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ARTICLE

Pharmacological management of chronic non-cancer pain in frail older people

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SUMMARY

Chronic non-cancer pain is a common problem among older people and has a significant impact on their quality of life. Medical comorbidities and polypharmacy are often additional challenges in managing these patients.

Appropriate assessment of chronic non-cancer pain is important for the development of a patient-centred, goal-directed management plan. When assessing patients with cognitive impairment, modified communication strategies and validated pain assessment tools can be useful.

The quantity and quality of the evidence supporting individual drugs in the management of chronic non-cancer pain varies and studies focused on frail older people are limited. Caution is generally advised when introducing drugs and escalating the doses.

Drugs that are not effective should be stopped. A shared decision-making approach is advised for deprescribing analgesics used for chronic non-cancer pain.

Introduction

Chronic non-cancer pain is defined as pain lasting beyond the time of tissue healing or for over three months.[1] It is a significant problem among older people, due to the high prevalence of conditions, such as osteoarthritis, in which pain is a predominant symptom. In Australia, almost one in four older adults aged 65 years and over suffer from chronic pain.[2]

Older people living with chronic pain are more likely to report significant limitation in their daily activities as compared to those without chronic pain.[3] Chronic non-cancer pain can have a negative impact on a person's psychological well-being, and vice versa.[4] However, it is under-recognised, undertreated and often challenging to manage. The presence of frailty in older people adds an extra layer of complexity, given these patients often have several comorbidities treated with multiple medicines and are prone to falls and adverse effects.[5] The relative lack of high-quality studies of using drug therapy in the management of chronic non-cancer pain in frail older people creates gaps in the evidence base which makes management a difficult task.

Assessment

The first step in the successful management of chronic non-cancer pain is recognising the presence of pain and accurately assessing its severity and impact on function, in conjunction with history and examination. Stoicism, and the expectation that pain is part of ageing, have been implicated in the under-reporting of pain in older people.[4] Cognitive and sensory impairments that affect communication can also limit the accurate identification of pain.

The initial assessment needs to identify or exclude serious and treatable causes of pain, before embarking on a symptom management approach. In a holistic assessment it is important to address the psychological and functional impact of chronic non-cancer pain.[4] Multiple functional assessment tools (e.g. SF36, Pain Disability Index) are validated and practical for use in older people. Understanding the impact of the pain can facilitate negotiating realistic and meaningful treatment goals. For example, in some cases improving self-care or mobility to enable the person to participate in certain life activities will be more achievable than complete pain relief.

Assessing pain in mild–moderate cognitive impairment

The current literature shows that even for patients with mild–moderately impaired cognition, self-reporting is still the most reliable and accurate way to obtain the pain history.[6] The Box shows strategies recommended by the UK National Guidelines and the Australian Pain Society for assessing pain in older people.[4]

Assessing pain in severe cognitive impairment

A behavioural-based pain assessment scale can be useful in assessing older people with severe cognitive impairment (Table 1).[4,5,7,8] Most scales are easy to use and only take a few minutes. The Abbey Pain Scale (APS) is widely used and validated for Australian settings. The Pain in Advanced Dementia

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Box Pain assessment in older people[4]

Provide adequate time to discuss their pain, process the question and to formulate a response.

Use open-ended questions when discussing pain, rephrase the questions to elicit the presence of pain, for example:

- Do you hurt anywhere?
- Do you have any aches, soreness or discomfort?
- What is stopping you from doing what you want to do?

Use a self-reported pain measurement tool to assist in evaluation e.g. brief pain inventory.

Arrange for someone who knows the patient well to do the pain assessment and use the same tool and standardised wording during each discussion.

Table 1 Standardised pain assessment tools for older people with cognitive impairment

Standardised pain assessment tool	Format	Comments and references
Tools appropriate for communicative patients		
Brief pain inventory – short form	15-item scale measures both the intensity of pain and impact of pain on the patient's life.	Validated in assessment of chronic non-cancer and cancer pain, available in multiple languages. Appropriate for older people with minimal–mild cognitive impairment.[7]
Numeric Rating Scale (NRS)	10-point scale to quantify pain. Clinician asks: 'On a scale of zero to 10, with zero meaning no pain and 10 meaning the worst pain possible, how much pain do you have now?'	Reliable with high validity in older people with mild–moderate cognitive impairment.[4,8]
Tools appropriate for non-communicative patients		
Abbey Pain Scale (APS)	Six domains of pain-related behaviour are rated on a four-point word descriptor scale (absent to severe): • vocalisation • facial expressions • change in body language • change in behaviour, physiological change, physical changes.	Takes 2–6 minutes to administer. Validated in an Australian residential aged-care setting.[5]
electronic Pain Assessment Tool (ePAT)	A point-of-care smartphone-enabled application that assesses 42 items across 6 domains: face, voice, movement, behaviour, activity and body	Validated against APS in Australian aged-care setting with high sensitivity (96.1%) and specificity (91.4%), with positive predictive value of 97.4% and negative predictive value of 87.6%.[9]
Pain in Advanced Dementia (PAINAD) Scale	Five-item scale assessing: • breathing independent of vocalisation • negative vocalisation • facial expression • body language • consolability. Each item scores 0–2, with higher total scores suggesting a higher probability of pain.	Originally validated in a group of 25 male nursing home residents with severe dementia in the USA. It has high sensitivity (92%) but low specificity (62%) for pain.[4] It was also validated in an Australian study with acceptable utility.[5]
Doloplus-2 Scale	10-item scale that assesses somatic, psychomotor and psychosocial reactions related to pain. Each item scores 0–3 for an overall score up to 30.	

and the Doloplus-2 scale are also recommended based on high reliability and validity.[4] The electronic Pain Assessment Tool (ePAT, or PainChek) adapts automated facial analysis technology to improve recognition of pain in this population and is validated against the APS.[9] It is important to include insights and observations from family members and familiar carers about behaviour that may be pain related. When reassessing the efficacy of pain management, the same scale should be used each time.

Drug treatment

Drugs only form part of a multidimensional management plan for chronic non-cancer pain, in conjunction with other strategies, such as physical exercise and cognitive behavioural therapy.[8,10,11] When a decision is made to prescribe, careful consideration should be taken of the age-related physiological changes and the impact of polypharmacy in older people (Table 2).[12-16] The World Health Organization Analgesic Ladder is still relevant in the management of chronic non-cancer pain, however pharmacological strategies that are effective in acute pain may be less effective in chronic pain. The harm–benefit ratio of pharmacotherapy is frequently higher in frail people, but these patients are often excluded from clinical studies.[17] Current guidelines recommend the following general principles when prescribing for older people:

- start one drug at a time, at a low dose, with slow-dose titration
- allow an adequate time interval to enable the drug to take effect, before introducing additional drugs
- constantly monitor efficacy and adverse effects and adjust or cease the drug if required
- consider deprescribing at regular intervals once self-management of pain is achieved
- review all analgesia, including over-the-counter products, for potential interactions.

The Royal Australian College of General Practitioners aged-care clinical guide (Silver Book) provides practical summaries on polypharmacy, medication management and pain management in older people.[18]

Table 2 **Analgesic dosing considerations in frail older people with chronic non-cancer pain**

Analgesic class	Dosing considerations
Paracetamol	Decreased volume of distribution (20%) and clearance (37%) in frail older people.[13] Harm associated with these changes is uncertain, however some local guidelines recommend reduced doses:[15,16] • 0.5–1 g every four to six hours, up to a maximum of 3 g in 24 hours, if weight >50 kg • 15 mg/kg/dose every four to six hours up to a maximum of four doses in 24 hours, if weight <50 kg. Accidental overdose can occur if taken in combination with over-the-counter products containing paracetamol.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Increased prevalence of chronic renal disease and co-prescription of anticoagulation and antiplatelet therapies in frail older people. Presence of these comorbidities should be considered before prescribing NSAIDs to frail older people. Consider dose reduction and co-administration of proton pump inhibitors if indicated. Accidental overdose can occur if taken in combination with over-the-counter products containing non-steroidal anti-inflammatory drugs. Avoid indometacin and ketorolac because of their higher risk profile.[13]
Adjuvant drugs	Adverse reactions such as sedation and anticholinergic effects limit use. Reduce starting dose and slow up-titration with close monitoring in frail older people and those with renal or hepatic impairment.
Opioids	Increased risk of falls and subsequent fractures, delirium and excessive sedation in older people. Additional risk associated with high-dose use and co-administration with benzodiazepines.

Paracetamol

Although paracetamol is the first-line analgesic, particularly for nociceptive pain, its efficacy is modest. Evidence supporting its long-term use in chronic non-cancer pain is limited, but it remains in multiple guidelines as the first-line drug, especially for older people, given that other options are often contraindicated.[19] Regular paracetamol for up to three months provided mean pain relief of 0.3 points (on a 10-point pain scale, 95% confidence interval −0.6 to −0.1 points) in a systematic review of five trials involving 1686 patients with knee or hip osteoarthritis. Its efficacy in other painful conditions is uncertain.[20]

In view of an increased risk of hepatotoxicity in older adults, sometimes at therapeutic doses,[21,22] and emerging evidence of a relative lack of efficacy of paracetamol, the benefits of long-term use need to be re-evaluated. Co-administration of paracetamol with other analgesics is common, however there is a lack of data on the efficacy of combination therapy in chronic non-cancer pain. A Canadian cohort study highlighted the potential additional risk of gastrointestinal bleeding among older people when paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are co-administered as compared to NSAIDs alone.[23] Prescription of paracetamol for a limited duration is recommended with a review of the response to therapy. Discontinue therapy if there is no response.[24,25]

Non-steroidal anti-inflammatory drugs

The gastrointestinal, renal and cardiovascular adverse effects of NSAIDs are well known. Upper gastrointestinal complications occur in 1% of older patients treated for 3–6 months and in 2–4% of those treated for one year. This risk continues with longer durations of use.[13] The efficacy of NSAIDs for knee osteoarthritis diminished and lost clinical significance by eight weeks of therapy.[26] International guideline recommendations do not exclude using NSAIDs in very old people for some musculoskeletal pains with an inflammatory component (e.g. osteoarthritis).[27] The harm and benefit of a short course of therapy should be evaluated carefully and discussed with the patient. Co-administration with a proton pump inhibitor is advised for patients at risk of gastrointestinal complications, such as a history of complicated or uncomplicated ulcers, concomitant use of certain drugs (anticoagulants or antiplatelet drugs, including low-dose aspirin), and the presence of *Helicobacter pylori* infection.[28]

Topical NSAIDs may be a safer alternative for localised pain. They are the preferred treatment for pain associated with osteoarthritis in the hands and knees.[24,25,29] The majority of reports on the safety of topical NSAIDs in older adults are limited by a short period of usage (mostly up to 12 weeks)[30,31] and high drop-out rates secondary to lack of efficacy or localised adverse effects.

