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CONTENTS

EDITORIAL

Risky business? Pharmaceutical industry sponsorship of health consumer groups

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conflict of interest, consumer organisations, medical education, pharmaceutical industry

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Health consumer organisations can include groups specific to a particular condition, such as the Heart Foundation, and health system advocacy groups, such as the Consumers Health Forum of Australia. They play an important role in health care in Australia. Consumer organisations raise awareness about diseases and treatments, fund or conduct research on particular topics, and engage in advocacy for regulatory and legislative reforms that benefit consumers. These groups also educate and provide support to people living with a health condition and gain media attention for consumer issues.

Pharmaceutical industry sponsorship of health consumer groups is common. Since 2013, Medicines Australia has publicly reported the amount of money that member pharmaceutical companies provide to consumer organisations. From 2013 to 2016, companies provided a total of $34,507,810 to 230 Australian health consumer organisations. However, nearly half of these organisations made no mention of industry sponsorship on their websites and fewer than one in five had policies governing sponsorship.[1]

In a US survey of 245 health consumer groups, two-thirds reported pharmaceutical industry sponsorship with about 10% taking over $1 million each.[2] Ties may not be only financial – another US study found that 36% of 104 consumer groups had industry executives on their governing boards.[3]

Health consumer groups may derive important benefits from relationships with pharmaceutical companies.[4] Financial support enables groups to cover administration costs and pursue activities such as education, research funding and advocacy. In-kind support from companies may help groups to grow their organisation.

Health consumer groups are confident that they are able to withstand influence from their pharmaceutical company sponsors.[5] However, this same level of confidence is seen in other health sectors that receive pharmaceutical industry funding and evidence shows that this confidence is often misplaced. For example, even small gifts from pharmaceutical companies influence health professionals' behaviour, despite them strongly believing that they are not influenced by pharmaceutical company money.[6]

Ties between pharmaceutical companies and health consumer groups can be perceived as a conflict of interest. Companies with a fiduciary responsibility to shareholders to increase product sales tend to fund consumer groups representing patients with the conditions treated by their products. Health consumer groups have a primary mandate to represent the interests of members living with a specific condition. Industry ties could influence the ability of consumer groups to fully represent members' interests.[7]

Consumer groups have an important role in advocating for policies that can benefit patients. Condition-specific consumer groups often promote policies that enable access to treatment, for example by lobbying for a drug to be subsidised. Pharmaceutical companies may be eager to sponsor groups whose focus and advocacy is aimed at the disease and the drugs the companies make, because if those drugs become more accessible, sales will increase.

An Australian study identified that the industry prioritised payments to health consumer groups that were focused on diseases for which there were new drugs available. Indeed, most of the companies sponsoring the most heavily funded consumer groups had drugs under review for listing on the Pharmaceutical Benefits Scheme.[8] Companies are particularly keen to sponsor group activities likely to lead to more sales, with the bulk of industry money going towards public involvement (communication, advocacy, campaigning, disease awareness) and policy engagement activities. Much less goes towards patient support or organisational maintenance.[8-10]

Many health consumer groups consider they have closely aligned interests with pharmaceutical companies, making the sponsorship relationship useful for both parties. In particular, both sectors may be interested in public access to affordable new drugs. However, there are important ways in which the interests of the two sectors may diverge, including the promotion of expensive drugs or drugs with questionable efficacy or poor adverse-effect profiles. Although their interests may appear aligned, consumer groups might be placed in a position to overemphasise the benefits and downplay the harms of their sponsors' products, ultimately putting consumers at risk. For example, a US study found that pharmaceutical industry-sponsored consumer groups that provided commentary on a proposed guideline to restrict the use of opioids for chronic, non-cancer pain were more

likely to oppose the guideline than groups without such sponsorship.[11] Industry-funded consumer representatives to the European Medicines Agency were more likely, than those without industry funding, to support a legislative proposal permitting some direct-to-consumer advertising of prescription medicines.[12]

By funding consumer groups whose views are aligned, the pharmaceutical industry may magnify consumer opinions pushing for access to drugs. This may effectively silence those who argue for non-pharmaceutical measures or express concerns about overdiagnosis and overtreatment. Pharmaceutical funders may also push consumer groups to lobby for drug subsidies. Such public lobbying can influence media coverage of new treatments, policies that affect the regulatory approval or financial coverage of medicines, and public opinion. Given the lack of transparency around pharmaceutical industry support for consumer groups, it is often difficult for members of the public to know whether consumer voices have financial links to the manufacturers of the products they support.

Consumer organisations have a mission to educate patients and the public about diseases and treatments. One advantage of pharmaceutical industry sponsorship of consumer groups could be financial support for patient 'educational' materials or events. However, these groups should be aware that, globally, pharmaceutical industry sponsorship has been linked to biases in clinical research, education and practice.[13,14] An Australian study found that sponsoring pharmaceutical companies sometimes request direct access to consumers at educational events and seek to influence group communications through newsletters and conference materials.[4] Internal pharmaceutical company documents have defined education as a 'marketing strategy'.[15] Marketing messages tend to emphasise a medicine's benefits and provide limited information on harms[16] while promoting high-cost, brand-name drugs over well-established, safer generic alternatives.[17]

Sponsorship of consumer groups could also allow direct marketing to patients through a back door. Direct-to-consumer advertising is illegal in Australia, but industry sponsorship could give companies direct access to patients through their attendance at industry-sponsored events or participation in industry-sponsored support groups. This access could be used to gather information for marketing or for new types of promotion, such as through social media.[18]

By building relationships with consumer groups, pharmaceutical companies can shift the focus from patients and health to their own corporate interests. In order to maintain the flow of industry money, consumer groups may align their priorities with those of their sponsors. The company priority of selling more medicines may not be the best for public health. Consumers need to be represented by truly independent groups that have consumer interests as their main concern.

Health consumer organisations looking for guidance on how to manage relationships with industry sponsors have limited options. The Consumers Health Forum of Australia has produced a document in conjunction with Medicines Australia, the main organisation for the pharmaceutical industry.[19] Consumer organisations might also look to the industry's own Code of Conduct, which includes information on how the industry expects its member companies to behave. There is room for independent guidance to support groups that are looking for more assistance with developing and enacting sponsorship policies. We recently convened a seminar on this topic in conjunction with Health Consumers NSW and the Consumers Health Forum of Australia. The meeting report is available online.[20]

We encourage health professionals to investigate funding sources for health consumer groups that they mention to patients or engage with as advisors and to educate themselves about the risks such funding can create. Health professionals can then engage in open discussions with patients about what it might mean for a given consumer group to be funded by a particular company.

We strongly support the global move towards greater transparency around industry funding in the health sector,[21] including for health consumer organisations.[22-24] If health consumer organisations made clear disclosures about the extent, amount and uses of pharmaceutical industry sponsorship, this would allow patients and referring health professionals to be much better informed about the impacts of industry influence. ◀

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Letters to the Editor

Antidepressants and sexual adverse effects

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I am writing to complain about the article 'Choosing an antidepressant'.[1] The article did not define mild–moderate depression and did not mention screening patients to exclude an organic cause of the depression. It mentioned agitated depression, but not that agitation suggests a mixed state that would be worsened by antidepressants.

Sexual adverse effects are a significant problem with antidepressants, but the article only recommended agomelatine to minimise these effects. Mirtazapine, moclobemide, reboxetine, vortioxetine and bupropion all have favourable adverse-effect profiles. Agomelatine is an antidepressant produced by Servier and one of the authors has received payments from that company. It is not enough that authors declare their conflicts of interest. They should avoid publishing articles that could be perceived to be influenced by payment.

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Philip Boyce and Cassandra Ma, the authors of the article, comment:

We thank Dr Nielsen for his comments. While we agree that we did not define mild–moderate depression, we assumed most GPs would understand the term. We later stated that antidepressants are indicated for depressed patients with marked symptoms and functional impairment.

Screening patients for an organic cause for depression is important and we hope this would be part of routine practice. However, *Australian Prescriber* commissioned us to write about choosing an antidepressant, not the assessment of patients with depression.

Agitated depression can indicate a 'mixed state',[1,2] and the possibility of bipolarity (a history of a manic episode) should be examined in any patient presenting with an agitated depression. However, our article was referring to the more common situation in which an agitated depression is not part of a bipolar illness.

Sexual adverse effects are a significant problem and we included them when we rated the limitations of the classes of antidepressants. These ratings were based on our review of the literature and gauging the opinion of experts (the mood disorders guideline working party[2]) using a Delphi process. Minimum limitations are found with moclobemide, mianserin and agomelatine, while reboxetine, mirtazapine and vortioxetine are rated as having more limitations. We suggested that agomelatine be used for patients with sexual dysfunction based on its efficacy and very low reported levels of sexual dysfunction.[3]

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LETTERS

Stopping antiepileptic drugs – other factors to consider

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I read the informative article 'Discontinuation of antiepileptic drugs in adults with epilepsy' by Hanka Laue-Gizzi[1] and would like to highlight a few points regarding the factors which can affect the outcomes for patients.

The author described factors associated with seizure recurrence. A few more factors worth mentioning include the type of seizure, neurological examination, and any family history of epilepsy. Patients who had a single seizure type have more chance of remaining seizure-free after drug withdrawal. Generalised seizures have a better prognosis compared to focal seizures. Patients with a normal neurological examination have more chances of remaining seizure-free after drug withdrawal as do patients with no family history of epilepsy.[2]

The article also described important considerations for counselling. Apart from driving, patients should refrain from potentially dangerous activities such as swimming during the first three months after discontinuing therapy.[2]

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ARTICLE

Managing hoarding and squalor

SUMMARY

Hoarding and squalor are complex conditions with a range of physical and mental comorbidities.

GPs play a key role in identifying people who experience these conditions, screening for safety risks, referral to specialist services and encouraging people to accept treatment and ongoing monitoring. Treatment for contributing and comorbid conditions should be optimised, with the help of specialist services when required. Medicines should be reviewed and adherence confirmed.

For moderate to severe hoarding and squalor, referral to specialist psychiatry, geriatrics and allied health services is recommended for thorough assessment, treatment of underlying conditions and ongoing management.

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bipolar disorder, dementia, hoarding disorder, obsessive compulsive disorder, schizophrenia

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Introduction

Hoarding and squalor are complex conditions with diverse underlying aetiologies. In both conditions there is an accumulation of possessions or rubbish. Intervention is recommended due to a risk to the health and safety of the individual or others.

Although hoarding and squalor can at times appear similar in the home environment, they are two different, albeit sometimes overlapping, conditions. Hoarding disorder is a mental illness whereas squalor describes an unsanitary living environment, which may be the end result of extreme domestic neglect or hoarding.[1,2] A quarter of people with hoarding and squalor have a physical health problem that contributes to the state of their living environment, such as incontinence, immobility, or severe visual impairment.[3]

Hoarding and squalor can pose safety risks to the individual, other household occupants, pets and neighbours.[4,5] People who hoard, and other household members, have been found dead after being trapped by falling items. Accumulated objects increase the risk of falls, and insect or rodent infestations lead to health hazards.[5] The risk of fire and associated mortality is high.[6]

Hoarding

Hoarding becomes a disorder when it is excessive, reduces usable living space and interferes with people's lives.[7] A central feature is the accumulation of possessions due to difficulty discarding them related to distress, as opposed to poor motivation or unawareness concerning the need to discard.[3] Hoarding disorder can occur in the absence of another physical or mental disorder and is a distinct diagnosis in DSM-5 (Box 1).[8] Hoarding behaviour can also occur in association with various medical conditions (Box 2).[9]

Box 1 DSM-5 hoarding disorder – abbreviated diagnostic criteria

A. Difficulty discarding or parting with possessions, regardless of their value.

B. This difficulty is due to a perceived need to save the items and to distress associated with discarding them.

C. The difficulty discarding possessions results in the accumulation of possessions that congest and clutter active living areas and substantially compromises their intended use.

D. The hoarding causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The hoarding is not attributable to another medical condition.

