®)</td>
</tr>
<tr>
<td>Will not be subsidised if patient also taking subsidised glycopyrronium. Special Authority criteria apply.⁸⁹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em><em>Glycopyrronium</em> (long-acting)</em>*</td>
<td>50 micrograms</td>
<td>Once daily</td>
<td>50 micrograms daily DPI, breath-activated device with each dose contained in a capsule (Breezhaler®)</td>
</tr>
<tr>
<td>Will not be subsidised if patient also taking subsidised tiotropium. Special Authority criteria apply.⁸⁹</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Combination inhalers

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
<th>Device Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Budesonide + formoterol</strong></td>
<td>200 + 6 micrograms</td>
<td>Twice daily</td>
<td>Four puffs daily DPI, breath-activated device (Turbuhaler®) and standard MDI</td>
</tr>
<tr>
<td>Special Authority criteria apply.⁹⁰</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>400 + 12 micrograms</td>
<td>Twice daily</td>
<td>Two puffs daily</td>
</tr>
<tr>
<td><strong>Ipratropium + Salbutamol</strong></td>
<td>20 + 100 micrograms</td>
<td>Four times daily</td>
<td>12 puffs in 24 hours MDI</td>
</tr>
<tr>
<td></td>
<td>Two puffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fluticasone + salmeterol</strong></td>
<td>125 + 25 micrograms</td>
<td>Twice daily</td>
<td>500 + 50 micrograms, twice daily MDI</td>
</tr>
<tr>
<td></td>
<td>Two puffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 + 25 micrograms</td>
<td>Twice daily</td>
<td>MDI</td>
</tr>
<tr>
<td></td>
<td>Two puffs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 + 50 micrograms</td>
<td>Twice daily</td>
<td>DPI, breath-activated device (Accuhaler®)</td>
</tr>
<tr>
<td></td>
<td>One puff</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Continues next page
### Corticosteroids

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage</th>
<th>Route</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>50 – 400 micrograms</td>
<td>Twice daily</td>
<td>400 micrograms, twice daily, MDI</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>100 – 500 micrograms</td>
<td>Twice daily</td>
<td>1 mg, twice daily, MDI, DPI</td>
</tr>
<tr>
<td>Budesonide</td>
<td>100 – 800 micrograms</td>
<td>Twice daily</td>
<td>800 micrograms, twice daily, DPI</td>
</tr>
</tbody>
</table>

MDI = metered dose inhaler, DPI = dry powder inhaler

* These medicines recently underwent a change in funding status and are now fully-subsidised, see: “Two newly funded medicines for COPD”, BPJ 65, Dec, 2014).

a Patient must have trialled a short-acting bronchodilator of at least 40 micrograms ipratropium, four times daily for one month; and have grade 4 or 5 breathlessness; and measured FEV₁ below 60% of predicted; and been offered smoking cessation counselling if appropriate; and offered influenza immunisation.

b Patients must aged over 12 years; and have been treated with inhaled corticosteroids of at least 800 micrograms per day beclomethasone or budesonide, or 500 micrograms per day fluticasone; and the prescriber considers that the patient would receive an additional clinical benefit from a combination product.

### Routine follow-up is essential

As the patient’s lung function can be expected to decline, routine follow-up is an important part of COPD management to assess efficacy of treatment and also reduce problematic polypharmacy. The success of treatment should be largely determined by the patient’s response as improvements in lung function may not be reliably detected on spirometry. A period of six weeks is reasonable to detect clinically significant changes in symptoms such as dyspnoea, however, longer periods are likely to be required to detect changes in the patient’s quality of life.²

### Managing exacerbations

Patients with COPD who have frequent exacerbations are more likely to experience a rapid decline in FEV₁ and are more likely to die of COPD-related complications.² Prompt treatment of exacerbations is important as a delay of greater than 24 hours in presentation for the treatment of an exacerbation approximately doubles the likelihood of hospital admission.² An exacerbation in the previous 12 months is the greatest risk factor for a future exacerbation.²
Management of a patient with an acute exacerbation of COPD includes:
- Inhaled bronchodilator (increased dose), every three to four hours
- Breathing relaxation techniques
- Oral corticosteroids for five days, if moderate to severe exacerbation
- Oral antibiotics for five to ten days, but only if signs of chest infection

**Symptom control during an exacerbation**

Advise patients to take increased doses of bronchodilators during exacerbations, e.g. salbutamol, 400 – 800 micrograms (four to eight puffs of a standard strength, 100 micrograms per puff inhaler), every three to four hours, titrated to response.\(^2\) If the patient requires an inhaled bronchodilator more frequently than three-hourly during an exacerbation they should be advised to seek medical assistance.\(^2\) Correct device usage is essential during an exacerbation.

If during an exacerbation the patient feels panicked and overwhelmed, the following advice may help them relax:

1. Stop what you are doing
2. Relax your shoulders and neck
3. Breathe low and slow using a pursed lip technique, i.e. in through the nose and out slowly through pursed lips, with the diaphragm moving and the chest and shoulders relaxed
4. In a comfortable position concentrate on a relaxed breathing rhythm

Airway clearing techniques, e.g. percussion, vibration, or active cycles of breathing, may be useful for patients if secretions are troublesome.\(^2\) The active cycle of breathing involves controlled breathing to relax the airways, then deep breathing to get air behind sputum lodged in the small airways, and finally huffing to dislodge sputum where it can then be removed by coughing.

**Five-day course of corticosteroids improves outcomes**

Oral corticosteroids reduce the severity of COPD exacerbations and improve recovery time for the patient. They have the advantage of being rapid-acting, more convenient, and may be more effective than intravenous corticosteroids.\(^2\) Prednisone 30 – 50 mg, once daily in the morning, for five days can be prescribed for patients with moderate or severe exacerbations.\(^2\) Prescribing corticosteroids for periods of 14 days to reduce the severity of exacerbations is no longer considered necessary.\(^8\) Corticosteroid use does not need to be tapered in patients prescribed treatment courses of less than two weeks.
For further information see: “Shorter courses of oral corticosteroids for the management of exacerbations in patients with COPD”.

**When to prescribe antibiotics**

If patients show clinical signs of infection, i.e. fever, increased volume or colour of sputum, they can be prescribed oral antibiotics for five to ten days. Bacterial infection is thought to be involved in approximately half of COPD exacerbations. Antibiotic regimens for the treatment of patients with infective COPD exacerbations vary. Recommended treatments include: amoxicillin, 500 mg, three times daily or doxycycline, 100 mg, twice daily*. Sputum culture is not routinely required unless the patient is not responding to antibiotic treatment or has had multiple bacterial infections over a period of several months. Intravenous antibiotics are unlikely to be required in a community setting and are only appropriate for patients with an impaired mental state, inability to swallow, or X-ray evidence of pneumonia requiring hospitalisation.

Prophylactic or continuous use of antibiotics is not currently recommended to prevent exacerbations in patients with COPD on the balance of benefits versus adverse effects.

* Recommended doses for doxycycline for acute exacerbations of COPD range from 100 – 200 mg, twice daily on day one, followed by 100 mg, once or twice daily, on days two to five.

**Consider “back-pocket” prescriptions for select patients**

Patients with COPD who are considered to have good self-management skills can be provided with “back-pocket” prescriptions for antibiotics and corticosteroids for the treatment of exacerbations. A written action plan should be provided to the patient that indicates how to recognise if their condition has changed, what to do if this occurs and the medicines, doses and action that should be taken.

**When to refer to hospital**

Patients with COPD who are experiencing an exacerbation should be considered for referral to hospital if they display:

- A significant increase in symptom intensity
- An inadequate response to community-based treatments
- An inability to walk between rooms when they were previously mobile
- Dyspnoea that is affecting their ability to sleep or eat
- An inability to cope at home
- Features suggestive of respiratory failure, i.e. confusion, drowsiness, restlessness, and cyanosis
- New-onset arrhythmia
- \( \text{SpO}_2 < 92\% \) on pulse oximetry
- Deteriorating cor pulmonale

Controlled oxygen, delivered at a rate of 0.5 – 2.0 L/min, is indicated for patients with hypoxaemia during a COPD exacerbation.\(^2\) High-flow oxygen is avoided in patients with COPD as this may cause hypoventilation and acute respiratory failure.\(^2\)

**Pulmonary embolism should be considered** if a patient’s condition merits hospitalisation, but the typical features of an exacerbation of COPD are absent, such as fever, productive cough and wheezing.\(^2\) It is estimated that as many as one in four patients with an atypical COPD exacerbation may have an underlying pulmonary embolism causing acute dyspnoea.\(^9\)

**Follow-up after discharge from hospital**

Following discharge from hospital it is reasonable for the primary care team to expect to receive a hospital discharge plan within 24 hours.\(^2\) The patient should then be followed-up by a member of the primary care team within seven days. Follow-up should include an assessment of the patient’s:\(^2\)

- Level of physical activity
- Coping ability
- \( \text{FEV}_1 \) (if equipment and skills to perform spirometry) and performance status (e.g. Modified Medical Research Council Dyspnoea Scale)
- Medicine adherence and ability to use inhaler devices
- Effectiveness of treatments, with optimisation if necessary using a stepwise approach
- Influenza and pneumococcal vaccination status
- Risk of osteoporosis
- Risk of future exacerbations with a review of the patient’s action plan

Following an exacerbation requiring hospitalisation, patients with COPD should be referred for pulmonary rehabilitation, once they are stable.\(^2\) Patients with abnormalities on X-ray should be followed up within four to six weeks of discharge from hospital.\(^2\) Depending on the clinical circumstances, a follow-up x-ray may be required.
Pharmacological treatment in patients with advanced COPD

Low-dose morphine, benzodiazepines, and eventually oxygen, may be considered for patients with COPD who have reached the stage when their lung function cannot be improved.

