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# EDICINEWISE

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# **Caution!** Diagnosis creep

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### Key words

conflict of interest, drug industry, guidelines, overdiagnosis

Aust Prescr 2016;39:30-1 http://dx.doi.org/10.18773/ austprescr.2016.021 Twenty years ago British GP Iona Heath observed that one of the key roles of the GP was to help protect people from the unnecessary diagnosis of disease.<sup>1</sup> Perhaps the biggest challenge for doctors who take that role seriously comes from expanding disease definitions. The current definition of 'chronic kidney disease' labels 10% of the adult population as having the condition.<sup>2</sup> New criteria almost triple the number of pregnant women labelled as having gestational diabetes.<sup>3</sup> Thresholds defining attention deficit hyperactivity disorder continue to fall, meaning more children and adults will be diagnosed.<sup>4</sup>

We are labelling more and more healthy people as sick and building bigger potential markets for those selling medicines. For some of the newly labelled patients there will no doubt be benefits, but for others with mild problems or at very low risk of illness, a diagnosis can bring more harm than good, leading to overtreatment and wasting precious resources that could be better directed to those in genuine need.

The process of broadening definitions can be described as 'diagnosis creep' and often results from guidelines prepared by expert panels. In 2013

colleagues and I analysed recent changes made by expert panels to the definitions of 14 common conditions, including hypertension, depression and Alzheimer's disease.<sup>5</sup> Of 16 publications from the panels, only one proposed a narrower definition, for five the impacts were unclear, and 10 proposed an expanded definition - pre-diseases were created, thresholds were lowered, or diagnostic processes changed to enable earlier diagnosis. In no case did a panel rigorously investigate and report on the potential danger that some people may be caught unnecessarily by the newly widened definitions. Among the panels that disclosed competing interests, 75% of panel members had multiple financial ties to a median of seven drug companies each. These members were paid by companies for activities like speaking, consulting, advising or researching. This is in direct contrast to recommendations from organisations like the US Institute of Medicine for more independence among those who write guidelines.6

For instance, among the blood pressure guideline panel that in 2003 created 'pre-hypertension', 80% of members disclosed ties to 12 companies each.<sup>5</sup> Eight of the 11 members had financial ties to pharmaceutical companies that sold drugs for hypertension.

Over half of the members of the 2011 joint US National Institute on Aging – Alzheimer's Association panel that described 'pre-dementia' and defined 'preclinical' Alzheimer's disease had financial ties to a median of five companies.<sup>5</sup> Similarly for the 2012 psychiatric panels, which widened the definitions of depression and attention deficit hyperactivity disorder, over half disclosed links to companies, including those that could directly benefit from expanded patient populations.<sup>5</sup>

The decisions made by these heavily conflicted panels are not abstract academic exercises. They ultimately influence whether or not an individual is labelled as 'diseased', changing their life's narrative. Moreover, decisions that expand patient populations profoundly affect where we spend our health resources.

Health professionals should be more aware, and patients and the public better informed, about the controversy surrounding many contemporary definitions of disease. Diagnostic criteria are not set in stone – they are regularly changed, often with the best of intentions, but are also often rigorously challenged because of the potential for unintended

# From the Editor



NPS MedicineWise, the publisher of *Australian Prescriber*, has decided to cease publication of the journal in print. In addition, the journal's website australianprescriber.com, established in 1996, will be replaced by a new website hosted by NPS MedicineWise. The *Australian Prescriber* team would like to thank Greg Buchberger (GBI Creative) who has been the journal's webmaster for over a decade. In future, health professionals who wish to continue to

read *Australian Prescriber* need to register at nps.org.au/australianprescriber.

This penultimate issue of the printed *Australian Prescriber* has a focus on osteoporosis. Angela Sheu and Terry Diamond discuss diagnosis, while Akhil Gupta and Lyn March review its management. Chris Daly describes the dental problems that can result from the treatment of osteoporosis.

While relatively few patients with minimal trauma fractures are investigated for osteoporosis, in other conditions there is overdiagnosis. Ray Moynihan discusses this diagnosis creep.

Borderline personality disorder is often undetected. While management can be challenging, Andrew Chanen and Katherine Thompson tell us that drugs are not first-line therapy.

Managing menstrual problems in women with intellectual disability may also seem challenging, but Jane Tracy, Sonia Grover and Sandra Macgibbon provide helpful advice. The approach to management should be the same as it is in other women.

harms. A peer-reviewed series in the BMJ is currently examining expanding disease definitions and the risk of overdiagnosis. The series has included articles on the evidence underpinning the controversy over gestational diabetes,<sup>3</sup> attention deficit hyperactivity disorder,<sup>4</sup> chronic kidney disease,<sup>7</sup> pre-dementia,<sup>8</sup> mild hypertension<sup>9</sup> and pulmonary embolism.<sup>10</sup>

With gestational diabetes for example, proposals to lower diagnostic thresholds and dramatically expand the patient population have generated ongoing criticism that too many women will be labelled unnecessarily.<sup>11</sup> The proposals have been rejected by an independent panel constituted under the US National Institutes of Health consensus development conference series.<sup>12</sup>

Health professionals can help to expose and challenge diagnosis creep, and improve disease definitions. A group of doctors in the UK has successfully lobbied the Royal College of General Practitioners to set up a standing committee to address overdiagnosis,<sup>13</sup> and similar moves are afoot in Australia. Across Europe the new 'quaternary prevention' movement is also gathering strength within primary care. This doctor-led movement is aimed at preventing people receiving diagnoses that may bring them more harm than good.<sup>14</sup>

Globally, efforts are underway from a range of organisations including the Guidelines International Network, to produce new guidelines for guidelines, to encourage expert panels to rigorously examine both benefits and harms before they shift diagnostic thresholds. In line with the Institute of Medicine's recommendations for more independence in guideline panels,<sup>6</sup> a new approach must surely also mean an end to panel members being speakers or consultants for companies that directly benefit from their deliberations on diagnosis. While it is more difficult to find unconflicted experts, practical models do exist, including the National Institutes of Health consensus development panels.<sup>12</sup>

These efforts to reform the way diseases and diagnostic thresholds are set are happening concurrently with related initiatives to combat medical excess, like the Choosing Wisely Australia campaign. This aims to reduce use of unnecessary tests and treatments.<sup>15</sup>

Finally, in the interest of protecting people from the dangers of diagnosis creep, one might take the provocative advice of Dr Iona Heath. Addressing a symposium about the problem of too much medicine in Canada in 2014, Dr Heath prescribed this solution: 'Whenever I see the sort of guidelines that are, right now, driving overdiagnosis and overtreatment, I think of this: our responsibility not to follow the rules.'<sup>16</sup>

Conflict of interest: Ray Moynihan is a member of the scientific committee that is organising the international scientific conference Preventing Overdiagnosis. He is also a member of the planning committee for the Australian Preventing Overdiagnosis and Overuse meetings.

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# Letters to the Editor

# Warfarin and beetroot

Aust Prescr 2016;39:32 http://dx.doi.org/10.18773/austprescr.2016.017

The recent Letter to the Editor about warfarin and beetroot by Louise Vanpraag and the response from Philip Tideman and colleagues' both miss the point about warfarin and beetroot. It is commonplace for those eating beetroot to have red urine (beeturia) or red faeces, or both, and such symptoms in those taking warfarin can be worrying. On many occasions, warfarin dosage has been adjusted unnecessarily and there have been many unnecessary urinary and bowel investigations. The beetroot-induced symptoms are of no importance and of course can occur in anyone eating beetroot.

John Raven Clinical haematologist Consultant physician Bunbury, Qld

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 Vanpraag L. Warfarin and beetroot [letter]. Aust Prescr 2015;38:150. http://dx.doi.org/10.18773/ austprescr.2015.061

Philip A Tideman, Rosy Tirimacco, Andrew St John and Gregory W Roberts, the authors of the article, comment:

This is an excellent point, and any counselling regarding the signs of bleeding should include alerting the patient to the possibility of red or pink urine or faeces after eating beetroot. Likewise, clinicians should enquire about beetroot consumption for any patient presenting with pink or red urine or faeces.

# Warfarin, St John's wort and INR

Aust Prescr 2016;39:32-3 http://dx.doi.org/10.18773/austprescr.2016.025

In regards to the article on the management of warfarin therapy,<sup>1</sup> the statement on page 46 'drugs that may increase INR – macrolide antibiotics, imidazole antifungals, sulfamethoxazole/ trimethoprim, amiodarone, statins, some nonsteroidal anti-inflammatory drugs and some complementary medicines such as St John's wort' may not be correct. In the literature, St John's wort *decreases* the INR through induction of cytochrome P450 (CYP)-mediated metabolism of warfarin and increases warfarin clearance.<sup>2-9</sup>

Angela Cattanach Siboniso Sibindi Clinical pharmacists Lismore Base Hospital Lismore, NSW

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# *Gregory Roberts, one of the authors of the article, comments:*

Thank you for pointing out the error in the article.<sup>1</sup> St John's wort induces CYP enzymes with a resultant increase in warfarin clearance and decrease in INR, not a possible increase in INR as described in the article. Decreases of 20% in AUC (area under the curve) have been noted in single warfarin dose studies,<sup>2</sup> so while prudent INR monitoring should be undertaken, the interaction is likely to be of clinically minor importance.

# 4

The Editorial Executive Committee welcomes letters. which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

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# Benzodiazepines

Aust Prescr 2016;39:33 http://dx.doi.org/10.18773/austprescr.2016.016

I congratulate the authors of the recent article on benzodiazepines<sup>1</sup> for highlighting that, although not as bad as in the 1980s,<sup>2</sup> benzodiazepine abuse and misprescribing remain a problem, especially in the area of polysubstance abuse.

I would like to make a suggestion. Regarding the Table, I tend to classify flunitrazepam (also now a Schedule 8 drug) and nitrazepam as long-acting benzodiazepines. There are usually three groups of benzodiazepine cited for clinical action: short-, intermediate- and long-acting. The authors have grouped short and intermediate, but this can give a misleading impression to prescribers, especially regarding these two benzodiazepines notorious for their accumulation and morning-after effects. For example, the product information for nitrazepam states 'elderly debilitated patients may show a significant increase in elimination half-life.'

The other minor point I would make is that the approximate half-life of diazepam in the Table (20–80 hours) is misleading. Its active metabolite nordiazepam has a half-life of 96 hours according to the product information, and is marketed as an active compound in some countries.

Finally, a little mnemonic to help students, GP trainees and addiction trainees with outpatient benzodiazepine withdrawal is TTT i.e. Ten per cent reduction in dose per week over Ten weeks with an exponential/terminal Taper.

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# *Bridin Murnion and Jonathan Brett, the authors of the article, comment:*

Thank you for your observations regarding the half-lives of nitrazepam and flunitrazepam. Indeed we feel that any use of benzodiazepines in elderly debilitated people carries a significant risk regardless of half-life. The Table is perhaps an arbitrary division of benzodiazepines based on halflife as there is a degree of inter-individual variability and, as you say, active metabolites are also important. The pharmacodynamic effects of each drug may also differ to some degree and this may also impact on toxicity.

# Prescribing for people in custody

Aust Prescr 2016;39:33-4 http://dx.doi.org/10.18773/austprescr.2016.013

I read the article on prescribing for people in custody<sup>1</sup> with interest. It raised many valid points and covered several narcotics and other sedatives among high-risk medicines. I would like to draw attention to antihyperglycaemic drugs, especially insulin which requires expertise on site to monitor its use and potential misuse. This is more important for inmates with type 1 diabetes in high-security facilities who mostly do not have access to diabetic meals, and where food provided after hours is mostly not diabetes friendly. In my experience dealing with patients on insulin in custody is really challenging. Rigid schedules and limited availability of healthcare staff add to the complexity of this situation.

It is unfortunate that in spite of the high prevalence of diabetes in the community, especially in those who are disadvantaged, there is no specific policy on management of people with diabetes in custody.

Santosh K Chaubey Staff specialist (Endocrinology) Gosford Hospital Gosford, NSW

# REFERENCE

 Hampton S, Blomgren D, Roberts J, Mackinnon T, Nicholls G. Prescribing for people in custody. Aust Prescr 2015;38:160-3. http://dx.doi.org/10.18773/ austprescr.2015.057 Stephen Hampton, Donna Blomgren, Jill Roberts, Tobias Mackinnon and Gary Nicholls, the authors of the article, comment:

We thank Dr Chaubey for his response. He has identified a number of challenges which make managing diabetes in the custodial environment more difficult when compared to the community. Systems vary between jurisdictions, facilities and patient security classifications, but the schedules mandated by the secure environment do not always coincide with the most appropriate testing and dosing times. Patients may not have access to glucometer testing without supervision by nurses. Meals can have high caloric loads and be given at unusual times. Also extra snacks can be 'purchased' by patients, which can be unhelpful for diabetic control. Specialist reviews may take some time to arrange through already burdened public systems and patients may be disinclined to travel to them.

Having said this, many of the people entering prisons have had little or no diabetic care or may not have known they are diabetic. Local chronic disease programs have been developed from national guidelines. Nursing care is available on a daily basis, and GPs and specialist nurses visit on a sessional basis. Finally, it should be said that staff and patients are very grateful for the support and advice from hospital specialist colleagues on the management of complex medical problems for people in custody.



# Bone mineral density: testing for osteoporosis

# SUMMARY

Primary osteoporosis is related to bone loss from ageing. Secondary osteoporosis results from specific conditions that may be reversible.

