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EDITORIAL

Reporting adverse drug events to the Therapeutic Goods Administration

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In Australia the Therapeutic Goods Administration (TGA) monitors the safety of medicines to improve the understanding of their possible adverse effects. Adverse events are the harmful and unintended consequences of medicine use. They are a leading cause of unplanned hospital admissions and deaths. Reporting adverse drug events to the TGA is therefore important for making the information known and widely available. Reports can come from health professionals, consumers and pharmaceutical companies. These reports are collected in the Database of Adverse Event Notifications (DAEN). This includes information about adverse events related to prescribed, over-the-counter and complementary medicines, and devices.

The TGA assesses potential signals and reports nationally and internationally to enable a clearer understanding of the risk of harm associated with a drug. It is important that health professionals report all suspected adverse events, including known adverse events (to monitor their frequency), for all drugs, no matter when they were registered. It is particularly important for detecting rare and potentially dangerous adverse effects, those occurring after prolonged exposure, and drug–drug and drug–disease interactions that may not have been observed in clinical trials.[1]

Although it is easy to send reports to the TGA, voluntary reporting is in decline. There are now less than 1000 reports by medical practitioners per year. Of the 11,662 reports in July–December 2019, only 4.6% were from medical practitioners. Although most prescribing is in general practice, few reports come from GPs. Reports from non-medical health practitioners comprised 15.3%, patients made 3.4% of notifications, pharmaceutical companies were responsible for 64.2% of reports and 12.5% were from other sources.[2]

It is unclear if the decline in reporting is because adverse events are truly declining, or there are behaviour changes regarding reporting. For example, health professionals used to receive printed copies of the publication Medicines Safety Update and the 'blue card'[3] reporting form. The blue card is now only available on the TGA website. If these hard copies, which are no longer printed, were visual cues for prescribers, perhaps raising expectations and awareness that adverse events are common and should be reported, their absence may have led to less reporting. Medicines Safety Update is now only published as relevant topics arise rather than in a bimonthly scheduled publication, as was previously the case, thereby reducing the profile of reporting.

Probably less than 5% of adverse reactions are reported, even in countries where reporting is mandatory.[4] A European systematic review found that the median rate of under-reporting by healthcare professionals was 94%.[5] Despite the limitations of voluntary adverse drug reaction reporting systems, they remain the most common and inexpensive method of collecting data to generate safety signals.

In Australia, it is mandatory for pharmaceutical companies to report all serious adverse events suspected of being related to their drugs, but reporting by health professionals has always been voluntary. Without robust reporting mechanisms supporting the detection of safety signals, rare adverse drug events may remain undetected for years, exposing patients to unanticipated risks. Examples of high-profile drug withdrawals include lumiracoxib (associated with severe hepatotoxicity), which only occurred after thousands of patients in Australia had been exposed.[6]

Neuropsychiatric adverse events associated with montelukast, and euglycaemic ketoacidosis associated with sodium-glucose co-transporter 2 inhibitors, are rare adverse effects detected only by careful pharmacovigilance analysis. The Australian pharmacovigilance system detected an outbreak of hyoscine hydrobromide toxicity due to wide variations in the concentration of the active ingredient.[7]

There is a need to understand the reasons for under-reporting. We need to consider the different motivators and barriers that influence the likelihood of completing and sending reports to the TGA. What has changed? For example, has the removal of the blue card reduced awareness of pharmacovigilance?

Recognising an adverse event is a key issue, however even when it is recognised it may not be reported. Definitions of medicine-related harm are multiple and varied[8] and this may make medical staff anxious if they are uncertain of the diagnosis. Available tools include the Naranjo Adverse Drug Reaction Probability Scale.[9] A possible solution is to have

standard descriptors adopted by practitioner groups and regulatory organisations to support better awareness, quality improvement and patient safety.[8]

Health professionals possibly report proportionally more serious adverse events, due to the impact on patient care, and because the TGA website stipulates particular interest in serious adverse events. However, this skews the reported data. This means that the DAEN may contain a higher ratio of serious to non-serious adverse event reports and also rare rather than common reactions. A further limitation is that a search of the DAEN will not provide information about the severity of adverse events, or the dose, strength or duration of use of a medicine. Reports for drugs accessed via the Special Access Scheme, Authorised Prescriber Scheme, Clinical Trial Notification Scheme or the Clinical Trial Exemption Scheme are not published in DAEN. This lack of publication may potentially be a disincentive to reporting.