Adjuvant drugs

In chronic non-cancer pain with a neuropathic component, there is evidence supporting the use of adjuvant drugs, such as gabapentinoids, tricyclic antidepressants and selective serotonin noradrenaline reuptake inhibitors. These drugs have been recommended as first-line therapy based on a meta-analysis of moderate- to high-quality trials in post-herpetic neuralgia and diabetic neuropathy. The number of patients who needed to be treated for one to benefit (NNT) in the general population was 3.6–7.7 over a period of 12 weeks or less.[32] However, these trials did not specifically involve older people, so caution is advised when prescribing these drugs in frail older patients, and tricyclic antidepressants are not advisable given the high risk of adverse effects.[33]

Topical capsaicin and lidocaine (lignocaine) patches can be considered as second-line drugs for localised neuropathic pain, however their efficacy is limited (NNT = 10.6 for capsaicin 8% patch, undetermined for lidocaine (lignocaine) patch).[32] The associated cost also prohibits ongoing use in some patients.

Opioids

Current guidelines do not support the long-term use of opioids in chronic non-cancer pain. There is a lack of evidence for long-term efficacy, but significant evidence of harm.[10,34] A recent meta-analysis of 30 studies associated opioid use with falls, fall injuries and fractures in older people.[35] Opioids are therefore not recommended other than in exceptional circumstances when other treatments have failed and the pain has been shown to be opioid-responsive.[10] High doses and co-administration with benzodiazepines should particularly be avoided in frail older people given the additional risk of harm.

Data on the use of newer opioids, such as tapentadol, for chronic non-cancer pain are limited. A Cochrane review of four studies in a general adult population showed tapentadol had a relatively small benefit in treating chronic musculoskeletal pain.[36] Data on long-term use in older people are scarce. A sponsored report on the tolerability of sustained-release tapentadol in patients aged 75 years or older showed a more favourable adverse-effect profile than conventional opioids, yet almost a third of patients discontinued by three weeks of usage due to an adverse event, with nausea, constipation, dizziness, and somnolence being the most common.[37] Similarly, the efficacy of buprenorphine in treating chronic non-cancer pain is poor.[38] It is poorly tolerated due to neurological and psychiatric adverse effects in frail older nursing home patients with dementia, especially those using antidepressants.[39] These issues are often not highlighted in clinical trials in which the frail older populations are often excluded.

Deprescribing

Regular review of the drug treatment of chronic non-cancer pain is recommended. Assess the effectiveness of analgesia using the '5As' principle:[10]

- analgesia
- activity
- affect
- adverse effects
- aberrant behaviours, such as unapproved increase of dose or use of the drug to treat other symptoms, or seeking additional prescriptions from other prescribers.

Consider deprescribing if there has been no meaningful improvement in function or pain, when the risk of harm outweighs benefit, or there are aberrant behaviours.[40] Starting a conversation about tapering ineffective drugs with patients can be challenging, especially if they believe the drugs are helpful. Adopt a shared decision-making and tailored approach and involve carers when appropriate.

NPS MedicineWise has developed several resources to assist GPs effectively communicate with patients about managing chronic non-cancer pain.[41,42] While these resources were developed around opioid treatment, the same strategy can be used for deprescribing other analgesics. Written information for patients can also aid the discussion of alternative management strategies.[43,44]

Doses should be reduced slowly in patients who have taken opioids or adjuvant drugs for longer than three months (Table 3).[10,45,46] Consider a faster dose reduction, with specialist input, when deprescribing for intolerable adverse effects or opioid misuse.

Conclusion

Managing chronic non-cancer pain, especially in frail older people, remains challenging. The altered harm versus benefit profiles of drugs in this group of patients need to be carefully considered and regularly reviewed when prescribing. If pain remains troublesome despite standard therapies, consideration should be given to seek support from a geriatrician, pain specialist or pain service. <

Conflicts of interest: none declared

Table 3 **General approach for weaning opioids and gabapentinoids**

Drug class	Duration of use	Weaning schedule
Opioids[10,45]	<3 months, or rapid wean required	Reduce dose by 5–25% every week
	>3 months	Reduce dose by 5–25% every 4 weeks
Gabapentinoids[46]	<3 months	Reduce dose by 25–30% every week
	>3 months	Reduce dose by 25–30% every 2 weeks

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LETTERS

Letters to the Editor

Complementary medicines: an alternative view

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The article on the safety of Australian complementary medicines[1] by Geraldine Moses is incorrect or misleading on many levels. There is not enough space to respond to each inaccuracy in detail here, but a fuller response can be found on the website of Complementary Medicines Australia.

Dr Moses downplays the strict regulation of Australian complementary medicines by the Therapeutic Goods Administration. However, this high level of regulation is one reason why Australia's complementary medicines industry is thriving at home and overseas.

The author states that most adults do not need supplements, but this is untrue. A myriad of evidence supports the existence of nutrient-dietary challenges for Australians, from iron-deficiency anaemia to vitamin D and B_{12} plus many more. Deficiency has many causes such as cultural practices, post-gut surgery, lifestyle factors, ageing, the use of certain drugs and, of course, dietary factors. A staggering 50% of adults do not consume sufficient fruit, and 93% of adults and 95% of children do not consume adequate vegetables, plus just one in five Australians consume enough omega-3s.

Surely engagement with clinicians, patients, academia, and industry can aid the understanding, benefits and risks of recognising and advancing complementary and all medicines? I suggest that a mutually respectful approach to conversation and ongoing education is needed to help Australians make the best decisions and deliver the most positive health outcomes for us all.

Carl Gibson
Chief Executive Officer, Complementary Medicines Australia, Canberra

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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.

Cariprazine pharmacokinetics

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In the new drug comment Cariprazine hydrochloride for schizophrenia there is a possible error.[1] The comment 'when deciding which drug to prescribe for controlling acute schizophrenia, it may be a consideration that cariprazine takes five days to reach 90% of its steady-state concentration' could be misleading. The product information states 'Cariprazine has two pharmacologically active metabolites with similar activities as cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Total cariprazine (sum of cariprazine + DCAR and DDCAR) exposure approaches 50% of steady state exposure in ~1 week of daily dosing while 90% of steady state is achieved in 3 weeks'. While the steady-state concentration of the parent compound may be reached in a week, that of the pharmacologically active metabolites (similar potency to parent compound) will take significantly longer.

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The Australian Prescriber Editorial Executive Committee comments:

Among the papers considered by the Editorial Executive Committee when discussing the new drug comment on cariprazine[1] was the Australian Public Assessment Report published by the Therapeutic Goods Administration. When assessing population pharmacokinetics, this states that the 'Median time to achieve 90% steady state for cariprazine and the metabolite DCAR was 5 days, and 21 days for the metabolite DDCAR'. The time to steady state will indeed be longer if all three molecules are considered.

From a practical perspective, it is probably cariprazine and desmethyl cariprazine that contribute to the early effects of the drug.[2]

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ARTICLE

Optimal use of smoking cessation pharmacotherapy

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Keywords
bupropion, nicotine replacement therapy, smoking cessation, vaping, varenicline

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SUMMARY

The most effective intervention for stopping smoking is a combination of professional counselling and pharmacotherapy. Medicines are recommended for all smokers who are motivated to quit and are nicotine dependent.

Combination nicotine replacement therapy with a patch and an oral product is more effective than the patch alone. An adequate dose of nicotine must be used for an adequate duration.

Varenicline is the most effective oral drug. It is safe in people with stable mental illness.

Vaping nicotine is a second-line treatment which can be considered for smokers who are unable to quit with other methods.

Introduction

Tobacco smoking remains Australia's leading preventable cause of death and illness, prematurely killing 21,000 people every year.[1] At any time, two in three smokers intend to quit.[2] Brief interventions by GPs can significantly increase quit rates.[3] The most effective intervention is professional support combined with pharmacotherapy.[4]

Assessment

All smokers should be offered a brief intervention, such as Ask-Advise-Help. This involves asking all patients if they smoke, advising all smokers to quit and offering treatment or referral.[4] If time allows, more detailed support can be given and follow-up visits arranged. Smokers who are ambivalent about quitting may benefit from motivational interviewing.[5]

Pharmacotherapy is indicated for all smokers who are motivated to quit and are nicotine dependent.[4] Their dependence on nicotine can be assessed using the Heaviness of Smoking Index (Table 1).[6] The sooner a patient smokes after waking and the more cigarettes smoked daily, the more benefit is generally expected from pharmacotherapy.[7]

Some smokers are driven more by the smoking ritual and behavioural triggers and less by nicotine dependence. These smokers may benefit from behavioural counselling or vaping, with or without nicotine.[8]

Table 1 **Heaviness of Smoking Index for assessing nicotine dependence**

Criterion	Scoring	Score
Average cigarettes per day	1–10 = 0 points 11–20 = 1 point 21–30 = 2 points ≥31 = 3 points	
Time to first cigarettes (minutes)	61+ = 0 points 31–60 = 1 point 5–30 = 2 points <5 = 3 points	
	Total score	

Nicotine dependence level:
total score 0–2 low, 3–4 moderate, 5–6 high

Pharmacotherapy

Table 2 shows the increase in smoking cessation with first- and second-line drugs compared to control interventions or placebo in systematic reviews of randomised controlled trials.[9-11] All treatments are more effective with behavioural support.[12]

Drugs only have a modest effect on quit rates so it is important to have realistic expectations of treatment. The key to long-term success is to keep trying to quit at every opportunity. For the best health outcomes, the most effective treatment should be used as soon as possible.

If a previous pharmacotherapy was effective and well tolerated, it is generally best to use the same drug again. Other factors guiding the choice of drug include effectiveness, personal preferences, contraindications, drug interactions and cost. Varenicline, bupropion, nicotine patches, gum and lozenges are all available on the Pharmaceutical Benefits Scheme. However, only one product is subsidised at a time.

This article is peer-reviewed

Table 2 **Efficacy of pharmacotherapy for smoking cessation at 6–12 months**

Drug	Effect size*	Quality of the evidence (grade)
Comparison to control or placebo		
Varenicline[9]	15%	High
Combination nicotine replacement therapy[9]	11%	High
Bupropion[9]	7%	High
Single nicotine replacement therapy[9]	6%	High
Comparison to nicotine replacement therapy		
Vaping nicotine[10]	3%	Moderate
Varenicline[11]	4.8%	Moderate

* Effect size is the increase in the efficacy of the drug compared to the comparator

Nicotine replacement therapy

Nicotine replacement therapy is the most widely used first-line treatment. It is approved for use by people from the age of 12 years. Nicotine replacement therapy temporarily replaces the nicotine from smoking, reducing cravings and withdrawal symptoms. The nicotine is delivered more slowly than from smoking and monotherapy generally achieves blood concentrations around half those of smoking.[13]

Two types of nicotine replacement therapy are available:

- The nicotine patch releases nicotine steadily through the day and relieves background cravings.[13]
- Oral preparations act more quickly but are shorter acting.[13] The gum, lozenge and inhalator are best used regularly, say hourly, or 20 minutes before a trigger is anticipated, such as before eating. The mouth spray starts to work within about a minute and can help manage unexpected cravings.