A thoracolumbar X-ray is useful in identifying vertebral fractures, and dual energy X-ray absorptiometry is the preferred method of calculating bone mineral density. The density of the total hip is the best predictor for a hip fracture, while the lumbar spine is the best site for monitoring the effect of treatment.

The T-score is a comparison of the patient's bone density with healthy, young individuals of the same sex. A negative T-score of -2.5 or less at the femoral neck defines osteoporosis.

The Z-score is a comparison with the bone density of people of the same age and sex as the patient. A negative Z-score of -2.5 or less should raise suspicion of a secondary cause of osteoporosis.

Clinical risk calculators can be used to predict the 10-year probability of a hip or major osteoporotic fracture. A probability of more than 5% for the hip or more than 20% for any fracture is abnormal and treatment may be warranted.

# Introduction

Osteoporosis is a common systemic skeletal disorder leading to decreased bone strength and increased susceptibility to osteofragility fracture. It is a significant health issue that affects up to one million Australians.<sup>1</sup>

Primary osteoporosis refers to bone loss that occurs due to the normal ageing process, while secondary osteoporosis results from specific clinical disorders that are potentially reversible. Correctly treating an underlying cause may ameliorate fracture risk and avoids unnecessary treatment with antiresorptive drugs.

The diagnosis of osteoporosis is based on the presence of a fracture after minimal trauma or by detecting low bone mineral density. There are different imaging modalities (Table) but dual energy X-ray absorptiometry is the preferred method.

Eligibility for treatment under the Pharmaceutical Benefits Scheme (PBS) requires confirmation of a minimal trauma fracture or low bone mineral density.

# Spinal radiography

Vertebral fractures are often missed and can be asymptomatic, or present with progressive kyphosis, loss of height, or chronic back pain. A vertebral fracture can be defined as a 20% or greater reduction in anterior height versus posterior vertebral body height (see Fig.). The presence of a vertebral fracture is highly predictive of a subsequent fracture, but if the fracture is asymptomatic the patient may be left untreated and at risk.

In a large Australian community-based study of women aged over 70 and not known to have osteoporosis, thoracolumbar X-ray detected at least one vertebral fracture in 24.7%. In the same cohort, dual energy X-ray absorptiometry found 21.8% had osteoporosis at the femoral neck or lumbar spine. However, only 7.3% had both osteoporosis on dual energy X-ray absorptiometry and a vertebral fracture on thoracolumbar X-ray.<sup>2</sup> Up to 50% of women with vertebral fractures have normal bone mineral density by dual energy X-ray absorptiometry, so potentially a third of women will not be diagnosed by this method.<sup>3</sup>

A thoracolumbar X-ray should therefore be performed in patients who have symptoms of a vertebral fracture, decreased bone mineral density on dual energy X-ray absorptiometry at the hip, or multiple clinical risk factors for osteoporosis. While spinal radiography is essential for diagnosing a vertebral fracture, it is important not to confuse the spinal deformity of an osteoporotic fracture from other causes including spondylosis.

Another method for detecting vertebral fractures is through vertebral fracture assessment using dual energy X-ray absorptiometry. Multiple studies have

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### Key words

bone densitometry, bone density, fracture of bone, osteoporosis

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Test	Radiation*	Sites	Advantages	Disadvantages	Clinical use
DXA	Minimal (4 microsievert)	Hip, spine, forearm	High precision, reproducible, correlates well with fracture risk	Affected by many artefacts, including previous fractures, spinal pathology, extrinsic artefacts, obesity	Hip bone mineral density best predictor for hip fracture. Lumbar spine bone mineral density best for monitoring treatment effect
QCT	High (200 microsievert at spine, 1200 microsievert at hip)	Hip, spine	Selective measurement of trabecular and cortical bone, true volumetric bone mineral density	Less reproducible, less standardisation, fewer analysis protocols	Sensitive for monitoring vertebral bone loss and treatment effect, especially in known spinal disease or artefacts
pQCT	Minimal (3–5 microsievert)	Distal bone (usually radius, tibia)	Compact and mobile machines	Small peripheral regions only, slow changes over time	Children
HR-pQCT	Minimal (5 microsievert)	Tibia, radius	Non-invasive measurement of microarchitecture, structure and mechanical strength	Small peripheral regions only, expensive machinery	Research tool for non-invasive determination of bone structure
QUS	None	Calcaneus, radius, tibia	Portable, no ionising radiation	Not standardised, operator dependent, poor reproducibility	May be able to predict fracture risk, but conflicting evidence for monitoring while on treatment
* Daily background radiation approximately 5 microsievert, standard chest X-ray 20–60 microsievert					

# Table Comparison of different technologies for measuring bone mineral density

DXA dual energy X-ray absorptiometry HR-pQCT high-resolution peripheral quantitative CT QCT quantitative CT QUS ultrasonography pQCT peripheral quantitative CT

# \_\_\_\_\_





shown moderately good concordance between absorptiometry and thoracolumbar X-ray in identifying vertebral fractures.<sup>4-6</sup> Limitations include adequate visualisation of the upper thoracic spine and potentially confounding spinal diseases.

# **Bone mineral density**

By current criteria, a bone mineral density at the femoral neck equal to or less than 2.5 standard deviations below the mean for a young person of the same sex is diagnostic of osteoporosis. This is reported as a T-score of -2.5 or less. Prescribing criteria for antiresorptive treatment are based predominantly on the T-score, so measuring bone mineral density is usually required before treatment.

A screening measurement is reimbursed by Medicare for patients over 70 years old, in the absence of a minimal trauma fracture or secondary cause of osteoporosis. For patients who have sustained a minimal trauma fracture, measuring bone mineral density is not required for the diagnosis of osteoporosis or to fulfil some PBS prescribing criteria for osteoporosis. However, a baseline measurement is useful before starting treatment.

The Z-score is the number of standard deviations away from the mean bone mineral density of a person of the same age and sex. A Z-score below -2.5 should raise suspicion of a secondary cause of osteoporosis.

# Dual energy X-ray absorptiometry

The most commonly used technique for measuring bone mineral density is dual energy X-ray absorptiometry. This harnesses the high sensitivity of calcium in absorbing X-rays to measure the relative amounts of bone and other soft tissue, in order to calculate bone mineral content and hence density (Table). Absolute measurements from different machines differ significantly so standardised reference ranges should be used. Serial measurements should be performed on the same machine to identify true changes in the patient's bone mineral density.

Dual energy X-ray absorptiometry is versatile and can be used to measure bone mineral density at various body sites. Of the four potential sites at the hip (total hip, femoral neck, trochanteric region and Ward's triangle), the density of the total hip is recommended due to its high precision, reproducibility and correlation with fracture risk.<sup>7</sup> Measurements at the lumbar spine are also highly reproducible, but can be heavily influenced by artefacts. The forearm may be used when the hip or spine cannot be measured or interpreted, but there can be a significant difference in bone mineral density between the dominant and non-dominant arm.8 Current evidence shows that bone mineral density at the hip is the most reliable for predicting hip fracture risk, and spinal bone mineral density should be used for monitoring treatment.9

Technical factors can affect measurements made by dual energy X-ray absorptiometry. Commonly there are false elevations due to vertebral disease, such as osteoarthritic spondylosis, osteophytes, scoliosis or vertebral fracture. or extrinsic artefacts from calcifications and surgical metalwork. Obesity may alter the calculated bone mineral density. Osteomalacia may lead to underestimates due to decreased bone mineralisation. Acquisition errors in patient positioning and other physical artefacts can usually be overcome by trained staff, guality control and regular services of the machines. Correct positioning is critical for accurate measurements and should be confirmed by the clinician. For optimal hip measurements, the femur should be internally rotated so that the lesser trochanter is not seen. Spine images should be centred, straight and not rotated.

# Computed tomography

Quantitative CT generates a reconstructed threedimensional image and calculates bone density when calibrated to a reference object of known density. It measures true volumetric bone mineral density and is not limited by the patient's size or vertebral deformities.<sup>10</sup> Results can occasionally be spuriously low in a patient with normal T-scores on dual energy X-ray absorptiometry. It is suspected this is due to increased marrow fat with advancing age which affects the assessment of bone density when measured by CT. Quantitative CT may also be used to assess a patient who is suspected of having a falsely elevated bone mineral density on dual energy X-ray absorptiometry due to osteoarthritis. Limitations of CT include higher doses of radiation, less reproducibility and fewer standardised reference ranges and analysis protocols.

Peripheral quantitative CT requires machines specifically designed for distal bone sites (usually radius or tibia). Its use is mostly limited to children. High-resolution CT has spatial resolution that allows imaging of individual trabeculae. This is a non-invasive method of viewing three-dimensional microarchitecture and trabecular and cortical structure. Radiation is minimal, scan time is relatively short (approximately three minutes) and scan precision is acceptable, making this an attractive method for determining bone structure, although it is currently limited to research centres.

# Ultrasound

Ultrasonography calculates bone stiffness as a surrogate for bone density and is most commonly used on the calcaneus.<sup>11</sup> Clinical studies suggest that ultrasonography can predict hip fractures<sup>12</sup> and vertebral fractures<sup>13</sup> in a similar way to bone mineral density. Benefits include no ionising radiation, and portability of the machine. Its limitations include significant manufacturer and operator differences. Ultrasound is not currently recommended for screening for osteoporosis.

# **Risk factors**

Apart from low bone mineral density, a number of clinical risk factors for fractures have been identified and should be used together with the bone mineral density to calculate an individual's fracture risk (Box 1).<sup>14,15</sup> Peak bone mass is achieved by age 30. Bone loss occurs steadily from the age of about 40 (0.3–0.5% per year), with accelerated loss in the perimenopausal period (4–6% per year) before slowing again after the age of 70 (1–2% per year).<sup>16</sup> Age is therefore the strongest predictor for fracture risk.

# Box 1 Clinical risk factors for fracture 14,15

# High fracture risk:

Age >70 years

Low body weight or significant weight loss

Physical inactivity (including secondary to chronic illness or spinal cord injury) Drugs: corticosteroids ( $\geq$ 5 mg prednisolone daily or equivalent for  $\geq$ 3 months), anticonvulsants, thiazolidinediones, selective serotonin reuptake inhibitors, thyroxine, aromatase inhibitors, chemotherapy

Current smoking

Alcohol (≥2 standard drinks/day) History of fragility fracture Parental history of hip fracture Low sunlight exposure

# DIAGNOSTIC TESTS

SELF-TEST

True or false?

chest X-ray.

2. Up to 50% of

QUESTIONS

1. The radiation dose

absorptiometry is

from dual energy X-ray

approximately double

the dose of a standard

women with vertebral fractures have normal

bone mineral density

when measured by

Answers on page 66

dual energy X-ray absorptiometry.

### Bone mineral density: testing for osteoporosis

# Assessing fracture risk

Although bone mineral density provides an estimation of osteoporosis, it is insufficient for predicting an individual's fracture risk. Clinical risk models, such as the FRAX tool<sup>17</sup> and the Garvan fracture risk calculator<sup>18</sup> use bone mineral density and clinical factors to predict an individual's absolute fracture risk. The patient's risk of falls is also essential in risk stratification.

FRAX\* has been the most extensively used tool worldwide and calculates the 10-year risk for a hip or major osteoporotic fracture (hip, clinical spine, humerus or wrist). By combining clinical risk factors with bone mineral density and age, the sensitivity of fracture prediction improves without reducing specificity. A 10-year probability of a hip fracture more than 5%, or of a major osteoporotic fracture more than 20%, is significant and antiresorptive treatment should be considered (see case study in Box 2). The main limitation of FRAX is the dichotomised risk factors (presence or absence of a parameter) rather than quantifying each risk factor. For example, two previous fractures increase the risk much more than a single previous fracture, and increased total consumption (duration and dose) of glucocorticoids, tobacco and alcohol are associated with greater fracture risk. A further limitation is that the algorithm only uses the T-score measured by femoral neck dual energy X-ray absorptiometry. The applicability of FRAX to patients

\* www.shef.ac.uk/FRAX/tool.aspx?country=31

with discordant T-scores at other sites or the use of different technologies has yet to be determined.

The Garvan fracture risk calculator can be used with or without a measurement of bone mineral density. It quantifies the number of fractures and takes into account the patient's history of falls. The calculator gives both a 5-year and 10-year risk for a hip or any fracture and is useful when a measurement of bone mineral density cannot be performed or interpreted. Its main limitation is the absence of other clinical risk factors in the risk calculation.

# Conclusion

Osteoporosis is a common disorder that affects many Australians. Preventing fractures is crucial to reducing the associated morbidity and healthcare costs.

Diagnosing osteoporosis requires a careful search for fragility fractures and measuring bone mineral density. Thoracolumbar X-ray may reveal an asymptomatic vertebral fracture, which significantly increases the individual's risk for a further fracture. Dual energy X-ray absorptiometry is the preferred method of measuring bone mineral density as it has excellent precision, minimal radiation and is useful in predicting a fracture and for monitoring treatment. Combining the bone mineral density with clinical risk factors in risk calculators can quantify a patient's fracture risk and can guide specific treatment.

Conflict of interest: none declared

# Box 2 Case study: calculating fracture probability <sup>17</sup>

A 72-year-old female with no personal or family history of a fracture and no other high-risk features and a femoral neck bone mineral density T-score of -2.7, has a 9.3% probability of any osteoporotic fracture and 4.2% probability of a hip fracture in 10 years (see A). If the same patient had previously sustained a fracture, her probabilities would increase to 14% and 6.2% (see B), placing her at high risk of hip fracture and therefore treatment would be warranted.