Whereas publicity about a possible adverse event may increase reporting, there is a well-characterised progressive decline in adverse event reporting, following an initial peak, after a drug's regulatory approval. Other factors potentially contributing to low reporting rates by health professionals include a lack of time relative to other clinical priorities,[8] their awareness and perceived importance of pharmacovigilance,[8,10] and a lack of feedback about pharmacovigilance activities.[11] There may be limited awareness of adverse drug event reporting mechanisms and uncertainty about the cause of events, particularly when there is multimorbidity and polypharmacy.[10] An adverse event may cause misplaced concern regarding potential legal liability.[11]

To improve safety for patients, health professionals should be encouraged to report adverse drug events. We suggest education, starting at university, that any suspected adverse event related to a medicine should be reported, even if the reaction is already known. A lack of awareness of the need to report adverse drug reactions may have led to some clinical pharmacology departments specifically teaching about pharmacovigilance and the importance of reporting. Role modelling by more senior clinicians demonstrating reporting on ward rounds, in the early postgraduate years, might also encourage new graduates to report adverse events.

A longer term strategy to improve reporting is to consider adding successful aspects of an international pharmacovigilance system to the current Australian system. For example, a collaboration between the European Medicines Agency, the European Medicines Regulatory Network and academic research centres, provisionally termed the Regulatory Science and Innovation Programme for Europe (ReScIPE),[12] is an interesting model and broader than pharmacovigilance reporting. This model could be explored for more in-depth and clinically relevant approaches to reporting. Other jurisdictions such as New Zealand also have specific pharmacovigilance committees. An Australian committee could be reinstated to raise the profile of drug safety in Australia.

For the present, reports can be made online via the TGA website or via email. There is an online blue card reporting form which can be downloaded from the TGA website and emailed, faxed or posted to the TGA. Medical practices can download and install templates in their software to create adverse drug reaction reports. Health professionals can subscribe to the online version of Medicines Safety Update for advice on drug safety and information about emerging safety concerns.

Conflict of interest: none declared

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EDITORIAL

Policing the promotion of prescription medicines – the new Medicines Australia Code of Conduct

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Keywords
advertising, conflict of interest, drug industry, Medicines Australia

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In 2020, Medicines Australia, the industry organisation for research-based pharmaceutical companies, launched its latest Code of Conduct for ethical marketing. This 19th edition covers the promotion of prescription medicines and public reporting of industry payments to health professionals and health consumer groups.[1]

The first overarching principle in the 19th edition is that 'all activities undertaken by companies have the purpose of supporting the quality use of medicines'.[1] Although this is an important aspirational goal, the evidence to date on the effects of promotion points to higher prescribing rates, increased costs and less appropriate prescribing.[2]

Regulation of pharmaceutical promotion matters to public health because inappropriate use of drugs can lead to serious harm. Intensive opioid marketing helped fuel the epidemic of opioid mortality in North America. In the USA, doctors with funding from opioid producers prescribed more opioids, and opioid-related mortality was higher in counties where more money was spent on marketing.[3] Promotion can also affect health systems by fuelling higher costs, for example by encouraging more prescribing of brand-name products.

The new edition of the Medicines Australia Code of Conduct is shorter and is described as more principle-based and less prescriptive than previous codes. Users are referred to the guidelines of the 18th edition as a benchmark, suggesting the two editions have broadly similar criteria. One striking difference is that this is the first Code since the 1970s not to be authorised by the Australian Competition and Consumer Commission (ACCC). Previously, Medicines Australia had sought ACCC oversight to ensure the Code was consistent with competition law.

The ACCC played an important role in strengthening the Code in 2015, when Medicines Australia began the public reporting of payments to individual health professionals. The ACCC rejected an opt-out clause allowing clinicians to refuse consent. It also urged Medicines Australia to set up a centralised searchable database of clinician reports instead of them being scattered in many separate company documents. The name of the health professional can be entered into a search which will reveal any payments they have received.