Optimising nicotine replacement therapy

As nicotine replacement therapy combined with counselling only has a modest effect on quit rates, it is important to optimise its use to increase the chance of success.

Combination nicotine replacement therapy

Combining the nicotine patch with an oral form of nicotine replacement therapy relieves both background and breakthrough cravings. This is more effective than using a single formulation.[14] Combination therapy should be considered for all smokers, especially those who are more nicotine dependent or when nicotine replacement monotherapy has not worked.

Address concerns about safety

Misinformed safety concerns are a major cause of poor adherence.[15] Patients should therefore be reassured about the safety and low addictive potential of nicotine replacement therapy. Explain that nicotine does not cause cancer or lung disease and only has a minor role in cardiovascular disease.[16] Nicotine replacement therapy is always safer than smoking.[16]

Correct use of oral products

It is important to give clear instructions on how to use oral products and to review the technique regularly, as most patients use them incorrectly.[17] All oral products including the inhalator are absorbed in the buccal cavity. Instruct patients not to eat or drink for 10 minutes before use as this reduces absorption.[18]

Explain the 'chew and park' technique for using gum and the importance of shallow, frequent puffs from the inhalator. Lozenges should be dissolved slowly in the mouth over about 20 minutes. The mouth spray is used under the tongue and swallowing should be delayed as long as possible.

Adequate dosing

Most patients do not use enough nicotine, often due to misperceptions about safety.[17] The dose should be sufficient to control withdrawal symptoms and cravings with frequent review to titrate the dose accordingly. More heavily dependent smokers should use combination nicotine replacement therapy, use 4 mg gum or lozenges instead of 2 mg and they may need two patches.[17] Too much nicotine causes nausea, but the risk of toxicity is very low.[19]

Pre-cessation patch

Starting the nicotine patch two weeks before the day the patient intends to stop smoking increases quit rates by 25% compared to starting on the quit day.[14]

Adequate duration

A course of at least 10 weeks is recommended.[4] At the end of the course abrupt cessation of nicotine replacement therapy is generally advised as the evidence does not support tapering.[14] Extending the course for 12–18 months may help prevent relapse.[20]

Adverse effects

Minor adverse effects are common with nicotine replacement therapy. They vary with the method of delivery (Table 3).

Precautions

Nicotine replacement therapy is safe in stable cardiovascular disease.[21] Oral nicotine replacement therapy is approved in pregnancy with informed consent if behavioural treatment has not been successful, although there is no clear evidence of effectiveness.[4] Larger doses are needed as nicotine clearance is accelerated in pregnancy. Nicotine is linked to harmful effects on the fetus in animal studies, but there is no evidence so far of harm to the human fetus. Nicotine replacement therapy can also be used while breastfeeding.[4] There are no relevant drug interactions with nicotine replacement therapy. As the pharmacokinetics of some drugs are affected by smoking, check if any dose adjustments are needed when quitting.[22]

Varenicline

Varenicline is the most effective monotherapy for smoking cessation.[9] It blocks nicotine receptors in the brain and relieves cravings and withdrawal symptoms. It also reduces the reward if a cigarette is smoked.

The dose of varenicline is up-titrated over the first week. It should always be taken with food to reduce the risk of nausea. A full course of 12 weeks is recommended and a second course can be considered to prevent relapse.[4]

There are two ways to take varenicline:

- Flexible option – start varenicline, then quit smoking between days 8 and 35 of treatment.
- Fixed option – set a quit date and start varenicline one or two weeks before that date.

Combining varenicline and a nicotine patch significantly increases quit rates compared to varenicline alone.[23] The combination is well tolerated and can be considered if monotherapy has failed.

Precautions

Adverse effects include nausea (usually self-limiting), headache, insomnia and disturbed dreams.[11] Varenicline has no known drug interactions, but is contraindicated in pregnancy and lactation and is only approved for adults. The dose should be reduced in severe renal impairment.

Varenicline is safe and effective in people with stable mental illness.[24] Although many patients are reluctant to take it because of reports of depression, behavioural changes and suicidal ideation, there is no definite evidence that varenicline causes these conditions. Everyone who quits smoking is at increased risk of psychological stress, especially those with mental illness.[24] All patients who quit smoking should be advised accordingly and monitored for mood or behavioural changes. Advise them to stop varenicline and contact their doctor if there is any concern.

Bupropion

Bupropion is an antidepressant that is also an effective aid for quitting smoking.[25] It is taken as an eight-week course with quitting in the second week.

Adverse effects include insomnia, dry mouth and nausea.[25] The main risk from bupropion is a one-in-a-thousand incidence of seizures.[26] Bupropion

Table 3 **Adverse effects of nicotine-containing products**

Product	Adverse effects	Management
Nicotine patch	Skin irritation, redness, itch	1% hydrocortisone Rotate application site daily
	Insomnia and vivid dreams (24-hour patch)	Use 16-hour patch or remove the 24-hour patch at bedtime
Gum, inhalator, lozenge	Dyspepsia, nausea and throat irritation	Avoid swallowing excessively
Mouth spray	Throat irritation, hiccups	Delay swallowing
Vaping nicotine liquid	Cough, dry throat, nausea, headache	Sips of water for dry throat

is contraindicated in patients with a raised seizure risk and should be used with caution in people taking drugs that can lower seizure threshold, such as antidepressants.[26] Pregnancy is also a contraindication.

Vaping nicotine

For smokers who have been unable to quit with other methods, vaping is considered a second-line option.[4] It is the most widely used quitting aid globally and in Australia.[2] Vaping provides the nicotine that smokers crave as well as the rituals and sensations of smoking, but without most of the toxins and carcinogens from burning tobacco. The cost of vaping nicotine is about 10% of the cost of smoking on average.

The Royal Australian College of General Practitioners (RACGP) guidelines state:[4]

> 'For people who have tried to achieve smoking cessation with first-line therapy (combination of behavioural support and Therapeutic Goods Administration-approved pharmacotherapy) but failed and are still motivated to quit smoking, nicotine vaping products may be a reasonable intervention to recommend along with behavioural support.'

Vaping can be used as a short-term quitting aid, but could have a long-term role for tobacco-harm reduction. Reviews of randomised controlled trials have found that vaping nicotine was about 50% more effective than nicotine replacement therapy.[27,28] In absolute terms, six out of 100 smokers will quit with nicotine replacement therapy and 9–10 will quit with vaping nicotine. More studies are needed to confirm the exact effect size. These findings are consistent with those of observational and large population studies.

Vaping is not risk-free, but it is considerably less harmful than smoking.[29] Vapour contains low doses of some toxic chemicals such as heavy metals, carbonyls and volatile organic compounds.

Some studies have associated vaping with impaired cell viability, impaired immune defences, increased inflammatory markers, oxidative stress and airways hyper-responsiveness. There is some evidence that vaping may worsen asthma and cause cough and lung irritation in non-smoking adolescents and cause school absenteeism.[30] However, asthma,[31] chronic obstructive pulmonary disease,[32] lung function[33] and respiratory symptoms[34] can improve when adult smokers switch to vaping.

While the long-term risk of vaping nicotine is unknown, it is unlikely to be more than 5% of the risk of smoking, according to the Royal College of Physicians.[29] There is also no evidence of significant harm from passive exposure.[29]

Patients should be advised that no products are currently approved by the Therapeutic Goods Administration. Short-term use is recommended, but long-term use to prevent relapse to smoking is likely to be far less harmful than relapse to smoking.[29] Continuing use of vaping and smoking (dual use) should be discouraged.

It is illegal in Australia to use nicotine liquid without a prescription, but it can be accessed by two legal pathways:

- Nicotine liquid can be dispensed by Australian pharmacies and online pharmacies with a prescription from a doctor who is an Authorised Prescriber of nicotine.
- It can also be imported from overseas under the Therapeutic Goods Administration's Personal Importation Scheme.[35] Individuals can order three months supply at a time for personal use, up to a total of 15 months supply each year. Patients must arrange for a copy of their prescription to be sent to the vendor and enclosed with their order.

More information about vaping regulations is available on the Therapeutic Goods Administration website.[36]

Conclusion

Pharmacotherapy combined with counselling can help smokers quit. The most effective first-line treatments are varenicline and combination nicotine replacement therapy. Vaping nicotine is considered a second-line option for smokers who are unable to quit with other therapies. <

Conflicts of interest: Colin Mendelsohn has received funding from Pfizer, GlaxoSmithKline, Johnson & Johnson (Pacific) and Perrigo Australia for teaching, consulting and conference expenses. He is on Pfizer's Champix Advisory Board.

Dr Mendelsohn has not received any payments from electronic cigarette or tobacco companies. He has a special interest in tobacco-harm reduction and vaping nicotine and was the founding chairman of the Australian Tobacco Harm Reduction Association (ATHRA), a health promotion charity established to raise awareness of safer alternatives to smoking, but is no longer on the Board. ATHRA received funding from the vape industry to establish the charity which was publicly declared. He is the author of a self-funded book called Stop Smoking Start Vaping.

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ARTICLE

Cluster headache in adults

SUMMARY

Cluster headache is characterised by attacks of very severe, unilateral headache lasting 15–180 minutes, up to eight times per day. The attacks are associated with cranial autonomic symptoms on the same side and a sense of agitation or restlessness.

First-line acute abortive treatments include intranasal or subcutaneous sumatriptan or high-flow oxygen. Neuromodulation may benefit some patients.

First-line preventive therapy is high-dose verapamil. Close monitoring is required for the adverse effect of arrhythmia.

There are several emerging therapies that have either proven efficacy, or possible benefit for cluster headache. They include drugs aimed at the calcitonin gene-related peptide.