### A. FRAX-calculated 10-year probability of a fracture



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# B. FRAX-calculated 10-year probability of a fracture for the same patient with the additional risk factor of a previous fracture



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# **Treating osteoporosis**

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### Key words

bisphosphonates, bone resorption inhibitor, calcium, vitamin D

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# SUMMARY

Osteoporotic fractures are common resulting in increased morbidity and mortality. Exercise can help prevent osteoporosis. It can also benefit patients with osteoporosis, but the exercises must be tailored to the patient.

Most Australians should be able to obtain adequate calcium in their diet and vitamin D from the sun. Supplements may be needed in some patients and they are recommended for use with other drugs for osteoporosis.

Bisphosphonates, and in some patients denosumab, are first-line drugs for osteoporosis. Raloxifene and strontium ranelate can be considered in patients who cannot take bisphosphonates or denosumab. Teriparatide is reserved for patients with severe osteoporosis and the use of strontium ranelate is declining because of cardiovascular safety concerns.

# Introduction

Osteoporosis is a common systemic skeletal condition among older people. Currently, 2.2 million Australians have osteoporosis and, for those aged 50 and over, up to one in four men and two in five women will experience a minimal trauma fracture.<sup>1</sup> Retrospective data show that fewer than 20% of these patients are investigated or treated for osteoporosis. Fractures cause significant pain, disability, reduced quality of life and even premature death.<sup>2</sup> In economic terms, the cost of osteoporosis to the Australian community is projected to be \$33.6 billion in the decade 2012–22.<sup>3</sup> There is some international evidence that early detection and treatment of osteoporosis in both men and women is cost-effective.<sup>4-6</sup>

# **Exercise**

Exercise can delay the onset of osteoporosis. There is strong evidence that 'impact exercises' in children such as hopping, skipping and jumping can lead to higher peak bone mass in adulthood.<sup>7,8</sup> Impact exercises are also beneficial for middle-aged and older adults for increasing or preventing age-related bone loss. Although the gains in bone mass are promising, there is insufficient evidence to suggest exercise might reduce fractures.

The frequency and severity of falls may be reduced by exercises that maintain muscle strength, muscle mass, flexibility, mobility, balance and ease of movement. For people with established osteoporosis, any exercise that promotes these characteristics is recommended. The Box lists exercises according to their 'osteogenic' profile and more detailed information is available at www.osteoporosis.org.au/exercise. Specifically, weight-bearing aerobic exercises and progressive resistance training improve bone mineral density.<sup>7-11</sup>

Any recommendation for exercise must be tailored to the individual. For example, in patients who have already sustained osteoporotic fractures, moderateto high-impact activities may be unsuitable. Patients

### Box The impact of exercises on bone health

Highly osteogenic Basketball, netball Impact aerobics Dancing, gymnastics Tennis Skipping with a rope

Moderately osteogenic Running, jogging Brisk walking, hill walking Resistance training Stair climbing Low osteogenic Leisure walking Lawn bowls Yoga, pilates, tai chi Non-osteogenic\* Swimming Cycling

(Adapted from Osteoporosis Australia with permission)

\* Although non-weight bearing exercises such as swimming and cycling do not increase bone density, they should not be discouraged, as they probably contribute to the overall maintenance of muscular and cardiovascular health.

with asymptomatic vertebral fractures can be at risk of further vertebral fractures and exercises involving forward flexion of the spine should be avoided. However these patients could benefit from postural strengthening exercises.

# Calcium

Adequate body calcium is crucial to prevent bone loss and fracture. The recommended dietary intake of calcium is between 1000 and 1300 mg per day, depending on age and sex. It is recommended that people get this through their diet by selecting foods that are naturally high in calcium, and including foods that have had calcium added. A dietary calcium calculator is available on the International Osteoporosis Foundation website.\*

Most Australians do not reach the recommended dietary intake so daily supplements of 500–600 mg of calcium are sometimes needed. This is because calcium supplementation, especially when combined with vitamin D, can reduce the rate of bone loss and fracture in people who are deficient in dietary calcium such as the frail elderly. Calcium supplementation in these people is also thought to optimise the effectiveness of osteoporosis treatments including bisphosphonates, strontium ranelate, denosumab, teriparatide and selective oestrogen receptor modulator therapy.

The controversy regarding the safety of calcium supplements has not yet been resolved. There is some concern regarding a possible increase in the rate of myocardial infarction,<sup>12-14</sup> however this has not been confirmed by other research.<sup>15,16</sup> A large European study appeared to show increased rates of myocardial infarction in people taking calcium supplements, but not in people who achieved their calcium intake through diet alone.<sup>17</sup> Taken as currently recommended, combined calcium and vitamin D supplements seem safe and effective for most people who require them. The risk of heart attack and stroke will be the subject of ongoing research.

# Vitamin D

Small amounts of vitamin D are found in some foods, but most adults are unlikely to get more than 5–10% of their requirement from food. Australians receive most of their vitamin D from direct sunlight. To maintain adequate vitamin D, those with fair skin need only expose the arms for 6–7 minutes mid-morning or mid-afternoon outdoors on most days during the Australian summer. Up to 30 minutes exposure will be required in winter. Advice regarding time of day and duration of exposure varies with latitude. A randomised trial of sunlight exposure in residential

\* www.iofbonehealth.org/calcium-calculator

aged-care facilities in Sydney found that compliance with the duration and amount of sunlight exposure required to reach optimal vitamin D concentrations was low.<sup>18</sup> Darker skinned people require 3–6 times longer exposure. Window glass, full-coverage clothing and sunscreen inhibit transmission of ultraviolet B and thus synthesis of vitamin D in the skin. Synthesis of vitamin D in the skin also becomes less efficient in older people.

If indicated, vitamin D is best measured at the end of winter or in early spring, when serum 25-hydroxyvitamin D is lowest. Optimal mineral metabolism, bone density and muscle function are achieved when serum 25-hydroxyvitamin D is greater than 50 nmol/L. If testing is carried out at the end of summer, the concentration should be 10–20 nmol/L higher.

Evidence suggests that 31% of Australians are vitamin D deficient.<sup>19</sup> In older people, deficiency is associated with loss of lower extremity muscle mass, strength and impaired balance. Rates of deficiency are higher in southern Australia compared to northern Australia, and in the winter months, 50% of all Australian women are vitamin D deficient.<sup>19</sup> Improving vitamin D status reduces the risk of falls and fractures in older people,<sup>20,21</sup> particularly when combined with adequate calcium.<sup>22</sup>

# Prevention of vitamin D deficiency

To prevent vitamin D deficiency in people who receive less than optimal sun exposure, supplementation is recommended:

- at least 600 IU per day for people under 70
- at least 800 IU per day for people over 70
- 1000–2000 IU per day may be required for sun avoiders or those at high risk of deficiency.

Higher doses are needed if there is vitamin D deficiency (Table 1). For all individuals taking a vitamin D supplement, a daily intake of 1000–1300 mg calcium, ideally dietary calcium, should be encouraged.

Vitamin D status should be re-assessed 3–5 months after commencing supplements as the full increase in serum 25-hydroxyvitamin D may not be seen until this time. Although there is no definitive evidence, it

# Table 1 Treatment of vitamin D deficiency

Vitamin D status	25-hydroxyvitamin D (end of winter)	Recommended vitamin D supplementation
Mild deficiency	30-49 nmol/L	1000-2000 IU per day
Moderate deficiency	12.5-29 nmol/L	3000-5000 IU per day (for 6-12 weeks)
Severe deficiency	<12.5 nmol/L	followed by maintenance dose of 1000–2000 IU per day

### **Treating osteoporosis**

is recommended that calcium and vitamin D status be checked annually in patients undergoing treatment for osteoporosis.

There are very few adverse effects related to vitamin D supplementation. When combined with calcium, there is a small risk of hypercalcaemia, which may lead to hypercalciuria and nephrolithiasis.

# **Drugs for osteoporosis**

When considering, and before starting, therapies ensure that all patients have adequate vitamin D and calcium concentrations and that any secondary causes for osteoporosis have been managed. The Figure provides an algorithm for the management of established osteoporosis.

# Fig. Osteoporosis drug treatment algorithm



PBS Pharmaceutical Benefits Scheme (authority prescriptions)

eGFR estimated glomerular filtration rate

Bone mineral density testing by dual energy X-ray absorptiometry is recommended every 2-3 years to help monitor adherence and response to therapy.<sup>23</sup> More frequent testing every 12 months may be needed if there is a significant change in therapy or the patient's health, or the use of drugs which decrease bone density, for example corticosteroids.23 The frequency of bone density testing has come under question. Given that changes to bone density generally occur slowly and allowing for measurement error of the testing, there is little evidence to support annual testing unless there have been major changes in treatment or health status. Some would argue that, once a diagnosis has been made and treatment started, no further testing is necessary given the weak concordance between fracture risk reduction and bone density changes, together with the lack of clear evidence that monitoring improves compliance.<sup>24</sup> However, most specialists still monitor bone mineral density to gauge adherence and response to treatment after two years and then again at five years to aid decisions about treatment duration.

Table 2 shows the number of patients that must be treated for 36 months in order to prevent one fracture.<sup>25-28</sup>

# Oral bisphosphonates

Bisphosphonates block osteoclast activation and thus slow bone resorption. They slow bone loss, improve bone mineral density and reduce fracture rates. Most bisphosphonates have similar degrees of efficacy, whether they are used intravenously or orally. Headto-head evidence for oral bisphosphonates is lacking. Oral drugs alendronate and risedronate are the preferred first choice due to their low cost and ease of use with once-weekly dosing. There are other oral bisphosphonates, however they are uncommonly used in the treatment of osteoporosis.

The use of oral bisphosphonates is limited by their adverse effects in renal impairment and they are absolutely contraindicated if the estimated glomerular filtration rate (eGFR) is below 35 mL/minute/1.73 m<sup>2</sup>. They also have significant upper gastrointestinal adverse effects. Dysphagia, achalasia, or an inability to remain upright for 30 minutes after tablet ingestion, are absolute contraindications.

# Intravenous bisphosphonates

Intravenous bisphosphonates can overcome the gastrointestinal limitations, however this therapy has other potential adverse effects, notably the risk of flulike reactions with intravenous infusions of zoledronic acid. Other symptoms such as joint and muscle pains can be prolonged. Patients with renal impairment can be at greater risk of these reactions, and in such cases the infusion rate could be reduced. Intravenous bisphosphonates are not recommended when the eGFR is below 35 mL/minute/1.73 m<sup>2</sup>. Zoledronic acid has not been tested to any great extent in people with eGFR below 30 mL/minute/1.73 m<sup>2</sup>. It may be directly nephrotoxic or may worsen already low bone turnover, however these issues do not appear to be of concern when using the osteoporosis regimen of 5 mg annually. Some clinical experience with zoledronic acid was reported in a cohort with eGFR in the 20-30 mL/minute/1.73 m<sup>2</sup> range without untoward

Drug	Vertebral fractures (NNT)	Hip fractures (NNT)	Patient population studied (to determine NNT)
Oral bisphosphonates <sup>25</sup>	15-20	91	Bone mineral density (T-score –2.0 to –4.0) Low-trauma fracture
Intravenous bisphosphonates <sup>25</sup>	14	91	Bone mineral density (T-score –2.0 to –4.0) Low-trauma fracture
Raloxifene <sup>26</sup>	29	n/a	Low bone mineral density (T-score less than –2.5) Low-trauma fracture
Denosumab <sup>27</sup>	21	200	Bone mineral density only (T-score -2.5 to -4.0)
Teriparatide <sup>28</sup>	11	n/a	Low bone mineral density (mean T-score –2.6) Low-trauma fracture

# Table 2Efficacy of antiresorptive drugs

NNT number needed to treat for three years to prevent fracture (all estimates based on drug effect compared to placebo)

### **Treating osteoporosis**

effects although reduced dosing was recommended. As zoledronic acid is renally cleared it has generally been recommended to use a reduced dose or a slower infusion rate in older patients with reduced renal function but no sound evidence exists for this.<sup>29</sup> A different class of drug that is not affected by renal function, such as denosumab, should be considered. There may also be a slight risk of atrial fibrillation with intravenous zoledronate.

The recommended duration of therapy with oral bisphosphonates is five years and perhaps less (3 years) for intravenous bisphosphonates.<sup>30-35</sup> Safety data are robust for up to five years of treatment, but extending treatment beyond this has questionable benefit and possible harm. Harms such as osteonecrosis of the jaws and atypical femoral fractures occur very infrequently but are more likely with longer periods of antiresorptive treatment. Osteonecrosis of the jaws is more likely to be seen in patients with cancer receiving frequent doses of bisphosphonates, but other risk factors include dental extractions, dental implants, poorly fitting dentures, and pre-existing dental disease, glucocorticoid use and smoking (see Dental note in this issue).

More research is required to determine optimum duration of bisphosphonate therapy. Each patient should be reviewed after five years and a decision regarding ongoing treatment based on their individual needs and fracture risk profile. If they remain at high risk, most specialists would continue treatment. Treatment may be safely extended or alternative treatments used if:

- the femoral neck T-score\*\* is less than -2.5 without prevalent vertebral fractures
- the femoral neck T-score is less than -2.0 with prevalent vertebral fractures
- there has been a recent fracture.