**Opioids can relieve dyspnoea at low-doses** by decreasing the patient’s respiratory rate without causing hypercapnia or hypoxia. Initially, low doses of morphine can be trialled on an “as needed” basis for refractory dyspnoea, e.g. 2 mg of morphine oral solution pre-measured in a syringe or 2.5 mg of an immediate-release tablet (one-quarter of a 10 mg tablet of morphine). If the patient requires regular dosing, 2 – 2.5 mg of morphine can given every four to six hours; this dose can increased in steps of 30% if tolerated. It is unknown what the exact mechanism for opioids relieving dyspnoea is. One possibility is that opioids modulate the patient’s perception of dyspnoea, in the same way they do for pain, without reducing the patient’s ventilation drive.

**Benzodiazepines can be very effective at reducing the anxiety associated with dyspnoea,** although there is no evidence that they can relieve breathlessness itself. Lorazepam 0.5 mg (half of a 1 mg tablet), every four to six hours, as required, is an appropriate starting dose.


**Oxygen treatment in a consistently hypoxic patient** may reduce polycythaemia, improve sleep quality, prevent right-sided heart failure and reduce mortality. Patients with COPD who are stable but have persistent hypoxaemia, consistent with a SpO₂ < 92% on pulse oximetry, should be referred to a respiratory physician to assess their need for long-term oxygen therapy. For patients to be eligible for long-term treatment with oxygen it is a requirement that the patient and their home be smoke-free.

**Nutritional advice for patients with COPD**

Weight loss and reduced muscle mass are common in people with advanced COPD as they need to exert more energy while breathing. This can result in a deterioration in lung and heart function, a reduced ability to exercise and increased mortality. People with COPD need to ensure that their nutritional intake is adequate enough to support their extra energy requirements. It is estimated that approximately 23% of people with COPD are malnourished, but it is unclear whether this is the cause of their deterioration or a part of the disease process.
Five key questions that can be asked to assess food intake and nutritional status are:16

- “How is your appetite?”
- “Are you managing to eat like you usually do?”
- “Have you noticed any change in your body weight?”
- “Have you noticed any other changes to your body shape or muscle strength?”
- “Do you have concerns about your diet or food intake?”

**Nutritional advice for patients with COPD**

Patients with BMI <20 kg/m² or any patients with unintentional weight or muscle loss:

1. **“Food First”**. Maximise nutritional intake from the diet:
   - Eat small, frequent meals that are high in protein (meat, chicken, fish, eggs, cheese and milk) and fat (cream, cheese, butter, peanut butter, gravy, sauces and fried foods)
   - Consume six to eight drinks per day; water, milk drinks and soup are better than tea or coffee
   - Offer referral to a “Meals-on-wheels” or a similar service


2. Oral nutritional supplements can be considered as an adjunct to the “food first” strategy in patients with a BMI <20 kg/m² or in any patients who continue to experience unintentional weight or muscle loss despite optimising dietary intake.16

The recommended dose of oral nutritional supplements is 600 kcal, daily, for three months, with monthly reviews where possible.16 If there is no improvement after three months referral to a dietitian is recommended.

Pulmocare is a high-fat, reduced-carbohydrate formula indicated for patients with CO₂-retentive respiratory conditions such as COPD.7 The formula is available subsidised with Special Authority on application from a vocationally registered general practitioner, specialist or dietitian for patients who have COPD and hypercapnia (CO₂ value of > 55 mmHg). It is designed to reduce carbon dioxide production and supply nutrients without compromising respiratory function.7
Planning end-of-life care with patients with COPD

As the goals of care change, patients with COPD and their family/whānau require realistic advice, as well as support, from health professionals to make informed decisions and to plan for the future appropriately.

Initiating conversations about end-of-life issues with patients who have COPD can feel daunting to many health professionals, especially in judging the right time to do so. However, it is best that these discussions take place early. Giving patients sufficient time, e.g. 12 months, before end-of-life care is required, allows them to plan with their family/whānau how they want their care to be managed.

Discussions about end-of-life issues are generally less stressful when patients are relatively well; it is reported that the majority of patients with life-limiting conditions prefer to discuss preferences for end-of-life care early. Increased communication with patients who have a terminal illness is also associated with better end-of-life care and a reduced number of medical interventions. Furthermore, the subject of end-of-life care is easier to revisit with patients and their family if it has been broached previously. In general, patients and their family/whānau want an honest conversation that is balanced between realistic information and appropriate hope. Current evidence does not support suggestions that discussing end-of-life care increases the patient’s feelings of anxiety, depression or hopelessness.

When is it appropriate to discuss “end-of-life care” with a patient with COPD?

The greater uncertainty in predicting mortality in patients with COPD compared to patients with other terminal respiratory conditions, such as lung cancer, makes it difficult for clinicians to know when it is appropriate to initiate end-of-life discussions.

The presence of two or more of the following markers is an indication for a discussion centred on the patient’s preferences for end-of-life care:

- FEV₁ < 30% of predicted
- Age over 70 years
- Dependence on oxygen treatment
- One or more hospitalisations in the previous year for an exacerbation
- Left heart failure
- Weight loss or cachexia
- Decreased ability to function
- Increasing dependence on family or carer
Another useful strategy when deciding if end-of-life discussions are appropriate is to consider the question: “Would I be surprised if this patient died in the next 12 months?”

Prognostic markers for COPD

It is also difficult to provide patients with COPD and/or their family with timeframes for disease progression. Decreasing FEV₁ is associated with worsening prognosis in patients with COPD, however, because this measure does not account for other factors affecting a patient’s health, e.g. co-morbidities, it is not a good predictor of outcomes when used in isolation. Exercise capacity is one of the most important prognostic markers in COPD and is directly related to how well the respiratory and cardiovascular systems are able to supply oxygen to the rest of the body. The six-minute walking test is an objective measure of a patient’s exercise ability. The Body Mass Index (BMI), Obstruction, Dyspnoea, and Exercise (BODE) scale is used to assess mortality risk in patients with COPD.

Biomarkers are not widely used for prognostic assessment in patients with COPD; biopsies and lavage are extremely invasive, breath sampling is highly variable, and serum markers have yet to be validated.

A copy of the BODE index for COPD can be found at: [www.pulmonaryrehab.com.au/pdfs/BodeIndexForCOPD.pdf](http://www.pulmonaryrehab.com.au/pdfs/BodeIndexForCOPD.pdf)

What does advanced care planning involve?

Advanced care planning refers to the process of assisting patients with terminal illnesses to:
- Gain a better understanding of their current and likely future health
- Consider their personal views and values regarding end-of-life care
- Understand the treatment and care options that are available to them
- Initiate discussions around end-of-life issues with their family/whānau

A suggested way to begin a conversation involving advanced care planning is: “What is your understanding of where you are now with your illness?”

What do most patients want to know?

Having entered into this discussion many patients will want to know what they can expect in the weeks and months ahead. For patients with COPD, advanced care planning should specifically prepare them for complications such as panic and severe dyspnoea. The patient should also be asked if they have any fears or concerns that they would like to discuss.
Encouraging patients to focus on what matters to them

Advanced care planning should identify the patient’s goals for treatment. This may be assessed by asking: “If your health worsens, what are your most important goals?”

Discussions on critical functions should also be attempted, e.g: “What abilities are so critical to your life that you cannot imagine living without them?”

Some patients may wish to discuss a ceiling of care with a respiratory physician.

During advanced care planning some patients may wish to create a “ceiling of care”. This is a document that is usually put together by a respiratory physician, and outlines interventions that in the context of the patient being severely incapacitated are considered futile, burdensome and contrary to the patient’s wishes. This can be particularly useful if the patient is admitted to hospital and is unable to contribute to decision-making at the time it is required; rather than focusing on intensive interventions to prolong life, other health professionals, who have never met the patient, are able to provide supportive care that is consistent with the patient’s desires and beliefs. For example, if the situation arose, would the patient wish to have a trial of mechanical ventilation for acute respiratory failure? A ceiling of care document is non-binding and patients are free to make alternative decisions about their treatment at any stage.

Asking: “If you become sicker, how much are you prepared to go through for the possibility of more time?”, is one way to encourage patients to think about the level of intensity of treatment they are prepared to tolerate in their last days.

It is important to ask patients with advanced COPD if their family is aware of their priorities and wishes, e.g. if the situation arose, would they want to be intubated or have cardiopulmonary resuscitation attempted? This allows patients to consider appointing a substitute decision maker (also known as an enduring power of attorney [medical]) in case they are admitted to intensive care and are unable to communicate their wishes.