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Introduction

Cluster headache is a type of trigeminal autonomic cephalalgia. It is known colloquially as the 'suicide headache' because it is among the worst pains that can be experienced and many patients contemplate suicide during the attacks.[1,2] Compounding the morbidity of the disease, there can be a significant delay in diagnosis of up to eight years, and therefore a delay in optimal treatment.[3]

Epidemiology

The pooled lifetime prevalence of cluster headache is 0.12%. There is an overall male predominance of 4.3:1, which is higher in chronic cluster headache (15:1) than in episodic cluster headache (3.8:1).[4] There is a significant genetic component with first-degree relatives having an 18 times higher risk of the disease.[5] Attacks are triggered by the interplay of endogenous and exogenous factors such as alcohol and seasonal and diurnal variation. Smoking is a well-known risk factor in chronic cluster headache.[6]

Diagnosis

Cluster headache accounts for 20% of headaches which always occur on the same side of the head (side-locked headache).[7] When evaluating a patient, secondary causes of headache should first be considered and excluded. An anterior location of pain, sense of internal restlessness or agitation, and ipsilateral autonomic features (conjunctival injection, lacrimation, rhinorrhoea, eyelid oedema, sweating, miosis or ptosis) are highly suggestive of one of the trigeminal autonomic cephalalgias. The duration of pain and response to treatment helps differentiate these conditions (see Fig.).[7]

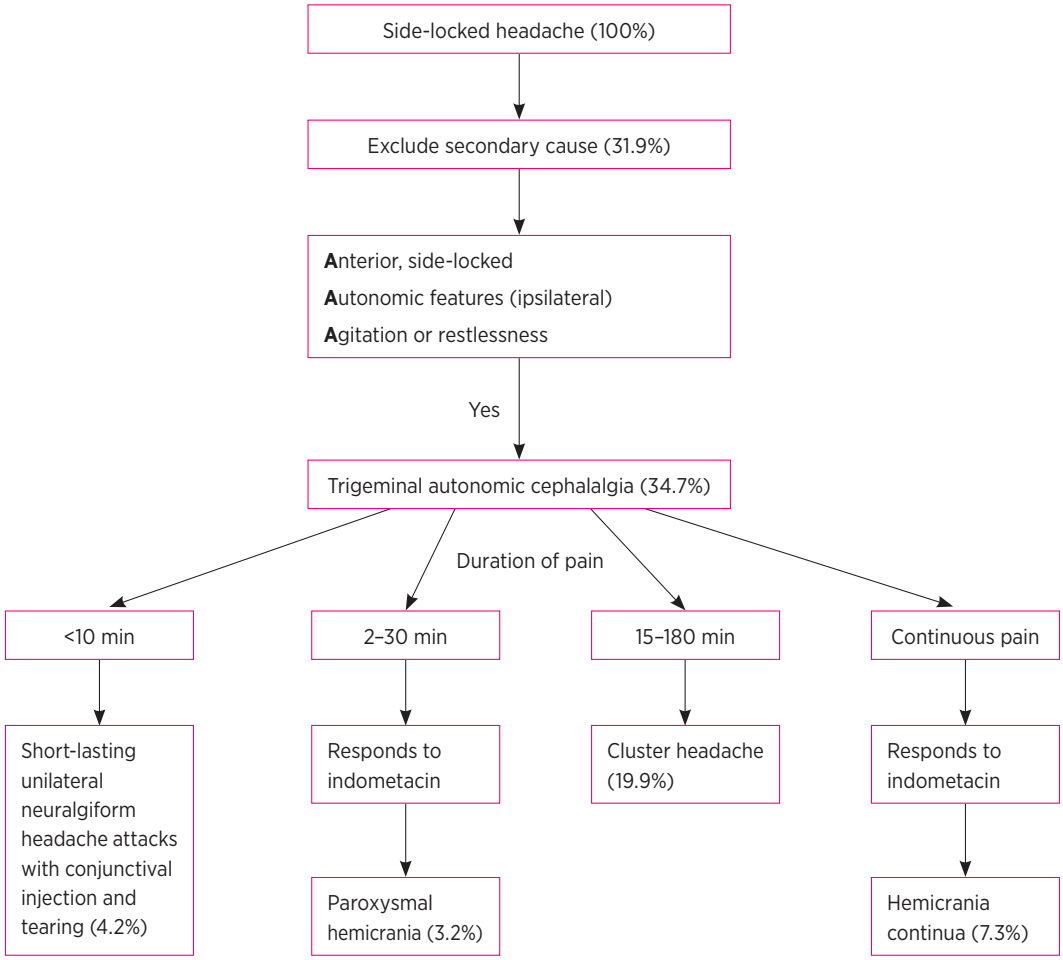
Cluster headaches are characterised by severe pain occurring over the orbit, supraorbital or temporal region lasting 15–180 minutes. They are associated with ipsilateral cranial autonomic features and a sense of internal restlessness or agitation (see Box).[8] During cluster periods, cluster headache attacks occur up to eight times per day, typically at night.[8] In episodic cluster headache the cluster periods last between seven days and one year and are separated by pain-free remission periods of three months or more. The 10–15% of patients who do not experience remission, or have a remission lasting less than three months, have chronic cluster headache.[5,8] All patients presenting with cluster headache require MRI of the brain, including the pituitary region to exclude a secondary cause mimicking cluster headache ('symptomatic cluster headache'). These include vascular causes, inflammatory pathology or a neoplasm.[9]

Paroxysmal hemicrania is another type of the trigeminal autonomic cephalalgia. The headache can be of similar duration to cluster headache, but there are more attacks (5–40/day) and no nocturnal emphasis. It responds to a trial of indometacin (25 mg three times a day then increasing, if there is no or only a partial effect, at three-day intervals to 50 mg, then 75 mg three times a day with gastric ulcer prophylaxis).[10] The gastric ulcer prophylaxis is stopped when the indometacin is stopped.

Pathophysiology

The pathophysiology of cluster headache is not completely understood. With advances in clinical and neuroimaging studies, the vascular theory of cluster headache is now considered incomplete.[11] There are vascular changes, but they are a consequence

Fig. **Evaluation of a side-locked headache**[7]



Box **Diagnostic criteria for cluster headache**[8]

A At least five attacks fulfilling criteria B–D

B Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)

C Either or both of the following:

1. At least one of the following symptoms or signs, ipsilateral to the headache:
   - conjunctival injection or lacrimation
   - nasal congestion or rhinorrhoea
   - eyelid oedema
   - forehead and facial sweating
   - miosis or ptosis
2. A sense of restlessness or agitation

D Occurring with a frequency between one every other day and eight per day

E Not better accounted for by another diagnosis

of neurological processes. While the precise mechanisms are still debated, recognition of three key structures involved in the pathophysiology aids in the understanding of the clinical features of the disease. These are the:

- trigeminovascular system
- parasympathetic system
- hypothalamus.[12]

The trigeminocervical complex connects the peripheral trigeminal neurons to the central nervous system. Activation of the trigeminal system results in release of several neuropeptides including calcitonin gene-related peptide, a potent vasodilator, through activation of transient receptor potential cation subfamily V_1 ($TRPV_1$).[5,13] As pain is perceived unilaterally in the ophthalmic division of the trigeminal nerve, the activation is theorised to be unilateral. However, this theory is unproven and the inefficacy of neurolysis of the trigeminal nerve serves as evidence that the origin of the perception of pain is incompletely understood.[5,11]

The trigeminal nerve connects through the superior salivatory nucleus to the parasympathetic fibres of the facial nerve, where they pass through the sphenopalatine ganglion. Activation of the parasympathetic system by the trigeminal nerve (termed the trigeminal autonomic reflex) is also responsible for the release of various neuropeptides including pituitary adenylate cyclase-activating polypeptide (PACAP)[5] and ipsilateral cranial autonomic symptoms.

Functional imaging shows that the hypothalamus is involved in the circadian and circannual rhythmicity of cluster headache.[14] The suprachiasmatic nucleus plays a critical role in circadian rhythm, and the nocturnal peak of melatonin is blunted in patients with cluster headache, however the significance of this is unclear.[5]

Approach to management

Management of cluster headache may be divided into acute abortive and preventive therapies, possibly with bridging therapy between them. The drugs used for the acute and preventive treatment of cluster headache are off label, but supported by clinical evidence. The majority of patients require preventive therapy, however patients with episodic cluster headache with seasonal bouts may only require abortive therapy, which provides symptomatic benefit but does not alter the cluster duration, or short-term prevention. Bridging therapies are frequently used at the start of a cluster to control attacks while up-titrating preventive therapy. During a bout of attacks, avoiding triggers such as alcohol, nitrate-containing foods and strong odours can be beneficial.[15]

Acute treatment

First-line, evidence-based, abortive treatments for cluster headache include triptans and high-flow 100% oxygen through a well-fitting mask (Table 1).[5,15-21] While several formulations of triptans have been studied in cluster headache, subcutaneous or intranasal preparations are recommended for their rapid onset of action. Triptans can be repeated after two hours. Although patients find both are helpful, there has been no head-to-head trial comparison of oxygen and subcutaneous sumatriptan.[22] Oxygen, which is delivered via a non-rebreather mask and oxygen cylinder at 7–12 L/minute for 15 minutes, may be ordered from medical gas supply companies in Australia with a prescription.

The choice of acute therapy depends on patient factors and cost. Oxygen is contraindicated in active smokers and patients with type 2 respiratory failure. Triptans are contraindicated in patients with ischaemic heart disease.

Other abortive treatments that have some supporting evidence in cluster headache include non-invasive stimulation of the vagal nerve.[23] Trials are investigating other forms of neuromodulation.

Table 1 **Acute abortive therapies for cluster headache**[5,15-21]

Therapy	Dose (maximum 24 h)	Efficacy Proportion with response (placebo response)	Possible mechanism of action
Sumatriptan (subcutaneous)	6 mg (12 mg)	Mild or no pain at 15 min: 75% (32%) Pain-free at 15 min: 48% (17%)	5-HT1$_{B/D/F}$ receptors – inhibit calcitonin gene-related peptide release and nociceptive signalling in trigeminocervical complex, and cause vasoconstriction of cerebral vessels which is possibly contributory
Sumatriptan (intranasal)	20 mg (40 mg)	Mild or no pain at 30 min: 57% (26%) Pain-free at 30 min: 47% (18%)	
Zolmitriptan (intranasal)*	5 mg (20 mg)	Mild or no pain at 15 min: 15% (7%), at 30 min: 45% (30%) Pain-free at 15 min: 8% (3%), at 30 min: 32% (18%)	
Zolmitriptan (intranasal)*	10 mg (20 mg)	Mild or no pain at 15 min: 28% (7%), at 30 min: 62% (30%) Pain-free at 15 min: 12% (3%), at 30 min: 48% (18%)	
High-flow oxygen	7–12 L/min for 15 min	Reduction in pain at 15 min: 78% (20%) Pain-free at 15 min: 78% (20%)	Vasoconstriction, blocks trigeminal autonomic reflex, inhibits protein release and activity in the superior salivatory nucleus
Non-invasive vagal nerve stimulation (episodic cluster headache only)	3 stimulations for 2 min	Mild or no pain at 15 min: 39% (12%)	Blocks trigeminal autonomic reflex, inhibits nociceptive signalling in trigeminocervical complex

* Intranasal zolmitriptan is currently not available in Australia.