Source: adapted from reference 8 (p. 247)

Box 2 Conditions in which hoarding behaviour can occur

- Acquired brain injury
- Attention deficit hyperactivity disorder
- Autism spectrum disorder
- Behavioural variant frontotemporal dementia
- Hoarding disorder
- Intellectual disability
- Obsessive compulsive disorder
- Obsessive compulsive personality disorder
- Parkinson's disease/dopamine agonist-associated impulse control disorder
- Prader-Willi syndrome
- Schizophrenia

Hoarding disorder tends to begin early in life and has a chronic, progressive course.[2,10] The prevalence is 1.5–5.8%.[11] Insight is limited in about half of cases.[10]

Approximately half of all people with hoarding disorder are impaired by a current physical health condition. Arthritis and sleep apnoea are common in older people who hoard.[12] Estimates of comorbid mental illness, such as mood, anxiety or attention deficit hyperactivity disorders, range from 56–85%.[11,13] Personality traits of perfectionism, indecisiveness and procrastination are associated with hoarding.[14] People with hoarding disorder often have a low quality of life and poor function.[15] The burden on family members is high.[16]

Squalor

Severe domestic squalor describes a home that is so unclean, messy and unhygienic that people of a similar culture and background would consider extensive clearing and cleaning essential.[17] This is not a diagnostic entity in current classification systems, but an epiphenomenon of other diagnoses. There are two main pathways to squalor – domestic neglect such as failure to remove rubbish, and hoarding such as excessive accumulation of items.[1]

People living in severe domestic squalor often refuse intervention, withdraw socially and lack insight into their living conditions.[1] About half are over 65 years old, and at least one in a 1000 people over 65 live in squalor.[1,18] Presentation is often precipitated by the loss of a partner, increasing frailty or symptoms of a neurocognitive disorder.[19] Neglect and elder abuse can also be potential factors.[20]

The majority of people living in squalor also have a psychiatric disorder (Box 3),[1] yet only half have had contact with a mental health service in the preceding year.[3] People living in squalor may be malnourished and mortality is high.[21,22]

Box 3 Conditions that can lead to squalor

- Vascular cognitive impairment
- Alzheimer's disease
- Frontotemporal dementia
- Acquired brain injury
- Alcohol or other substance misuse
- Depressive disorders
- Bipolar disorder
- Schizophrenia, other psychotic disorders
- Intellectual disability
- Autism spectrum disorder
- Personality disorders

Cognitive impairment

Cognitive impairment, specifically executive dysfunction (also known as frontal lobe impairment), is almost universal in people living in severe domestic squalor.[18] Executive dysfunction leads to deficits in planning, organisation, abstract reasoning, insight and decision making.[23] Similarly, hoarding is also associated with specific deficits in information processing, particularly attention, memory and executive functioning.[24,25] Hoarding and squalor may both arise from a frontal dysexecutive process.[26]

Getting help for individuals

It is uncommon for GPs to receive referrals for hoarding and squalor, but it is important for them to be aware of how to screen for the severity of hoarding and squalor along with the risk to safety, and pathways for assessment and referral.

Unless GPs do home visits, it is often not immediately obvious that a patient has hoarding disorder. Hoarding behaviour may first come to light through a variety of sources including neighbours, relatives, service providers, police, fire services, local council and accommodation providers. The person tasked with the initial assessment may be from a general or aged-care health service, mental health, welfare and community services or the local council.[27]

Assessment

Detailed multidisciplinary assessment is important in moderate to severe cases (Box 4). The team undertaking the initial assessment screens for underlying health issues, evaluates individual needs and can then refer on to specialist services for more targeted assessment and management. The assessment includes:

- the environment and symptom severity (including use of hoarding/clutter and squalor severity-specific tools)
- the person and contributing conditions (mental and physical health, cognition)
- functional impairment due to hoarding or squalor
- safety risks (including readiness for change and assessment of capacity).

Capacity to refuse treatment

Many people with hoarding disorder or living in squalor lack insight into their condition and refuse treatment.[28] If intervention is needed (because there is a risk to the person's health or to others) but declined, assessment of their capacity to refuse treatment is indicated. Given the high prevalence of executive impairment, it is not acceptable to withhold treatment out of a purported respect for the person's autonomy

Box 4 Principles of assessment of hoarding and squalor [30,33,40]

- **Engagement:** Build trust. Reframe your role in terms of meeting the person's perceived needs.
- **Home visit:** Beforehand, obtain information to identify safety issues.
- **Environment/symptom severity:** Assess the degree of hoarding/squalor and document it – take photos if the person permits, or use validated tools such as the Environmental Cleanliness and Clutter Scale (ECCS), Clutter Image Rating Scale (CIRS), Hoarding Rating Scale (HRS).
- **Contributing conditions:** Assess the factors underlying hoarding/squalor and possible comorbidities:
  A. **Physical health problems.**
  B. **Cognitive problems**: Executive function should be assessed. Mini Mental State Exam alone is insufficient and may be normal.
  C. **Mental health problems**: Assessment and usual treatment of comorbidities may need to be undertaken before or simultaneously, as they may interfere with addressing hoarding. For example, treatment for anxiety may assist with interventions to discard items.
- **Function:** Screen for impact on daily activities. For example, does the person:
  - sleep in their bed
  - have somewhere to sit
  - have a place to prepare food and a place to eat
  - use their toilet, shower, appliances/utilities e.g. fridge, water
  - move throughout the home safely
  - if there was a fire or a need for an ambulance, are the hallways clear?
- **Potential for harm/safety risks:** Assess the consequences of hoarding/squalor:
  - risks to the person themselves (e.g. risk of self-harm/suicide, imminent safety hazards like fire or falls, acute medical illness, ability to receive emergency services in the home)
  - risks to dependents (e.g. children and young people, adults in the household with a disability or frailty, pets)
  - risk of eviction/homelessness
  - medication safety.
- **Legal and ethical issues/capacity:** Assess the person's decision-making capacity in relation to hoarding/squalor. Are there other legal considerations? For example, does the council or another organisation have the power to override the person's wishes? Consider the person's readiness for change, and the safety risks, and capacity to refuse treatment in relation to the risks.
- **Collateral history** should be obtained.

without conducting a capacity assessment.[29] Attempts to engage affected individuals and promote capacity should be maximised. There are three main scenarios:

1. If the person has decision-making capacity but initially refuses assistance, there should be ongoing attempts to engage them. Over time the person may recognise the consequences of this decision and be more receptive towards help. Education and support for relatives are useful in preparation for when a person is ready to accept help or to respect their decision. If there are safety issues regarding the person's living conditions that cannot be addressed voluntarily, referral may be needed.[30]
2. If decision-making capacity cannot be assessed (e.g. the person will not open the door or engage), there are a few options. If there are signs of a mental illness, the person can be referred to a local psychiatric service for assessment. Guardianship legislation may be relevant if there are concerns about serious physical health issues and suspected lack of capacity. Aged Care Assessment Services may assist. Police may be asked to perform a welfare check. In some jurisdictions, local councils can order an inspection. Property inspections may also be conducted under residential tenancy legislation.[30]
3. If the person lacks decision-making capacity and there is a risk to safety or welfare, it may be necessary to appoint a substitute decision-maker or guardian through the local guardianship tribunal. The guardian can make decisions about interventions including medical treatment, services for cleaning and other domestic support, and moving into a residential aged-care facility where applicable. If decision-making incapacity is related to an underlying psychiatric illness, the local Mental Health Act may be more appropriate to enable treatment of the illness, which may lead to the person regaining capacity.[30]

Management of hoarding and squalor

The majority of evidence for specific management strategies in severe domestic squalor comes from case reports.[1] Management guidelines are consensus based.[1] A summary of interventions to manage hoarding and squalor is provided in Box 5. If another medical or psychiatric condition is the main driver of hoarding, this should be treated first.[1]

Box 5 Interventions for hoarding and squalor

- **Coordination of services**: they need to work together to deliver a consistent approach. A case manager or key worker should be identified to lead the response. Ideally, there is one coordinated intervention plan across agencies to facilitate collaboration and clear communication (including clear goals, support and timeframes).
- **Match the assessment to specific specialist services and interventions**, including:
  - Treat comorbidity and the underlying causes of the hoarding and squalor.
  - Arrange for community services to support people with functional impairment. Some people may not be able to have their complex or high needs met at home and may need to enter a residential aged-care facility or supported accommodation. Occupational or functional assessment may assist.
  - Arrange for services to assist with cleaning.
  - Consider making a cleaning agreement with the person and actively involve them, where appropriate, to reduce trauma.
  - Arrange or notify services as indicated e.g. Child Protection Services, RSPCA, Ageing and Disability Abuse Helpline.
- **A Team Care Arrangement** may help keep track of the numerous referrals and agencies involved and review outcomes.
- **Support the individual, their carers and relatives**. Interventions are often experienced as very stressful and there may be multiple unsuccessful attempts. When someone is not ready for change, relatives may need support. Resources and strategies for families and carers may be found in the book 'Digging Out' by Michael Tompkins et al.,[31] or online e.g. Hoarder.org.
- **Arrange ongoing funding** source (e.g. National Disability Insurance Scheme, My Aged Care), with **ongoing home-visit-based case management and domestic assistance** for support and monitoring to ensure maintenance of treatment gains.

Non-drug interventions

Cognitive Behavioural Therapy for Hoarding Disorder (CBT-H) reduces disease severity, but functional impairment may persist.[5,32] Therapy should target specific symptoms, such as emotional attachment to items, patterns of avoidance and neuropsychological deficits.[5] Behavioural approaches include:

- goal setting
- training in organising and problem-solving skills
- practice in sorting and discarding, and graded exposure to discarding.[5,33]

Motivational interviewing techniques may be useful.[5] Emerging approaches for moderate to severe hoarding include harm reduction[34] and community-based interventions[35] which focus on safety interventions with multidisciplinary and multi-agency responses.

Drug treatments

Clinical trials of drug treatments for hoarding disorder are of poor methodological quality but show modest benefit (Table).[36] Open-label trials suggest improvement with paroxetine in obsessive compulsive disorder with hoarding,[37] and with venlafaxine,[38] adjunctive methylphenidate[39] and atomoxetine in hoarding disorder.[40]

A coordinated approach

GPs, often with established long-term relationships with their patients, can play an important role in both the detection and management of hoarding and squalor (Box 6).[41] A coordinated approach should be provided to ensure the home is safe for the patient, others living in the same residence and any carers (Box 4). This can include developing safety goals with the individual, and regular home-visit support

Table Pharmacotherapy studies for hoarding

Study	Population	Intervention	Outcome
Saxena, et al[37]	OCD (n=32 with hoarding, n=47 without)	Paroxetine (open label, titrated to target dose of 40 mg/day), no other treatment	Both groups improved with no significant differences between groups. Hoarding symptoms improved as much as other OCD symptoms.
Saxena and Sumner[38]	Hoarding disorder (n=24)	Venlafaxine (open label, titrated to 150–300 mg/day), no other treatment	36% decrease in UCLA Hoarding Severity Scale score, 70% classified as 'responders'
Rodriguez, et al[39]	Hoarding disorder (n=4), one with comorbid OCD	Methylphenidate (open label, 18–72 mg/day), usual medicines continued	2 of the 4 subjects had a modest reduction in hoarding symptoms
Grassi, et al[40]	Hoarding disorder (n=12)	Atomoxetine (open label, flexible dose of 40–80 mg/day)	Statistically significant reduction on UCLA Hoarding Severity Scale for the group, 6 classified as 'responders' and 3 'partial responders'

OCD obsessive compulsive disorder

Box 6 General practice strategies for hoarding and squalor

- The general practice role is vital. A couple of questions can encourage a patient to consider making their home safer, receive assistance with their health, or start recovery. GPs can lead or be key advocates for intervention with other providers, making a significant difference in their patient's life.
- GPs can be alert for signs of hoarding and squalor e.g. patients with bags overstuffed or filled with a variety of objects, or problems with personal hygiene. GPs may have established relationships with patients and can connect them with services to address these problems.
- Initial screening in the medical centre or home can inform discussions about needed intervention and this information, with consent, can be shared with other services.
- Provide education on relevant medical complications associated with hoarding or squalor. Motivational interviewing assists readiness for change. Effects on physical health can help with motivation to start to make homes safe and comfortable.
- Collaborate with other service providers to coordinate services and develop a management plan. Where possible share information on the severity and impact on daily activities and function to assist with establishing priorities.

Source: adapted from reference 41

to declutter key areas, motivational interviewing, emotional support, and physical assistance or cleaning if the person is frail. GPs are also well placed to ensure underlying physical and mental health conditions are being managed, and to check on medication adherence, use-by date and storage.

In severe cases, specialised cleaning and pest eradication may be needed, particularly for squalor. Cleaning and decluttering can be distressing. Emotional support, a written cleaning agreement, and a slow clean approach where possible are recommended.[34] One-off cleaning is usually inadequate and does not address excessive acquisition.[42] When a one-off clean has occurred, a thorough ongoing management plan should be developed including follow-up and support to prevent recurrence, such as ongoing home-based case management, community treatment orders for underlying mental illness, and monitoring by GPs and other health professionals.[30] Where possible, the management plan should be shared across services to prevent or reduce the likelihood of recurrence or deterioration in mental health.

Some non-governmental organisations in Australia, such as Catholic Healthcare, have hoarding and squalor programs and support groups (e.g. hsru.com.au). Some allied health professionals such as occupational therapists, social workers and psychologists identify as having specialist skills in hoarding and squalor. Private allied health professionals can provide specific programs for hoarding and squalor, particularly when the person has a funding source, such as under a National Disability Insurance Scheme or My Aged Care package in Australia.

Conclusion

Severe hoarding disorder and squalor are complex and challenging to manage. These conditions can often be debilitating for a person and their family. Health workers and people from social services who provide care often feel overwhelmed. Hoarding and squalor can lead to violation of health, housing and sanitation laws. A multiservice, multidisciplinary approach is often required. Medical, social and ethical dimensions need to be considered, and ideally clinical and environmental assessments should occur. <

Conflicts of interest: none declared

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ARTICLE

Drugs in secondary stroke prevention

SUMMARY

After an ischaemic stroke or transient ischaemic attack, patients have a high risk of having another stroke. Secondary stroke prevention includes antiplatelet therapy, statins and antihypertensives.