# Denosumab

Denosumab is a monoclonal antibody that reversibly inhibits bone resorption by reducing osteoclast formation and differentiation while increasing osteoclast apoptosis. It increases bone mineral density at the lumbar spine and hip, and reduces vertebral, non-vertebral and hip fractures. In contrast to bisphosphonates, denosumab can be used in chronic kidney disease, however these patients are particularly at risk of hypocalcaemia so baseline assessment of calcium and vitamin D status should be undertaken before starting therapy. Denosumab's effect will wear off as it does not accumulate. It is therefore given regularly as a six-monthly subcutaneous injection.

# Raloxifene

Raloxifene is a selective oestrogen receptor modulator that reduces postmenopausal bone loss. It reduces the risk of vertebral fractures, but it does not reduce non-vertebral fractures. Raloxifene is an alternative to bisphosphonates or denosumab (if they cannot be tolerated) for women with postmenopausal osteoporosis and is most appropriate for treating younger postmenopausal women with spinal osteoporosis. It increases the incidence of hot flushes, which can be a significant problem in young postmenopausal women. Raloxifene reduces the risk of breast cancer, so it can be considered in women with a high risk of breast cancer. It is, however, known to increase the risk of deep venous thrombosis and other evidence suggests a slightly increased mortality after stroke.

# Strontium

Strontium ranelate reduces bone resorption but its mechanism of action is unknown. A 2008 Cochrane systematic review<sup>36</sup> of three randomised controlled trials reported a 37% reduction in vertebral fractures and a 14% reduction in non-vertebral fractures over three years when strontium was used for established osteoporosis. However, monitoring of bone mineral density while on therapy is difficult to interpret. Up to 50% of any increase in spinal bone mineral density is due to the atomic weight of strontium and the distribution across the skeleton can be highly variable.

Recent data have raised significant safety concerns, particularly the risk of myocardial infarction. This has curtailed the use of strontium with contraindications in patients with a history of ischaemic heart disease, venous thromboembolism, peripheral vascular or cerebrovascular disease. Strontium use is declining in Australia, but it remains an option for people unable to tolerate other drugs and who have a low cardiovascular risk.<sup>37</sup>

# Teriparatide

Teriparatide is a synthetic form of parathyroid hormone and is the only currently available drug that increases bone formation. As a last line of therapy, teriparatide is used to treat severe osteoporosis and is subsidised in Australia when people continue to fracture despite receiving at least 12 months treatment with first-line therapies.

The rate of vertebral fractures may be reduced by up to 65%. There is an overall reduction in nonvertebral fractures, but the rate of hip fractures is not reduced.

<sup>\*\*</sup> T-score: the number of standard deviations that bone mineral density differs from that of a young adult of the same sex

Contraindications include patients younger than 25 years, known or suspected Paget's disease or previous radiotherapy to bone. Additional contraindications include pre-existing hypercalcaemia, malignancy, kidney disease and primary hyperparathyroidism. Rat studies have shown a risk of bone sarcomas and this is the only basis for the recommended lifetime exposure to teriparatide being limited to 18 months. Following a course of teriparatide, patients should receive antiresorptive therapy (e.g. raloxifene, a bisphosphonate, denosumab, strontium ranelate) to further increase bone mineral density and maintain the anti-fracture effect.

# New drugs

There are some drugs in development, but their role is currently uncertain. Cathepsin K is elevated in women with postmenopausal osteoporosis. It is a cysteine protease that cleaves collagen 1, the major collagen type in bone. Bone mass can therefore be preserved by inhibiting cathepsin. Clinical trials with cathepsin K inhibitors, such as odanacatib, have shown improvements in bone mineral density at the spine and hip. These trials have also found a reduction in bone resorption markers with minimal effect on bone formation.

Another target for therapy is sclerostin. It is produced by osteocytes as a glycoprotein inhibitor of osteoblast signalling. Romosozumab is an anti-sclerostin monoclonal antibody that increased bone formation and bone mineral density in phase I and phase II trials. Further evaluation of the efficacy and safety of this drug in a large phase III controlled study is awaited. These interventions appear to be promising drugs for the treatment of osteoporosis.<sup>38,39</sup>

# Conclusion

As our population ages, osteoporotic fractures are likely to occur more frequently. While preventive measures in the form of exercise are ideal and lifestyle measures play their role, they have limited efficacy in established osteoporosis. There are readily available screening tests along with effective treatments to prevent fractures. All men and women over the age of 50 who sustain a fracture should be assessed for antiresorptive therapy.

Therapy can and should be tailored to the individual. Bisphosphonates are by far the preferred treatment from a cost-effectiveness perspective. Newer treatments are available for patients who cannot use bisphosphonates.

Surveillance for the potential adverse effects of therapy and the need for the continuation of therapy is essential.

*Conflict of interest: Lyn March received consultancy fees from Servier.* 

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# SELF-TEST QUESTIONS

True or false?

3. Intravenousbisphosphonates havegreater efficacy thanoral bisphosphonates.4. Vitamin Dconcentrations are best

measured at the end of summer.

Answers on page 66

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# **Dental note**

# Osteoporosis treatment and medication-related osteonecrosis of the jaws

Antiresorptive drugs are used widely for the prevention and management of primary and secondary osteoporosis. The bisphosphonates<sup>1</sup> and newer drugs such as denosumab<sup>2</sup> have been associated with osteonecrosis of the jaws. This condition is characterised by the presence of exposed, non-healing bone for more than eight weeks in the absence of radiotherapy or other pathology in the jaws. Extraction of teeth has been identified as the trigger factor in 60–87% of cases.<sup>1,3-5</sup> Dentoalveolar surgery has also been identified as a trigger<sup>1</sup> and is considered a major risk factor for osteonecrosis.<sup>6</sup>

When osteonecrosis occurs with antiresorptive therapy, it is termed medication-related osteonecrosis of the jaws (MRONJ).<sup>6</sup> There has been much debate over the incidence of MRONJ associated with bisphosphonate use. A widely quoted paper by the American Society for Bone and Mineral Research said it was rare, at between 1 in 10 000 and less than 1 in 100 000 patient-treatment years.<sup>7</sup> Detailed independent studies that take into account dental extractions have reported a much higher incidence at around 1 in 1000 patients.<sup>3,8</sup> When the duration of oral bisphosphonate therapy is taken into account, the incidence has been found to double to 2.1 in 1000 patients for those with four or more years of drug exposure.<sup>8</sup> A recent UK national survey<sup>4</sup> over a two-year period estimated that the incidence in a population of postmenopausal women with osteoporosis was between 1 in 1262 and 1 in 4419.

The incidence is much higher in cancer patients on antiresorptive drugs, with the risk being 1 in 15 for extractions in patients on intravenous bisphosphonates.<sup>3</sup> Compared to patients receiving monthly intravenous antiresorptive therapy for metastatic bone disease, multiple myeloma or giant cell tumours of bone, the 6-monthly or 12-monthly intravenous regimens used for patients with osteoporosis have a lower incidence of MRONJ.<sup>6</sup>

An Australian case-control study<sup>9</sup> investigated 950 consecutive patients taking oral bisphosphonates for osteoporosis who underwent dental extractions. There were four cases of MRONJ versus none in a control group of patients not taking bisphosphonates. All four cases had a low bone turnover as assessed by a fasted C-terminal crosslinking telopeptide (CTX) concentration of less than 150 pg/mL immediately before dental extraction. The incidence in patients with a CTX value less than 150 pg/mL was 1 in 45. All the affected patients were aged 70 or above and had chronic health problems requiring medication but which did not affect bone healing. No patients were immunocompromised, taking corticosteroids or undergoing cancer chemotherapy.

The exact pathogenesis by which antiresorptive therapy may result in MRONJ is unclear. Several mechanisms have been proposed<sup>6,10</sup> including anti-osteoclast activity, inhibition of angiogenesis, uncoupling of osteoblast-osteoclast activity in jaw bones, and soft tissue toxicity. Reduction of bone cellularity and vascularity may not support hard or soft tissue healing following dental extraction. This can lead to exposure of avascular bone which is readily colonised by oral bacteria. These mechanisms may also explain why MRONJ can occur spontaneously when normal function (eating or toothbrushing) traumatises the thin mucosa overlying jawbone exostoses or the mylohyoid ridge of the mandible, or when dentures are ill-fitting and traumatise the oral mucosa. Local factors such as periodontal disease or periapical pathology, and systemic factors such as corticosteroid use may contribute to the risk of MRONJ.6

The management of MRONJ is problematic and patients do not respond well to established protocols used for the treatment of osteomyelitis or osteoradionecrosis.<sup>10</sup> Patients may benefit from drug withdrawal until the area of osteonecrosis heals.<sup>1</sup> For patients with exposed or necrotic bone who are asymptomatic and have no evidence of infection, antibacterial mouth rinses are indicated. Patients with soft tissue infection require treatment with broadspectrum antibiotics such as penicillin, cephalexin or clindamycin.<sup>10</sup> With time, the dead bone will sequestrate and should be removed without exposing uninvolved bone.<sup>6</sup> Treatment is dictated by the clinical stages of MRONJ and should be provided by an oral and maxillofacial surgeon. The MRONJ staging system developed by the American Association of Oral and Maxillofacial Surgeons<sup>6</sup> is the one used most commonly to guide treatment strategies and is available online.

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# DENTAL NOTE

### Osteonecrosis of the jaws

Patients with osteoporosis who are to begin antiresorptive drug therapy by either the oral or intravenous route should be informed by their medical practitioner of the potential risks of MRONJ. They should also be informed of the need to ensure optimal oral health so as to prevent dental and periodontal disease which might require extraction of teeth in the future. Before starting treatment, the patient should therefore be seen by a dentist for a comprehensive oral examination.

Australian<sup>11</sup> and American<sup>6</sup> guidelines recommend that any teeth requiring extraction should be removed and dental caries and periodontal disease treated to ensure optimal oral health, and that the patient is dentally fit, before beginning antiresorptive therapy. During therapy, it is important that the patient's oral health is monitored regularly by their dentist. The less invasive treatments such as restorative dentistry, endodontics and non-surgical periodontal therapy are not risk factors for MRONJ and may also be used as safe alternatives to extractions if clinically feasible.

For patients on oral bisphosphonates who are to undergo dental extractions or other dentoalveolar surgery, a low bone turnover as shown by CTX testing may be used as a trigger to cease drug therapy until the fasted CTX exceeds 150 pg/mL.<sup>11</sup> Such cessation of therapy is termed a 'drug holiday'. In contrast with this approach, American guidelines<sup>6</sup> recommend a blanket two-month drug holiday before invasive dental procedures for patients with more than four years exposure to oral bisphosphonates. Drug holidays for osteoporotic patients should only be instituted following discussion with the patient's treating physician. The risk of MRONJ should be weighed against the risk of fracture on a case-bycase basis.

Conflict of interest: none declared

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# SUMMARY

Accurate diagnosis is fundamental to effective management of borderline personality disorder, but many patients remain undetected.

The first-line management for borderline personality disorder is psychosocial treatment, not drugs. There are major prescribing hazards including polypharmacy, overdose and misuse.

Drug treatment might be warranted for patients who have a co-occurring mental disorder such as major depression.

If a drug is prescribed for borderline personality disorder, it should only be as an adjunct to psychosocial treatment. There should be clear and collaborative goals that are regularly reviewed with the patient.

Use single drugs prescribed in limited quantities for a limited time. Stop drugs that are ineffective.

# Introduction

Borderline personality disorder is a severe mental disorder that has its onset during adolescence and emerging adulthood.<sup>1</sup> It affects up to 3% of the population<sup>2.3</sup> and occurs almost equally among males and females.<sup>4</sup>

The disorder has a fourfold higher prevalence among primary care patients than among the general population.<sup>5</sup> It affects around one-quarter of primary care patients with depression<sup>6</sup> and one in five psychiatric outpatients.<sup>7.8</sup> In these settings females outnumber males by a ratio of up to 4:1.

Borderline personality disorder is a leading contributor to the burden of disease in our community. It is associated with adverse longterm outcomes that include severe and persistent functional disability,<sup>9</sup> high family and carer burden,<sup>10</sup> physical ill health,<sup>11</sup> and premature mortality,<sup>12</sup> including a suicide rate of 8%.<sup>13</sup> People with the disorder use mental health services continuously for long periods of time.<sup>14</sup> After schizophrenia, borderline personality disorder is the most costly psychiatric disorder to treat in Australia on a per case basis.<sup>15</sup>

Psychosocial treatment is the primary therapy but access to this is poor. Despite the effectiveness of treatment, persisting psychopathology (e.g. borderline personality disorder features, depressive and anxiety symptoms) and functional impairment remain clinically problematic. While it is easier to provide prescriptions than psychosocial treatments, evidence does not support the use of drugs as first-line or sole treatment.<sup>16</sup> Nevertheless, psychotropic drug use is common and needs careful management and review.

# **Clinical presentation**

Borderline personality disorder is characterised by a pervasive pattern of instability in emotional regulation, interpersonal relationships and self-image, along with marked impulsivity.<sup>17</sup> Clinically, this often manifests as recurrent self-harm and suicide attempts. The person frequently describes a chaotic lifestyle and relationships, reckless behaviours likely to harm the individual (e.g. impulsive substance use, unsafe sex), chronic dysphoria and anxiety, severe mood instability and reactive aggression.