Bridging therapies

Despite a lack of supportive randomised data, prednisolone is commonly used as a bridging preventive strategy to allow the up-titration of safer long-term preventive therapies. A variety of prednisolone regimens have been successful in uncontrolled studies, however prolonged use should be minimised because of its adverse effects. Starting at 1 mg/kg (maximum dose 75 mg daily) with gastric ulcer prophylaxis, and down-titrating over two weeks, is one reasonable strategy.[15,16]

An alternative strategy is a greater occipital nerve block with an injection of local anaesthetic and depot-methylprednisolone. This combination can reduce attacks for on average four weeks and avoids the adverse effects of a course of oral steroids.[24]

Preventive therapy

Preventive therapy may be indicated long term in patients with chronic cluster headache, or seasonally, in patients with episodic cluster headache, depending on their history. Immediate-release or controlled-release verapamil is first line, and its use is supported by a randomised controlled trial, in which 80% of patients had a halving of attack frequency and 26% were attack free.[25] Its efficacy is dose-dependent and the doses required for disease control can be in excess of the usual dose. Specialists can sometimes use up to 960 mg per day in divided doses (Table 2).[5,15,16] Patients therefore require ECG monitoring before starting verapamil, during titration, and even after reaching a stable dose. One in five patients will develop an arrhythmia and delayed-onset arrhythmias have been reported.[26,27] Arrhythmias include first-degree heart block, second-degree heart block, junctional rhythms, right bundle branch block and bradycardia.[26] There is a need to check for drug interactions. Once a bout of cluster headache has finished, the patient can be weaned cautiously off verapamil, by 80 mg every one to two weeks.

Lithium is considered second-line for the prevention of cluster headache. There are limited controlled

Table 2 **Preventive therapy for cluster headache**[5,15,16]

Drug	Dosing	Monitoring	Possible adverse effects	Possible mechanism of action
Verapamil (immediate-release formulation*) (Grade 1B)	Start: 80 mg three times a day for **at least** 2 weeks Titrate: increase by 80 mg every 2 weeks Range: 240–960 mg	ECG: before starting and at every dose change Repeat at stable dose after 10 days, every 1–2 months then every 6 months	Constipation, peripheral oedema, bradycardia, conduction abnormalities. Cytochrome P450 3A4 inhibitor. There is a potential for drug interactions	Voltage-gated calcium channels: decreases calcitonin gene-related peptide release, alters circadian rhythm
Lithium (Grade 1B)	Start: 300 mg daily for **at least** 1 week Titrate: increase by 300 mg every week Range: 300–1200 mg	Monitor thyroid, kidney function, calcium, magnesium Monitor lithium concentration (initial aim 0.6–0.8 mmol/L)	Include tremor, dizziness, dry mouth, weight gain, fatigue, anorexia, ataxia, gastrointestinal upset	Alters glutamate, dopamine, gamma aminobutyric acid, circadian rhythm
Galcanezumab (episodic)	Start: 240 mg subcutaneous Continue: 120 mg every 4 weeks	Not required	Constipation, local injection site reaction, nasopharyngitis	Inhibition of calcitonin gene-related peptide
Topiramate (Grade 1B)	Start: 25 mg daily for ≥1 week Titrate: increase by 25–50 mg/week Range: 100–200 mg	Monitor kidney function	Cognitive slowing, paraesthesia, kidney stones, gastrointestinal upset	Inhibits trigeminal nociception, enhances gamma aminobutyric acid
Melatonin (Grade 2C)	Start: 4 mg daily for ≥1 week Titrate: increase by 4 mg every week Range: typically 8–10 mg, compounded	Monitor sedation	Drowsiness, gastrointestinal upset	Alters circadian rhythm, enhances gamma aminobutyric acid

* Controlled-release formulation may also be used with twice-daily dosing

Grade 1 strong recommendation Grade 2 weak recommendation
Grade A high-level evidence Grade B moderate-level evidence Grade C low-level evidence

data on its use, however in one trial it had similar efficacy to verapamil, but more adverse effects (29% vs 12%).[28] The use of lithium is limited by its long-term adverse effects, toxicity and the need for strict monitoring.

Topiramate showed efficacy in a single open-label trial, but while it is a reasonable third-line option, cognitive adverse effects may limit its use.[29] There is also weaker evidence for pizotifen and gabapentin, and conflicting evidence for melatonin and valproate. They are generally used as adjuvant therapies to other preventive drugs.[5,15,30]

Neuromodulation

Several invasive and non-invasive neuromodulatory techniques have been investigated in cluster headache. Electrical stimulation of the sphenopalatine ganglion, occipital nerve and vagal nerve have all been effective at reducing attack frequency. However, these procedures are reserved for drug-refractory cluster headache due to the need for surgery, their cost and the risk of complications.[5] Access to invasive neuromodulatory techniques in Australia is limited.

Neuromodulation can be highly effective in select groups. In a randomised controlled trial of sphenopalatine ganglion neurostimulation (involving implantation of a device not available in Australia) for refractory cluster headache, 67% of patients achieved pain relief.[31] Other trials studied radiofrequency ablation of the sphenopalatine ganglion. In the largest case series of 66 patients there was pain relief in 60% of those with episodic cluster headache and in 30% of those with chronic cluster headache.[31,32]

A phase III trial of occipital nerve stimulation has been completed. It compared low- (30%) and high-intensity (100%) stimulation for refractory chronic cluster headache. Overall, the median weekly mean attack frequency reduced to 7.4. The reduction was greater in the high-stimulation group. However, the difference between the groups was –2.42 (95% confidence interval –5.17 to 3.33). Serious adverse events, such as pain, were reported in 26% of the high-stimulation and 12% of the low-stimulation groups.[33]

Non-invasive stimulation of the vagus nerve has been studied for acute treatment of cluster headache in two randomised, sham-controlled trials. There was a significant response in episodic cluster headache, but not chronic cluster headache.[34,35] In one trial of non-invasive stimulation of the vagus nerve for prevention, the number of weekly attacks reduced by 5.9 compared to 2.1 with sham treatment.[36]

Emerging therapies

Galcanezumab is a monoclonal antibody against calcitonin gene-related peptide. In episodic cluster headache galcanezumab reduced weekly attacks by 71%. Fremanezumab, another calcitonin gene-related peptide monoclonal antibody, was not effective in episodic cluster headache. Neither drug was effective for chronic cluster headache.[37] This may have been due to poor trial design and differing neurobiology between episodic cluster headache and chronic cluster headache.[37,38] Trials of eptinezumab, an intravenous calcitonin gene-related peptide monoclonal antibody, in episodic cluster headache are ongoing (NCT04688775).

Three prospective studies of onabotulinum toxin A using a variety of protocols have provided low-quality evidence that it may reduce attack frequency in cluster headache by up to 50%.[39] A phase I–II trial of onabotulinum toxin A injected towards the otic ganglia found it to be safe in chronic cluster headache, but there was no significant reduction in attack frequency.[40] A phase III trial is studying injections towards the sphenopalatine ganglion (NCT03944876).

Referral

Early specialist referral and co-management are recommended if there is any diagnostic uncertainty about the condition. A suboptimal response to management or a need for second- or third-line treatments are also indications for referral.

Conclusion

A cluster headache is one of the most excruciating pains imaginable. Recognising the condition and empowering patients with a plan for managing acute attacks and bridging therapies while titrating preventive therapy is key to limiting the morbidity of the disease.

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Richard Stark has served on advisory boards for Novartis, Teva, Eli Lilly, Allergan, Lundbeck and has received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis.

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ARTICLE

Home oxygen therapy

SUMMARY

Long-term home oxygen therapy improves survival in patients with chronic obstructive pulmonary disease and persistent, severe hypoxaemia. It is uncertain that this benefit extends to patients with other chronic lung diseases.

Oxygen is a treatment for hypoxaemia, not breathlessness. To confirm hypoxaemia, blood gas analysis is recommended before prescribing oxygen.

There is limited and conflicting evidence that portable oxygen for exertional use is of benefit to patients with chronic obstructive pulmonary disease who do not have severe hypoxaemia. Laboratory studies show improvements in exercise capacity and dyspnoea, but these do not translate into significant benefits in the home setting.

Patients should be educated regarding the expected benefits, risks and burdens of home oxygen therapy. It is particularly important that the patient does not smoke.

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Introduction

Oxygen is a drug that is often used in medical emergencies.[1] The gas may also be prescribed for longer term use by patients with chronic respiratory conditions. Oxygen is indicated for the treatment of hypoxaemia, but not for the symptom of breathlessness.

Long-term oxygen therapy is most frequently prescribed for patients with chronic obstructive pulmonary disease (COPD). While oxygen can improve survival, not all patients will benefit, therefore the prescription of oxygen therapy should be guided by the evidence from clinical trials. While the results of studies in COPD have been extrapolated to hypoxaemic patients with other lung diseases, the evidence for benefit is lacking.

Long-term continuous oxygen therapy

The prescription of long-term continuous oxygen therapy is based on two studies that showed improved survival in patients with COPD and severe hypoxaemia.[2,3] In the UK Medical Research Council study, patients were prescribed 15 hours of oxygen per day or no oxygen. Mortality at three years was 66% in the control group and 42.5% in the oxygen group.[2] Patients in the US Nocturnal Oxygen Treatment Trial (NOTT) were prescribed continuous oxygen (averaging about 18 hours/day) or nocturnal oxygen. Mortality in the nocturnal oxygen therapy group was 1.94 times that of the continuous oxygen therapy group (p=0.01).[3]

The results of these trials significantly altered the treatment of hypoxaemic COPD. Domiciliary oxygen was until recently the only therapy (apart from smoking cessation) known to significantly reduce mortality. Most international guidelines are based on the entry criteria for these trials. They recommend that oxygen should be considered for patients with stable COPD, who have an oxygen partial pressure in arterial blood (PaO_2) of:

- 55 mmHg or less at rest when awake and breathing air
- 56–59 mmHg if they have polycythaemia (haematocrit >0.55) or clinical, electrocardiographic or echocardiographic evidence of pulmonary hypertension or right heart failure.

Before prescribing oxygen, the patient's condition must be stable and all reversible factors, such as the underlying lung disease and comorbidities, for example anaemia or sleep apnoea, should have been treated as much as possible. Continuous oxygen is delivered via a stationary concentrator – an electrically powered device that extracts nitrogen from room air – and should be prescribed for at least 15 hours per day. The flow rate should be set to maintain PaO_2 above 60 mmHg, at rest. Consideration may be given to increasing flow rates by 1 L/minute during sleep, exertion and air travel.