Aspirin, clopidogrel, or a combination of aspirin with dipyridamole are first-line options for secondary stroke prevention in the absence of atrial fibrillation.

Dual antiplatelet therapy has a benefit in the first three weeks after stroke, but patients should change to a single antiplatelet drug after this time.

Anticoagulants are indicated if the patient has atrial fibrillation. Avoid combinations of anticoagulants and antiplatelet drugs.

Patients should be started on statins after an ischaemic stroke. High doses are recommended even if cholesterol concentrations are normal.

Antihypertensive drugs are recommended for all patients with systolic blood pressures greater than 140/90 mmHg. ACE inhibitors, calcium channel blockers and diuretics are first-line options.

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anticoagulants, antiplatelet drugs, cerebrovascular disease, stroke

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Introduction

Each year almost 20,000 Australians have a stroke, the majority of which are ischaemic.[1] The 10-year recurrence rate following a first stroke is over 40%.[2] To prevent recurrences patients are managed with a combination of drugs and lifestyle modification. Pharmacotherapy is critical for optimising outcomes for patients after an ischaemic stroke or transient ischaemic attack (see Fig.). Treatment recommendations change regularly, and as such there are a set of living guidelines for secondary stroke prevention that are continually reviewed and updated.[3] Adherence to treatment is also important.

Antiplatelet drugs

The efficacy of antiplatelet drugs for secondary stroke prevention is well established.[4] Antiplatelet therapy should start as soon as possible following a stroke or transient ischaemic attack.[5] Current Australian guidelines recommend either aspirin, clopidogrel or a combination of aspirin and dipyridamole (see Table). Antiplatelets carry some risk of gastrointestinal bleeding. The routine use of proton pump inhibitors is restricted to those considered higher risk, for example patients with a history of gastrointestinal ulcer, or those over 60 years with gastro-oesophageal reflux disease.[6]

Aspirin

A 2016 meta-analysis found that aspirin at daily doses of 75–162 mg or 500–1500 mg reduced long-term recurrence of stroke more than placebo.[7] However, there was an increased risk of bleeding with the increased dose range, so typically doses of 75–150 mg are used. The benefit of aspirin has been shown to be even more marked for secondary stroke prevention in the first six weeks post stroke.[5]

Aspirin/dipyridamole

Dipyridamole should not be used alone in stroke prevention. In trials it was combined with aspirin, typically as aspirin 25 mg and dipyridamole 200 mg. This is an acceptable antiplatelet combination for patients with non-cardioembolic ischaemic stroke or transient ischaemic attack.

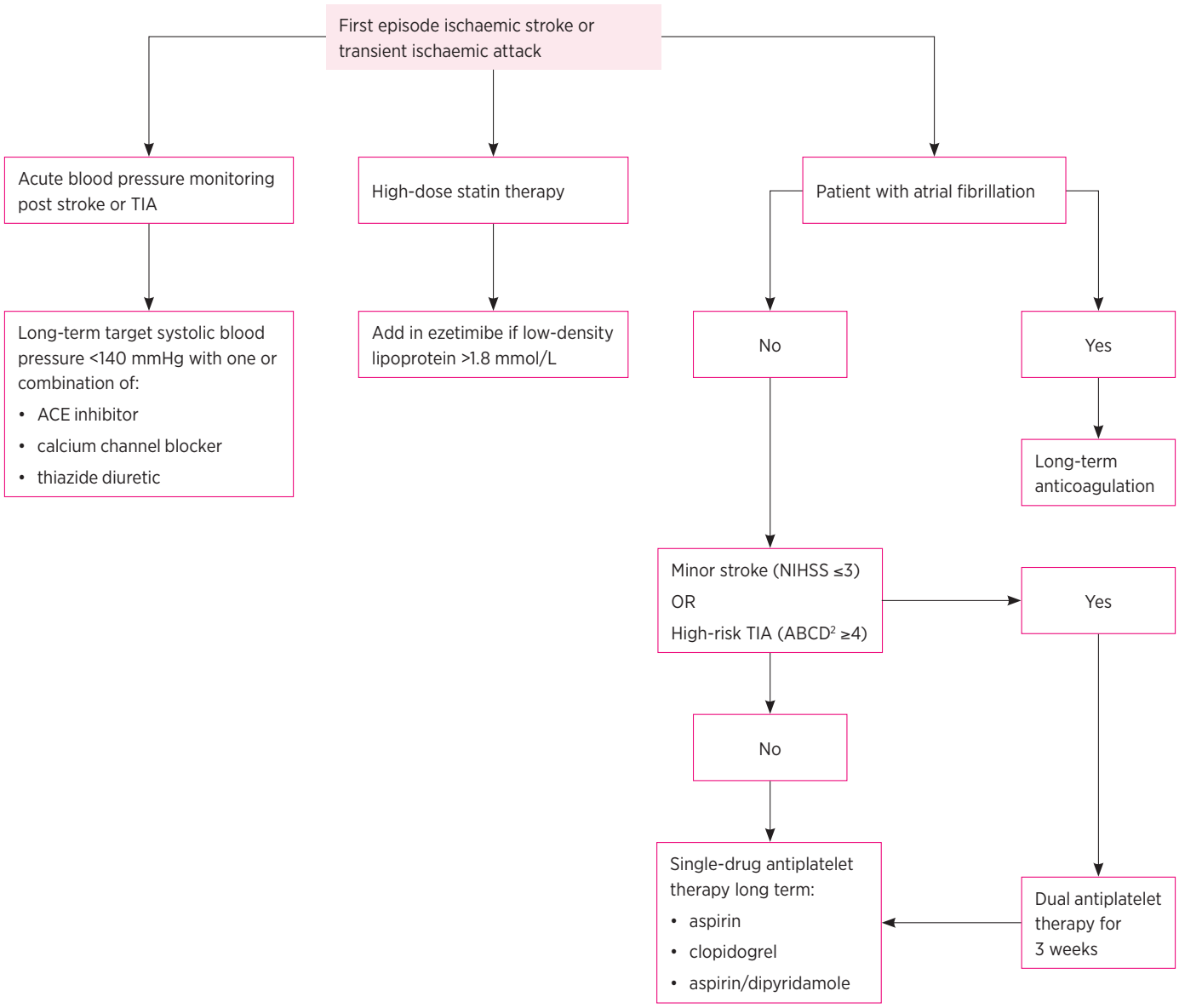
The 2006 ESPRIT trial found that the combination of aspirin and dipyridamole had a benefit over aspirin alone with regard to secondary stroke risk, and non-fatal bleeding.[8] It is worth noting however that the majority of patients were randomised after more than one month, and so it is unclear if aspirin/dipyridamole has benefit over aspirin immediately after a stroke.

Dipyridamole has a vasodilatory action and headache is a common adverse effect which may lower adherence to treatment.[9] Dipyridamole's vasodilatory effect also means care should be used in patients with unstable angina or aortic stenosis.

$P2Y_{12}$ inhibitors

Clopidogrel, a $P2Y_{12}$ inhibitor, has efficacy for secondary stroke prevention at doses of 75 mg.[10] A 2019 meta-analysis found a benefit for clopidogrel over aspirin and aspirin/dipyridamole for reducing major bleeding and intracranial haemorrhage.[11]

Fig. **Drugs for secondary stroke prevention**



NIHSS National Institutes of Health Stroke Scale

Table **Comparative efficacy of antiplatelet drugs for secondary stroke prevention**

	Aspirin versus placebo	Clopidogrel versus placebo	Aspirin/dipyridamole versus placebo
Recurrent stroke (up to 27 months)	Odds ratio 0.78 (95% CI 0.63–0.99)	Odds ratio 0.68 (95% CI 0.53-0.92)	Odds ratio 0.69 (95% CI 0.56-0.89)
Bleeding (up to 27 months)	Odds ratio 2.33 (95% CI 1.73–3.30)	Odds ratio 1.79 (95% CI 1.23-2.78)	Odds ratio 1.95 (95% CI 1.43-2.78)
Serious vascular event (up to 27 months)	Odds ratio 0.83 (95% CI 0.71-0.96)	Odds ratio 0.74 (95% CI 0.65-0.86)	Odds ratio 0.72 (95% CI 0.63-0.83)

Adapted from reference 3
CI confidence interval

Ticagrelor, another $P2Y_{12}$ antagonist, has not been shown to offer a benefit over aspirin for monotherapy.[12] It is not recommended in guidelines or approved by the Therapeutic Goods Administration for stroke prevention in Australia.

Recurrent stroke while on antiplatelet therapy

Patients may have 'breakthrough' cryptogenic strokes despite antiplatelet therapy. It is worth discussing the patient's adherence to treatment and working with them on strategies to improve this if there is a problem.[13]

Studies have shown that patients adherent with aspirin benefit from a change to a different antiplatelet drug if they have a breakthrough ischaemic stroke.[14,15] 'Clopidogrel resistance' is a phenomenon well studied in acute coronary syndrome, but less so in stroke, making it a challenge to guide management of breakthrough stroke on clopidogrel.[16] Screening for clopidogrel resistance is not currently recommended.[17]

Dual antiplatelet therapy

Dual antiplatelet therapy in secondary stroke prevention has received increased attention due to two major randomised controlled trials – CHANCE and POINT. CHANCE found aspirin and clopidogrel given together for the first 21 days after a high-risk transient ischaemic attack ($ABCD^2 \geq 4$)[18] or minor stroke (National Institutes of Health Stroke Scale ≤3)[19] reduced recurrence without a risk of increased bleeding compared to aspirin alone.[20] The POINT study showed a reduction in ischaemic stroke at 90 days for patients on the aspirin/clopidogrel combination compared to aspirin alone in minor stroke or high-risk transient ischaemic attack, at the cost of an increased rate of major haemorrhage.[21] A subsequent meta-analysis including both trials has suggested that dual antiplatelets appear to be most beneficial in the first three weeks following minor stroke.[22] In Australia, the Stroke Foundation currently advises using dual antiplatelet therapy for three weeks after a non-valvular, non-arrhythmic, minor ischaemic stroke or high-risk transient ischaemic attack then switching to monotherapy.[3] There is no evidence to continue dual therapy beyond 90 days. For larger strokes (NIHSS >3), the risk of bleeding from dual antiplatelet therapy outweighs the benefits and is not routine practice.

The combination of aspirin with ticagrelor was recently compared to aspirin alone in the first 30 days after a stroke. This THALES study found the combination to be superior for prevention of stroke or death, but with an increased risk of major bleeding.[23] Ticagrelor is not currently listed on the Pharmaceutical Benefits Scheme for stroke prevention, and like other combinations, the combination with aspirin has no evidence beyond 30 days.

Dual antiplatelet therapy will typically be used for 30 days after carotid artery stenting. However, there is no evidence to support dual antiplatelet therapy after carotid endarterectomy.[24]

Anticoagulants and atrial fibrillation

The evidence for anticoagulants for the secondary prevention of ischaemic stroke in a patient with non-rheumatic atrial fibrillation without mechanical heart valves is unequivocal.[25,26] The direct oral anticoagulants are now preferred to warfarin for secondary stroke prevention. This is because a meta-analysis found non-inferiority for preventing ischaemic stroke and superiority for rates of haemorrhagic stroke.[27] Warfarin does have some advantages in the risk of gastrointestinal bleeding, and can also be used in patients with an estimated glomerular filtration rate (eGFR) below 15 mL/minute. The choice of direct oral anticoagulant is individualised based on renal function, ability to adhere to the dosing schedule and the likely need for reversal of anticoagulation.[28]

There are concerns that cryptogenic strokes may be due to undiagnosed paroxysmal atrial fibrillation,[29,30] creating the idea that anticoagulants may have a role even if the arrhythmia is not detected.[31,32] However, evidence to support this is lacking, and anticoagulants post stroke without evidence of atrial fibrillation are not recommended for secondary stroke prevention due to the increased risk of bleeding.[33]

There is no role for antiplatelets in secondary stroke prevention in patients with atrial fibrillation as they should be anticoagulated. After a stroke, patients taking anticoagulants for atrial fibrillation should stop antiplatelet drugs, unless there is another indication for antiplatelet therapy, such as previous acute myocardial infarction or coronary stents. Clinicians should liaise with the patient's cardiologist with a view to stopping the antiplatelet drugs when possible.

Blood pressure management

The Australian Clinical Guidelines for Stroke Management currently recommend a reduction of systolic blood pressure to less than 140 mmHg.[3] A target of below 130 mmHg has been suggested to offer a small additional benefit in secondary stroke prevention for patients with lacunar infarcts. This comes at the risk of increased unsteadiness, especially in older patients.[34,35] The blood pressure target will also depend on evidence of other sequelae of hypertension, such as renal impairment.