Further information on advanced care planning, including resources that can be provided to patients, can be found at: www.advancecareplanning.org.nz

Acknowledgement: Thank you to Professor John Kolbe, Respiratory Medicine Physician, University of Auckland and Auckland DHB for expert review of this article.
References
The interventions with the greatest potential to prevent further deterioration in patients with COPD are:

1. Smoking cessation; maintenance of abstinence and living in a smoke-free environment
2. Daily exercise; most effective when initiated as part of a pulmonary rehabilitation programme
3. Annual influenza vaccination to reduce the risk of exacerbations

Smoking cessation will improve quality of life

Achieving and maintaining a smoke-free status is the most important intervention for all people with COPD and a history of smoking. Quitting smoking helps to preserve remaining lung function, and delay the onset of disability. Patients with COPD who smoke should be offered cessation support every time that they consult with a health professional. The combination of brief advice to quit and an offer of cessation support increases the chance that a patient who smokes will be able to quit.

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

Exercise and pulmonary rehabilitation is beneficial for all people with COPD

All people with COPD who are able to, should be encouraged to walk for 30 minutes daily, for five days a week. The person should walk until they feel too breathless to go on, rest to recover, and then continue.
Pulmonary rehabilitation involves a programme of exercise and education for groups, lasting for at least six weeks. This is appropriate to recommended for all patients with COPD, regardless of their level of severity, although it is particularly important for patients who experience troublesome dyspnoea following exertion. Patients who participate in pulmonary rehabilitation programmes have reduced dyspnoea and fatigue, improved exercise capacity and fewer hospitalisations, therefore improving quality of life. The benefits of pulmonary rehabilitation often begin to decline once the patient completes the programme. The primary care team plays an important role in encouraging patients to remain active and to maintain fitness levels.

Pulmonary rehabilitation programmes are usually run by local DHB respiratory services, although community-based programmes are available in some areas. The local Asthma Society or Trust has information about what programmes are available in each area. For further information, visit: www.asthmafoundation.org.nz/about/who-we-are/affiliated-asthma-societies/

**Annual influenza vaccinations should be strongly encouraged**

Annual influenza vaccination is strongly recommended for all patients with COPD. Patients with COPD who receive influenza vaccinations are less likely to experience COPD exacerbations, hospitalisation and death. Pneumococcal vaccination is also recommended for patients with COPD, however, there is no evidence that this reduces their risk of exacerbations.

**References**

Overuse of benzodiazepines: still an issue?
Benzodiazepines may be considered as a short-term treatment for insomnia and anxiety; zopiclone, a benzodiazepine-like medicine, is indicated for the treatment of insomnia only. Benzodiazepines are also used in the treatment of epilepsy and as sedatives during medical procedures. Long-term use of these medicines for insomnia or anxiety is discouraged as they are associated with dependency, an increased risk of falls and dementia in elderly people, cognitive difficulties and an increased risk of motor vehicle accidents. Data from New Zealand show that patients are currently being prescribed large volumes of benzodiazepines and zopiclone.

Benzodiazepines and benzodiazepine-like hypnotics and anxiolytics are medicines which bring about a state of sedation, increased sleepiness, relaxation and impaired memory formation, depending on the drug and formulation used. Benzodiazepine-like hypnotics are often referred to as z-drugs due to the alliteration in their naming (zopiclone, zolpidem, zaleplon) and indication as hypnotics. Zopiclone is the only z-drug available in New Zealand. Benzodiazepines are Class C controlled drugs; zopiclone is not a controlled drug.

Benzodiazepines and zopiclone are used frequently in New Zealand

New Zealand pharmaceutical dispensing data shows that zopiclone is the most widely used funded hypnotic medicine. The number of patients dispensed zopiclone in 2013/14 was approximately equal to the total number of patients dispensed any benzodiazepine. Zopiclone was the 14th highest volume medicine dispensed in New Zealand in 2013/14, with 120.2 dispensings (initial) per 1000 registered patients. In comparison, there were 30.8 dispensings of lorazepam per 1000 registered patients in 2013/14 and 25.6 dispensings of diazepam; the two highest volume benzodiazepines dispensed.

Benzodiazepine and zopiclone use in New Zealand is particularly prevalent in older people. A study on dispensing rates in 2011/2012 found that on average one in ten people aged 65 years and over, and one in five people aged 85 years and over, were dispensed a benzodiazepine in any quarter over this time period. A recent assessment of medicine use in older people living in the community in New Zealand involved interviews with 316 participants aged 75 years and over. This study identified that 15% of participants were likely to be inappropriately using benzodiazepines and 9% inappropriately using zopiclone. Inappropriate use included patients prescribed benzodiazepines long-term, at high-doses or using long-acting formulations, which should be avoided in elderly people.
Large volumes of benzodiazepines and zopiclone are being dispensed

Analysis of New Zealand dispensing data shows that there are many patients being prescribed large quantities of benzodiazepines and zopiclone (for any indication). It is uncertain to what extent these medicines are being used by the patients for whom they are prescribed, as opposed to being stockpiled, shared or even on-sold.

Zopiclone use in 2013
The recommended dosing regimen of zopiclone is up to one tablet (7.5 mg) at night, for a period of up to four weeks. Therefore a patient could be dispensed up to 28 tablets for a single short course of use.

Among patients dispensed zopiclone in 2013:
- 50% were dispensed 30 tablets or less
- 27% were dispensed between 30 and 150 tablets
- 23% were dispensed over 150 tablets (a total of 44,365 patients)

This suggests that half of patients were dispensed more zopiclone than is necessary for one treatment course in a one year period. While patients should only take zopiclone or benzodiazepines short-term for the treatment of insomnia, there are no clear clinical guidelines regarding an appropriate medicine-free interval before another short course is tried. Patients dispensed a large volume of tablets in one year may have taken several short courses of zopiclone, or may have been taking zopiclone on an as required ongoing basis throughout the year. Almost one-quarter of patients dispensed zopiclone received more than 150 tablets; this is the equivalent of (assuming the patient is taking one tablet, daily, as indicated):
- One tablet per day for at least five months if taken continuously
- At least three tablets per week taken over the entire year

There were 944 patients who received over 900 zopiclone tablets in 2013.

Similar trends of dispensing are seen for triazolam and temazepam, benzodiazepines which are indicated for short-term use in the treatment of patients with insomnia (Table 1).
Table 1: The % (number) of patients dispensed zopiclone, temazepam or triazolam in 2013, by volume⁴,⁵

<table>
<thead>
<tr>
<th>Recommended volume of tablets for one course of treatment</th>
<th>Zopiclone</th>
<th>Temazepam</th>
<th>Triazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 28 tablets: 7.5 mg at night, for up to four weeks; 7.5 mg tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 30 tablets</td>
<td>50.2% (97585)</td>
<td>51.5% (14130)</td>
<td>39.2% (10150)</td>
</tr>
<tr>
<td>31–90 tablets</td>
<td>19.5% (37868)</td>
<td>18.8% (5161)</td>
<td>20.2% (5223)</td>
</tr>
<tr>
<td>91–150 tablets</td>
<td>7.5% (14585)</td>
<td>6.5% (1790)</td>
<td>8.7% (2253)</td>
</tr>
<tr>
<td>151–300 tablets</td>
<td>10.1% (19663)</td>
<td>7.8% (2131)</td>
<td>11.6% (3006)</td>
</tr>
<tr>
<td>&gt; 300 tablets</td>
<td>12.7% (24702)</td>
<td>15.4% (4236)</td>
<td>20.4% (5273)</td>
</tr>
</tbody>
</table>

Prescribing points for benzodiazepines and zopiclone for insomnia or anxiety

Prescriptions for benzodiazepines or zopiclone should be written to take account of the risk of uncontrolled and escalating use, e.g. limited quantities with regular review. Prescribers should be vigilant for drug-seeking behaviour, such as early requests for repeat prescriptions.

For further information, see: “Prescription drug misuse: How to identify and manage drug seekers”, BPJ 16 (Sep, 2008).

Prior to starting the medicine, patients should be given information about adverse effects, and understand that they are for short-term use only (if prescribed for insomnia or generalised anxiety) and educated about the importance of not becoming reliant on these medicines. Consider a treatment contract which covers treatment duration, dose parameters, outcome measures, adverse effects and review dates. This helps the patient to understand the expectations of their treatment and provides a safeguard for the clinician to avoid escalation of prescribing.

Prescription of benzodiazepines and zopiclone needs to be carefully considered as patients may perceive that the rapid symptom relief that is often gained when using these medicines outweighs any adverse effects and risks. Patients may be less willing to try other treatments.
that are not as instantly gratifying, such as SSRIs for anxiety or non-medical interventions for insomnia, but these are likely to be safer and more appropriate in the long-term.

**For the treatment of anxiety**

Benzodiazepines:
- Should not be routinely used to treat anxiety disorder unless there are specific reasons to believe they could offer short-term benefit\(^6\)
- Are not recommended for the treatment of stress following a traumatic event\(^7\)
- Are only recommended for short-term use

In addition to psychological support and counselling, pharmacological treatment options for anxiety include SSRIs, tricyclic antidepressants, buspirone and benzodiazepines. When considering prescribing benzodiazepines to a patient for short-term benefit, this should be balanced against the risk that even a brief prescription may encourage the patient to become reliant on a medicine to manage their anxiety. This may deter commitment to later psychological intervention.

For further information, see: “Generalised anxiety disorder in adults”, BPJ 25 (Dec, 2009).