Oxygen from a portable cylinder or battery-powered portable oxygen concentrator may be provided for use outside the house for patients who are physically active and wish to maximise the number of hours they receive oxygen.

Ambulatory oxygen therapy

Ambulatory oxygen may be provided for patients who have:

- severe resting hypoxaemia and are physically active – in order to maximise the survival benefit by increasing the duration of their therapy
- an improvement in exercise capacity in response to ambulatory oxygen in a laboratory-based functional exercise test (usually a 6-minute walk test).

Despite some small acute benefits during laboratory-based tests, an Australian double-blind randomised controlled trial of oxygen therapy or air in patients with COPD without significant resting hypoxaemia found no greater relief of dyspnoea during activities of daily living in the oxygen group.[4] This raises the possibility that the small benefits in both groups were related to a placebo effect or an effect of gas flow on the face.[5]

Oxygen therapy during pulmonary rehabilitation

Oxygen supplementation during pulmonary rehabilitation in patients with COPD who desaturate with exertion is no more beneficial than supplemental air. This was shown in a double-blind randomised controlled trial, comparing oxygen and air delivered at 6 L/minute.[6] These results accord with those of a previous meta-analysis.[7]

Nocturnal oxygen therapy

Two small studies, reported over 20 years ago, investigated the impact of nocturnal oxygen therapy in patients with COPD who desaturated below 85% or 90% for more than a third of the night. Although one study showed a trend to improved pulmonary artery pressures in those randomised to receive nocturnal oxygen, no benefit was observed in the other study.[8,9]

The International Nocturnal Oxygen (INOX) trial also investigated patients with COPD and nocturnal desaturation. It was designed to test whether supplemental oxygen delivered via a concentrator would delay death or progression to long-term continuous oxygen therapy for longer than sham oxygen (air delivered via the identical device).[10] Recruitment and retention difficulties led to premature stopping of the trial, after recruitment of only 243 out of a projected 600 patients, with no benefits observed. Overall, the evidence to date does not support the use of nocturnal oxygen in patients without severe daytime hypoxaemia.

Oxygen for moderate hypoxaemia

The Long-Term Oxygen Treatment Trial originally aimed to test whether supplemental oxygen would improve survival in patients with COPD and moderate resting hypoxaemia (pulse oximetry: SpO_2 89–93%). Recruitment difficulties led to extension of the entry criteria to include exercise-induced desaturation and modification of the outcome measure to also include first hospitalisation for any cause. Compared to patients who did not use oxygen, there were no differences in any of the primary or secondary outcomes of the trial. The conclusion was that long-term supplemental oxygen in patients with stable COPD and resting or exercise-induced moderate desaturation has no benefit.[11] These results were consistent with a small study with similar entry criteria which found that oxygen had no mortality benefit in patients with moderate hypoxaemia.[12]

Palliative oxygen therapy

Home oxygen is often sought for managing intractable dyspnoea, but, in the absence of significant hypoxaemia, there is no convincing evidence that it provides greater benefit than sham oxygen.[13] Even in the presence of hypoxaemia and where underlying therapies have been maximised, oxygen may not relieve dyspnoea. Other palliative therapies including fans and opioids may be more appropriate for symptom management.

Assessment of oxygen requirements

Physicians often first become aware of a patient's hypoxaemia when the patient is admitted to hospital for an exacerbation of COPD. Oxygen is then often prescribed at hospital discharge, but this practice is not evidence-based. A New Zealand study reported that over a third of patients found to fulfil the criteria for long-term continuous oxygen therapy at hospital discharge no longer did so two months later.[14] Guidelines therefore recommend reviewing patients 4–8 weeks after discharge to assess their requirements for oxygen.[15]

To determine eligibility for long-term continuous oxygen therapy, the Thoracic Society of Australia and New Zealand (TSANZ) Adult Domiciliary Oxygen Therapy Clinical Practice Guideline recommends arterial blood gas analysis while the patient is breathing room air. This is because of the known inherent variability of measuring oxygen saturation with pulse oximetry.[15]

Assessments should be made at least one month after the patient has quit smoking. There should also be regular reviews to confirm any ongoing need and the adequacy of oxygen therapy, or the need for patients using oxygen for exertion to progress to long-term continuous oxygen therapy.[15]

For patients who do not fulfil the criteria for long-term continuous oxygen therapy, but who desaturate on exertion, a blinded trial of portable oxygen versus air may be appropriate to determine whether there is any improvement in dyspnoea or distance walked. Then,

after discussion with the patient, a trial at home may be in order, with a review to assess any benefit and the need for ongoing therapy.

Contraindications, adverse effects and dangers

Oxygen therapy is an absolute contraindication in patients who smoke because it is a fire risk. Open flames in the house such as from gas stoves or open fires may also present a risk. Identified issues surrounding the burden of therapy include decreased mobility, discomfort relating to the nasal prongs and noise relating to the device, to name a few.[16]

It is important that patients are aware that oxygen is a drug and should not be adjusted without consultation with the prescribing physician or therapist.

There is accumulating evidence regarding the burden placed on patients and carers by oxygen therapy, particularly ambulatory oxygen. Education about the potential benefits (or lack thereof) and burdens should occur when patients undergo assessment for home oxygen therapy. Patients benefit from discussing their beliefs and concerns, as their beliefs about oxygen influence its use.[17]

Oxygen supplies

In Australia there are three main methods of oxygen delivery. These are stationary concentrators for continuous use, and portable cylinders or portable concentrators for use during exertion.

While the TSANZ Guideline provides evidence-based guidance, the Australian states and territories vary in their interpretations and application of this advice and in their provision of oxygen therapy.[18] There are different programs across the country to access home oxygen, for example the State-Wide Equipment Program in Victoria and the Medical Aids Subsidy Scheme in Queensland.

Further information on programs for oxygen supply in various states in Australia is available from:

- State-wide Equipment Program (Vic.)
- Medical Aids Subsidy Scheme (Qld)
- Enable NSW (NSW)
- Respiratory Health Network (WA)
- SA Health Home Oxygen Therapy (SA)

Useful information for patients is available through the Lung Foundation Australia.

Conclusion

Oxygen therapy improves mortality in patients with COPD and severe hypoxaemia. The results of trials in COPD during the 1980s have been extrapolated to patients with other lung conditions. Any benefits of oxygen in patients with milder degrees of hypoxaemia who may desaturate on exertion or nocturnally are unclear and require further study. Adequate discussion of patients' beliefs and concerns about oxygen therapy is important and impacts their use of home therapy. ◀

Conflicts of interest: none declared

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New drugs

Burosumab

Approved indication: X-linked hypophosphataemia

Crysvita (Kyowa Kirin)
vials containing 10 mg/mL, 20 mg/mL, 30 mg/mL

X-linked hypophosphataemia is a rare cause of defective mineralisation of bone. The genetic mutation results in increased concentrations of fibroblast growth factor 23. This suppresses renal reabsorption of phosphate and inhibits the renal synthesis of 1,25-dihydroxyvitamin D. X-linked hypophosphataemia is a cause of rickets in children and osteomalacia in adults. Current management includes supplements of phosphate and vitamin D.

Burosumab is a monoclonal antibody that has been engineered to bind to fibroblast growth factor 23. By inhibiting the growth factor, burosumab increases concentrations of phosphate and 1,25-dihydroxyvitamin D.

The dose of burosumab is determined by the weight of the patient and fasting serum phosphate concentrations. It is given by subcutaneous injection every two weeks in children and every four weeks in adults. After the injection, it takes 7–13 days to reach the maximum concentration of burosumab. It is probably cleared like other antibodies and has a half-life of about 18 days. Burosumab should not be used in patients with severe renal impairment. Another contraindication is co-administration with phosphate and vitamin D. These supplements should be stopped one week before starting burosumab.

Phase II trials in children showed that burosumab increased serum phosphorous and reduced the severity of rickets.[1,2] An open-label phase III trial randomised 29 children to receive burosumab and 32 to continue conventional treatment. The average age of the children was approximately six years and they had a mean score of 3.2 on a 0–10 scale of rickets severity. After 40 weeks there was radiographic evidence of greater improvement in the children given burosumab. Their rickets severity score declined by 2.0 compared with a reduction of 0.7 in the control group. The difference between treatments was still present after 64 weeks.[3]

A double-blind phase III trial in adults randomised 68 patients to injections of burosumab and 66 to injections of placebo. These patients with X-linked hypophosphataemia were experiencing skeletal pain with most requiring analgesics. X-rays revealed nearly all patients had enthesopathy and 85 had a history of osteoarthritis. Fractures were present in 70 patients at the start of the study. A primary analysis after 24 weeks found a serum phosphate concentration above the lower limit of normal had been achieved by 94.1% of the burosumab group versus 7.6% of the placebo group. Concentrations of 1,25-dihydroxyvitamin D also increased. Stiffness was reduced with burosumab and more fractures had healed (43.1% vs 7.7%) during treatment. However, there was no clear benefit over placebo for pain or physical function.[4] An open-label extension of this trial treated all (119) patients with burosumab. Compared to baseline, patients reported improvements in pain, stiffness and physical function at 96 weeks.[5]

Injecting burosumab caused an injection-site reaction in 56% of the children and 12% of the adults. The site of injection should be rotated and no more than 1.5 mL should be injected into one site. In the paediatric phase III trial 38% of the children given burosumab had a hypersensitivity reaction, but these were not severe and treatment continued. Compared to conventional therapy, they also experienced more fever, headache, cough, arthralgia, diarrhoea and vomiting.[3] Dental infections were very common in children[3] and adults.[4] If hyperphosphataemia develops, the next dose should be withheld and a lower dose will be required when treatment resumes.

In animal studies burosumab had adverse effects during pregnancy. There are no data from pregnant women.

In children burosumab had favourable effects, but it is unclear which statistical differences from conventional treatment will be clinically significant. Longer term follow-up will be needed to see the effects on growth and deformity. In adults it is uncertain how burosumab compares with conventional treatment. Before the double-blind phase III trial, phosphate and vitamin D supplements had to be stopped.[4] Again, long-term monitoring of long-term treatment will be required.

T manufacturer provided the product information

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The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed 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.

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

Esketamine hydrochloride

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Approved indication: treatment-resistant depression

Spravato (Janssen-Cilag)
nasal spray containing 32.3 mg/0.2 mL

Some patients with major depressive disorder will not respond to antidepressant therapy, even if they have adhered to treatment with an adequate dose for an adequate duration. These patients then need to switch to another antidepressant.[1] In such treatment-resistant cases augmentation of antidepressant therapy may also be considered. One drug that has been used, off label, for augmentation is the anaesthetic drug ketamine.