People with borderline personality disorder typically present to health services during times of crisis, following self-harm, because of the consequences of impulsive and self-damaging behaviour, or because of poor physical, sexual and reproductive health. Interpersonal problems are at the very heart of borderline personality disorder and these are usually magnified during crises. For example an individual might have unrealistically high expectations or demands of care from health practitioners and when these are not met, he or she might respond aggressively. It is important to remember that clinicians are likely to see patients at their lowest ebb, but this is when they are in greatest need of timely and coherent assistance.

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# Key words

antidepressant, antipsychotic agent, borderline personality disorder, polypharmacy, psychosocial intervention strategy

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### Prescribing and borderline personality disorder

# Assessment

The DSM-5 criteria for borderline personality disorder are listed in Box 1.<sup>18</sup> Although the DSM-5 requires any five of these nine criteria in order to make a diagnosis, even low levels of borderline pathology (e.g. one criterion) are associated with substantial increases in psychosocial impairment.<sup>19</sup>

Despite the evidence of the reliability and validity of the diagnosis, and the treatability of the condition,<sup>20</sup> many people with borderline personality disorder remain undiagnosed in clinical practice. This places them at risk of being given treatments that are ineffective or even harmful.<sup>21</sup> The central task for diagnosing personality disorder is to separate 'state' (transient aberrations in mental state) from 'trait' (long-standing patterns of thinking, feeling, behaving, perceiving and relating). Many mental state disorders can present with features that are similar to borderline personality disorder. For example, affective dysregulation is characteristic of both bipolar disorder and borderline personality disorder. Also, the current definition of depression incorporates non-specific forms of dysphoria that overlap with borderline personality disorder. What distinguishes borderline personality from these other disorders is that the features are present most of the time and comprise part of the patient's 'usual self'. These patients will tell you that this is how they 'usually are'. Although various tools are available to aid the diagnosis of borderline personality disorder, clinical application of the DSM-5 criteria is sufficient in a busy clinical practice. Each of the nine criteria should be enquired about and considered in turn.

# Box 1 Diagnostic criteria for borderline personality disorder <sup>18</sup>

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

- 1. Frantic efforts to avoid real or imagined abandonment (do not include suicidal or selfmutilating behaviour covered in criterion 5)
- 2. A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation
- 3. Identity disturbance: markedly and persistently unstable self-image or sense of self
- 4. Impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating do not include suicidal or self-mutilating behaviour covered in criterion 5)
- 5. Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour
- 6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
- 7. Chronic feelings of emptiness
- 8. Inappropriate, intense anger or difficulty controlling anger (e.g. frequent displays of temper, constant anger, recurrent physical fights)
- 9. Transient, stress-related paranoid ideation or severe dissociative symptoms

A common cause of misdiagnosis of borderline personality disorder is to rely on 'gut feeling' when a patient presents as interpersonally abrasive, sullen or hostile, particularly if the individual also engages in self-harm. Such diagnoses are often unreliable because they do not assess each of the DSM-5 borderline personality disorder criteria and do not take into account other reasons for such presentations, such as temporary aberrations in mental state, depression or other disorders.

Another cause of diagnostic confusion is the high rate of comorbid conditions. Comorbidity with other personality disorders and with mental state disorders is the norm. At times, these other disorders (e.g. mood, anxiety, eating and substance use disorders) can overwhelm the clinical picture, but this does not indicate that the underlying personality pathology is unimportant or should be a secondary concern.<sup>21</sup> Rather, there is evidence to suggest that personality disorder might be a key vulnerability factor for recurrent mental state disorders.<sup>22,23</sup> Patients with borderline personality disorder who have these co-occurring conditions should be treated for these conditions in accordance with best practice. However, there should not be a disproportionate emphasis given to the immediate relief of mental state pathology at the expense of managing the borderline personality disorder.

# Treatment

Since the 1990s there has been growing optimism and enthusiasm for the treatment of borderline personality disorder. There is now a variety of effective evidencebased psychosocial treatments (Box 2). Referral for one of these first-line treatments is recommended.<sup>16,24</sup> No single treatment is recommended over another and they have common core features (Box 2).<sup>25</sup> Treatment guidelines include one published by the Australian National Health and Medical Research Council (NHMRC).<sup>16</sup>

Despite advances in psychosocial treatment for borderline personality disorder, improvements remain suboptimal.<sup>24,25</sup> Access to treatment is limited, and dropout rates are high (15–77%).<sup>26</sup> The NHMRC guidelines provide advice that can be implemented when referral to specialist services for borderline personality disorder is unavailable.

# Evidence for drug therapy

Pharmacotherapy has been investigated as a standalone or adjunctive treatment option for borderline personality disorder. There are many high-quality reviews<sup>16,27,28</sup> including a Cochrane review.<sup>27,29</sup> The Cochrane group found 33 randomised controlled trials in adults with borderline personality disorder,<sup>27,29</sup> but commented that the overall evidence base for prescribing is unsatisfactory. The literature is hampered by small trials (less than 50 patients) of numerous drugs, short treatment periods (mean duration of 12 weeks), diverse outcome measures, infrequent replication of findings, and lack of independence from the pharmaceutical industry.<sup>30,31</sup> In addition, controversy has surrounded the methods of one research group and the integrity of the findings.<sup>29</sup>

The available evidence<sup>16,27-29</sup> does not support a prominent role for selective serotonin reuptake inhibitors in the treatment of borderline personality disorder, despite their widespread use. Other drugs require further investigation. Mood stabilisers (topiramate, sodium valproate, lamotrigine) have shown some effect in reducing affective dysregulation and impulsive aggression. Antipsychotics such as aripiprazole, olanzapine and quetiapine have shown some effect in reducing cognitive–perceptual symptoms and affective dysregulation. Omega-3 polyunsaturated fatty acids might reduce the overall severity of borderline personality disorder.<sup>27</sup>

Although the evidence for drug therapy is less conclusive than for the psychosocial interventions, US data indicate that prescribing rates for borderline personality disorder are paradoxically high. Drugs are prescribed for 78% of patients for more than 75% of

# Box 2 Psychosocial treatments and their common characteristics

### Treatments

Dialectical behaviour therapy Mentalisation-based treatment Schema-focused therapy Cognitive behavioural therapy Cognitive analytic therapy Transference-focused therapy Systems training for emotional predictability and problem solving Dynamic deconstructive psychotherapy

# **Common characteristics**<sup>25</sup>

Approaches to prototypic borderline personality disorder problems are structured (manual-directed)

Patients are encouraged to adopt self-control (i.e. sense of agency)

Therapists help patients to connect feelings to events and actions

Therapists are active, responsive and validating

Therapists discuss cases, including personal reactions, with others

the time over a six-year period and polypharmacy occurs in 37% of patients,<sup>32</sup> perhaps reflecting clinical needs and pressures. To date, there has been no study of Australian prescribing practices, but clinical experience suggests that the situation might be similar.

# Guidelines

In light of the clinical needs and pressures, and the harm associated with prescribing for these patients, the NHMRC<sup>16</sup> and UK National Institute for Health and Care Excellence (NICE)<sup>28</sup> have considered the controlled trial evidence. In general, both groups recommend against prescribing psychotropic drugs for treating borderline personality disorder.

Importantly, the NHMRC guideline recognises that the absence of evidence can lead to heterogeneity of practice. It therefore provides some guidance for those who wish to try empirical treatment (Box 3).

Drugs should not be used as primary therapy for borderline personality disorder

# *Box 3* Key recommendations for treating borderline personality disorder <sup>16</sup>

- People with borderline personality disorder should be provided with structured psychological therapies that are specifically designed for borderline personality disorder, and conducted by one or more adequately trained and supervised health professionals.
- Drugs should not be used as primary therapy for borderline personality disorder, because they have only modest and inconsistent effects, and do not change the nature and course of the disorder.
- The time-limited use of drugs can be considered as an adjunct to psychological therapy, to manage specific symptoms.
- Caution should be used if prescribing drugs that may be lethal in overdose, because of high suicide risk with prescribed drugs in people with borderline personality disorder.
- Caution should be used if prescribing medicines associated with substance dependence.
- Before starting time-limited pharmacotherapy for people with borderline personality disorder:
- ensure that a drug is not used in place of other more appropriate interventions
- take account of the psychological meaning of prescribing (both for the individual and for the prescriber) and the impact that prescribing decisions may have on the therapeutic relationship and the overall borderline personality disorder management plan, including long-term treatment strategies
- use a single drug and avoid polypharmacy if possible
- ensure that there is consensus among prescribers about the drug used, and collaboration with other health professionals involved in the person's care, and that the main prescriber is identified
- establish likely risks of prescribing, including interactions with alcohol and other substances.
- The use of drugs can be considered in acute crisis situations where psychological approaches are not sufficient.
- If drugs have been prescribed to manage a crisis, they should be withdrawn once the crisis is resolved.

# The doctor-patient relationship

All prescribing occurs in the context of the doctorpatient relationship. However, this takes on particular significance when the condition being treated is fundamentally a relational disorder. Interpersonal difficulties and challenges, particularly maladaptive help-seeking, are part of the everyday work of caring for people with borderline personality disorder. This need not be a deterrent to becoming involved in their care, but it does require a degree of self-reflection and self-monitoring.

In caring for patients with borderline personality disorder, strong thoughts or feelings on the part of the doctor can be used as a reminder to reflect on what is happening in the doctor-patient relationship: Am I feeling 'pulled' or 'pushed' to respond in particular ways? Why won't the patient do what they need to? Who is responsible for change? Am I doing all the work? Am I responding as I might usually do, or am I treating this patient differently? Some patients will invite clinicians to behave differently with them and we can be aware of these invitations without automatically feeling 'cheated' or 'manipulated' and becoming more rigid and inflexible.

Some strategies to assist in this task can be drawn from the common characteristics of evidencebased treatments in Box 2, e.g. encouraging patients to develop a sense of self-control, and helping patients to connect feelings to events and actions. Collaborative goal setting is fundamental to successful prescribing. This involves being clear about what it is that the patient is seeking, and agreeing to common goals. A key role for the clinician is to keep one's eye on these goals, assisting the patient to persist with the chosen strategy, without becoming too rigid. Clinicians need to be aware of their own limits and needs and should be willing to communicate these to the patient, rather than dress them up as the patient's needs. For example, the doctor's responsibility to prescribe safely, legally and ethically might be at odds with the patient's demands for immediate relief from distressing symptoms.

Clinicians also need to admit and be willing to openly discuss difficulties. It is often much easier to start prescribing than to stop it. Honest and open discussion about whether a trial of a drug is warranted or has been effective is fundamental.

# Conclusion

Borderline personality disorder is a leading cause of disability and mortality and is common in clinical practice. Although it was once considered 'untreatable', the outlook for patients with borderline personality disorder is much improved, with a range of effective psychosocial treatments available for the disorder. However, access to these treatments is limited in the Australian healthcare system. Despite this, drugs should not be used as primary therapy for borderline personality disorder because they have only modest and inconsistent effects. They do not change the nature or course of the disorder. A time-limited trial of a drug can be considered as an adjunct to psychological therapy, to manage specific symptoms, but caution is needed. ◄

Conflict of interest: Andrew Chanen was a member of the development group for the National Health and Medical Research Council's Clinical Practice Guideline for the Management of Borderline Personality Disorder.

Acknowledgement: The authors would like to thank Dr Louise McCutcheon for comments on an earlier version of this manuscript.

QUESTIONS True or false?

SELF-TEST

5. Selective serotonin reuptake inhibitors are the first-line treatment for borderline personality disorder.

6. Binge eating may be a feature of borderline personality disorder.

Answers on page 66

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# **Book review**

# Handbook of drug administration via enteral feeding tubes. 3rd ed.

# White R, Bradnam V

London: Pharmaceutical Press; 2015. 732 pages

This new edition covers over 400 drugs and includes 29 new monographs. It aims to support safe and effective prescribing by providing practical recommendations on the administration of drugs via enteral tubes. Information in the book comes from pharmaceutical companies, published information (which is limited), and research undertaken largely by pharmacists.

The introductory chapters cover technical and pharmaceutical issues with tubes, drugs and administration, as well as tube blockage, drug errors and occupational exposure.

The monographs list UK formulations and relevant data for each drug. Information is provided on sites of oral absorption, alternative routes, interactions with food and enteral feeds, health and safety precautions, altering available products, and intragastric and intrajejunal administration procedures. The products listed may differ from those available in Australia. The print is very small, and the book does not cover administration to patients with swallowing difficulties. A publication by the Society of Hospital Pharmacists of Australia, the Australian Don't Rush to Crush Handbook, covers administration via enteral tubes in less detail, but includes information on swallowing difficulty and products available in Australia. There is some overlap between the two books, but each contains unique content.

This is a practical book which contains more detail on drug administration via enteral tubes than is readily available elsewhere. Because such administration is generally 'off-label' (outside the approved product information), those prescribing, dispensing or administering drugs via enteral tubes may be liable if the patient experiences adverse effects due to the route or alteration of the product. This makes reliable information on the topic particularly valuable. The handbook would be useful to nurses, pharmacists, doctors and dietitians who regularly deal with patients on enteral feeds.

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# Key words

contraception, dysmenorrhoea, intellectual disability, menstruation

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# Menstrual issues for women with intellectual disability

# SUMMARY

The approach to menstrual management in girls with intellectual disabilities should be the same as it is for other girls. Advice may need to be tailored according to the severity of the disability.

Girls who can manage their own toilet hygiene can usually learn to manage their menses independently. They need preparation for the menarche with information appropriate to their level of understanding.