N.B. Benzodiazepines may be considered for reducing anxiety associated with breathlessness in patients during end-of-life care, if non-pharmacological treatments and morphine have not been effective.

For further information, see: “Managing breathlessness in palliative care”, BPJ 47 (Oct, 2012).

**For the treatment of insomnia**

Benzodiazepines and zopiclone are not preferred treatment options, because:
- Cognitive-behavioural approaches (e.g. “sleep hygiene”) have high levels of efficacy, are supported by a good evidence base, and achieve better outcomes in the long-term\(^8\)
- Benzodiazepines are known to alter sleep architecture, with a reduced amount of time spent in slow wave sleep, reducing overall sleep quality compared to the equivalent duration of sleep achieved by cognitive-behavioural approaches\(^9\)

If a benzodiazepine or zopiclone is being considered, because other interventions have been unsuccessful, a short-acting preparation should be chosen (Table 2) and prescribed at the lowest effective dose for a short duration; no more than four weeks, and preferably five to ten days.
Table 2: Key prescribing information for benzodiazepines and zopiclone approved in New Zealand for the treatment of insomnia and anxiety.4

<table>
<thead>
<tr>
<th>Key medical indication for use in primary care</th>
<th>Half life</th>
<th>Recommended dose for healthy adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insomnia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>long</td>
<td>5 – 15 mg at bedtime (insomnia)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>medium</td>
<td>1 – 2 mg at bedtime (insomnia)</td>
</tr>
<tr>
<td>Lormetazepam c</td>
<td>medium</td>
<td>0.5 – 1.5 mg at bedtime</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>long</td>
<td>5 – 10 mg at bedtime</td>
</tr>
<tr>
<td>Temazepam</td>
<td>short</td>
<td>10 – 30 mg half an hour before bedtime</td>
</tr>
<tr>
<td>Triazolam c</td>
<td>short</td>
<td>125 – 250 micrograms at bedtime</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>short</td>
<td>3.75 – 7.5 mg at bedtime</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>short</td>
<td>0.5 – 4.5 mg daily</td>
</tr>
<tr>
<td>Diazepam</td>
<td>long</td>
<td>15 – 30 mg daily (anxiety)</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>medium</td>
<td>1 – 4 mg (anxiety)</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>short</td>
<td>30 – 120 mg daily</td>
</tr>
</tbody>
</table>

a  Half-life definitions – short: less than 12 hours, medium: 12 – 24 hours, long: >24 hours. Half-life is likely to be longer in elderly or patients with renal impairment. The use of benzodiazepines with long half lives is not recommended in elderly patients.

b Elderly patients or those with co-morbidities such as renal impairment may require lower doses, often recommended as half the normal adult dose, see New Zealand Formulary for more details.

c Partly subsidised; all other medicines in the table are fully subsidised.

N.B. Clonazepam is not included in this table as its approved indication is for the treatment of epilepsy. However, in practice some clinicians use clonazepam to treat anxiety. It is a long-acting benzodiazepine; NZF does not list a dose for use in anxiety.
Adverse effects of hypnotics can range from subtle to serious

Benzodiazepines and zopiclone can cause a range of adverse effects, which include:

- Vertigo
- Muscle weakness
- Effects on cognition
- Dependency
- Increased risk of dementia and possible increased risk of Alzheimer’s disease
- Sleep automatism (in the case of z-drugs), including food binging, and even driving, while still asleep or in a sleep-like state

These adverse effects can lead to clinical outcomes, such as an increased risk of falls, and increased risk of motor vehicle accidents. There is some evidence that discontinuing the benzodiazepine or zopiclone reverses some of these effects, e.g. improvements in motor performance, cognition, and a reduction in dementia risk.

Concomitant use of benzodiazepines or zopiclone with opioids or alcohol increases many risks, such as lack of judgement, sexual disinhibition, criminal activity and fatal overdose.

**Elderly patients** have reduced clearance of medicines from their body and are likely to need a lower dose of benzodiazepines or zopiclone to minimise adverse effects, such as half the normal adult dose. Benzodiazepines with a long half-life, e.g. diazepam and nitrazepam (Table 2), should be avoided due to an increased risk of falls with next-day drowsiness. Particular care needs to be taken with diazepam, which has both a long half-life and active metabolites.

**Withdrawing patients from long-term use of benzodiazepines or zopiclone**

Strategies to encourage patients to stop a benzodiazepine or zopiclone should involve attempting to realign their perceptions of risks and benefits. Interventions which can be used in primary care to help change the way people perceive these medicines, and have been reported to increase rates of stopping hypnotic use, include:

- Patient education with information brochures or booklets about discontinuing benzodiazepines, e.g.:
- Regular follow-up letters to patients informing or reminding them of the risks of benzodiazepine use and the benefits of withdrawal
- Fortnightly consultations during withdrawal
- Psychological support: counselling or referral to psychological support services substantially improves rates of discontinuation over and above patient education or follow-up approaches

**Withdrawal should be “slow but sure”**

Rapid withdrawal of benzodiazepines is associated with an increased risk of seizures, therefore patients should be counselled against stopping their medicine abruptly.

Acute withdrawal can result in physiological and psychological effects, and a dose reduction strategy that aims to gradually wean patients off benzodiazepines and zopiclone is best practice. A gradual taper has been shown to improve the rate of successful discontinuation and avoid effects of withdrawal. There is little evidence, however, of how frequently doses should be reduced, by how much, or the desired overall duration of weaning off these medicines.

Usual recommendations for benzodiazepine or zopiclone withdrawal are:

- Dose reductions every one to two weeks, e.g. 10–15% of the initial dose depending on current dose and tablet strength/formulation
- Provide documentation of the treatment plan so that both patient and clinician can keep track of the planned reduction strategy. This is especially useful for patients who may be experiencing cognitive adverse effects.
- Monitor patient progress with frequent contact
- Be flexible – adjust reduction intervals according to how well a patient is tolerating the process. Some patients may manage a relatively quick reduction while others require a longer withdrawal process.
- If patients are experiencing difficulty, encourage them to remain on the lower dose they have achieved at that point, rather than increase the dose again. Recommence dose reduction when the patient feels able to resume.
- Patients should expect the possible occurrence of tremor, irritability, insomnia and anxiety during withdrawal stages, but these symptoms should alleviate once the withdrawal process is complete
- For patients with ongoing symptoms of anxiety or depression, the use of alternative anxiolytics or antidepressants in addition to psychological support may be required
For patients who have difficulty withdrawing from benzodiazepines or zopiclone, such as those who find the process psychologically distressing or who develop strong withdrawal symptoms, consider discussing their situation with an addiction specialist or referring to addiction services; these patients may need more in-depth assistance than can be easily offered in a general practice setting.

Patients who have been taking benzodiazepines or zopiclone at high doses (e.g. > 20 mg diazepam per day) or for a long period of time (e.g. > ten years) are best discussed with an addiction specialist. These patients are likely to require a lengthy withdrawal period and more intensive psychological support and counselling.

N.B. Be aware that some patients may be taking very little, or any, of a seemingly large volume of benzodiazepines or zopiclone prescribed to them; drug-seeking rings commonly include older women who may raise less suspicion than younger males.

Patient support for benzodiazepine and hypnotic withdrawal

Patients may find benefit from interacting with others in a similar situation, or those who have prior experience with hypnotic addiction. This may be in the form of face-to-face patient-focused support groups or online support. Other support within the health care system or wider community is also available for patients with addiction to medicines.

New Zealand drug and addiction resources and services:

- Drug help: www.drughelp.org.nz
- Addictions treatment directory: www.addictionshelp.org.nz/Services/Home
- New Zealand Drug Foundation: www.nzdf.org.nz
- Alcohol drug help line: 0800 787 797
- Salvation Army addiction support: 0800 530 000

Online information and support groups:

- www.benzobuddies.org
- www.benzosupport.org
Acknowledgement: Thank you to Dr Jeremy McMinn, Consultant Psychiatrist and Addiction Specialist, Wellington for expert review of this article.

References:
The detection and management of patients with chronic kidney disease in primary care
A New Zealand consensus statement for the management of chronic kidney disease (CKD) in primary care has recently been developed. The statement reinforces the need to view CKD as a significant contributor to cardiovascular risk and recommends that targeted testing for CKD should be linked to routine cardiovascular risk assessments and diabetes testing. Earlier detection of CKD in high-risk groups, e.g. Māori and Pacific peoples and people with diabetes, is a clinical priority. A major challenge is identifying those patients with progressive CKD who require early and intensive intervention to prevent kidney failure and the eventual need for dialysis and/or kidney transplantation.

Chronic kidney disease in New Zealand

A consensus statement on the identification and management of chronic kidney disease (CKD) in primary care was agreed upon following the National Consensus Conference on CKD held in 2013 at Matakana. Discussions involved general practitioners, nurses, diabetes specialists and nephrologists. The CKD consensus statement has been reviewed by stakeholder groups. In this article we present the key points for health professionals working in primary care.

The challenge of chronic kidney disease

Chronic kidney disease is a general term used to describe any long-term condition that affects kidney structure and function, e.g. diabetic nephropathy, IgA nephropathy or polycystic kidney disease. However, declining kidney function is also a natural part of the ageing process. It is estimated that by the age of 70 years approximately 30% of the population will meet classification criteria for CKD. The clinical challenge of CKD is to distinguish patients with progressively declining renal function due to disease from those with uncomplicated, age-related declining renal function. Patients with untreated progressive CKD are at extremely high risk of experiencing a cardiovascular event, and if they live long enough they are likely to require dialysis and/or kidney transplantation.