ACE inhibitors, calcium channel blockers and thiazide diuretics are first-line options for blood pressure control

after a stroke.[36] The choice should be individualised for each patient. A large meta-analysis of cardiovascular outcomes found beta blockers may be inferior to other antihypertensive drugs in stroke prevention.[37]

Adherence to diuretics has been shown repeatedly to be worse than with other antihypertensives.[38] The adherence to the other drugs is around 80% one year after the stroke. Programs designed to increase patient adherence and improve blood pressure long term have shown some benefit on adherence, but not on blood pressure.[39] Of concern, however, is evidence that people who remain hypertensive after a stroke are under-prescribed antihypertensive drugs despite a clear benefit in stroke prevention.[40]

Cholesterol management

High-dose statins, such as atorvastatin 80 mg or rosuvastatin 40 mg, are first-line treatment for all patients following ischaemic strokes regardless of their cholesterol.[3] This is because a meta-analysis found high-dose statins offered a protective effect against further ischaemic strokes even when cholesterol was not elevated.[41] There had been concerns that statins may cause an increase in intracerebral haemorrhage based on results from the SPARCL trial and the Heart Protection Study.[42,43] However, this was not borne out in a subsequent meta-analysis, which also reported that statins improved all-cause mortality, functional outcome, and the risk of stroke regardless of type.[44] In patients who cannot tolerate high-dose statins, low-dose statins should still be tried.

A 2020 randomised controlled trial found that a target low-density lipoprotein concentration of less than 1.8 mmol/L had benefit in protecting patients post stroke from cardiovascular events, compared to a target of 2.3–2.8 mmol/L.[45] Patients in the lower target group typically received ezetimibe if their cholesterol remained elevated, although there was no fixed regimen. Ezetimibe is also recommended for patients who are statin intolerant as second-line therapy.[46] This is mainly based on the IMPROVE-IT trial, which studied patients with acute coronary syndrome.[47] It is unclear if ezetimibe works as monotherapy.[48] The main adverse effects of ezetimibe include myalgias, headaches and hepatitis.

Fibrates have not been shown to be beneficial in secondary stroke prevention. They are not recommended in treatment guidelines.[49,50]

Conclusion

After a stroke, patients are at risk of further ischaemic strokes, particularly in the first few weeks. Antiplatelet drugs, statins and antihypertensive drugs are the mainstay of pharmacotherapy for secondary stroke prevention. If dual antiplatelet therapy is used after a stroke, clinicians should ensure patients return to single drug therapy three weeks later. Patients with atrial fibrillation should be anticoagulated. Combinations of anticoagulants and antiplatelets should be avoided if possible. Liaise with the patient's neurologist and cardiologist if the patient is taking anticoagulants and antiplatelets to confirm whether combined treatment is intended.

The target blood pressure should be less than 140 mmHg systolic. ACE inhibitors, calcium channel blockers or thiazide diuretics can be used. Statins are first-line treatment and a target low-density lipoprotein of less than 1.8 mmol/L is now recommended.

Conflicts of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. After a stroke, all patients should take an anticoagulant for secondary stroke prevention.

2. After a stroke, normotensive patients should be started on antihypertensive drugs.

Answers on page 113

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ARTICLE

Updated anaphylaxis guidelines: management in infants and children

SUMMARY

Severe allergic reactions (anaphylaxis) are unpredictable, and initial signs of what could be fatal anaphylaxis can be mild.

Adrenaline (epinephrine) remains the first-line drug of choice for the acute management of anaphylaxis and should be administered early.

There are no contraindications to intramuscular adrenaline in the treatment of anaphylaxis.

Correct positioning of the patient is vital as death can occur within minutes if a patient stands, walks or sits up suddenly. Position the patient correctly first and then promptly administer intramuscular adrenaline.

Updated guidelines by the Australasian Society of Clinical Immunology and Allergy now recommend that the 0.15 mg adrenaline injector device may be prescribed for infants and children weighing 7.5–10 kg. The recommendation to use the 0.3 mg adrenaline injector device for those over 20 kg remains unchanged.

The adrenaline doses in Australian Prescriber's anaphylaxis wallchart remain valid.

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Introduction

Anaphylaxis is a potentially life-threatening severe allergic reaction and adrenaline (epinephrine) remains the first-line treatment. The Australasian Society of Clinical Immunology and Allergy (ASCIA) has recently updated its dose recommendations for adrenaline injectors in children.[1]

Rates of hospital admission for anaphylaxis in Australia are increasing, particularly for food-related anaphylaxis in older children and adolescents.[2] There has been a similar increase in all-cause fatal anaphylaxis in Australia in the last two decades. In keeping with the increasing incidence in children and adolescents, these age groups have the highest risk of fatality from food-related anaphylaxis.[3]

Anaphylaxis – presenting symptoms

ASCIA defines anaphylaxis as:

- any acute onset illness with typical skin features (e.g. urticarial rash or erythema or flushing with or without angioedema), plus involvement of respiratory or cardiovascular symptoms with or without persistent severe gastrointestinal symptoms, OR
- any acute onset of hypotension or bronchospasm or upper airway obstruction where anaphylaxis is considered possible, even if typical skin features are not present.[1]

Gastrointestinal symptoms of any severity including abdominal pain or vomiting may be signs of anaphylaxis from an insect sting or injected drug allergy. However, severe, persistent gastrointestinal symptoms may be a feature of anaphylaxis from any cause (see Box 1).[1,4-6]

Anaphylaxis is unpredictable and signs of a potentially fatal anaphylaxis can initially appear mild.[3,7] However, mild or moderate allergic symptoms may not always precede anaphylaxis.[4,5,7] Risk factors for fatal anaphylaxis include upright posture during and after anaphylaxis, delayed administration of adrenaline, concomitant asthma and delayed initiation of CPR after collapse.[3,8]

Management

Adrenaline is the first-line drug for anaphylaxis.[5,9-11] It works by reducing airway mucosal oedema, inducing bronchodilation and vasoconstriction and increasing cardiac contraction strength. Intramuscular adrenaline should be administered without delay into the outer mid-thigh if features of anaphylaxis are present.[1,5,9] There are no contraindications to intramuscular adrenaline in the treatment of anaphylaxis.[11-13]

Given the rapid onset of anaphylaxis, its potential severity and ethical issues, there are no published pharmacodynamic dose response studies of adrenaline in anaphylaxis. Adrenaline dosage is based on common practice and limited studies in healthy volunteers.[12,14]

Box 1 **Signs and symptoms of allergic reactions in infants**[6]

Mild to moderate reaction	Severe reaction (anaphylaxis)
Cutaneous • urticaria • angioedema	Respiratory • swelling of tongue • swelling in throat (e.g. hoarseness, croakiness or difficulty vocalising) • wheeze, stridor or persistent cough • laboured or noisy breathing • low oxygen saturation • rapid respiratory rate for age • low respiratory rate may indicate impending respiratory arrest
Gastrointestinal • tingling mouth • abdominal pain • vomiting*	Cardiovascular • hypotension is a late sign in infants due to high peripheral vascular resistance and can represent a pre-arrest sign • collapse • pallor and floppiness • tachycardia – rapid resting heart rate for age may signal hypotension
Other signs • face (eye, ear, nose) rubbing • sneezing • sudden onset of clear nasal discharge • conjunctival redness • irritability • clinging to caregiver	Behavioural changes • sudden drowsiness • unresponsiveness • loss of consciousness

* abdominal pain and vomiting are signs of anaphylaxis in insect sting or injected drug allergy

Intramuscular adrenaline is first line

In patients of all ages using adrenaline 1:1000, 0.01 mL/kg up to 0.5 mL (0.5 mg) per dose is recommended using an adrenaline ampoule and syringe or an adrenaline injector device (Table).[1,5,9,10,13] Repeat doses are recommended at five minute intervals if there are ongoing symptoms. An adrenaline infusion should be considered if signs persist despite administration of two or more doses, if skills and equipment are available.[1,5,9,11-13]

Boluses of intravenous adrenaline are associated with a significantly increased risk of adverse effects and overdose, and should be avoided.[15,16] Subcutaneous adrenaline is not as reliably absorbed as intramuscular and should also be avoided.[17]

A person with both known asthma and an allergy to food, insects or a medicine who has a sudden onset of difficulty breathing (including wheeze, persistent cough or hoarse voice) should always be given adrenaline first, then a bronchodilator, even in the absence of cutaneous symptoms.

Adrenaline injectors

Adrenaline injectors allow rapid, reliable delivery of intramuscular adrenaline. They were designed to make it easier for non-medical people to administer adrenaline in an emergency. Adrenaline injectors also reduce the risk of dosing errors associated with adrenaline ampoules and syringes, especially in the community.[14,18]

Up to two adrenaline injectors can be prescribed on the Pharmaceutical Benefits Scheme (PBS) for patients at risk of anaphylaxis. The initial PBS authority requires either discharge from the emergency department or hospital after treatment with adrenaline for anaphylaxis or consultation with a clinical immunologist or allergy specialist, paediatrician or respiratory physician. Additional devices can be purchased over-the-counter at full cost.

Updated guidelines for infants and small children

From 1 September 2021, injector devices will be available in three dose sizes containing 0.15 mg, 0.3 mg and 0.5 mg adrenaline. In infants and young children weighing less than 10 kg, this poses a challenge for prescribing an adrenaline injector. ASCIA recently updated the weight recommendations for the use of an adrenaline injector in children.[1] A 0.15 mg device may now be prescribed for an infant weighing 7.5–10 kg, following a considered assessment. Previously this device was only recommended for children weighing 10–20 kg. This update is based on the safety of intramuscular adrenaline in children at the recommended doses and is supported by international professional consensus.[5,9,11,13,14]

The use of a 0.15 mg adrenaline injector device for infants weighing 7.5 kg will deliver up to 200% of the recommended 0.01 mg/kg adrenaline dose. However, delivering it via an injector poses less risk than using an adrenaline ampoule and syringe where dosing errors and delays in administration increase the risk of harm, particularly when used without medical training.[14,18]

There are no published cases of bone injury or adrenaline delivery failure from an adrenaline injector needle tip striking the femur in children weighing less than 10 kg, despite theoretical risks. Bunching the skin and muscle of the mid-thigh may help to reduce this risk.[14,19] The ASCIA recommendation to prescribe a 0.3 mg adrenaline injector to individuals weighing at least 20 kg to reduce the risk of under-dosing adrenaline remains unchanged.[1,11,14]

Infants with anaphylaxis may remain pale despite 2–3 doses of adrenaline. This can resolve without further doses[6] so persistent pallor alone is not an

indication for more adrenaline. In addition, more than 2–3 doses of adrenaline in infants may cause hypertension and tachycardia, and the tachycardia is often misinterpreted as an ongoing cardiovascular compromise or anaphylaxis.[6] To check if additional doses of adrenaline are required, measuring blood pressure can provide a guide to the effectiveness of treatment.[6,16]

Positioning of the patient

Correct positioning of a patient being treated for anaphylaxis is vital (see Fig.) as death can occur within minutes if a patient stands, walks or sits up suddenly.[3] Laying the patient flat improves venous blood return to the heart. A patient must not walk or stand, even if they appear to have recovered. A wheelchair, stretcher or trolley should always be used to transfer the patient to and from the ambulance, treatment room bed and toilet.[1] The left lateral (recovery) position is recommended if someone with anaphylaxis is vomiting.

Patients with respiratory symptoms, which are the most common feature of anaphylaxis in children, may prefer to sit to help with breathing and improve ventilation. They should sit with their legs outstretched in front of them, not in a chair, and must be monitored closely as even sitting may trigger hypotension.

Infants with anaphylaxis may appear pale and floppy and should be held horizontally in the carer's arms and not upright over the shoulder. The left lateral (recovery) position is recommended for pregnant patients as this reduces the risk of compression of the inferior vena cava by the uterus and improves venous return to the heart.[20]

Other drug options after adrenaline

Bronchodilators such as salbutamol may be given for persistent wheeze after adrenaline. Antihistamines and corticosteroids should not be given before or in place of adrenaline in the treatment of anaphylaxis. Antihistamines do not treat or prevent anaphylaxis or biphasic reactions but may reduce pruritis and can be given after adrenaline.[1,5,9] The benefit of corticosteroids is unproven in anaphylaxis, but they are sometimes given after adrenaline in people with a history of reactive airways or to help prevent biphasic reactions. However, the evidence of benefit is scant.[1,2,9] Intravenous promethazine should not be used in anaphylaxis because it can cause hypotension and muscle necrosis.