The effect of ketamine in depression is thought to be related to its action on the N-methyl-D-aspartate (NMDA) receptor. By antagonising the NMDA receptor, ketamine may increase glutamate release and improve synaptic functioning.

Esketamine is the S-enantiomer of ketamine. It has a higher affinity for the NMDA receptor and can be given in a nasal spray. The bioavailability of an intranasal dose is approximately 48% with a peak plasma concentration 20–40 minutes later. Most of the dose is metabolised in the liver with most of the metabolites being excreted in the urine. The terminal half-life is 7–12 hours. Esketamine metabolism includes the cytochrome (CYP) P450 system, particularly CYP2B6 and CYP3A4. There are potential interactions with other drugs metabolised by these enzymes. No dose adjustment is needed in renal impairment or mild–moderate hepatic impairment.

Animal studies show that ketamine can cause developmental neurotoxicity during pregnancy. Women taking esketamine should use effective contraception during treatment and for six weeks afterwards. The risk of harm during breastfeeding is unknown.

Esketamine is a Schedule 8 drug and must be taken in the presence of a health professional. One spray is given into each nostril. When starting the drug, a dose determined by age is given twice weekly. After four weeks esketamine can be reduced to once weekly. Depending on the response, insufflation can possibly be reduced to fortnightly from week nine. If the patient improves, the recommendation is to continue treatment for at least six months.

The main clinical trials supporting the approval of esketamine have been included in a meta-analysis.[2] These five trials used changes in the 60-point Montgomery-Asberg Depression Rating Scale (MADRS) to assess efficacy. They involved 774 patients with major depressive disorder. In this pooled sample there was a response to augmentation of antidepressant treatment in 53.2% of the 442 patients who took esketamine and 38.5% achieved remission. For the 332 patients in the placebo group the response rate was 36.4% with 24.7% achieving remission. For patients starting a new antidepressant, approximately six need to be treated with esketamine for four weeks for one to benefit.[2]

In addition to the trials in the meta-analysis, the safety of esketamine was assessed in a long-term open-label study. This enrolled 802 patients with treatment-resistant depression and followed them for up to one year. The median treatment with esketamine was approximately 23 weeks. Most patients had adverse events with the most frequent being dizziness, dissociation, nausea, headache and somnolence. Adverse events led to 9.5% of the patients stopping esketamine.[3]

Esketamine can temporarily increase blood pressure so this should be measured before insufflation and about 40 minutes afterwards. The blood pressure usually returns towards pre-dose levels after about 90 minutes.[4] Emergency care is needed if there is a hypertensive crisis. Esketamine is contraindicated in patients with a history of aneurysm or intracerebral haemorrhage. After each dose patients should also be monitored for sedation and dissociation for at least two hours. They should not eat for at least two hours before a dose and should not drive or operate machinery until the following day.

Caution will be needed if prescribing for a patient with a history of substance abuse, including alcohol. Ketamine has been misused, but this may be less likely with esketamine. The risk of dependence with esketamine is uncertain.

While the meta-analysis showed a benefit, not all of the trials of esketamine have reported a clear advantage in treatment-resistant depression. In a study of 138 patients over the age of 65 years the MADRS score had declined after 28 days by 10 points with esketamine and by 6.3 points with placebo.[4] The rapid action of esketamine may be an advantage in managing patients with an imminent risk of suicide. A placebo-controlled trial involving 66 of these patients reported a mean decrease of 13.4 points in the MADRS score four hours after a dose of esketamine. The reduction in the placebo group was 9.1 points, but by 24 hours there was no difference between the groups in suicidal thoughts.[5]

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.

Lemborexant

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Approved indication: insomnia

Dayvigo (Eisai)
5 mg and 10 mg film-coated tablets

Lemborexant is a dual orexin receptor antagonist indicated for the treatment of insomnia, characterised by difficulties with sleep onset or sleep maintenance. Orexins are neuropeptides involved in regulating sleep and arousal by promoting wakefulness. Lemborexant blocks the binding of orexins A and B to their receptors 1 and 2 thereby reducing wakefulness and promoting sleep. Suvorexant is the other orexin receptor antagonist marketed in Australia for insomnia.

A single dose of lemborexant is taken a few minutes before going to bed, with at least seven hours remaining before the planned time of awakening. Lemborexant is rapidly absorbed with a time to peak concentration of 1–3 hours. The time to sleep onset may increase if lemborexant is taken with or soon after a meal. Lemborexant is mainly metabolised by cytochrome P450 (CYP) 3A4 with most of the metabolites being excreted in the faeces. The concomitant use of moderate or strong CYP3A inhibitors or inducers should be avoided. The effective half-life is 17 hours for lemborexant 5 mg and is 19 hours for lemborexant 10 mg.

Lemborexant is not recommended for patients with severe hepatic impairment. However, severe renal impairment has little effect on drug concentrations. Lemborexant has not been studied in patients with chronic obstructive pulmonary disease or moderate to severe obstructive sleep apnoea.

In a pivotal phase III trial of lemborexant, 1006 participants 55 years and older with insomnia received lemborexant, 5 mg or 10 mg, or zolpidem extended-release 6.25 mg or a placebo for one month at bedtime. The effect of treatment was assessed using polysomnography. Before treatment, the time to persistent sleep was approximately 45 minutes. After four weeks, this reduced to 25.8 minutes with lemborexant 5 mg, 22.8 minutes with lemborexant 10 mg, 37.1 minutes with zolpidem and 36 minutes with placebo. The sleep efficiency increased by 13–14% corresponding to an increase in the total sleep time of at least 60 minutes with lemborexant.[1]

Another phase III trial of lemborexant analysed 949 participants 18 years and older with insomnia who received placebo or lemborexant, 5 mg or 10 mg, for six months, followed by six months of lemborexant 5 mg or 10 mg. Patients who had received placebo in the first six months were re-randomised to lemborexant 5 mg or 10 mg. The patients maintained daily sleep diaries. After six months, participants taking lemborexant were falling asleep 22–28 minutes faster and sleeping for 70–74 minutes longer compared with baseline.[2] These results were maintained after 12 months of treatment. There were no reports of rebound insomnia or withdrawal following treatment discontinuation after 12 months.[3]

There were no statistically significant differences in adverse events across the placebo and lemborexant groups in the six-month analysis.[2] Adverse events caused discontinuation in 3.8% of the placebo group, 4.1% of the lemborexant 5 mg group, and 8.3% of the lemborexant 10 mg group. The most common adverse event was somnolence, which was more common in patients 65 years and older who received the 10 mg dose (2.3% vs 1.1% for lemborexant 5 mg vs 0.6% for placebo). Other less common adverse events included headache and fatigue.[2]

The incidence of suicidal ideation increases after taking lemborexant (0.3% for lemborexant 10 mg, 0.4% for lemborexant 5 mg, and 0.2% for placebo). Alcohol and other drugs that depress the central nervous system should be avoided. The safety of lemborexant in children and pregnant women is unknown. Lemborexant is contraindicated in narcolepsy.

A company-funded network meta-analysis of 45 studies compared lemborexant with 15 other insomnia treatments. Although the confidence intervals overlapped, patients receiving lemborexant were found to have the longest total sleep time, shortest time to persistent sleep and highest sleep efficiency. Treatment outcomes were similar in older adults. The safety profile, severe adverse events and rates of withdrawals due to adverse events were similar for lemborexant and all the other treatments.[4]

Lemborexant is effective and well tolerated for the treatment of insomnia. The lowest number of tablets feasible should be prescribed for the shortest possible time. To minimise the risk of discontinuation due to adverse events such as somnolence, the starting dose of lemborexant should be 5 mg.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

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Lurbinectedin

Aust Prescr 2022;45:31
https://doi.org/10.18773/austprescr.2021.064
First published 10 December 2021

Approved indication: small cell lung cancer

Zepzelca (Specialised Therapeutics)
vials containing 4 mg powder for reconstitution

Metastatic small cell lung cancer has a poor prognosis. Although many patients will have a response to chemotherapy, the cancer soon relapses. Their median survival can then be less than a year, so there is a need for effective second-line treatments.

Lurbinectedin is a cytotoxic drug with some similarity to trabectedin. It binds to DNA, affecting DNA repair and transcription leading to cell death.

The drug has to be reconstituted and diluted before being given by intravenous infusion over an hour. Lurbinectedin is thought to be metabolised by cytochrome P450 (CYP) 3A4. It is therefore recommended that strong inhibitors of CYP3A, such as the azole antifungals, be avoided. Moderate inhibitors, such as ciprofloxacin and erythromycin, should be avoided too, but if they have to be used the dose of lurbinectedin may need to be reduced. Strong inducers of CYP3A, such as phenytoin, and moderate inducers, such as phenobarbital, should be avoided. There are no clinical drug–drug interaction studies. The effect of severe hepatic or renal disease is unknown, but no changes in dose are required in mild disease. Most of the dose is metabolised then excreted in the faeces. The half-life is 51 hours.

The activity of lurbinectedin was investigated in several different cancers. An open-label phase II trial included 105 patients with small cell lung cancer that had progressed despite platinum-based chemotherapy. They were infused with lurbinectedin every three weeks. After a median follow-up of 17.1 months, the investigators thought that 35.2% of the patients met the criteria for a partial response. The median duration of the response was 5.3 months. Although the responders tended to survive longer, the median overall survival for all patients was 9.3 months.[1]

The results of this trial led to the phase III ATLANTIS trial of lurbinectedin in combination with doxorubicin for the treatment of small cell lung cancer that had progressed after platinum-based chemotherapy. This trial was also open-label, but patients were randomised to the regimen or the investigators' choice of treatment. At the time of writing the full results for the 631 patients in the ATLANTIS trial have not been published, but it is reported not to have met its primary end point. The median progression-free survival was four months with both treatments. The median overall survival was 8.6 months with lurbinectedin and doxorubicin compared with 7.6 months for the other treatments.[2]

Some of the toxicity of lurbinectedin can be predicted from its mechanism of action. Many patients develop myelosuppression, and neutropenia or thrombocytopenia require the dose of lurbinectedin to be modified. It should also be modified if hepatotoxicity emerges. Other adverse effects seen in the phase II trial included infections such as pneumonia, peripheral neuropathy, dyspnoea, fatigue, nausea, vomiting and diarrhoea.[1] Prophylactic antiemetic drugs may be given before the infusion.

Lurbinectedin has only been given provisional approval for use in Australia. More study is needed to work out how to use it and which patients may benefit. While the ATLANTIS trial did not show any survival advantage for lurbinectedin, the dose prescribed was less than that used in the phase II trial.[1,2]

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, 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.