Chronic kidney disease is a growing problem

The number of people in New Zealand with CKD is currently unknown, although based on overseas populations an estimate of 7–10% of the population would seem reasonable. It has also been estimated that one in three people in the general population are at risk of developing CKD. The burden of CKD on New Zealand communities is increasing and the number of people requiring dialysis has almost doubled since 2000; in 2012 there were reported to be 2469 people undergoing dialysis and 1520 people who had a successful kidney transplant. Approximately half of all people in New Zealand requiring dialysis have diabetes as a primary cause of their condition.
The impact of CKD in New Zealand is felt particularly among Māori and Pacific peoples as end stage kidney disease (stage 5 CKD – Figure 1) is reportedly three to four times more common in these groups compared with people of European descent. Earlier detection of CKD in high-risk groups is a health priority for primary care. The cost per annum for each patient undergoing dialysis ranges from $30 000 to $60 000.

Defining and classifying chronic kidney disease

Chronic kidney disease is defined as the presence of structural or functional renal abnormalities, present for periods greater than three months, with implications for the patient’s health.

The Kidney Disease Improving Global Outcomes (KDIGO) criteria are used to classify CKD according to the patient’s estimated Glomerular Filtration Rate (eGFR) and degree of albuminuria (Figure 1). The KDIGO classification criteria do not include the cause of the patient’s CKD. The term progressive CKD is used to describe patients with CKD whose eGFR is declining at a rate > 5 mL/min/year.

In people with CKD the criteria used to classify stage 1 – 2 CKD differs from that used to classify stages 3 – 5. Patients who have stage 1 or stage 2 CKD must have some form of documented kidney disease, e.g. diabetic nephropathy or polycystic kidney disease as shown by imaging or biopsy abnormalities, or persistent proteinuria with or without haematuria. A patient’s eGFR is then used to distinguish stage 1 CKD from stage 2 CKD, i.e. ≥ 90 mL/min/1.73m² (stage 1) or 60 – 80 mL/min/1.73m² (stage 2). Patients with stages 3 – 5 of CKD have an eGFR ≤ 59 mL/min/1.73m², and evidence of kidney damage is not required (Figure 1). It is important to note that the patient’s eGFR will underestimate true GFR if the eGFR > 60 mL/min/1.73m², most likely due to the composition of the study population used to develop the equation from which eGFR is derived.

Age is included in the formula that calculates eGFR. Therefore in the general population eGFR declines by approximately 1 mL/min per year and many older patients will fulfil the criteria for stage 3 CKD without having any evidence of active or structural kidney disease. In these patients histology is likely to show age-related sclerotic changes to renal blood vessels, glomeruli and interstitium following biopsy.

The kidneys are the canary in the coal mine

The risk of a person experiencing a cardiovascular event increases as their renal function declines. Between 40 – 50% of people with kidney failure die of cardiovascular disease (Figure 2). The association between CKD and cardiovascular disease exists in part because
Prognosis of CKD and by eGFR and Albuminuria Categories: 
KDIGO 2012

<table>
<thead>
<tr>
<th>Persistent albuminuria categories</th>
<th>Urine ACR (mg/mmol)</th>
<th>Description and range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Normal male &lt; 2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>female &lt; 3.5</td>
<td></td>
</tr>
<tr>
<td>A2</td>
<td>Microalbuminuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>male 2.5 – 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>female 3.5 – 35</td>
<td></td>
</tr>
<tr>
<td>A3</td>
<td>Macroalbuminuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>male &gt; 25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>female &gt; 35</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Classification and prognostic risk of chronic kidney disease (CKD) according to estimated Glomerular Filtration Rate (eGFR – mL/min/1.73m²) and presence of albuminuria (mg/mmol) adapted from KDIGO clinical guidelines, 2012

<table>
<thead>
<tr>
<th>eGFR categories (mL/min/1.73m²)</th>
<th>Description and range</th>
<th>Low risk if no other markers of kidney disease, no CKD</th>
<th>Moderately increased risk</th>
<th>High risk</th>
<th>Very high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Normal or high</td>
<td>&gt;90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>Mildly decreased</td>
<td>60–89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3a</td>
<td>Mildly to moderately decreased</td>
<td>45–59</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased</td>
<td>30–44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G4</td>
<td>Severely decreased</td>
<td>15–29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Risk of death due to a cardiovascular cause according to KDIGO criteria relative to a “healthy” person with an eGFR 90 – 105 mL/min/1.73m² and ACR < 10 mg/mmol, from the National Consensus Statement.

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two of the largest risk factors for CKD – diabetes and hypertension – are also associated with left ventricular hypertrophy and left ventricular diastolic dysfunction, both of which are predictive of myocardial infarction and stroke. Coronary artery calcification, hyperlipidaemia, inflammatory processes, thrombosis, altered blood viscosity and endothelial dysfunction have also been suggested as mechanisms for the increased cardiovascular risk in people with CKD. Albuminuria/proteinuria are markers of increased cardiovascular risk and renal injury.

Detecting patients with chronic kidney disease in primary care

Most people with CKD stage 1 or 2 have no symptoms. Therefore to increase detection of people with CKD it is recommended that primary care clinicians routinely offer kidney function testing for patients as part of routine CVD risk assessments and diabetes checks.

Risk factors for chronic kidney disease

The major risk factors for CKD are:

- Hypertension
- Proteinuria
- Diabetes
- Age over 60 years
- Body mass index (BMI) > 35
- Family history of CKD
- Māori, Pacific or Indo Asian ethnicity
- Cardiovascular disease resulting in reduced renal perfusion and endothelial dysfunction
- Prostatic syndrome/urologic disease which has the potential to cause obstructive nephropathy

Patients with risk factors for CKD should be assessed at least every one to two years. For patients with diabetes this assessment should be performed at least annually. Population screening for CKD in isolation is not recommended.

Diagnosing chronic kidney disease

Patients with stage 3 CKD may be asymptomatic, or may report nocturia, mild malaise or anorexia. The signs and symptoms of stage 4 and 5 CKD are usually more obvious and include nausea, pruritus, restless legs and dyspnoea.
Patients with CKD can be identified in primary care by requesting both:¹

- A serum creatinine, which automatically generates an eGFR from the laboratory
- An ACR test; if a first void urine specimen, when the urine is most concentrated, is not possible then a random urine sample can be used²

Blood pressure measurements for patients at risk of developing CKD should also be performed where there is not a recent measurement recorded in the patient’s notes.

**Evaluating kidney test results**

In patients with an eGFR < 60 mL/min/1.73m² testing should be repeated. Be mindful when performing follow-up tests that small fluctuations in eGFR occur naturally and these may not necessarily indicate that the patient’s renal function is progressively declining.² A decline of 20% or greater in a patient’s eGFR from baseline is considered to be clinically significant.² An eGFR < 45 mL/min/1.73m² is associated with an increased risk of renal and cardiovascular complications regardless of the patient’s age.² When evaluating patients with suspected CKD it is particularly important to detect patients with progressive CKD whose kidney function decline may be as high as 10 – 20 mL/min per year.¹

**Albumin:creatinine ratio testing is recommended** in preference to protein:creatinine ratio (PCR) (mg/mmol) testing because ACR testing is considered to be a more sensitive and specific measure of changes in glomerular permeability than total urinary protein.⁵ Albuminuria is classified according to Table 1.

**Table 1: Staging of albuminuria for males and females²**

<table>
<thead>
<tr>
<th>Stage of kidney damage</th>
<th>Male ACR (mg/mmol)</th>
<th>Female ACR (mg/mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalalbuminuria</td>
<td>&lt;2.5</td>
<td>&lt;3.5</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>2.5 – 25</td>
<td>3.5 – 35</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;25</td>
<td>&gt;35</td>
</tr>
</tbody>
</table>

If the patient has microalbuminuria or macroalbuminuria (see referral criteria below) then this result should be repeated one to two times over the next three months to confirm a result.² If the patient has established macroalbuminura/proteinuria then the PCR needs to be quantitated as the proteinuria is usually non-selective and albumin will only comprise 50–60% of the proteinuria. Persistent proteinuria needs to be investigated.
The combination of a low eGFR and albuminuria/proteinuria means that the patient is at greater risk of developing end-stage renal failure, compared with patients who have a low eGFR, but no albuminuria or proteinuria.\(^1\)

**Referral to nephrology**

General practitioners need to make the decision on an individual basis as to when to refer a patient with CKD to a nephrologist and/or diabetes services, and local guidelines may vary.\(^2\) In younger patients a lower threshold for referral is usually appropriate. All patients with the following should be referred to a nephrologist:\(^1\)

- Progressive CKD in patients with an eGFR < 45 mL/min/1.73\(^2\)
- Evidence of intrinsic kidney disease, e.g. glomerulonephritis, polycystic kidney disease or interstitial nephritis
- Resistant hypertension and/or significant issues with blood glucose control and/or multiple vascular complications

If there is uncertainty concerning referral or management then telephone consultations and/or “virtual” referrals are highly recommended.\(^1\) In general referral to a nephrologist is not necessary for patients who have:

- Stable eGFR ≥ 30 mL/min/1.73m\(^2\); and
- ACR < 30 mg/mmol with no haematuria; and
- Normal or controlled blood pressure

As CKD progresses alterations in bone mineral metabolism and calcium and phosphate homeostasis develop.\(^5\) Anaemia will often occur in patients with severely reduced kidney function due to reduced renal synthesis of erythropoietin. Complications of advanced CKD will be managed by a renal team (Table 2), e.g. acidosis, metabolic bone disease, anaemia, malnutrition, infection risk and acute kidney injury (AKI).\(^2\) Each patient should have an eGFR, serum electrolytes and quantification of proteinuria, and ideally have a recent renal ultrasound before being referred to a nephrologist. Consider discussing patients with a nephrologist if there is uncertainty regarding referral.\(^2\)
Managing patients with chronic kidney disease in primary care

Most patients with stable CKD can be fully managed in primary care, particularly patients with stable stage 3 CKD or those patients aged over 75 years with early and stable stage 4 CKD. The most important aspects of CKD management are:

1. Controlling blood pressure; and if the patient has diabetes
2. Controlling blood glucose

Patients with stable CKD (stage 3 – 4) have a five-year cardiovascular risk > 15%, if they do not have diabetes, which increases to > 20% if diabetes is also present. These patients need appropriate cardiovascular disease management and it is important that additional medicines, e.g. statins and aspirin, are initiated according to cardiovascular guidelines to reduce cardiovascular risk.

Complementary community-based care strategies involving nurse-led teams have been shown to improve outcomes in patients with moderate CKD who are at high-risk of progressing to kidney failure (see: “Delaying nephropathy in Māori and Pacific patients”).

Software-based decision support, audit and patient recall systems are an important part of best practice in the management of CKD.

Delivering nephropathy in Māori and Pacific patients: the DEFEND trial

General practices can produce clinically significant improvements in outcomes for patients at high-risk of progressing to kidney failure by instigating relatively simple complementary nurse-led interventions.

The DElay Future End-stage Nephropathy due to Diabetes (DEFEND) trial involved 65 Māori and Pacific patients aged from 47 – 75 years with type 2 diabetes, moderate CKD and hypertension. Half the patients were randomised to usual-care (routine family doctor and renal/diabetes hospital outpatient care). The remaining patients received community care with monthly visits for one year by a member of a nurse-led team for blood pressure measurements, treatment compliance checks as well as monitoring for adverse effects. The study found that the community care resulted in clinically significant reductions in systolic blood pressure and proteinuria as well as delaying progression of left ventricular hypertrophy and diastolic dysfunction. The success of the programme was attributed to Māori and Pacific health-care assistants providing culturally appropriate care, more frequent follow-up, frequent prompting for patients to take medicines, and reduced costs to the patients because of home visits.
Lifestyle management of chronic kidney disease

Patients with CKD are able to reduce their rate of renal function decline through lifestyle modifications. Reductions in systolic blood pressure are often used to quantify the benefits of lifestyle modification in patients with CKD because this is known to have a renal-protective effect. Examples of lifestyle modifications and their approximate effect on systolic blood pressure include:\(^2\)

- Reducing BMI to at least $\leq 30 \text{ kg/m}^2$ with an ideal target of $\leq 25 \text{ kg/m}^2$. Alternatively a waist circumference for males $< 102 \text{ cm}$ and a circumference $< 88 \text{ cm}$ for females. A 10 kg reduction in weight results in a reduction in systolic blood pressure of 5 – 20 mmHg.
- Moderate intensity physical activity $\geq 30$ minutes/day results in a 4 – 9 mmHg reduction in systolic blood pressure.
- Reducing dietary salt intake to $\leq 6 \text{ g/day}$ results in a systolic blood pressure of 2 – 8 mmHg. This can be achieved by choosing to consume fresh vegetables and fruit, fish, milk, unprocessed meats, and using less salt in cooking and at the dinner table.
- All patients with CKD can be advised to observe at least two alcohol-free days per week. Upper limits for alcohol consumption for females are no more than two standard drinks per day, and no more than ten standard drinks a week. Males should be encouraged to drink no more than three standard drinks per day, and no more than 15 standard drinks per week. Reducing alcohol consumption to moderate levels can result in a 2 – 4 mmHg reduction in systolic blood pressure.

Smoking is an important modifiable risk factor for CKD progression.\(^9\) The few studies that have been conducted on the effects of smoking cessation in patients with CKD have found that albuminuria is significantly decreased and progression of diabetic nephropathy slowed.\(^9\) Encouraging smoking cessation in any patients with CKD is a priority of care.

Patients with CKD can be advised to maintain a normal daily intake of protein, i.e. 0.75 – 1 g/kg/day.\(^2\) This equates to 60 – 80 g of protein a day for an 80 kg person, e.g. approximately 250 g of lean beef or chicken breast or 300 g of canned tuna.\(^10\) High-protein diets, i.e. $> 1.3 \text{ g/kg/day}$, are not recommended in patients with CKD at risk of progression due to the risk of further kidney damage.\(^5\) Low-protein diets are also not recommended as insufficient dietary protein can lead to malnutrition, particularly in older patients.\(^5\)

For further information see: [www.nutritionfoundation.org.nz/nutrition-facts/Nutrients/protein](http://www.nutritionfoundation.org.nz/nutrition-facts/Nutrients/protein)
Identifying patients at risk of progressive chronic kidney disease

Patients with progressive CKD require close supervision and will often need to be intensely managed. Patients with CKD and risk factors should be regularly monitored (Table 2) for clinically significant reductions in renal function. These risk factors include:

- Hypertension
- Proteinuria
- Obesity
- Diabetes
- Current smoker
- Aged over 60 years
- Family history of CKD
- Māori, Pacific or Indo-Asian ancestry

Pharmacological treatment of chronic kidney disease

Managing blood pressure is a cornerstone of CKD management both to slow the rate of CKD progression and to reduce the patient’s cardiovascular risk.

The target blood pressure for patients with CKD is:2

- ≤ 130/80 mmHg for patients with diabetes or proteinuria with an ACR > 30 mg/mmol
- ≤ 140/90 mmHg for most other patients

However, blood pressure targets may need to be flexible and in older patients, e.g. aged over 70 years, a blood pressure target of < 150/90 mmHg may be reasonable. When prescribing antihypertensive medicines to older patients doses should be gradually increased and the patient monitored for adverse effects such as dizziness, orthostatic hypotension, electrolyte imbalances and acute kidney injury (AKI). Blood pressure control should also aim to reduce the levels of proteinuria by more than 50%.

Angiotensin converting enzyme (ACE) inhibitors are the first-line treatment for controlling blood pressure in patients with CKD. Angiotensin II receptor blockers (ARBs) are an alternative if ACE inhibitors are not tolerated. The combination of ACE inhibitors and ARBs should be avoided when treating patients with CKD in primary care. Follow-up in the early stages of treatment, i.e. two to four weeks, is useful to ensure the patient is responding adequately to antihypertensive treatment.

Many patients will require multiple medicines to achieve blood pressure targets and this need increases as a patient’s eGFR declines. It is recommended that a calcium channel
blocker be added to an ACE inhibitor or ARB as the second stage in managing hypertension in patients with CKD.\textsuperscript{11}


\textbf{Glycaemic control}

In patients with CKD and diabetes, glycaemic control is essential to prevent or delay the progression of the microvascular complications of diabetes, including diabetic nephropathy, and to reduce cardiovascular risk.\textsuperscript{5} A HbA\textsubscript{1c} target < 53 mmol/mol is generally appropriate for patients with CKD and diabetes, although in patients at risk of hypoglycaemia, e.g. older patients living alone, or in patients with co-morbidities or limited life expectancy, a target HbA\textsubscript{1c} ≥ 53 mmol/mol may be more appropriate; this should be discussed with patients using a shared-decision making approach.\textsuperscript{5}

In patients with advanced stage 4 and stage 5 CKD the risk of hypoglycaemia is also clinically relevant, and less intensive glycaemic control but with close monitoring is often required.\textsuperscript{1}

\textbf{The maximum dose of metformin in patients with an eGFR < 60 \text{mL/min/1.73m}^2} is metformin 1 g, daily.\textsuperscript{12} Metformin should be avoided altogether in patients with an eGFR < 30 \text{mL/min/1.73m}^2 except under the close supervision of a nephrologist.\textsuperscript{12}

For further information see: “Getting to know patients with type 2 diabetes and poor glycaemic control: One size does not fit all” BPJ 58 (Feb, 2014).