For hypotensive patients, give intravenous fluids (normal saline 20 mL/kg to a maximum of 1 L in the first 30 minutes) and consider an adrenaline infusion. In patients with cardiogenic shock despite

Table **Adrenaline (epinephrine) dosing for the treatment of anaphylaxis**

Approximate age (years)	Weight (kg)	Vol. adrenaline 1:1000	Adrenaline injector
<1	<7.5	0.1 mL	0.1 mg device (not currently available in Australia or New Zealand)
1–2	10	0.1 mL	7.5-20 kg (~<5yrs) 0.15mg device
2–3	15	0.15 mL	
4–6	20	0.2 mL	
7–10	30	0.3 mL	>20kg (~>5yrs) 0.3mg device
10–12	40	0.4 mL	
>12 and adults	>50	0.5 mL	>50kg (~>12 years) 0.3mg or 0.5mg devices

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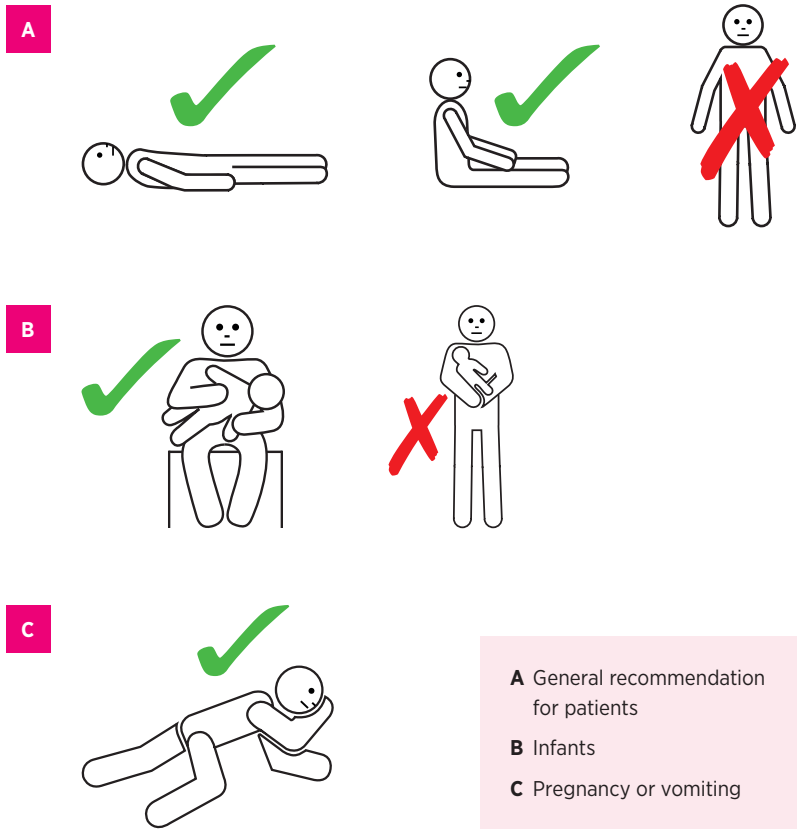
Fig. **Correct and incorrect positioning of the patient with anaphylaxis**



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these measures (especially if taking beta blockers) glucagon may improve cardiac output. Consider an intravenous glucagon bolus of 1–2 mg in adults or 20–30 microgram/kg up to 1 mg in children and seek specialist advice.

Duration of monitoring

Patients with anaphylaxis can experience protracted or biphasic reactions[7,9] and should be transported to hospital or other medical facility via ambulance (where possible) to allow management of these possibilities. Currently there is little evidence to guide the optimal duration of observation. True biphasic reactions are estimated to occur in 3–20% of patients at a median of 11 hours after the initial reaction (range 0.5–72 hours).[9,21] ASCIA recommends clinical monitoring of a patient for a minimum of four hours after the last dose of adrenaline.[1]

Patients should strongly be considered for overnight hospital admission if they:

- present with severe or protracted anaphylaxis (e.g. required repeated doses of adrenaline or intravenous fluid resuscitation)
- have a history of severe or protracted anaphylaxis
- have other concomitant illness (e.g. severe asthma, history of arrhythmia, systemic mastocytosis)
- live alone or are remote from medical care
- present for medical care late in the evening.[1,5,9]

Follow-up

On discharge from hospital following anaphylaxis, patients at risk of re-exposure (e.g. to stings, foods, unknown cause) should be prescribed and ideally dispensed an adrenaline injector device pending specialist review.[1,5,9,13] Patients should be provided with education about using the adrenaline injector and given an ASCIA Action Plan for Anaphylaxis so they can recognise and manage potential future reactions.

All patients who present with anaphylaxis should be referred for clinical immunology/allergy specialist review to confirm the cause of their reaction and discuss avoidance strategies and management of comorbidities. Patients should be advised to document episodes of anaphylaxis. This helps identify causes and co-factors like exercise in the 6–8 hours preceding the onset of symptoms. The ASCIA allergic reactions event record and clinical history forms can be used to collect and document this information. These and other anaphylaxis resources are available to download (see Box 2).

Conclusion

Anaphylaxis is a potentially life-threatening allergic reaction and adrenaline remains the first-line treatment. ASCIA recently updated guidelines to recommend 0.15 mg adrenaline injectors for infants and children weighing 7.5–10 kg. Correct positioning of a patient experiencing anaphylaxis is vital as death can occur within minutes if a patient stands, walks or sits up suddenly. <

Conflicts of interest: none declared

Box 2 Evidence-based anaphylaxis resources for clinicians and patients

Australasian Society of Clinical Immunology and Allergy (ASCIA) resources: https://www.allergy.org.au/hp/anaphylaxis

Nip Allergies in the Bub: https://preventallergies.org.au/healthcare-professionals

Anaphylaxis: emergency management for health professionals. Aust Prescr 2018;41:54. https://doi.org/10.18773/austprescr.2018.014. **Order a free Anaphylaxis Wallchart online.**

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ARTICLE

Managing medicines in alcohol-associated liver disease: a practical review

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SUMMARY

People with alcohol-associated liver disease often take medicines to manage complications of liver disease and comorbidities. However, patients may be at increased risk of drug-related harm.

Assessing the severity of liver disease is fundamental to management, as disease staging (steatosis, early fibrosis, cirrhosis) affects medication safety and guides treatment.

While clinically significant pharmacokinetic and pharmacodynamic changes predominantly occur in cirrhosis, people with early alcohol-associated liver disease may still experience adverse events with potentially inappropriate medicines such as proton pump inhibitors, opioids and benzodiazepines.

Regular medication review is essential to ensure ongoing appropriateness and safety.

Alcoholic hepatitis and cirrhosis require specialist gastroenterology or hepatology management. However, general practitioners will remain the cornerstone of day-to-day medication management.

Introduction

Alcohol-associated liver disease is one of the major causes of chronic liver disease in Australia. National guidelines recommend healthy adults consume no more than 10 standard drinks per week and a maximum of four standard drinks on any one day.[1] However, the Australian Bureau of Statistics 2017–18 National Health Survey found that 16.1% of adults drank an average of at least two standard drinks per day, and 42.1% consumed more than four standard drinks on one occasion in the past year.[2]

Alcohol use disorder is a severe chronic drinking problem that is characterised by impaired ability to stop or control alcohol use despite adverse social, occupational or health consequences.[3] The risk of developing alcohol-associated liver disease increases with the amount of alcohol consumed.[4] Between 10 and 35% of excessive drinkers will develop advanced disease.[4] People with alcohol-associated liver disease are also at greater risk of cirrhosis-related complications ('decompensation') and liver-related death compared to other chronic liver diseases.[5] It is important to note that there are no safe limits of alcohol use in patients with alcohol-associated liver disease.

Optimising medicines to manage complications of liver disease and comorbidities can be difficult due to:

- heterogeneity in patient behaviour (variable medication adherence, compliance with monitoring tests and scans, engagement with health services)
- limited pharmacotherapy options to manage alcohol use disorder and treat certain complications of advanced disease
- changes to pharmacokinetic and pharmacodynamic characteristics (due to liver disease and malnourishment)
- the potential for interactions with alcohol itself.

Primary care clinicians are ideally placed to improve medication safety by reviewing and monitoring a patient's medicines and reducing use of potentially inappropriate medicines.

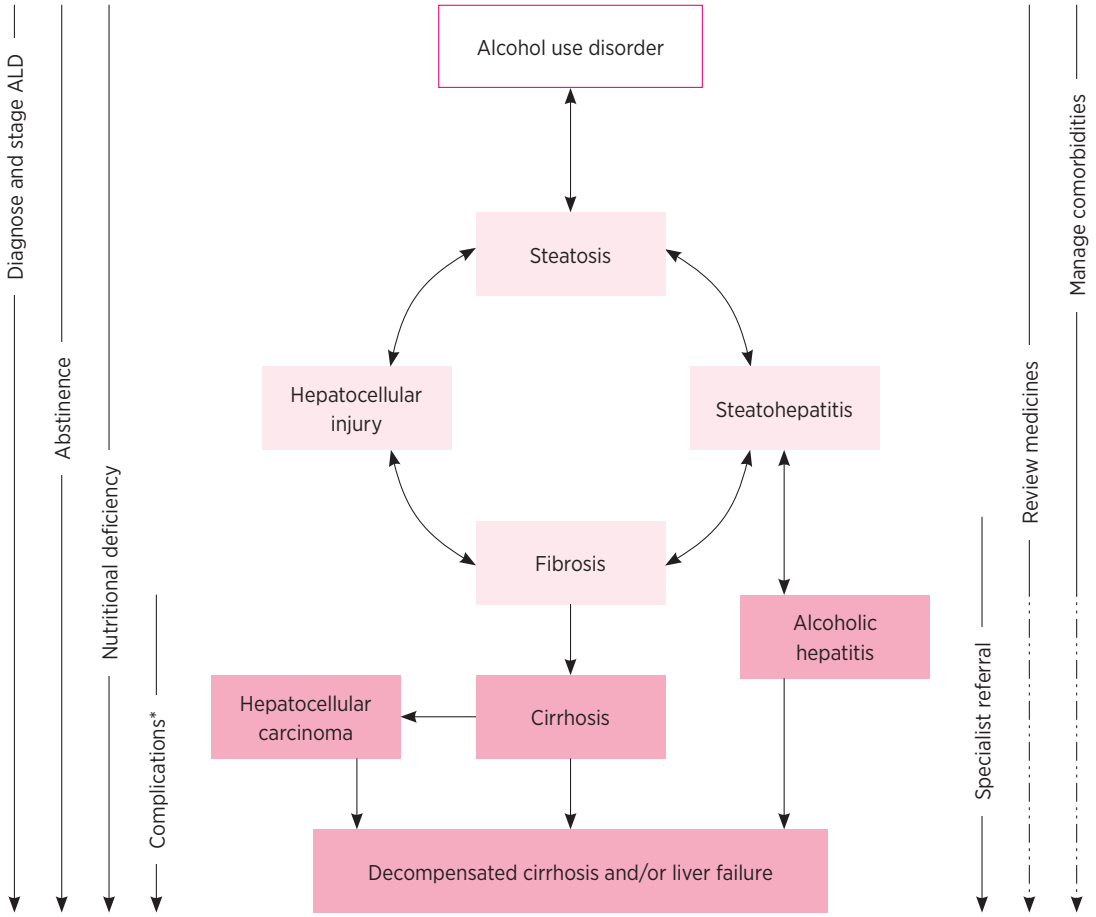
Diagnosis and staging of alcohol-associated liver disease

The role of medicines in alcohol-associated liver disease and the goals of treatment evolve with progression of disease. Optimisation of medicine use and minimisation of medicine-related harm therefore relies on appropriate staging.

The pathogenesis of alcohol-associated liver disease is complex. The disease spectrum ranges from simple hepatic steatosis to more advanced forms, including alcoholic hepatitis, alcoholic cirrhosis, and acute-on-chronic liver failure (see Fig.).[6] Investigations to assist with staging include medical imaging (ultrasound, magnetic resonance imaging, computed tomography), transient elastography (FibroScan), and tests such as Fibrosis-4, aspartate aminotransferase:alanine aminotransferase ratio, and aspartate aminotransferase platelet ratio index.[7,8]

Unlike renal disease, in which there are relatively reliable measures of glomerular filtration, there is no simple measure of hepatic function to guide drug dosing in liver disease. However, patterns and markers

Fig. **Progression of alcohol-associated liver disease**



Key:

——— Patient management goal

-·-·-·- Dose adjustment may be required

* Complications of cirrhosis and portal hypertension, including ascites, spontaneous bacterial peritonitis, hepatic encephalopathy and variceal bleeding

Risk factors for progressive liver injury include pattern of alcohol consumption (daily drinking, drinking while fasting, binge drinking), comorbid conditions (chronic viral hepatitis, haemochromatosis, non-alcoholic fatty liver disease), smoking cigarettes, female gender, increased body mass index, and genetic factors.

ALD alcohol-associated liver disease

in common blood tests can suggest acute hepatic inflammation or impaired synthetic function and may assist decision making regarding the safety of medicines (Table 1).[9-17]

Medicines in active drinkers

Interactions between alcohol and medicines can occur in active drinkers. For example, drugs that accelerate gastric emptying (e.g. metoclopramide, domperidone, erythromycin) and those that inhibit alcohol dehydrogenase activity (e.g. aspirin, ranitidine) may result in higher blood alcohol concentrations.[18] This can subsequently increase the risk of pharmacodynamic interactions with sedatives, anticholinergics and antidepressants, and cause symptoms such as increased drowsiness, sedation and decreased motor skills.