NEW DRUGS

Aust Prescr 2022;45:32
https://doi.org/10.18773/austprescr.2021.065
First published 10 December 2021

Satralizumab

Approved indication: neuromyelitis optica spectrum disorder

Enspryng (Roche)
pre-filled syringes containing 120 mg/mL

Neuromyelitis optic spectrum disorder is an autoimmune disease that causes inflammation and demyelination in the central nervous system. It is distinct from multiple sclerosis and can cause permanent disability. Symptoms include loss of vision, paralysis, pain and bladder dysfunction. The treatments for multiple sclerosis are ineffective so acute management includes intravenous corticosteroids and plasma exchange. There is therefore interest in finding therapies to prevent attacks.

Many of the patients who have neuromyelitis optica spectrum disorder have AQP4 autoantibodies. Interleukin-6 has a role in the production of these autoantibodies and also aids their penetration of the blood–brain barrier by increasing its permeability. One strategy to prevent this process is to block the interleukin-6 signalling pathways. Satralizumab is a monoclonal antibody that has been genetically engineered to reduce the activity of interleukin-6 by binding to its receptors.

Satralizumab has to be given as a subcutaneous injection. The regimen begins with loading doses, followed by a monthly maintenance dose. Satralizumab has a half-life of about 30 days and is mainly cleared by catabolism.

There have been two randomised, double-blind, placebo-controlled, phase III trials of satralizumab.[1,2] The patients had experienced at least one relapse of neuromyelitis optica in the previous year. One trial[1] allowed the 83 participants to continue any immunosuppressive therapy, while the other did not.[2] In both trials the primary end point was the occurrence of a relapse. There were fewer relapses in the patients randomised to inject satralizumab. After 48 weeks, 76% and 89% of these patients had not had a relapse compared with 62% and 66% of the placebo groups (see Table).[1,2] Across both studies the hazard ratio was 0.42 (95% confidence interval 0.25, 0.71) representing a 58% reduction in the risk of relapse for patients injecting satralizumab. Patients who were seropositive for AQP4 autoantibodies tended to have more benefit from satralizumab.[1,2]

Injecting a monoclonal antibody can cause injection-site and hypersensitivity reactions. Patients should rotate where they inject between the abdomen and thighs. In the clinical trials adverse reactions that were more frequent with satralizumab than with placebo included headache, arthralgia and rashes.[1,2] Neutrophil numbers may decrease so the white blood cell count should be monitored. It may be necessary to withhold satralizumab, particularly if an infection develops. Treatment may also need to be halted if liver enzymes increase.

Satralizumab reduces relapses in patients with neuromyelitis optica spectrum disorder, but it is a rare disease so data are limited. A benefit on outcomes such as pain and fatigue was not seen in the trials.[1,2] There were few adolescents in the trials so efficacy and safety in patients younger than 18 years old is uncertain. Its safety in pregnancy is also unknown. The Australian approval of satralizumab is restricted to adults who are seropositive for the AQP4 autoantibody.

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

Table **Efficacy of satralizumab in phase III trials**

	Number of patients	Median duration of treatment	Patients with relapse	Annualised relapse rate	Proportion of patients free of relapse	
					48 weeks	96 weeks
Trial 1[1]	Satralizumab 41	107.4 weeks	8 (20%)	0.11	89%	78%
	Placebo 42	32.5 weeks	18 (43%)	0.32	66%	59%
Trial 2[2]	Satralizumab 63	92.3 weeks	19 (30%)	0.17	76%	72%
	Placebo 32	54.6 weeks	16 (50%)	0.41	62%	51%

Voretigene neparvovec

Aust Prescr 2022;45:33
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First published 10 December 2021

Approved indication: inherited retinal dystrophy

Luxturna (Novartis)
vials containing concentrate for dilution before subretinal injection

Conditions such as retinitis pigmentosa are now known to be due to the lack of an enzyme in the retinal pigment epithelium. This enzyme (RPE65) is involved in the processes that convert light to an electrical signal. An enzyme deficiency mainly affects the rods, so patients lose peripheral vision and the ability to see in low-light conditions. There is continuing retinal degeneration, so most affected children become blind. As genetic mutations can cause the absence of RPE65, there has been research into the possible role of gene therapy for the inherited retinal dystrophies.

Voretigene neparvovec is engineered to provide a copy of the gene that codes for RPE65. It is delivered to the retinal pigment epithelium by the subretinal injection of a viral vector. One dose is given into each eye, but there should be a gap of at least six days between injections. Patients require immunomodulation with prednisolone before and after the procedure. DNA from the vector may be detected in tears for a few days after the injection.

The main study of voretigene was an open-label phase III trial involving patients with biallelic mutations of the RPE65 gene. These patients had a visual acuity of 20/60 or less, or visual fields less than 20° in any meridian. They were unable to pass a multi-luminance mobility test (MLMT) at a light level of 1 lux. Nearly half the patients needed a light level of at least 125 lux to pass the test. Their average age at randomisation was 15.1 years. A group of 21 patients was given subretinal injections under general anaesthetic while another 10 acted as a control group. Within one month patients given voretigene were better able to see in low-light conditions. After one year, 65% of these patients were able to pass the MLMT at 1 lux. There was little change in the control group. The best corrected visual acuity increased by an average of 8.1 letters with treatment compared with 1.6 letters in the control group.[1]

The results for these patients were reviewed after two years, along with the outcomes for those involved in phase I trials. Patients in the control group of the phase III trial had the option of having injections of voretigene, so a total of 40 patients have been reviewed. The improvements in the MLMT were maintained. Sensitivity to light improved across the visual fields.[2]

Most of the adverse events with voretigene were associated with the procedure, for example retinal tears and haemorrhage. Other events reported in the phase III trial include raised intraocular pressure, cataract and inflammation of the eye. There is a risk of endophthalmitis. The immunomodulatory regimen may reduce the immune reaction to the injection of a viral vector. As the vector may be shed, waste material, such as dressings, should be stored in sealed bags before disposal. Patients should not donate blood. They should also avoid air travel soon after the injection as the treatment will leave an air bubble within the eye. This dissipates over time.

Only a small number of patients will be eligible to be treated with voretigene neparvovec. They will need to have genetic testing to confirm that they have a biallelic RPE65 mutation. It is also a requirement that they have an adequate number of viable retinal cells. Treatment improves the patients' ability to function in low-light conditions and this may be sustained for four years.[2] The changes in visual acuity may not be significant, but if visual acuity remains stable this would be an improvement on the natural history of inherited retinal dystrophy. The patients in the trials are going to be followed up for 15 years[2] so the long-term effects of treatment will become clearer.

T manufacturer provided the AusPAR

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At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

Zanubrutinib

Aust Prescr 2022;45:34–5
https://doi.org/10.18773/austprescr.2021.066
First published 10 December 2021

Approved indications: mantle cell lymphoma, Waldenström's macroglobulinaemia

Brukinsa (BeiGene)
80 mg capsules

Zanubrutinib is an inhibitor of Bruton's tyrosine kinase. This kinase is involved in amplifying the signals from B-cell receptors. It is essential for B-cell maturation and proliferation. Bruton's tyrosine kinase is therefore a target for the treatment of cancers that involve B cells for example non-Hodgkin lymphomas, including Waldenström's macroglobulinaemia and mantle cell lymphoma. Like the previously approved ibrutinib and acalabrutinib, zanubrutinib irreversibly binds to the kinase resulting in a prolonged inhibition of its activity.

The capsules are taken once or twice a day. Food has no effect on absorption. Zanubrutinib has a half-life of two to four hours with most of the dose being metabolised. As this metabolism involves cytochrome P450 (CYP) 3A, zanubrutinib will interact with inhibitors of this enzyme such as the azole antifungals, erythromycin and grapefruit juice. Inducers of CYP3A, such as rifampicin, phenytoin and St John's wort, should be avoided. A reduced dose of zanubrutinib is recommended for patients with severe hepatic impairment.

The efficacy and safety of zanubrutinib in mantle cell lymphoma was investigated in a phase II open-label trial. All 86 patients in the trial had been previously treated, but the lymphoma was refractory or had relapsed. They were all given zanubrutinib 160 mg twice daily. After a median follow-up of 18.4 months there had been an objective response, according to the international criteria for assessing lymphomas, in 72 (84%) of the patients. There was a complete response in 59 (68.6%). The estimated median duration of the response was 19.5 months with a median progression-free survival of 22.1 months. Overall survival at 12 months was 84.1%.[1]

Following a favourable response in preliminary studies of zanubrutinib in Waldenström's macroglobulinaemia, an open-label phase III trial enrolled 201 patients who were unsuitable for immunochemotherapy or had relapsed or refractory disease. They were randomised to receive zanubrutinib 160 mg twice daily (102 patients) or ibrutinib 420 mg once daily (99 patients). The response to treatment was assessed by an independent review committee using international consensus criteria. After a median follow-up of 19.4 months no patients had achieved a complete response. In the zanubrutinib group 28% were judged to have had a 'very good partial response' compared with 19% of the ibrutinib group. After 18 months, 97% of the zanubrutinib group and 93% of the ibrutinib group were still alive. The median duration of response and median progression-free survival had not been reached when the results were published.[2]

A three-year follow-up of 77 patients with Waldenström's macroglobulinaemia, who had participated in a preliminary study of zanubrutinib, reported an overall response rate of 45.2%. The estimated progression-free survival rate was 80.5% and overall survival was 84.8%.[3]

Pooled safety data from 779 patients showed that the most common adverse reactions include neutropenia, thrombocytopenia, anaemia, haemorrhage, pneumonia and diarrhoea. Some of these reactions were fatal. The dose regimen of zanubrutinib needs to be modified if haematological toxicity occurs. Some patients will develop atrial fibrillation, so particular caution is needed in patients with hypertension or other cardiovascular risk factors. Monitor for signs and symptoms of atrial fibrillation or flutter. During treatment with zanubrutinib secondary cancers can emerge. These are mostly skin cancers so sun protection is important. Overall, 3.6% of the trial participants withdrew because of adverse effects.

Like many new anticancer drugs, the optimum use of zanubrutinib still needs to be determined. It is not yet clear that favourable response rates will lead to improved survival. While more patients with Waldenström's macroglobulinaemia responded to zanubrutinib, the difference from ibrutinib was not statistically significant (risk difference 10.2%, 95% confidence interval –1.5, 22.0). Adverse effects such as atrial fibrillation, hypertension and diarrhoea were more frequent with ibrutinib, but zanubrutinib caused more cases of neutropenia including febrile neutropenia.[2]

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At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration.

Update

Antipsychotic switching tool [Update 4]

Aust Prescr 2022;45:35
https://doi.org/10.18773/austprescr.2022.008

The online tool by Nicholas Keks et al has been updated. View updated tool (v5).

It includes the new oral drug cariprazine hydrochloride, which was recently approved for use in Australia for schizophrenia.

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