When assessing menstrual problems, it may help to chart any symptoms against the menstrual cycle to confirm that they are related. The management options for problems such as dysmenorrhoea or heavy bleeding are the same as they are for other women.

# Introduction

Girls with intellectual disability usually go through puberty at the same time as those without disabilities.<sup>1,2</sup> Their level of understanding, however, may present a challenge to learning the skills needed to manage their menses.

# Implications of intellectual disability

Women with intellectual disability may have difficulty with a range of cognitively based tasks (described in DSM-5<sup>3</sup>) including:

- conceptual understanding and skills (language, literacy, numeracy, reasoning, knowledge, memory)
- social understanding and skills (empathy, social judgement, interpersonal communication, relationships)
- practical understanding and skills (selfmanagement, personal care, money and time management, recreation, organisation, implementation of school and work tasks).

The impact on daily life (adaptive functioning) depends both on the severity of her intellectual disability and on the education, resources and supports available to her.

As a rule of thumb, if a girl can learn to be independent in her toilet hygiene, she can learn to be independent in the management of her menses. For those unable to do so, their menstrual hygiene is managed with continence products and the support of carers, in the same way as bladder and bowel function.

# Preparation for menarche

All girls benefit from preparation before the menarche to understand what is happening in their body. This applies equally to girls with intellectual disabilities. All girls need information provided in ways that are appropriate to their level of understanding.

Girls with intellectual disabilities require clear, direct information, and opportunities to practise new skills. Resources such as the Special Girls' Business picture book are very helpful for them, their families and for professionals working with them (see Box).

# **Menstrual difficulties**

Girls with intellectual disabilities may take longer to learn the skills required for menstrual management. Problems may reflect a lack of understanding of the practical steps required or appropriate social behaviours. When issues arise, such as blood on clothing, pads put in inappropriate places, or disclosure of private information at inappropriate times or places, the reactions of school staff, other students and parents can be highly charged. The assessment of these difficulties includes ensuring the young woman has the information, support and opportunity to learn and practise the skills she requires to be as independent as possible in her self-care (see Box).

Changes in a young woman's behaviour may be attributed to the menstrual cycle, whether or not this is actually the case. For women not able to clearly express their experiences in words, links between changes in behaviour and the menstrual cycle, which may indicate dysmenorrhoea or premenstrual syndrome, should be confirmed. This can be done by charting behaviour changes over several months in relation to the menstrual cycle.

# Sexual maturity

Menarche signals reproductive maturity and concerns around menstrual management may become intertwined with concerns around vulnerability to sexual abuse and pregnancy. These are quite separate issues and it is important to explore the presenting problem to clarify the issues and ensure the real underlying concerns are addressed.

Young women who have the capacity to choose to participate in sexual relationships require education around sexual activity, intimate relationships, sexual health and pregnancy. Consideration of contraceptive options is a part of this discussion.

Issues of vulnerability must be addressed to ensure girls and women live free from abuse. This is achieved through education, teaching of protective behaviours and the provision of appropriate environments with adequate social and personal support.

Sexual abuse is a crime. This includes situations in which a woman does not have capacity to consent to sexual activity. When she does not have this capacity and is found to be pregnant or have a sexually transmitted disease, the crime of abuse must have occurred. This should be reported to the police.

# Epilepsy and cyclic seizures

The prevalence of epilepsy is approximately 20–40% in people with intellectual disability.<sup>4</sup> In catamenial epilepsy the seizures are linked to the hormonal changes of the menstrual cycle. This link may be suspected by carers, but it is important to confirm the association by charting seizures in relation to the menstrual cycle over several months.

# Other medical conditions

There is a range of medical conditions that can impact on the menstrual cycle. Some genetic syndromes are associated with abnormalities of reproductive function. Prader-Willi syndrome and Laurence-Moon syndrome, for example, are both associated with intellectual disability and hypogonadism. Being underweight from any cause may result in amenorrhoea, while obesity may be associated with heavy or irregular menses. Thyroid dysfunction may also alter menstrual patterns. Drugs associated with menstrual irregularities include anticonvulsants (weight) and antipsychotics (weight and prolactin).

# **Medical management**

Respect the autonomy, dignity and privacy of all women. Invite the young woman to be seen alone (without parents or carers) for at least part of

# Box Resources on menstrual issues for women with intellectual disabilities

# **Special Girls' Business**

A puberty resource picture book written for school-aged girls with special needs and their carers

www.secretgb.com/special-girls-business™

# Supporting Women

Free downloadable resources for GPs and carers:

- Supporting Women: Information and resources for general practitioners supporting women to manage their menstruation http://cddh.monash.org/assets/supporting-women-gp.pdf
- Supporting Women: Information and resources for carers supporting women to manage their menstruation http://cddh.monash.org/assets/supporting-women-carer.pdf

# **Sexual and Reproductive Health**

Improving sexual and reproductive health for people with disability. Report from the SH&FPA Disability Special Interest Group. 2013. www.shinesa.org.au/media/product/2015/04/ImprovingSexualandReproductiveHealth forPeoplewithDisability.pdf

# Intellectual disability and healthcare

- Useful information, services and resources for [Victorian] health professionals working with people with developmental disability www.cddh.monash.org/assets/documents/healthcare-and-people-with-intellectualdisabilities.pdf
- Working with people with intellectual disability in healthcare settings http://www.cddh.monash.org/assets/documents/2015/working-with-people-withintellectual-disabilities.pdf

# Legal information

Contact the relevant state public advocate office for information on consent and disability.

www.advokit.org.au/decision-making/public-advocates/

the consultation. Collect information to confirm the diagnosis of menstrual or cyclic disorders by charting symptoms against the menstrual cycle. If the cycle is irregular then a longer recording period will be required.

If there is no underlying pathology, reassure the woman, educate her about her menstrual cycle and explain the reasons for any symptoms. Suggest simple strategies that may help, including rest, diet, exercise, weight management and relaxation.

# Menstrual problems

First clarify the problem. Is it heavy bleeding or dysmenorrhoea? Quantify by asking how many pads she uses. Possible investigations include a sexually transmitted infection screen (endometritis may increase bleeding, pelvic inflammatory disease may cause pain). Consider ultrasonography if symptoms are persistent or the woman is older.

# Menstrual issues and intellectual disability

ARTICLE

Management includes:

- simple non-pharmacological strategies such as warm packs, rest
- simple analgesic (paracetamol) or non-steroidal anti-inflammatory drugs such as mefenamic acid
- non-steroidal anti-inflammatory drugs or tranexamic acid to reduce heavy menstrual loss (30–50% reduction respectively)<sup>5</sup>
- combined low-dose monophasic oral contraceptive pill which can be used continuously long term, no break being required<sup>5</sup>
- long-acting reversible contraception such as the levonorgestrel-releasing intrauterine system and medroxyprogesterone acetate as these reduce menstrual loss (etonogestrel implants are associated with irregular bleeding in 33% of women and are therefore not recommended for women with intellectual disability<sup>5</sup>)
- surgical techniques these are irreversible and require special court or board approval for a woman with an intellectual disability.

# Cyclic behavioural problems

Communication challenges may make it difficult to distinguish discomfort from mood changes in women who respond to pain with altered behaviour. Management includes:

- explanation and education
- non-pharmacological interventions including physical activity, stress management, healthy lifestyle (diet, exercise, sleep), quitting smoking, low or no alcohol consumption
- trial of the management options for dysmenorrhoea with charting of behaviour to monitor response.

# Amenorrhoea

Primary amenorrhoea may occur if the young woman is underweight, or as a consequence of significant brain injury or disease process, either congenital or acquired. Delayed puberty should be investigated at 14 years and delayed menarche at 16 years, as for young women without a disability.

The most common cause of secondary amenorrhoea is pregnancy. Other causes include weight loss, obesity, pituitary tumours, drugs (e.g. antipsychotics), hyperthyroidism and, rarely, severe emotional disturbance.

# Working with carers

Statistically, most women with intellectual disability have a mild impairment. They can discuss their symptoms and management options with their doctor, as long as adequate time is allowed and the language used is appropriate for their level of understanding. Some women require the support of others (family or paid support workers) to access and participate in the consultation and implement management recommendations. Support workers, like most family members, do not have any health training and so clear language (without medical jargon) is required.

Family members usually have an extensive knowledge of the person's social and medical history, personality and function. They are a valuable source of information.

Disability workers support people in their personal and community activities. Their training is in working with people with disability, but not in health. The level of knowledge and experience is highly variable. Staff turnover is often high and staff work in shifts. It is therefore important to check how well the person accompanying the woman knows her (regular or casual staff member, length of relationship). Staff will often come with a medical file with information about past history and current health issues, but if more information is required contact the manager or house supervisor.

When implementing a management plan, work in partnership with the person's support network. Write a clear summary of management recommendations. Discuss, explain and write down the key points of diagnosis, investigations, management, expected response and potential adverse effects, and follow up to ensure accurate transmission of information to all involved in care. Review regularly to ensure management recommendations are implemented, expected outcomes are achieved and adverse effects are detected.

# Legal considerations

- Capacity to consent should be assessed individually for each decision required. A woman can legally consent if she is able to understand, retain, believe, evaluate, weigh relevant information and express her decision. Capacity to consent is therefore related both to the woman's cognitive ability and to the complexity of the decision (e.g. insertion of an intrauterine device or ablation of endometriotic lesions).
- Most women with intellectual disability have a mild cognitive impairment and can legally consent to treatments for menstrual disorders if information is provided in an accessible format and language.
- Women who have impaired capacity to consent may require the support of another, for example Person Responsible (Victoria), to make decisions about medical treatment. Paid carers are not able to give consent on behalf of the person they are paid to support.

The consent of the Family Court (children) or the relevant state Guardianship Tribunal (adults) is required for major medical procedures such as termination of pregnancy and sterilisation.

# Conclusion

Women with intellectual disability have the same menstrual problems as other women. The starting point for management should therefore be just

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the same as it would be for another woman of the same age.

Modifications to that strategy may be warranted when tailoring the intervention to the individual's needs and her decision-making capacity. These modifications should be justifiable in terms of being in the woman's best interests, the least restrictive option, and complying with any legal requirements.

Conflict of interest: none declared

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# **FURTHER READING**

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# New drugs

# Asunaprevir

Aust Prescr 2016;39:58–60 http://dx.doi.org/10.18773/austprescr.2016.009 First published online 19 November 2015

# Approved indication: hepatitis C

# Sunvepra (Bristol-Myers Squibb) 100 mg capsules Australian Medicines Handbook section 5.5

Asunaprevir is a direct-acting antiviral drug for hepatitis C.<sup>1</sup> It works by inhibiting the viral nonstructural 3/4A serine protease required for viral replication. Asunaprevir is indicated in combination with daclatasvir<sup>2</sup> for people with compensated liver disease, including cirrhosis. Daclatasvir is also a direct-acting antiviral and works by inhibiting the non-structural 5A protein involved in viral replication.

The safety and efficacy of asunaprevir (100 mg twice daily) with daclatasvir (60 mg daily) have been assessed in three main trials (see Table).<sup>3-5</sup> An open-label study of 643 patients with genotype 1b infection<sup>3</sup> enrolled three types of participants:

- treatment-naïve patients
- patients who had not responded or only partially responded to previous peginterferon and ribavirin
- patients intolerant to, and/or ineligible for, peginterferon and ribavirin (this included patients with depression, anaemia, or neutropenia, or compensated advanced fibrosis or cirrhosis with thrombocytopenia).

Patients with cirrhosis were present in all three groups (16%, 31% and 47%). After 24 weeks of asunaprevir and daclatasvir, most patients had a sustained virological response (see Table). This was defined as a viral RNA concentration less than the lower limit of quantification in serum 12 weeks after the end of treatment. Rates of sustained responses were similar in patients with cirrhosis and without cirrhosis (84% vs 85%). A high viral titre at baseline (≥800 000 IU/mL) or the presence of viral variants associated with non-structural 5A protein resistance predicted a poor response to treatment.<sup>3</sup>

Another open-label trial enrolled 222 patients with genotype 1b disease.<sup>4</sup> They were classified as non-responders to previous interferon and ribavirin or as intolerant to, or ineligible for, interferon-based

# 4

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication and little experience in Australia of their safety or efficacy. However, the Editorial **Executive Committee** believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information. a drug information centre or some other appropriate source.