Pharmacokinetic interactions with aldehyde dehydrogenase (e.g. disulfiram, metronidazole) can lead to rapid accumulation of ethanol's bioactive metabolite acetaldehyde and significant adverse effects.[18,19] Upregulation of cytochrome P450 2E1 in chronic alcohol use can also affect the metabolism of other drugs (e.g. paracetamol, phenobarbital).[18,20] These interactions depend on genetic variability and the presence or absence of alcohol as a competitive substrate.

Table 1 **Abnormal blood tests and medication considerations in people with alcohol-associated liver disease**[9-17]

Parameter	Test result	Comment
Aspartate aminotransferase (AST)*	Usually <8 times upper limit of normal.† AST is often higher than ALT with a ratio >1:1. Typically between 50–400 IU/mL in alcoholic hepatitis with AST often higher than ALT (ratio >2:1). May be 'normal' in cirrhosis.	Review drugs that may contribute to liver function test derangement and hyperbilirubinaemia: • antibiotics • antiepileptics • herbal and dietary supplements • paracetamol • statins. These tests do not reflect hepatic capacity to metabolise or clear medications, except where acute liver failure or cirrhosis is suspected.
Alanine aminotransferase (ALT)*	Usually <5 times upper limit of normal.† Elevated in alcoholic hepatitis but usually <400 IU/mL with ALT often lower than AST as above. May be 'normal' in cirrhosis.	
Alkaline phosphatase	Usually <2–3 times upper limit of normal.	
Gamma-glutamyl transferase	Often elevated in heavy drinkers, but non-specific. Other causes of elevation include: • biliary obstruction/disease • medications (e.g. phenytoin, barbiturates).	
Bilirubin	Often elevated (>50 micromol/L) in alcoholic hepatitis and cirrhosis due to impaired liver synthetic function. Higher bilirubin concentrations indicate more severe alcoholic hepatitis and onset of jaundice usually occurs within the preceding 8 weeks.‡ Elevation can signify decompensation in cirrhosis.	
Haemoglobin	May be low in all stages of alcohol-associated liver disease due to multiple factors.	Check iron studies and replace if deficient. Anticoagulant and antiplatelet therapies for comorbidities should be continued (if indicated) unless bleeding is suspected.
Lymphocytes and neutrophils	May be reduced in portal hypertension and cirrhosis due to hypersplenism. White cell count is elevated in alcoholic hepatitis, but usually <20 x 10^9/L (largely neutrophils).	Use drugs that can impair immunity with caution and monitor regularly: • corticosteroids • azathioprine.
International normalised ratio/ prothrombin time	Often elevated in alcoholic hepatitis and cirrhosis due to impaired synthetic function and reduced hepatic production of coagulation factors.	INR is a good measure of liver synthetic function but not bleeding risk. Decompensated cirrhosis is a prothrombotic state. Monitoring parameters for anticoagulant therapies (warfarin, heparin, low-molecular-weight heparin) may be less reliable. Vitamin K supplementation is only helpful in deficiency.
Albumin	May be reduced in alcoholic hepatitis and cirrhosis due to impaired synthetic function and reduced hepatic production of proteins.	Distribution of highly protein-bound drugs may be altered: • valproate, phenytoin • warfarin • diazepam.

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Table 1 **Abnormal blood tests and medication considerations in people with alcohol-associated liver disease[9-17] (continued)**

Parameter	Test result	Comment
Platelets	Often low in cirrhosis due to bone marrow suppression and splenic sequestration associated with portal hypertension.	Prophylactic use of heparin and low-molecular-weight heparin is usually avoided, particularly when platelet count <50 x 10^9/L. Use of aspirin in coronary artery disease appears safe.
Sodium	May be low in alcoholic hepatitis and cirrhosis due to altered renal haemodynamics, renin–angiotensin–aldosterone system dysregulation and fluid accumulation.	Avoid or carefully monitor drugs that may worsen hyponatraemia or renal function: • ACE inhibitors, sartans • diuretics.
Creatinine	May be elevated in decompensation, hepatorenal syndrome and severe alcoholic hepatitis. Baseline creatinine may be low in cirrhosis due to low muscle mass.	Have a low index of suspicion for acute renal impairment in people with cirrhosis due to low baseline creatinine. Use medicines that may affect renal function with caution and monitor required therapies regularly (e.g. diuretics). Nephrotoxic drugs are often withheld in severe alcoholic hepatitis to prevent or manage acute kidney injury and hepatorenal syndrome, which negatively impact survival.

* Transaminases >400 IU/mL should raise suspicion of other causes of acute liver injury.
† Degree of elevation does not correlate with alcohol-associated liver disease severity.
‡ Clinical history usually includes heavy alcohol use (>40 g/day in women, >60 g/day in men) for at least 6 months with fewer than 60 days of abstinence before onset of jaundice.

Despite the potential for increased bioactivation to its toxic metabolite, paracetamol is generally considered safe for most people with alcohol-associated liver disease and is preferred over non-steroidal anti-inflammatory drugs in advanced disease.[21] Dose reduction to a maximum 2–3 g of paracetamol daily is recommended for malnourished patients and those with cirrhosis.[20,21]

Abstinence and withdrawal

Intervention to support abstinence is essential, as cessation of drinking reduces the risk of liver disease progression, and cirrhosis-related complications, and it improves clinical outcomes at all stages.[6,22,23] In addition to psychosocial treatments, pharmacotherapy may be prescribed to support abstinence.[24] Therapies available on the Pharmaceutical Benefits Scheme in Australia include naltrexone and acamprosate. Disulfiram is also used but is only available on private prescription (Table 2).[9,16,19,24-31] These medicines have modest efficacy and most have limited or no published safety data in people with cirrhosis and should only be considered under specialist guidance.[6] Other medicines including gabapentin, baclofen and topiramate may be prescribed off label by specialists to assist relapse prevention, but evidence for their effectiveness is limited.[6,24]

Benzodiazepines

In heavy drinkers who suddenly discontinue or decrease alcohol consumption, benzodiazepines may be used short term with other supportive measures to manage withdrawal symptoms.[28] The Clinical Institute Withdrawal Assessment for Alcohol Revised (CIWA-Ar) Score[32] can assist the evaluation of alcohol withdrawal syndrome severity and benzodiazepine requirements. Patients with moderate or severe alcohol withdrawal syndrome are usually managed in hospital, but small doses of benzodiazepine may be continued for a short duration on discharge. Diazepam is usually preferred because of its long half-life, although oxazepam may be safer in cirrhosis.[28]

Outside the setting of alcohol withdrawal, benzodiazepines are potentially inappropriate. They should be prescribed with extreme caution (especially in cirrhosis) as the risk of adverse effects may outweigh the benefits. The decision to prescribe benzodiazepines in alcohol-associated liver disease should be made on a case-by-case basis as patients may be at increased risk of harm due to pharmacodynamic interactions. Benzodiazepines have also been associated with an increased risk of first-time hepatic encephalopathy in cirrhosis when taken for 3–10 days.[29]

Table 2 **Commonly used medicines in different stages of alcohol-associated liver disease** [9,16,19,24-31]

Drugs	Indication and mechanism of action	Precautions and contraindications	Comments
Alcohol abstinence			
Acamprosate	Reduces symptoms of alcohol withdrawal (e.g. anxiety, irritability, insomnia, cravings, neuronal hyperexcitability). Modulates the glutamatergic receptor system.	Contraindicated: Child-Pugh C cirrhosis, renal impairment (serum creatinine >120 micromol/L or creatinine clearance ≤30 mL/min). Caution: acute alcohol withdrawal, pregnancy.	Not hepatically metabolised but requires dose adjustment in renal impairment. Alcohol-induced psychomotor impairment will still occur if alcohol is consumed. Commence after the acute phase of alcohol withdrawal has passed (i.e. 1 week after the last drink).
Naltrexone	Attenuates cravings and reduces pleasurable effects following alcohol consumption. Reversible inhibition of opioid receptors.	Contraindicated: opioid dependence, severe hepatic impairment, acute hepatitis. Caution: renal impairment, liver enzymes >3 times upper limit of normal.	Risk of hepatotoxicity in hepatic and renal impairment. Alcohol-induced psychomotor impairment will still occur if alcohol is consumed. Use non-opioid analgesics (e.g. paracetamol) if pain relief is required.
Disulfiram	Interference with alcohol metabolism. Irreversible inhibition of aldehyde dehydrogenase results in raised blood acetaldehyde concentrations and unpleasant effects if alcohol is consumed.	Contraindicated: current alcohol intoxication, ischaemic heart disease, severe myocardial disease, severe renal impairment, severe hepatic impairment, acute psychosis, cirrhosis. Caution: cardiovascular disease, diabetes, hypothyroidism, epilepsy, chronic kidney disease, hepatic impairment.	Not recommended in moderate–severe liver disease due to lack of safety data. Extensive patient and carer education required before starting disulfiram. Adverse effects of a disulfiram–alcohol reaction can be severe, including respiratory depression, seizures, arrhythmia, myocardial infarction and worsening of acute congestive heart failure in patents with pre-existing cardiac conditions. Numerous potential drug–drug interactions.
Alcohol withdrawal syndrome			
Benzodiazepines: • diazepam, oxazepam	Reduce acute alcohol withdrawal symptoms and seizure risk. Modulate neuronal hyperexcitability by stimulating gamma-aminobutyric acid (GABA) receptors.	Caution: may precipitate hepatic encephalopathy in patients with cirrhosis or acute liver failure.	Short-acting benzodiazepines with uncomplicated hepatic metabolism (e.g. oxazepam) are preferred in people with cirrhosis and the elderly.
Alcoholic hepatitis			
Corticosteroids: • prednisolone	Modulate inflammatory response. May improve short-term survival in severe alcoholic hepatitis.	Contraindicated: untreated infection, gastrointestinal bleeding, renal failure, acute psychosis, pancreatitis (uncontrolled hyperglycaemia). Caution: diabetes, peptic ulcer disease.	Started in hospital with other supportive care. Short-term use only (up to 4 weeks with optional 3-week taper thereafter).
Nutritional deficiency			
Thiamine (B_1)	Chronic thiamine deficiency can lead to nutritional encephalopathy (Wernicke-Korsakoff's syndrome).		Thiamine doses contained in over-the-counter oral supplements may be insufficient.
Other B vitamins: • pyridoxine (B_6), folic acid (B_9), cyanocobalamin (B_{12})	Prevent complications of deficiency including cognitive dysfunction, peripheral neuropathy, and anaemia. Vitamin B deficiencies are common in alcohol-associated liver disease.	Caution: folic acid supplementation should be avoided in megaloblastic anaemia until B_{12} deficiency is corrected.	Specific deficiencies should be corrected, but evidence is lacking for long-term use.

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Table 2 **Commonly used medicines in different stages of alcohol-associated liver disease [9,16,19,24-31] (continued)**

Drugs	Indication and mechanism of action	Precautions and contraindications	Comments
Nutritional deficiency (continued)			
Vitamin D	Regulates absorption of essential minerals including calcium, magnesium and phosphate. Vitamin D deficiency is common in patients with cirrhosis.	Caution: severe renal impairment, hypercalcaemia.	Evidence for vitamin D supplementation in chronic liver disease is inconclusive. Supplement if deficient or in the presence of other indications (e.g. bone disease).
Zinc	Prevents complications of deficiency including cognitive dysfunction, hypogonadism, altered immune function and impaired wound healing. Improves gut-mucosal barrier integrity. Zinc deficiency is common and worsens with disease progression.	Caution: severe renal impairment.	Evidence supports zinc supplementation to correct deficiency in alcohol-associated liver disease, especially in people with cirrhosis and alcoholic hepatitis.
Complications of advanced liver disease (managed by a specialist)			
Non-selective beta blockers: • propranolol, carvedilol	Prevent bleeding from gastro-oesophageal varices. Induce splanchnic vasoconstriction, thereby decreasing portal blood flow and reducing portal hypertension.	Caution: bradycardia (45–50 beats/min), severe hypotension, peripheral arterial disease, diabetes, poorly controlled asthma, severe hepatic impairment (carvedilol).	Usually started at a low dose (propranolol and carvedilol are hepatically metabolised) and titrated to achieve a resting heart rate of 55–60 beats/min while maintaining systolic blood pressure ≥90 mmHg. Selective beta blockers (metoprolol, bisoprolol) are not effective. Carvedilol is not PBS-listed for this indication.
Diuretics: • spironolactone, furosemide (frusemide)	Treat fluid overload (e.g. ascites, hepatic hydrothorax). Promote excretion of sodium and water.	Contraindicated: renal failure, severe sodium and fluid depletion. Caution: renal impairment (creatinine clearance <30 mL/min), electrolyte derangement.	No significant pharmacokinetic changes in liver impairment, but patients may be at increased risk of harmful pharmacodynamic interactions. Regular monitoring of fluid status, renal function and electrolytes is required. Patients are usually on a salt-restricted diet.
Antibiotic prophylaxis: • trimethoprim/sulfamethoxazole, quinolones	Prevent recurrence of spontaneous bacterial peritonitis. Reduce pathogenic gut flora.	Caution: renal impairment (creatinine clearance <30 mL/min).	Usually started by a specialist following an episode of spontaneous bacterial peritonitis in patients with persistent ascites. Proton pump inhibitors can increase the risk of spontaneous bacterial peritonitis.
Non-absorbable disaccharides: • lactulose	Treat and prevent recurrence of hepatic encephalopathy. Acidify the gut and promote healthy gut flora (prebiotic), thereby reducing production and absorption of ammonia.	Contraindicated: intestinal obstruction.	In patients with genuine intolerance to lactulose, macrogol-containing laxatives can be used. Usually titrated to achieve 2–3 loose bowel motions each day.
Non-absorbable antibiotics: • rifaximin	Prevent recurrent hepatic encephalopathy. Modify gut flora and reduce production of ammonia.	Contraindicated: intestinal obstruction. Caution: Child-Pugh C cirrhosis (increased systemic activity).	Must be started by (or in consultation with) a gastroenterologist or hepatologist. Use concomitantly with lactulose if tolerated.