\textbf{Treat hyperlipidaemia according to cardiovascular risk}

Statin treatment for hyperlipidaemia should be discussed, where appropriate, with patients with CKD. The benefits of statin treatment in patients with CKD is relatively consistent in patients with a broad range of LDL cholesterol levels.\textsuperscript{5} However, statins are less effective in patients with advanced CKD.\textsuperscript{2} Fibrates should be avoided in patients with reduced renal function due to the increased risk of a myositis-like syndrome occurring.\textsuperscript{12} The optimal lipid levels for patients with CKD are:\textsuperscript{2}

- Total cholesterol < 4.0 mmol/L
- LDL cholesterol < 2.0 mmol/L
- HDL cholesterol ≥ 1.0 mmol/L
- Triglycerides < 1.7 mmol/L

\textbf{Gout is common in people with chronic kidney disease}

Chronic kidney disease is reported to be the third most prevalent risk factor for gout, following obesity and hypertension.\textsuperscript{13} This is because reduced renal function in patients with
CKD can result in uric acid levels being raised, causing gout symptoms in some patients.\textsuperscript{14} According to international estimates 40 – 50\% of patients with gout also have CKD.\textsuperscript{15} Gout is associated with increased cardiovascular risk in patients with CKD. Gout is present in 11.7\% and 13.5\% of Māori and Pacific males, compared to 3.7\% of European males, and 4\% of Māori and Pacific females, compared to less than 1\% of European females.\textsuperscript{16}

Monitoring of renal function in patients with CKD and gout is particularly important as many of the medicines used to treat patients with gout are potentially nephrotoxic. Allopurinol is the first-line medicine used to reduce uric acid levels. Initial doses of allopurinol should be low and determined by eGFR in patients with CKD, and then slowly titrated to achieve a serum uric acid level of < 0.36 mmol/L.\textsuperscript{17} This slow titration of allopurinol reduces the risk of patients experiencing the relatively rare allopurinol hypersensitivity syndrome. All non-steroidal anti-inflammatory drugs (NSAIDs) are associated with potentially nephrotoxic effects and should be used with caution to treat attacks of acute gout in patients with CKD. Oral prednisone is a treatment option for the management of acute gout attacks in patients with CKD.\textsuperscript{12} Colchicine remains a useful treatment option in patients with stage 1 or 2 CKD, but should be avoided in patients with an eGFR < 60 mL/min/1.73m\textsuperscript{2}.\textsuperscript{12}

For further information see: “Allopurinol dosing in renal impairment” BPJ 61 (Jun, 2014).

### Monitoring patients with established chronic kidney disease

Patients with established CKD should have their eGFR and albuminuria assessed at least annually.\textsuperscript{2} Albuminuria and eGFR measurements should be recorded more regularly for

### Table 2: Monitoring and investigation schedule for patients with chronic kidney disease according to staging\textsuperscript{2}

<table>
<thead>
<tr>
<th>CKD staging</th>
<th>Frequency of review</th>
<th>Investigations requested</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1 – 2</strong></td>
<td>6 – 12 months; less frequently if the patient’s eGFR is stable and risk factors controlled</td>
<td>Serum creatinine, ACR (or PCR), serum electrolytes, serum urate, HbA\textsubscript{1c} and lipids</td>
</tr>
<tr>
<td><strong>Stage 3</strong></td>
<td>Three to six-monthly</td>
<td>In addition to the above: FBC, serum ferritin, calcium, phosphate and parathyroid hormone</td>
</tr>
<tr>
<td><strong>Stage 4</strong></td>
<td>Three-monthly</td>
<td>In addition to the above: plasma bicarbonate</td>
</tr>
<tr>
<td><strong>Stage 5</strong></td>
<td>Monthly</td>
<td>Investigations usually determined in conjunction with a nephrologist</td>
</tr>
</tbody>
</table>
patients with an increased risk of progressive CKD. Patients with progressive stage 3 – 4 CKD have a much greater risk of developing renal failure. These patients require intensive management with weekly or fortnightly review of risk factor management until their condition is stable. Table 2 provides a recommended monitoring schedule for patients with established chronic kidney disease according to the degree of renal dysfunction.

**Preventing acute kidney injury**

Most people who experience AKI have some degree of pre-existing CKD. Medicines are a common cause of AKI in people with CKD and patients with an acute illness (e.g. a gastrointestinal illness, sepsis, and respiratory or urinary tract infection causing hypovolaemia) are at particular risk. In this context some medicines should be used with caution. For example the triple combination of NSAIDs, ACE inhibitors (or ARBs) and diuretics can cause AKI by interfering with homeostatic mechanisms needed to preserve kidney perfusion during acute illness. Fluid and electrolyte maintenance is an important preventative strategy in people with CKD who are acutely unwell. People with established CKD should be advised to cease taking antihypertensive and oral hypoglycaemic medicines, especially metformin, if they develop acute illness with vomiting and diarrhoea, until they have recovered.

People with CKD are also at an increased risk of developing AKI when they undergo procedures involving radiocontrast media. It may be necessary to temporarily withdraw potentially nephrotoxic medicines from patients with CKD who are undergoing contrast-enhanced imaging, particularly if they also have diabetes. The use of metformin is contraindicated in patients undergoing procedures involving iodine-containing contrast media, e.g. when investigating some cancers.

For further information see: “Acute-on-chronic kidney disease: prevention, diagnosis, management and referral in primary care” BPJ 46 (Sep, 2012).

**Acknowledgement:** Thank you to Professor Rob Walker, Nephrologist, Mary Glendining Chair in Medicine, Head of Department of Medicine, University of Otago and Southern DHB and Dr Helen Rodenburg, Clinical Director, Long-Term Conditions, Ministry of Health and General Practitioner, Wellington for expert review of this article.

**References**

Shorter courses of oral corticosteroids for the management of exacerbations in patients with COPD

Practice point
Prednisone 30 – 50 mg daily can be prescribed for five days for patients with acute moderate or severe exacerbations of chronic obstructive pulmonary disease (COPD). Previously, 10 – 14 days of oral prednisone treatment was recommended, but recent literature has reported that five days of treatment is equally effective for both treating the current exacerbation and preventing subsequent exacerbations.

Tapering of corticosteroid treatment is not necessary for treatment periods of less than two weeks in patients with acute exacerbations of COPD.

The evidence
The Reduction in the Use of Corticosteroids in Exacerbated COPD (REDUCE) study reported that five days of corticosteroid treatment was clinically non-inferior to 14 days of corticosteroid treatment in patients with an acute exacerbation of COPD, seen at the emergency department in five hospitals in Switzerland.

The high-quality, double-blind, non-inferiority study randomised 314 patients with an acute exacerbation of COPD to either five days (short) or 14 days (conventional) of prednisone 40 mg, daily.
There were no significant differences found between patients receiving short or conventional courses in terms of overall survival, FEV₁, patient-assessed overall performance, quality of life, the need for mechanical ventilation or the use of additional corticosteroids to control symptoms.²

Patients who received five days of prednisone treatment were as likely to experience an exacerbation within the next six months (primary endpoint) as those who received 14 days of treatment (36% vs. 37% of patients; p<0.01 for non-inferiority).² These results were consistent across all Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories of disease severity, i.e. for stage I/II (mild/moderate), III (severe) and IV (very severe) disease.² In those patients who did experience a subsequent exacerbation, the median time to the re-exacerbation was longer in those who received five days of treatment compared to those who received 14 days treatment (44 vs. 29 days).²

Patients who received the five-day regimen were less likely to have new or worsening hypertension at discharge (12% vs. 18%), although this was not statistically significant.² The rates of other adverse events including infection and new or worsening hyperglycaemia at discharge were similar in patients in both treatment groups.²

A 2014 systematic review, which included the REDUCE study, also supported the use of shorter duration (less than seven days) oral corticosteroid treatment over longer duration (greater than seven days) in patients with exacerbations of COPD.³

The systematic review concluded that there were no significant differences between patients treated with shorter or longer durations of corticosteroids in regards to the rate of treatment failure, the time to the next exacerbation, the duration of hospital stay, lung function tests, adverse effects or death.³

References
Diet and the risk of COPD

Relatively little is known about the influence diet has on COPD pathogenesis. A recent study used nutritional data collected from over 73,000 female nurses, between 1984 and 2000, and over 47,000 males, between 1986 and 1998, to correlate the quality of the participants' diet with the likelihood of them being newly diagnosed with COPD. It was found that a diet rich in whole grains, polyunsaturated and omega-3 fats and low in red and processed meats, refined grains, and sugar-sweetened drinks was associated with a reduced risk of COPD. The negative association between a healthy diet and COPD persisted when smoking status and relative exposure to tobacco smoke were accounted for. An association between a “Western” diet and specifically a high intake of cured and red meat had been previously noted by the same authors. This study adds strength to the hypothesis that diets rich in foods with high levels of antioxidants may provide a protective effect in the high-oxygen environment of the lung where inflammatory processes in patients with COPD lead to the proteolytic destruction of elastic fibres.

Reference
Milk and bone density

Dear Editor

Can bpac nz substantiate its claim that “consumption of milk, yoghurt or cheese is associated with improved bone density and a reduced risk of ischaemic heart disease, myocardial infarction and stroke”? [“Managing patients who are obese”, BPJ 65, Dec 2014] A recent cohort study of 107,000 Swedish adults found almost twice the overall mortality rate and significantly more fractures among women drinking three or more glasses of milk a day. Both men and women had higher rates of cardiovascular mortality with increasing milk consumption. The authors found such a claim may be true for fermented dairy products such as yoghurt and cheese (perhaps because of lower levels of D-galactose) but saying “milk, yoghurt or cheese” may no longer be accurate.