# TableEfficacy of asunaprevir (100 mg twice daily) and daclatasvir (60 mg daily)regimens in hepatitis C

Study Treatment		Viral	Sustained virological response $\ddagger$		
	regimen <sup>s</sup> geno		Treatment-naïve patients	Treatment-experienced patients	Intolerance/ ineligible patients
Manns <sup>3</sup>	asunaprevir +	16	90% (182/203)	82% (168/205)	82% (192/235)
Kumada⁴	daclatasvir	di	-	80% (70/87)	88% (119/135)
		1 (including 1a and 1b)	-	Overall 93% (329/354)	-
asunaprevir + daclatasvir +			Patients with cirrhosis 90% (66/73)		
Jensen	peginterferon + 4 ribavirin		-	Overall 98% (43/44)	-
				Patients with cirrhosis 95% (19/20)	

<sup>‡</sup> Defined as the proportion of patients with viral RNA less than the lower limit of quantification in serum measured 12 weeks after the end of treatment

<sup>§</sup> Treatment given for 24 weeks

treatment. They were given 24 weeks of asunaprevir and daclatasvir. Up to 88% of participants had a sustained viral response (see Table), including 20 of the 22 patients with cirrhosis.<sup>4</sup>

A third trial investigated asunaprevir and daclatasvir with peginterferon and ribavirin in 398 patients with genotype 1 or 4 infection.<sup>5</sup> Participants had been previously treated with peginterferon and ribavirin but had either not responded or had only partially responded. After 24 weeks of treatment with the new regimen, most of them had a sustained virological response (see Table).<sup>5</sup>

A preliminary trial of 75 people who were co-infected with HIV and hepatitis C (genotype 1 or 4) has also been conducted. Patients were all receiving raltegravir-based regimens. After 24 weeks of daclatasvir and asunaprevir with peginterferon and ribavirin, 96% of participants had a sustained virological response.<sup>6</sup>

In the safety cohort of 918 patients, the most common adverse events were headache (23%), fatigue (17%), diarrhoea (15%), nasopharyngitis (14%) and nausea (10%). In one of the trials, 10/643 patients discontinued because of an adverse event. Reasons included increased liver enzymes (7 patients) and prolonged QT interval (1 patient).<sup>3</sup> In another trial, 10/222 patients discontinued because of elevations in liver enzymes and one because of myasthenia gravis.<sup>4</sup> When peginterferon and ribavirin were added to daclatasvir and asunaprevir, 18/398 patients discontinued. The most common reasons were rash, malaise, neutropenia and vertigo (2 cases of each).<sup>5</sup>

Liver enzymes were elevated (at least 5 times the upper limit of normal) in 3–4% of patients and bilirubin was increased (at least 2.6 times the upper limit of normal) in 1% of patients. Liver enzymes and bilirubin concentrations should be monitored at least every two weeks for the first 12 weeks of treatment and then monthly after that until therapy is finished. Treatment should be stopped immediately if alanine aminotransferase increases tenfold or more, and if alanine aminotransferase increases fivefold or more with a total bilirubin increase of twofold or more.

Asunaprevir in combination with daclatasvir is not recommended in pregnancy as maternal and embryofetal toxicity has been observed with daclatasvir. The combination should only be used with adequate contraception. In animal studies, asunaprevir was excreted in breast milk and is not recommended during breastfeeding.

Asunaprevir can interact with the oral contraceptive pill and women receiving asunaprevir should be advised to take a pill containing at least 30 microgram of ethinylestradiol combined with norethisterone. The safety and efficacy of asunaprevir in people who are co-infected with hepatitis B have not been established as these patients were generally excluded from the trials.

Resistance to daclatasvir can occur. If patients experience an increase in viral RNA during treatment, their treatment should be reviewed to ascertain if resistance is a factor.

The recommended dose of asunaprevir is 100 mg twice daily. The dose should be reduced to once daily in patients with renal impairment (creatinine clearance <30 mL/min). Although asunaprevir is indicated for patients with compensated liver disease (including cirrhosis), it is contraindicated in those with moderate to severe hepatic impairment or decompensated liver disease.

After oral administration, peak plasma concentrations are reached in 1–4 hours and steady state is reached after seven days. The dose is extensively metabolised.

Asunaprevir and daclatasvir are metabolised by cytochrome P450 (CYP) 3A and asunaprevir is a moderate inhibitor of CYP2D6 so there is a potential for numerous drug interactions. The combination is contraindicated with moderate and strong inducers of CYP3A, such as phenytoin, carbamazepine, rifampicin, dexamethasone and St John's wort as these drugs may reduce as naprevir and daclatasvir concentrations. CYP3A inhibitors such as ketoconazole, clarithromycin, verapamil, and several HIV drugs are also contraindicated. Organic anion transporting polypeptide 1B1 (OATP 1B1) is involved in the distribution of asunaprevir in the liver so strong inhibitors of this transporter are contraindicated (e.g. rifampicin, cyclosporin and gemfibrozil). Other drugs that may interact include dabigatran, tricyclic antidepressants, dextromethorphan, digoxin, midazolam and statins.

Asunaprevir appears to be effective when used in combination with daclatasvir in patients with genotype 1b disease, and with daclatasvir, peginterferon and ribavirin in those with genotype 1 or 4. This included those who had not adequately responded to previous treatments and patients with cirrhosis. Preliminary results suggest it is also effective in patients co-infected with HIV. However, there are numerous potential drug interactions with asunaprevir and daclatasvir and the product information should be consulted before prescribing. In short, concomitant use of many CYP3A inducers and inhibitors are contraindicated, as are inhibitors of the OATP 1B1 transporter. Other co-administered drugs may need close monitoring or dose adjustment.

**T** manufacturer provided the product information

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# Idelalisib

Aust Prescr 2016;39:60–2 http://dx.doi.org/10.18773/austprescr.2016.010 *First published online 19 November 2015* 

# Approved indication: chronic lymphocytic leukaemia, follicular lymphoma

Zydelig (Gilead) 100 mg and 150 mg tablets Australian Medicines Handbook section 14.2.4

Like ibrutinib,<sup>1</sup> idelalisib is an oral anticancer drug that targets B-cell cancers. It works by inhibiting phosphatidylinositol 3-kinase. This enzyme is overactive in B-cell cancers and is involved in driving proliferation, migration and survival of malignant cells. Idelalisib is registered for two indications:

- in combination with rituximab for chronic lymphocytic leukaemia and small lymphocytic lymphoma when chemotherapy is not suitable, in people who have relapsed after treatment or have
- monotherapy for refractory follicular lymphoma.

the chromosome 17p deletion or TP53 mutation

# Chronic lymphocytic leukaemia

The approval of idelalisib for relapsed chronic lymphocytic leukaemia is based on a pivotal phase III trial of 220 patients.<sup>2</sup> The median age of randomised patients was 71 years. Two-thirds of them had advanced disease and the median time since initial diagnosis was nine years. Patients were heavily pre-treated (regimens included rituximab, cyclophosphamide, fludarabine and bendamustine) and were considered too unwell for chemotherapy.

In total, 80% of the patients lacked somatic hypermutation of the gene encoding the immunoglobulin heavy-chain variable region, and 40% carried the 17p deletion or TP53 mutation. These genetic characteristics are generally associated with poorer outcomes.

Patients received intravenous rituximab with either oral idelalisib or placebo. After 24 weeks, the rate of progression-free survival was significantly higher with idelalisib than with placebo (p<0.001, see Table 1). The overall response rate, assessed using serial CT or MRI of the neck, chest, abdomen and pelvis, was significantly higher in the idelalisib group compared to the placebo group (81% vs 13%, p<0.001). These were all partial responses.<sup>2</sup>

Idelalisib was also better than placebo in subgroup analyses of patients with unmutated immunoglobulin

# Table 1 Efficacy of idelalisib in relapsed chronic lymphocytic leukaemia<sup>2</sup>

Outcome	ldelalisib‡ plus rituximab <sup>§</sup> (110 patients)	Placebo plus rituximab <sup>§</sup> (110 patients)
Progression-free survival after 24 weeks	93%	46%
Median duration of progression-free survival	Not reached	5.5 months
Overall survival after one year	92%	80%
Overall response rate (all partial responses)#	81% (of a total of 88 patients that could be evaluated)	13% (of a total of 88 patients that could be evaluated)

‡ Oral idelalisib 150 mg twice a day

Intravenous rituximab 375 mg/m<sup>2</sup> body surface area, followed by 500 mg/m<sup>2</sup> body surface area every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions

# Assessed using serial CT or MRI of the neck, chest, abdomen and pelvis

heavy-chain variable region, or the 17p deletion or TP53 mutation. The trial was terminated at the interim analysis because of the superior efficacy of idelalisib combined with rituximab.

Single-arm trials of idelalisib combined with chemotherapy or immunotherapy generally found similar overall response rates (72% or above). However at the time of writing, these trials do not appear to have been published in full.

# **Follicular lymphoma**

The approval of idelalisib as a monotherapy for refractory follicular lymphoma was based on a pivotal phase II uncontrolled trial of 125 patients with relapsed indolent lymphoma.<sup>3</sup> Of the participants, 72 had follicular lymphoma, 28 had small lymphocytic lymphoma, 15 had marginal-zone lymphoma and 10 had lymphoblastic lymphoma. Patients had received a median of four previous regimens and most of them were refractory to rituximab and an alkylating agent such as cyclophosphamide. Their median age was 64 years.

The median duration of treatment was 6.6 months. More than half of patients responded to treatment – these were mainly partial responses (see Table 2). Rates of response seemed to be comparable across the different disease subtypes.

# Adverse effects and precautions

The most common adverse reactions (any grade) to idelalisib include neutropenia (50%), increased transaminases (50%), diarrhoea (38%), fever (32%), rash (24%) and pneumonitis (3%). These events can be serious (grade 3) in some cases and increased monitoring, dose interruption or treatment discontinuation may be needed.

In the indolent lymphoma trial there were 28 deaths. Most were related to disease progression (20 deaths). Other causes included pneumonia (3 patients), cardiac arrest, cardiac failure, splenic infarction, septic shock and pneumonitis (1 patient each).<sup>3</sup>

As elevated liver enzymes are so common, it is important to monitor alanine transaminase, aspartate transaminase and bilirubin fortnightly, at least for the first three months of treatment. Reactivation of hepatitis has occurred with idelalisib and all patients should be screened for hepatitis B and C before they start treatment. Close monitoring for toxicity is recommended if idelalisib is initiated in patients with severe hepatic impairment.

Severe diarrhoea or colitis occurred in 14% of patients across the trials. If diarrhoea occurs, make sure the patient is adequately hydrated, particularly those with pre-existing renal failure. Infections such as *Clostridium difficile* should be excluded. Intestinal perforation has been reported with idelalisib. This was fatal in some cases. Treatment should be stopped if perforation occurs.

Although live vaccines are not recommended during idelalisib treatment, they can be given to high-risk patients before treatment is started.

# **Pharmacokinetics**

The recommended dose of idelalisib is 150 mg orally twice a day. Peak plasma concentrations are reached within 2–4 hours after oral administration. Idelalisib is mainly metabolised by aldehyde oxidase, but also by cytochrome P450 (CYP) 3A and UGT1A4. The elimination half-life is around eight hours and metabolites are excreted in the faeces (78%) and urine (15%).

# **Drug interactions**

Concomitant strong CYP3A inducers (e.g. rifampicin, phenytoin, carbamazepine, St John's wort) may reduce plasma concentrations of idelalisib and should be avoided. Strong inhibitors may elevate idelalisib concentrations so increased monitoring for toxicity is recommended.

Caution is urged if idelalisib is given to patients taking CYP3A substrates with a narrow therapeutic index (e.g. cisapride, fentanyl). Idelalisib is a strong inhibitor of CYP3A and may increase exposure to substrates such as warfarin, some antiarrhythmic drugs, calcium channel blockers and statins.

# Conclusions

Idelalisib seems to benefit pre-treated, older patients with chronic lymphocytic leukaemia and follicular lymphoma. However, adverse effects are common and often limit treatment. In chronic lymphocytic

# Table 2Efficacy of idelalisib in relapsed<br/>indolent lymphoma 3

Outcome ‡	Idelalisib monotherapy $^{\S}$
Overall response rate	57% (71/125 patients) – 7 complete responses, 63 partial responses, 1 minor response
Median duration of response	12.5 months
Median progression-free survival	11 months
Median overall survival	20.3 months

<sup>‡</sup> Tumour response and progression assessed by serial

CT, laboratory testing and physical examination

<sup>§</sup> Oral idelalisib 150 mg twice a day

leukaemia, the long-term safety and effectiveness of idelalisib remains to be determined.

**T** manufacturer provided additional useful information

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# Nintedanib

Aust Prescr 2016;39:62-3 http://dx.doi.org/10.18773/austprescr.2016.031

First published online 22 February 2016

# Approved indications: idiopathic pulmonary fibrosis, non-small cell lung cancer

# Ofev (Boehringer Ingelheim) 100 mg and 150 mg capsules Australian Medicines Handbook section 14.2.3

Growth factors contribute to the proliferation of cells in cancers and conditions such as pulmonary fibrosis. This proliferation involves tyrosine kinases such as fibroblast growth factor, vascular endothelial growth factor and platelet-derived growth factor. Nintedanib inhibits these growth factors by binding to their receptors intracellularly. This disrupts the signalling needed for cell proliferation.

Nintedanib capsules are taken twice daily with food. There is extensive first-pass metabolism so the bioavailability is under 5%. The drug is also mainly cleared by metabolism with most of the metabolites being excreted in the faeces. The terminal halflife is 10–15 hours. As nintedanib is a substrate of P-glycoprotein, inducers of this transporter, such as phenytoin and St John's wort, will reduce the concentration of nintedanib. Its plasma concentration will be increased by inhibitors of P-glycoprotein such as ketoconazole.

# Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is one of the interstitial lung diseases. A proliferation of fibroblasts leads to progressive breathlessness. The median survival is 3–5 years.

The main clinical trials of nintedanib in pulmonary fibrosis were INPULSIS-1 and -2.<sup>1</sup> In these trials a

total of 638 patients were randomised to take 150 mg nintedanib twice daily for 52 weeks and 423 were given a placebo. These patients all had a forced vital capacity (FVC) that was at least 50% of the predicted value. In INPULSIS-1 the FVC fell by 239.9 mL/year with placebo and by 114.7 mL/year with nintedanib. The respective figures in INPULSIS-2 were reductions of 207.3 mL/year and 113.6 mL/year. The smaller decline in lung function with nintedanib was statistically significant.