PBS Pharmaceutical Benefits Scheme

Alcoholic hepatitis

Alcoholic hepatitis can be a life-threatening condition associated with heavy alcohol use. It usually presents with jaundice and a characteristic pattern of liver biochemistry (Table 1).[9,17] Symptoms can include fever, right upper-quadrant or epigastric pain and tenderness, and occasionally ascites or hepatic encephalopathy. Infection and sepsis are relatively common and severe complications of alcoholic hepatitis leading to poor outcomes.[22] Mortality associated with alcoholic hepatitis is high and immediate referral to hospital for assessment, support and treatment is essential.[9,16]

Treatment of alcoholic hepatitis focuses on nutritional support and complete abstinence from alcohol. In severe cases corticosteroids may be considered, although evidence for their effectiveness remains inconclusive.[33] Patients may be discharged with oral prednisolone to complete a 28-day course, followed by an optional three-week taper.[22] Following discharge from hospital, GP review and timely cessation of temporary concomitant therapies such as proton pump inhibitors may be helpful to prevent inappropriate long-term use. Re-introduction of temporarily withheld medications (e.g. nephrotoxic drugs including diuretics, ACE inhibitors and sartans) can be considered when renal function has stabilised.

Nutritional deficiency

Malnourishment is prevalent in alcohol-associated liver disease due to poor oral intake, hypermetabolism, altered nutritional requirements and malabsorption of fats.[34] Correction of pancreatic insufficiency (e.g. pancreatic enzyme replacement) and nutritional support may be required to maintain muscle mass and prevent catabolism (energy intake 25–40 kcal/kg/day and protein intake 1–1.5 g/kg/day).[34,35] Multivitamins and supplements to correct specific deficiencies are also commonly used in clinical practice.

In all stages of alcohol-associated liver disease, vitamin B_1 (thiamine) supplementation is strongly recommended to prevent neurological complications like Wernicke-Korsakoff's syndrome.[31] If Wernicke-Korsakoff's syndrome is suspected (e.g. acute confusion, delirium), immediate referral to hospital is required. Vitamin B_{12} supplementation is also recommended in deficiency to prevent neuropathies and megaloblastic anaemia.[31]

Supplementation of fat-soluble vitamins (A, D, E and K) is not routinely recommended, except for vitamin D deficient patients with cirrhosis or bone disease.[25,31] The benefits of supplementing other micronutrients including ascorbic acid, magnesium and selenium are debated and they are not routinely recommended in clinical practice. Antioxidants including beta-carotene, vitamin A, vitamin C, vitamin E and selenium have been trialled to reduce oxidative stress and liver damage. However, a Cochrane review found no evidence to support these supplements in patients with liver disease.[36]

Alcoholic cirrhosis

Progression of liver disease in the setting of ongoing alcohol consumption and other risk factors can lead to cirrhosis (Fig.). These patients may experience asymptomatic disease ('compensated') or present with complications of portal hypertension and liver insufficiency ('decompensated').[26,37] All patients with suspected cirrhosis should be referred for specialist evaluation.

Cirrhosis can potentially reduce clearance and increase exposure to certain drugs or metabolites[38] due to:

- altered drug absorption (rate and extent of absorption)
- abnormal distribution and impaired synthetic function (fluid accumulation and hypoalbuminaemia)
- reduced metabolism of endogenous and exogenous substances
- altered elimination processes via hepatic and renal pathways.

Consequently, people with cirrhosis are at greater risk of experiencing adverse drug reactions compared to those with non-cirrhotic liver disease.[39] This is especially the case for patients with complications like ascites, hepatic encephalopathy, jaundice and variceal bleeding who are at higher risk of pharmacodynamic interactions.

Practical prescribing recommendations for individual medicines (based on pharmacokinetic changes) are available to guide drug selection and dose adjustments for people with cirrhosis.[40,41] Progression to Child-Pugh B/C cirrhosis increases the likelihood of pharmacokinetic changes and pharmacodynamic interactions,[41] especially among potentially inappropriate medicines (Table 3).[15,18,20,21,29,40-44] Even medicines that are regularly used to manage the complications of cirrhosis such as diuretics, lactulose and non-selective beta blockers require regular titration and monitoring to prevent medication-related harm due to pharmacodynamic changes (e.g. dehydration, electrolyte derangement, hypotension).

Table 3 **Potentially inappropriate medicines in alcohol-associated liver disease** [15,18,20,21,29,40-44]

Drug	Stage to avoid use	Medication safety considerations
ACE inhibitors and sartans: • e.g. ramipril, perindopril, irbesartan, telmisartan	Alcoholic hepatitis Cirrhosis Especially patients with ascites or renal impairment	Increased risk of interactions with increasing severity of liver disease due to progressive alteration in renal haemodynamics. Commence at a low dose and titrate slowly. The risk of harm in Child-Pugh C cirrhosis may outweigh benefits.
Antibiotics: • metronidazole, nitrofurantoin, sulfamethoxazole	Alcohol use disorder	Interaction with alcohol may lead to disulfiram-like reactions (nausea, vomiting, flushing, headache, palpitations). Patients should avoid consuming alcohol during treatment and for 24 hours after finishing the course. Nitrofurantoin may cause drug-induced liver injury.
Antiplatelets and anticoagulants: • e.g. ticagrelor, dabigatran, rivaroxaban	Cirrhosis (varies by drug class)	Standard markers of haemostasis (INR, prothrombin time, platelet count) do not accurately reflect coagulative status. Low-molecular-weight heparins and vitamin K antagonists are preferred to manage venous thromboembolism. Limited experience with direct-acting oral anticoagulants. Avoid use in advanced cirrhosis. Clopidogrel and prasugrel appear safe in Child-Pugh A and B cirrhosis. Safety of ticagrelor in advanced cirrhosis is unknown. Aspirin appears safe.
Benzodiazepines: • e.g. diazepam, oxazepam, temazepam	Alcohol use disorder Cirrhosis Especially patients with history of hepatic encephalopathy	Alcohol consumption enhances the sedative effect of benzodiazepines including drowsiness, sedation and impaired motor skills. Even short-term use can precipitate hepatic encephalopathy. If a benzodiazepine is indicated, oxazepam or temazepam are preferred due to the comparatively simple hepatic metabolism.
Calcium channel blockers: • e.g. felodipine, lercanidipine, verapamil	Cirrhosis Especially patients with symptomatic hypotension or those co-prescribed non-selective beta blockers	If a calcium channel blocker is indicated, amlodipine, nifedipine and diltiazem appear safe if commenced at a low dose and titrated slowly. Felodipine, lercanidipine and verapamil should be avoided in Child-Pugh C cirrhosis.
Non-steroidal anti-inflammatory drugs: • e.g. ibuprofen, diclofenac, celecoxib	Alcohol use disorder Alcoholic hepatitis Cirrhosis Especially patients with ascites or renal impairment	Alcohol consumption increases the risk of peptic ulcer disease and gastrointestinal bleeding. Increased risk of renal impairment, acute kidney injury and hepatorenal syndrome in acute and chronic hepatic impairment. All non-steroidal anti-inflammatory drugs should be avoided. Paracetamol is a safe alternative (maximum 2–3 g daily in malnourished patients and those with cirrhosis).

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Table 3 **Potentially inappropriate medicines in alcohol-associated liver disease** [15,18,20,21,29,40-44] **(continued)**

Drug	Stage to avoid use	Medication safety considerations
Opioids: • e.g. oxycodone, tramadol, morphine, tapentadol	Alcohol use disorder Cirrhosis Especially patients with history of hepatic encephalopathy	Alcohol consumption enhances the sedative effect of opioids including drowsiness, sedation and impaired motor skills. May precipitate hepatic encephalopathy, especially in patients not taking appropriate laxatives. All slow-release formulations (especially patches) should be avoided due to reversal difficulties if hepatic encephalopathy occurs. If an opioid is indicated, immediate-release tramadol or oxycodone appear safe if commenced at a low dose and titrated slowly. Use paracetamol as an opioid-sparing drug. Avoid tapentadol in Child-Pugh C cirrhosis.
Proton pump inhibitors: • e.g. pantoprazole, rabeprazole, omeprazole	Nutritional deficiency Cirrhosis Especially patients with ascites, history of hepatic encephalopathy, or recurrent infections	Inhibition of gastric acid secretion alters bioavailability and absorption of vitamins and minerals. If a proton pump inhibitor is indicated, (es) omeprazole and rabeprazole appear safe at low doses. Esomeprazole may be safest in Child-Pugh C cirrhosis. People with cirrhosis often have impaired immunity. Inhibition of gastric acid secretion further increases infection risk, especially spontaneous bacterial peritonitis and *Clostridium difficile* infection.
Oral hypoglycaemic drugs: • e.g. metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, sodium-glucose co-transporter 2 inhibitors, pioglitazone	Cirrhosis (varies by drug class)	Metformin has a favourable safety profile and numerous benefits in chronic liver disease. There is conflicting evidence about the risk of lactic acidosis in advanced cirrhosis. Avoid sulfonylureas in cirrhosis due to the risk of hypoglycaemia. Avoid pioglitazone in advanced cirrhosis. Limited experience with dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors in cirrhosis. Dose reduction is often required. Avoid use in advanced cirrhosis.

Comorbidities and polypharmacy

While the comorbidity burden is often lower in alcohol-associated liver disease compared to other types of chronic liver disease (e.g. non-alcoholic fatty liver disease), the prevalence of hypertension (32–41%), ischaemic heart disease (5–20%), heart failure (5–12%) and type 2 diabetes (26–29%) is notable.[45,46] Concomitant drugs prescribed for these conditions may require additional monitoring, especially in people with cirrhosis. In those with decompensated cirrhosis who are ineligible for liver transplant, deprescribing medicines for which benefit is with long-term use (e.g. statins) could be considered. This will reduce the medication burden for these patients who will likely follow a palliative course, with a median survival of approximately two years.[37]

Conclusion

Doctors, nurses, and pharmacists in the primary care setting have an important role in the management of patients with alcohol-associated liver disease. In addition to supporting abstinence, optimising medicine use is imperative to improve outcomes and minimise harm. <

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MEDICINAL MISHAP

Death from diltiazem–ibrutinib interaction

Case study

A 68-year-old male presented to the emergency department because he woke with shortness of breath, central chest pain and dizziness. He had a past history of hypertension and gastro-oesophageal reflux disease and had been taking ibrutinib (560 mg daily) for the previous three months for mantle cell lymphoma.

The patient was diagnosed with a pulmonary embolism and anticoagulated with rivaroxaban. He was found to have atrial fibrillation with a rapid heart rate. This was attributed to ibrutinib therapy. Metoprolol, digoxin and diltiazem were started to control the heart rate. A haematologist advised withholding ibrutinib while the patient was in hospital.

The patient was discharged after one week, on all three drugs for rate control. Ibrutinib was recommenced on hospital discharge after consultation with the haematology team.

Two weeks after discharge he was reviewed in the haematology clinic and was managing well. The patient was to be closely monitored with two-monthly haematology reviews.

Three months after discharge the patient was hospitalised following a cardiac arrest. Despite intensive care, he suffered extensive neurological injuries and died three days later. While no autopsy was conducted, a CT pulmonary angiogram following the cardiac arrest did not show another pulmonary embolism. The patient's arrhythmias and subsequent cardiac arrest were deemed to be secondary to ibrutinib toxicity as a result of concomitant treatment with oral diltiazem.