Dr Stephen Hoskin, General Practitioner
Te Anau

Response from BPJ editorial team: Milk, yoghurt and cheese are recommended by the Australian Dietary Guidelines (2013) as one of five food groups that people choose from daily to create a varied and nutritious diet.¹ This guideline was the principle source of information for the healthy eating guidance provided in our article “Managing patients who are obese”, BPJ 65 (Dec, 2014). Milk, cheese and yoghurt are widely recognised as being good sources of easily absorbed calcium, protein, iodine, vitamin A, vitamin D, riboflavin, vitamin B12 and zinc. However, it is recommended that reduced fat versions of these dairy foods should be chosen on most occasions as full fat milk, cheese and yoghurts increase total fat, saturated fat and overall energy intake.¹

Specifically regarding milk, yogurt and cheese consumption and cardiovascular risk, the guidelines state:¹

“Coronary heart disease: It is probable that the consumption of at least two serves per day of milk, cheese and yoghurt is associated with a reduced risk of ischaemic heart disease and myocardial infarction.”²

Stroke: It is probable that the consumption of two or more serves per day of milk, cheese and yoghurt is associated with reduced risk of stroke, particularly reduced fat varieties.”²,³
Hypertension: It is probable that consumption of three serves of low fat milk, cheese and yoghurt is associated with reduced risk of hypertension. The evidence also suggests that consumption of three serves of any milk, cheese or yoghurt products per day is associated with reduced risk of hypertension.4, 5, 6, 7

The article by Michaelsson et al that found an association between milk intake, all-cause mortality and fracture risk was published in October 2014, and therefore would not have been available when the Australian guidelines were compiled. Michaelsson et al provided two large patient cohorts in Sweden with food frequency questionnaires which were used to correlate milk intake, either low or full fat, with health outcomes. A dose-dependent increased rate of mortality in females and males was observed, as well as a increased rate of bone fracture in females.8 This pattern of association was not detected with the consumption of other dairy products.8 The authors also noted that fermented milk products, such as yogurt and cheese, were associated with reduced mortality and rates of fracture.8 This observation, combined with other experimental data mainly from animal studies, led the authors to suggest that milk may be harmful due to the potential inflammatory and oxidative properties of D-galactose, a metabolite of lactose.8 However, currently there is limited evidence concerning the cardiovascular effect of D-galactose.9 It is possible that the increased fracture rate associated with milk consumption was due to females who were at increased risk of fractures voluntarily increasing their milk consumption and therefore creating a reverse causation phenomenon.

Dietary guidelines are based on rigorous methods of data analysis to ensure that recommendations are a balanced reflection of current evidence. Michaelsson et al note that as their study was observational in design their conclusion that milk consumption within recommended daily quantities may be harmful should be interpreted cautiously. Independent replication is required before these results can be incorporated into population-wide dietary recommendations. As one commentator remarked “a fascinating possibility” has been raised, and randomised controlled trials will assist in determining if this observation is correlation or causation.9

References

Is phentermine addictive?
Re: “Managing patients who are obese”, BPJ 65 (Dec, 2014)

This article is poorly researched and should be re-written. Phentermine abuse or psychological dependence (addiction) does not occur in patients treated with phentermine for obesity. Phentermine treatment does not induce phentermine drug craving, a hallmark sign of addiction. Amphetamine-like withdrawal does not occur upon abrupt treatment cessation even at doses much higher than commonly recommended and after treatment durations of up to 21 years.1

In 2005 a randomised, double-blind, placebo-controlled study was performed on 68 relatively healthy obese adults whose body mass index was 25 kg/m² or greater. They received phentermine-HCl 37.5 mg or placebo once daily with behavioural therapy for obesity. Mean decrease of both body weight and waist circumference in phentermine-treated subjects were significantly greater than that of placebo group (weight: −6.7 ± 2.5 kg, p < 0.001; waist circumference: −6.2 ± 3.5 cm, p < 0.001).2

Insufficient evidence exists for the use of metformin as treatment of overweight or obese adults who do not have diabetes mellitus or polycystic ovary syndrome.3

Dr Nicholas Cooper, General Practitioner
[online comment]

Response from BPJ editorial team and Dr Jeremy McMinn, Addiction Specialist: The role of phentermine in the management of patients who are obese is a controversial, and at times polarising, subject; perhaps due to the relatively limited evidence available. There is concern among some addiction experts in New Zealand, about the risks of phentermine. They advise general practitioners not to prescribe phentermine. However, some obesity
specialists advocate its use as a short-term, adjunctive treatment for patients who are obese. In the article “Managing patients who are obese: Encouraging and maintaining healthy weight-loss” (BPJ 65) we have attempted to present a balanced view on the subject.

Phentermine is a dopaminergic agonist that acts as an appetite suppressant. Like amphetamine, phentermine is classified as a sympathomimetic drug because it mimics the actions of neurotransmitters of the sympathetic nervous system.

Phentermine was approved for the short-term treatment of obese patients in the United States in 1959. It is subject to the controlled substances act as the United States Drug Enforcement Agency believes that the use of phentermine is associated with a risk of habituation or addiction. However, recently the United States Federal Drug Administration approved the combination of phentermine and topiramate for the long-term treatment of patients who are obese. In Europe, phentermine is not approved for the treatment of patients who are obese due to concerns about its potential to cause addiction, tachycardia and increased blood pressure. In New Zealand, phentermine is indicated as a short-term adjunctive treatment for weight loss in patients with a BMI greater 30 kg/m², although it is unsubsidised.

The decision of whether or not to initiate phentermine treatment should take into account the following factors, and should not focus entirely on the medicine’s addictive potential or lack of it:

- Phentermine has a substantial number of contraindications
- There is a paucity of research assessing the safety and effectiveness of phentermine
- The studies that have been conducted on phentermine report relatively modest reductions in weight by patients
- Phentermine is not subsidised and the cost of treatment limits the number of patients who this medicine can be prescribed to

Phentermine is contraindicated in patients with: pulmonary artery hypertension, severe cardiac disease, heart valve abnormalities or heart murmurs, moderate to severe arterial hypertension, cerebrovascular disease, hyperthyroidism, a history of psychiatric illness, glaucoma, a history or drug or alcohol abuse, or use of a monoamine oxidase inhibitor in within the past 14 days. Phentermine can be prescribed at 15 – 30 mg, once daily, in the morning. Patients should be advised to contact a health professional immediately if they experience symptoms such as breathlessness, chest pain, fainting, swelling in the lower limbs, or a decreased ability to exercise. Prescribers are recommended to consider withdrawing treatment of phentermine at 12 weeks if the patient has lost less than 5% of their pre-treatment bodyweight.
Phentermine is a generic medicine, therefore it is highly unlikely that any industry-sponsored trials will be conducted in the future and the available evidence relating to the use of phentermine is relatively limited. Early studies in monkeys did not indicate that phentermine was associated with addictive potential. A study of 117 obese patients who had been treated with phentermine long-term (1.1 – 21.1 years) at a private obesity centre, and 152 obese patients from the same centre who had been treated with phentermine short-term (4 – 22 days), found that, following neuropsychiatric interviews, all patients were negative for phentermine abuse or psychological dependence. While this study does provide some evidence that phentermine can be used safely, it will need to be replicated in larger patient cohorts before the medicine can be recommended routinely for the treatment of obesity. This study must also be balanced against reports that in Europe phentermine is known as a “street drug”, and that it is sold for considerable sums of money both overseas and in New Zealand. Addiction clinicians find that phentermine prescribing is sought disproportionally by patients with addiction difficulties, frequently for reasons that do not reflect a managed weight control programme.

The phentermine debate should also be focused on the medicine’s effectiveness as an anti-obesity medicine. A meta-analysis of nine studies published between 1975 and 1999 found that over a treatment period ranging from two to 24 weeks patients treated with phentermine lost an average of 3.6 kg of additional weight compared with placebo. It was concluded that phentermine can produce statistically significant but modest increases in weight loss, in addition to lifestyle interventions. The small 2005 study referred to by Dr Cooper investigated weight loss following a 14-week course of phentermine. Results were compared between 24 people who completed the course of phentermine and 12 people who completed a course of placebo treatment. However, the entry criteria for this study was a BMI > 25 kg/m² and the mean BMI for patients allocated phentermine was 29.3 kg/m². Therefore this study has questionable relevance to obesity management as many of the patients, although overweight, were not obese. The commonly accepted definition of obesity is a BMI > 30 kg/m².

The two key questions for clinicians who are considering prescribing phentermine are:
- Has the patient adequately trialled lifestyle change previously?
- Are the modest increases in weight loss associated with phentermine clinically significant enough to outweigh any concerns over the cardiovascular adverse effects and/or addictive potential?

These questions can only be answered on an individual patient basis. A patient’s addictive potential includes consideration of present or past history of addiction to any substance; family history of addiction and present or past history of mental illness. The prescriber and
patient should have an agreed contract including duration of treatment, treatment goals and how outcomes will be measured. If the benefits of treatment are judged to outweigh the risks then the financial cost to the patient of treatment must also be considered.

In regards to the correspondents comment about metformin, it has not been recommended as an anti-obesity treatment for patients without type 2 diabetes. Weight-loss was highlighted as a beneficial side effect of metformin treatment in patients with diabetes, as diabetes is a common co-morbidity in patients who are obese.

“Metformin is associated with clinically significant weight-loss in patients with type 2 diabetes and is fully-subsidised as an anti-diabetic medicine, however, it is not approved for use as an anti-obesity medicine.”

References

We value your feedback. Write to us at:
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