In INPULSIS-1, 21% of the patients had to discontinue nintedanib because of adverse events. In both trials more than 60% of the patients taking nintedanib developed diarrhoea compared with about 18% of the placebo group. Other adverse events that were more common with nintedanib than with placebo included nausea, vomiting, weight loss and elevated liver enzymes.<sup>1</sup>

# Lung cancer

The inhibition of growth factors by nintedanib has been studied in patients with non-small cell lung cancer of different histological types. The LUME-Lung 1 trial involved 1314 patients with locally advanced, metastatic or recurrent disease that had not responded to first-line chemotherapy. All the patients were given an infusion of docetaxel every 21 days and 652 also took 200 mg nintedanib twice daily on days 2–21 of the cycle. The median duration of treatment was 2.8 months with docetaxel alone and 3.4 months with the combination. After a median follow-up of 7.1 months, progression-free survival was 2.7 months in the control group and 3.4 months in the combination group. This difference is statistically significant.<sup>2</sup>

Adverse events led to 21.7% of the patients taking docetaxel and 22.7% of those taking docetaxel and nintedanib withdrawing from the trial. Deaths from adverse events were more frequent with the combination treatment. Nausea, vomiting, diarrhoea, altered liver function and febrile neutropenia were also more frequent.<sup>2</sup>

# Precautions

The adverse effects of nintedanib may require treatment to be interrupted or reduced. Blood counts and liver function should be regularly monitored. Nintedanib is not recommended for patients with moderate or severe liver disease. In addition to the common adverse effects, there may also be an increased risk of gastrointestinal perforation, impaired wound healing, bleeding and thromboembolism. Although patients with a history of myocardial infarction or stroke were excluded from the INPULSIS trials, myocardial infarctions were more frequent with nintedanib than placebo (1.6 vs 0.5%).

# Conclusion

Idiopathic pulmonary fibrosis has a poor prognosis, so reducing the decline in lung function is a benefit. However, in a pooled analysis of the INPULSIS trials, nintedanib had no significant advantage over placebo in preventing acute exacerbations in pulmonary fibrosis or in health-related quality of life.<sup>1</sup>

In non-small cell lung cancer adding nintedanib to docetaxel increases progression-free survival, but the median overall survival is not significantly increased unless the cancer is an adenocarcinoma. The median overall survival for patients with an adenocarcinoma given the combination was 12.6 months compared with 10.3 months for patients treated with docetaxel alone. Pemetrexed is another drug that can be used to treat non-small cell lung cancer. In March 2015 the Pharmaceutical Benefits Advisory Committee concluded that an indirect comparison did not show that the effectiveness of nintedanib and docetaxel was non-inferior to pemetrexed.<sup>3</sup>

**T** manufacturer provided additional useful information

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# Ramucirumab

Aust Prescr 2016;39:63–4 http://dx.doi.org/10.18773/austprescr.2016.030 First published online 22 February 2016

# Approved indication: gastric cancer

Cyramza (Eli Lilly) vials containing 100 mg in 10 mL and 500 mg in 50 mL as concentrate Australian Medicines Handbook section 14.2.1 Ramucirumab is indicated for patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma when the disease has progressed after cytotoxic chemotherapy. This drug is used in combination with paclitaxel or as monotherapy if paclitaxel cannot be given.

Ramucirumab is a monoclonal antibody that binds to the vascular endothelial growth factor (VEGF) receptor 2. This blocks the binding of several vascular endothelial growth factors (A, C and D) to the receptor. Signalling mediated by these growth factors in endothelial cells is important in the progression of gastric cancer.

The efficacy and safety of ramucirumab has been assessed in two trials – RAINBOW<sup>1</sup> and REGARD.<sup>2</sup> The trials enrolled patients who had locally advanced or metastatic gastric adenocarcinoma which had progressed after chemotherapy with platinum, fluoropyrimidine or both. Patients with a history of arterial thromboembolic events, gastrointestinal bleeding, or uncontrolled hypertension were excluded from the trials. Participants received treatment until their disease progressed (confirmed by radiography) or they had unacceptable adverse effects. In both trials, the primary end point was overall survival.

The RAINBOW trial randomised patients to ramucirumab plus paclitaxel or placebo plus paclitaxel. Ramucirumab (8 mg/kg) or placebo was given on day 1 and 15 and paclitaxel (80 mg/m<sup>2</sup>) was given on days 1, 8 and 15 of a 28-day cycle. Median overall survival was significantly longer in the ramucirumab arm than in the placebo arm (9.6 vs 7.4 months) (see Table).<sup>1</sup>

# Table Efficacy of ramucirumab alone and in combination with paclitaxel for gastric cancer

RAINBOW trial <sup>1</sup>	Ramucirumab + paclitaxel	Placebo + paclitaxel
Number of patients	330	335
Median duration of treatment	18 weeks	12 weeks
Median duration of overall survival	9.6 months	7.4 months
Overall survival at 12 months	40%	30%
Median progression-free survival	4.4 months	2.9 months
REGARD trial <sup>2</sup>	Ramucirumab	Placebo
Number of patients	238	117
Median duration of treatment	8 weeks	6 weeks
Median duration of overall survival	5.2 months	3.8 months
	5.2 11011115	5.0 11011113
Overall survival at 12 months	17.6%	11.8%

In the REGARD trial, patients were randomised to ramucirumab monotherapy (8 mg/kg fortnightly) or placebo. All participants received best supportive care. Although median overall survival times were generally shorter in this trial, ramucirumab significantly prolonged survival compared with placebo (5.2 months vs 3.8 months) (see Table).<sup>2</sup>

In the RAINBOW trial, the most common adverse events with ramucirumab were fatigue (56.8%), neutropenia (54.4%), decreased appetite (40%), abdominal pain (36%), nausea (35.1%), leucopenia (33.9%), diarrhoea (32.4%), epitaxis (30.6%), vomiting (26.9%), peripheral oedema (25%), hypertension (23.8%), stomatitis (18%), proteinuria (16.5%) and thrombocytopenia (13.1%). All of these events were more common with ramucirumab than with placebo. There were six deaths that were thought to be related to ramucirumab plus paclitaxel. Causes included sepsis, septic shock, malabsorption, gastrointestinal haemorrhage and pulmonary embolism.<sup>1</sup>

The most common adverse events with ramucirumab in the REGARD trial included fatigue (35.5%), abdominal pain (28.8%), decreased appetite (24.1%), vomiting (19.9%), hypertension (16.1%) and bleeding (12.7%). The five deaths thought to be related to ramucirumab were due to myocardial infarction, gastric haemorrhage, intestinal perforation (2 cases) and pneumonia.<sup>2</sup>

As hypertension can be a problem with ramucirumab, blood pressure should be monitored regularly. If it occurs, treatment should be interrupted until blood pressure is controlled.

Although patients with a history of thromboembolic events or gastrointestinal bleeding were excluded, myocardial infarction, cardiac arrest, cerebrovascular accident, cerebral ischaemia, gastrointestinal perforations and gastrointestinal bleeding have been reported with ramucirumab. These events have been fatal in some cases and treatment should be stopped if patients show symptoms. Blood clotting should be monitored in those with an increased risk of bleeding. Regular blood counts are also important as neutropenia was common with combination ramucirumab therapy.

As ramucirumab can affect angiogenesis, the drug could potentially reduce wound healing. Treatment should be stopped four weeks before elective surgery and only started again after adequate healing.

Interactions with other drugs have not been observed with ramucirumab. The drug is diluted and given by intravenous infusion over 60 minutes. Infusion reactions can occur and are more common during the first and second infusion. Premedication to prevent infusion reactions is recommended. Antibodies to ramucirumab were detected in 2–3% of patients. However, these were found not to be neutralising antibodies.<sup>1,2</sup>

Although ramucirumab improves the survival times of patients with advanced or metastatic gastric cancer, the benefit is modest. In the trials, median survival was prolonged by 8–9 weeks with ramucirumab and paclitaxel, and by 5–6 weeks with ramucirumab alone. Adverse reactions are common with ramucirumab and some are fatal so patient monitoring is essential.

🕅 manufacturer did not respond to request for data

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# Secukinumab

Aust Prescr 2016;39:64–6 http://dx.doi.org/10.18773/austprescr.2016.011

First published online 19 November 2015

# Approved indication: psoriasis

### Cosentyx (Novartis)

# prefilled syringe or pen containing 150 mg/mL for injection

# Australian Medicines Handbook section 8.2

Psoriasis is known to be an immune-mediated inflammatory skin disease. While many patients can be managed with topical treatments, systemic therapy may be needed in patients with moderate or severe disease. Severe plaque psoriasis has been treated with tumour necrosis factor antagonists such as etanercept, and immunosuppressant drugs such as methotrexate, cyclosporin and ustekinumab.

Like ustekinumab, secukinumab is a monoclonal antibody produced by genetic engineering. It binds with the cytokine interleukin 17A. This prevents interleukin 17A from binding to its receptors thereby modifying immune and inflammatory responses.

Secukinumab has to be injected. As the recommended dose is 300 mg, two subcutaneous injections are required. It then takes approximately six days to reach the peak concentration. Monthly injections produce a steady state after 24 weeks of treatment. As secukinumab is an antibody, it is probably catabolised like other peptides. It has a half-life of 22–31 days.

A placebo-controlled trial (ERASURE) studied 150 mg and 300 mg doses of secukinumab injected weekly for five weeks then once every four weeks. Although the 737 patients were followed up for 52 weeks, the primary end points were assessed after 12 weeks. These end points were the investigators' global assessments and a reduction in the Psoriasis Area and Severity Index (PASI). A reduction of at least 75% of the PASI score was achieved by significantly more of the patients taking secukinumab (see Table). A 100% reduction was achieved by 28.6% of the patients injecting 300 mg, 12.8% of those injecting 150 mg, but only 0.8% of the placebo group. These significant differences were reflected in the investigators' global assessments.<sup>1</sup>

Another placebo-controlled trial (FIXTURE), involving 1306 patients, studied the same regimens, but included subcutaneous etanercept as an active control. These patients were also followed up for 52 weeks and efficacy was assessed at week 12. The response to secukinumab was significantly greater than the response to placebo and etanercept whether assessed by the PASI or the investigator (see Table). There was a 100% reduction in the PASI score in 24.1% of the secukinumab 300 mg group and 14.4% of the 150 mg group, compared with 4.3% of the etanercept group and none of the placebo group.<sup>1</sup>

# Table Efficacy of secukinumab in plaque psoriasis<sup>1</sup>

Trial	Treatment (patients)	Proportion achieving primary end point $\ensuremath{^\ddagger}$
ERASURE	secukinumab	01.00/
	300 mg (245)	81.6%
	150 mg (243)	71.6%
	placebo (246)	4.5%
FIXTURE	secukinumab	
	300 mg (323)	77.1%
	150 mg (327)	67.0%
	etanercept	
	50 mg (323)	44.0%
	placebo (324)	4.9%

<sup>‡</sup> The primary end point was the proportion of patients, at 12 weeks, who had a reduction from baseline of at least 75% on the (0–72) Psoriasis Area and Severity Index (PASI). In both trials response to therapy was sustained in most (72–84%) patients treated for up to 52 weeks. The statistically significant advantage over etanercept was also maintained.<sup>1</sup>

Two trials have studied the feasibility of patients injecting themselves using prefilled devices. A total of 359 patients were randomised. They injected themselves with secukinumab 150 mg or 300 mg, or a placebo weekly for five weeks and then monthly, with efficacy assessed at 12 weeks. In the trial of prefilled syringes, a reduction of 75% on the PASI score was achieved by 75.9% of patients injecting 300 mg, 69.5% of those injecting 150 mg and none of the placebo group.<sup>2</sup> The corresponding responses in the trial of an autoinjector pen were 86.7%, 71.7% and 3.3%.<sup>3</sup> All the patients were able to use the devices.

The main adverse effects reported in the trials were nasopharyngitis and other upper respiratory symptoms. Patients taking secukinumab were also more prone to develop diarrhoea than those taking placebo. Neutropenia developed in 1% of patients.<sup>1</sup> As secukinumab affects the immune system, there is an increased risk of infections such as candidiasis and oral herpes. Patients should be tested for tuberculosis before treatment. Live vaccines should not be given. Patients can have hypersensitivity reactions to secukinumab, but only 1% of patients developed antibodies to the drug during a year of treatment. There are no studies of drug interactions and secukinumab has not been assessed in pregnant or breastfeeding women.

Secukinumab has been shown to be effective for the treatment of plaque psoriasis for at least 52 weeks. Longer term studies will report on the efficacy and safety of continued treatment. While secukinumab appears to have an advantage over etanercept, the full results of a comparison with ustekinumab in 676 patients were not published at the time of writing. Results at 16 weeks showed a 90% improvement in the PASI score for 79% of the secukinumab group and 57.6% of the ustekinumab group.<sup>4</sup> Other drugs acting on interleukin 17A are also likely to emerge in the future.

**T** manufacturer provided additional useful information

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# NEW DRUGS

# **A:**

# ANSWERS TO SELF-TEST QUESTIONS

1	False	2	True
3	False	4	False
5	False	6	True

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The Transparency score (**T**) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

- \* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).
- <sup>+</sup> At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).
- A the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm).

# Correction

# How to manage warfarin therapy

Aust Prescr 2015;38:44-8

In the section on 'Maintenance therapy', the phrase 'and some complementary medicines such as St John's wort' has been removed from the list of drugs that may increase INR, because St John's wort decreases INR.

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