Comment

Ibrutinib is an immune modulator indicated for the treatment of certain lymphoma subtypes.[1] It is metabolised primarily by cytochrome P450 (CYP) 3A4, to produce a prominent dihydrodiol metabolite that inhibits the enzyme Bruton's tyrosine kinase, thereby inhibiting B-cell receptor signalling. This kinase has a key role in survival for patients with B-cell malignancies.[2]

A notable adverse effect of ibrutinib is atrial fibrillation. It is a common reason for ceasing ibrutinib. Regular cardiac monitoring during treatment is recommended for patients with cardiac risk factors.[1] Atrial fibrillation is thought to occur due to the inhibition of Bruton's tyrosine kinase and tec protein tyrosine kinase, expressed in the heart, reducing phosphoinositide 3-kinase-protein kinase B signalling, which has a cardio-protective role during cardiac stress.[3]

While there is increasing awareness of the cardiovascular adverse effects of ibrutinib therapy, what is less well recognised is the potential for severe drug–drug interactions with drugs, such as diltiazem, used to treat arrhythmias. As diltiazem is a moderate inhibitor of CYP3A4 and ibrutinib is a substrate of this enzyme, prolonged co-administration of the two drugs is likely to result in reduced ibrutinib clearance and subsequent cardiotoxicity.[4] Given the grave consequences of this interaction, treatment guidelines for ibrutinib-induced atrial fibrillation should be updated to clearly state the risks of drug interactions and which drugs to avoid.

This case highlights the essential role of a clinical review of the drugs taken, particularly by patients at high risk, at every transition in care. For patients who present with atrial fibrillation requiring rate control while taking ibrutinib, the recommended treatment sequence is:

- beta blockers (with optimisation of dosage as tolerated)
- digoxin if required (doses should be spaced six hours apart from ibrutinib to minimise the potential for P-glycoprotein interactions in the gastrointestinal tract).

If further rate control therapy is needed and diltiazem is prescribed, the dose of ibrutinib should be reduced by 50% to 75%, depending on the patient's clinical requirements.[2,4]

For patients on high-risk drugs, with the potential for interactions, clinicians should consider searching beyond traditional interaction checking software, which may underestimate the risk of drug–drug interactions. Instead, consult a specialist pharmacist for advice and always consider the pharmacokinetic and pharmacodynamic effects of the combination therapy.

Conclusion

With increased prescribing of tyrosine kinase inhibitors, it is likely that clinicians less familiar with these drugs will be involved in managing patients

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Keywords
antiarrhythmic drugs, atrial fibrillation, diltiazem, drug interactions, ibrutinib

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taking ibrutinib. This highlights the need for education related to drug interactions with targeted therapies, as well as practice guidelines. These guidelines should include recommendations on baseline cardiac assessments for high-risk patients as well as management of new onset cardiac toxicities, developed in collaboration with haematologists, cardiologists and pharmacists to optimise the management of cardiovascular drugs in patients receiving ibrutinib.

Conflicts of interest: none declared

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New drugs

Romosozumab

Approved indication: osteoporosis

Evenity (Amgen)
syringe containing 105 mg/1.17 mL

Osteoporotic fractures increase morbidity and mortality so osteoporosis in patients with a high risk of fractures should be treated. In addition to calcium and vitamin D, management of osteoporosis can include drugs, such as bisphosphonates and denosumab, which reduce bone resorption, or anabolic drugs such as teriparatide which increase bone formation. As these treatments may not be effective, other options are being studied.

One area of research has been a substance called sclerostin, which is produced by osteocytes. Its effect is to increase bone resorption and decrease bone formation. Bone density may therefore increase if the effects of sclerostin can be blocked.

Romosozumab is a monoclonal antibody that binds to sclerostin and inhibits its action. The drug has to be given by monthly subcutaneous injections. A practical consideration for patients is that the available formulation contains half the recommended monthly dose (210 mg). This means that two injections will be required. It takes about three months to reach a steady-state concentration. Like other antibodies, romosozumab is thought to be cleared by catabolism.

The ability of romosozumab to prevent vertebral fractures was studied in the FRAME trial. This enrolled postmenopausal women with reduced bone mineral density. One group of 3589 women received monthly injections of romosozumab while another group of 3591 women received placebo. After one year all the women were given injections of denosumab every six months for a further year. Bone density increased with romosozumab and the changes from baseline in the lumbar spine and hip were greater than in the placebo group throughout the trial. In the first 12 months of the trial, 1.8% of the women in the placebo group had a new vertebral fracture compared with 0.5% of the romosozumab group. The corresponding results at 24 months were 2.5% and 0.6%.[1]

Romosozumab was compared with oral alendronate in 4093 postmenopausal women, with low bone mineral density and a history of fractures, in the ARCH trial. After one year of treatment, the 2046 women randomised to receive romosozumab switched to alendronate. These women had greater increases in bone density than those who had only taken alendronate throughout the trial. Over 24 months, 6.2% of the women treated with romosozumab had a new vertebral fracture compared with 11.9% of the alendronate group. Non-vertebral fractures occurred in 8.7% of the romosozumab group and 10.6% of the alendronate group.[2]

Women who have not had a good response to bisphosphonates may be switched to an anabolic drug. The STRUCTURE trial compared the outcomes of switching to teriparatide or romosozumab. The 436 women in the trial had taken alendronate in the previous year and had used bisphosphonates for postmenopausal osteoporosis for at least three years. They also had a history of low bone mineral density and fracture. After 12 months, bone density at the hip had increased by 2.6% in the 218 women randomised to romosozumab compared with a decrease of 0.6% with teriparatide.[3]

Osteoporosis can also occur in men. The BRIDGE trial investigated whether romosozumab has an effect in men with low bone mineral density and a history of fracture. In this trial, 163 men received romosozumab and 82 men were given injections of placebo for 12 months. Bone density in the lumbar spine increased by 12.1% with romosozumab and by 1.2% with placebo. The corresponding changes at the hip were 2.5% and −0.5%.[4]

Common adverse events in the trials included arthralgia, muscle spasms and headache. Injection-site reactions were more frequent with romosozumab than with placebo.[1,4] Hypersensitivity reactions can occur. Approximately 18% of patients develop antibodies to romosozumab including 4.7% who develop neutralising antibodies. As osteonecrosis of the jaw has been reported, patients should have a dental examination before starting romosozumab.

During the ARCH[2] and BRIDGE[4] trials there were increases in serious cardiovascular adverse events with romosozumab. In the first year of the ARCH trial 2.5% of the women had serious events, including death, compared with 1.9% of the alendronate group.[2] Among the men taking romosozumab in the BRIDGE trial 4.9% had a serious event compared with 2.5% of the placebo group.[4] A possible explanation is that sclerostin could have a role in vascular calcification. Whatever the mechanism, romosozumab should not be used in patients who have had a stroke or myocardial infarction in the previous year.

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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.

NEW DRUGS

While romosozumab was more effective than placebo at reducing the incidence of vertebral fractures in postmenopausal women with low bone mineral density, the difference in non-vertebral fractures did not reach statistical significance.[1] For women who have had a fracture, romosozumab appears to have an advantage over alendronate for preventing future fractures.[2] Whether the greater improvement in bone density, compared to teriparatide, in women switching from bisphosphonates results in fewer fractures remains to be seen.[3] As denosumab is often used when bisphosphonates are unsuitable, a comparative trial between denosumab and romosozumab would have been useful. As the effect of romosozumab subsequently declines, the drug should be stopped after 12 months.

T manufacturer provided the AusPAR

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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.

Trientine dihydrochloride

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Approved indication: Wilson's disease

Trientine Waymade (Waymade)
250 mg capsules

Wilson's disease is an autosomal recessive disorder. This genetic defect affects the transport of copper. Free copper is toxic so it causes cell damage as it accumulates, firstly in the liver and then in the brain. The disease is therefore also known as hepatolenticular degeneration.

The treatment of Wilson's disease aims to keep copper concentrations low. This can include using zinc, to reduce the absorption of copper from the gut, and chelating agents, such as penicillamine, to increase excretion. Treatment is lifelong but, in the absence of advanced liver disease, life expectancy can be normal.

Trientine dihydrochloride is a chelating agent which forms a complex with copper. It is taken orally, but is not well absorbed and should not be taken with food. The absorbed portion of the dose is widely distributed. The molecule is metabolised and its main metabolites can also chelate copper. Absorbed trientine has a half-life of 13.5 hours and is excreted with its metabolites in the urine. The dose is determined by the serum concentration of free copper.

Various forms of trientine have been available for a number of years. The approval of trientine dihydrochloride in Australia appears to be mainly based on a retrospective observational study. This used data from 405 children and adults with Wilson's disease who had been followed for an average of 13.3 years. As patients could change treatment, the analysis involved 326 treatments with penicillamine and 141 with trientine. Most patients took trientine as a second-line therapy. In second-line therapy stable liver disease was achieved with 25% of penicillamine treatments and 22.2% of trientine treatments. The corresponding figures for stable neurological disease were 69.2% and 33.3%.[1]

During the study 28.8% of the treatments with penicillamine were stopped because of adverse events, compared with 7.1% for trientine. The adverse effects of trientine include nausea, arthralgia and rashes. Neurological symptoms may get worse at the start of treatment. Trientine can reduce serum iron so some patients may develop anaemia. As trientine and zinc may interact, they should not be used together. Trientine is teratogenic.

The approved indication for trientine dihydrochloride in Australia is for adults and children with Wilson's disease who are unable to tolerate penicillamine.

[X] manufacturer did not respond to request for data

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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 European Medicines Agency and the Therapeutic Goods Administration.

NEW DRUGS

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Ripretinib

Approved indication: gastrointestinal stromal tumours

Qinlock (Specialised Therapeutics)
50 mg tablets

Ripretinib is a tyrosine kinase inhibitor indicated for adults with advanced gastrointestinal stromal tumours who have already had treatment with at least three other kinase inhibitors (e.g. imatinib, sunitinib and regorafenib). These tumours often have oncogenic mutations in the tyrosine kinases or platelet-derived growth factor receptor alpha. This makes the kinases overactive and causes uncontrolled multiplication of the cells. Ripretinib is a switch-control kinase inhibitor which locks the kinases in an inactive state and prevents downstream signalling and cell proliferation.

The efficacy and safety of ripretinib as a fourth-line therapy has been investigated in a placebo-controlled trial called INVICTUS.[1] Patients were randomised to oral ripretinib 150 mg once a day (n=85) or a matching placebo (n=44) in conjunction with best supportive care. In the event of progressive disease, patients receiving ripretinib were permitted to increase the dose to 150 mg twice a day and patients receiving placebo could cross over to ripretinib. In the ripretinib group, 9.4% of patients (8/85) responded to treatment (all partial responses) versus none of the patients in the placebo group. Ripretinib also improved median progression-free survival (6.3 vs 1 month) and overall survival (median 15.1 vs 6.6 months) compared to placebo.

Dose interruption (23.5% of patients), dose reduction (7.1%) and permanent discontinuation (8.2%) of ripretinib because of an adverse reaction was common in the trial. The most frequently reported treatment-emergent adverse events were alopecia (52% of patients), fatigue (42%), nausea (39%), abdominal pain (36%), constipation (34%), myalgia (32%), diarrhoea (28%), decreased appetite (27%), palmar-plantar erythrodysaesthesia syndrome (21%) and vomiting (21%). Treatment-emergent laboratory abnormalities included increases in activated partial thromboplastin time (35% of patients), lipase (32%) and triglycerides (26%), and decreases in phosphate (26%) and calcium (23%). Elevations in blood bilirubin (22% of patients) and creatine phosphokinase (21%) were also observed.

Hypertension was reported in 14% of patients taking ripretinib – half of these cases were severe (grades 3–4). It is therefore important to monitor patients' blood pressure before and during treatment. Cutaneous squamous cell carcinoma and melanoma occurred in 4.7% and 2.4% of patients who received ripretinib, so skin assessment is also recommended.

Cardiac dysfunction, including cardiac failure, occurred in 1.7% of patients, with decreased ejection fraction (grade 3) in 3.4% of those who had echocardiograms. Ejection fraction should be assessed before starting ripretinib and treatment should be permanently discontinued if grade 3 or 4 left ventricular systolic dysfunction occurs.

The recommended dose of ripretinib is 150 mg once a day with or without food. Tablets should be taken at the same time each day. Following oral administration, peak plasma concentrations are reached after four hours and steady state is reached after 15 days. The elimination half-life is approximately 15 hours and the main route of excretion is via the faeces.

Ripretinib is mainly metabolised by cytochrome P450 (CYP) 3A4 so inhibitors and inducers of this enzyme could affect plasma concentrations. The drug is also a substrate of P-glycoprotein so inhibitors of this transporter may increase ripretinib exposure. Ripretinib and its metabolite (DP-5439) inhibit CYP2C8 so may affect other medicines that are cleared by this enzyme.

Based on the results of animal studies, ripretinib may affect fertility in men. It may also cause embryo–fetal harm (pregnancy category D drug) and should not be used in pregnancy. Breastfeeding is not recommended until at least a week after the final dose of ripretinib.

For patients with advanced gastrointestinal stromal tumours who have no other treatment options, ripretinib can improve survival by approximately eight months. However, it causes considerable adverse effects which can be treatment limiting.

T manufacturer provided the product information

REFERENCE

1. Blay J-Y, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923-34. https://doi.org/10.1016/s1470-2045(20)30168-6

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.

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ANSWERS TO SELF-TEST QUESTIONS

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