Promotion is ubiquitous in clinical practice. Industry funds most medical research and much continuing medical education. Many clinical experts are paid by the industry to be 'key opinion leaders'. In Australia an average of 608 industry-sponsored events for clinicians are held each week, with food and drink provided at over 90%.[4]

In recent years more information about drug promotion has come to light because of public reports of industry payments to clinicians, especially through the US Open Payments database. There has also been the public release of internal company documents in whistle-blower legal cases concerning fraudulent marketing.[5] The issues addressed in these legal cases have implications that are relevant to the quality use of medicines in Australia. These include off-label prescribing of antipsychotic drugs and overuse of gabapentinoids and opioids. Financing of clinician key opinion leaders, sponsored continuing medical education and ghost-writing have been identified as key marketing tools.[5] There are many examples of ghost-writing in the medical literature. For example, dozens of reviews and commentaries promoted unproven benefits and downplayed the harms of menopausal hormone replacement therapy.[6] The new Medicines Australia Code does not mention ghost-writing. There are no new restrictions on allowable payments to clinicians and no firewalls to prevent company input into the content of continuing medical education or the choice of speakers.

Research linking the US Open Payments database with prescribing data has revealed the effects of industry payments on prescribing. One important finding is that even small gifts of food and drink affect prescribing. In an analysis in four drug classes, doctors who received one industry-funded meal, costing on average less than US$20 (A$28), wrote more prescriptions for the promoted drugs. More meals were associated with more prescribing.[7] In Australia, the Medicines Australia Code allows payments for meals up to A$120, but companies are not required to report publicly on food and drink payments. Free samples and payments for research contracts are also not disclosed.

Australia was at the forefront of transparency reporting in 2007, when public reporting of industry-sponsored events was introduced. Reporting of payments to individual clinicians, introduced in 2015, was an

important advance. Transparency about industry payments to clinicians allows the public to know the nature and extent of financial links and could lead some clinicians to avoid questionable payments. However, individual reporting was accompanied by a step backwards in terms of the types of funding disclosed, with costs of food and drink left out. As a result, the total amounts of funding disclosed dropped by one-third.[8] The only hospitality that must be reported under the current Code is airfares and accommodation. Current reporting is less comprehensive than in several European countries where the transparency of industry payments is mandated by law.[9] Additionally, companies that are not members of Medicines Australia may not adhere to the principles of the Code.

What about advertising standards? The Code specifies that information should be accurate, balanced and '...not mislead directly, by implication or by omission'.[1] However, an Australian analysis of advertising claims in 290 pharmacy journal advertisements found only nine (1.5%) of the 598 included claims were unambiguous clinical claims supported by strong published research evidence.[10] A comparison of Australian, Canadian and US advertisements in general practice journals gave Australian advertisements the lowest quality score, mainly due to limited information about harm or quantified benefits.[11] The new Code mainly differs from previous standards in no longer specifying required minimum font sizes. It does not require quantified clinical evidence or a balance of benefits and harms in advertising copy, nor does it prohibit ambiguous or non-clinical claims. It is therefore unlikely to address the key quality concerns raised in these analyses.

Medicines Australia receives few complaints about breaches of the Code. Most complaints come from competing companies. Within a complaints-based system, why most clinicians do not submit complaints is an open question. It could be due to a lack of observed breaches, lack of awareness, lack of time, or differing priorities. Medicines Australia's Code Monitoring Committee also reviews compliance of company policies and promotional materials submitted on request. The Committee is limited to three reviews per company per year. Overall, monitoring is limited in scope and cannot assess more generally whether misleading or inaccurate information is reaching clinicians.

If the regulation of promotion is to encourage the quality use of medicines, influential payments to clinicians and commercial biases in research and education must all be addressed. This would require visionary change. The new Medicines Australia Code of Conduct largely retains existing standards despite the international research evidence showing the adverse effects of promotion, such as the concerning experience with opioids. Gaps in transparency reporting persist, especially compared with national legislated public reporting systems overseas. From a public health perspective, more robust regulation is needed. <

Conflict of interest: In 2020, Barbara Mintzes acted as an expert witness for Health Canada in a legal case on marketing of an unapproved product. She is also a member of Health Action International (HAI-Europe), a non-profit organisation supporting rational medicine use and access to essential medicines.

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LETTERS

Letters to the Editor

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

More prescribing resources for medicinal cannabis

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We commend the authors for their informative article on prescribing medicinal cannabis in this rapidly evolving therapeutic area.[1] In 2019, given the absence of information on medicinal cannabis in usual reference texts such as the Australian Medicines Handbook, the NSW Therapeutic Advisory Group (NSW TAG) identified a resource gap for NSW public hospital clinicians. In collaboration with the NSW Cannabis Medicines Advisory Service, NSW TAG developed an information primer for Cannabis Medicines Use in Hospitals. This outlines information regarding access, general principles, active ingredients and scheduling for cannabis medicines. It also provides more detail regarding the dispensing processes for hospital pharmacists as well as storage considerations and links to other policy documents and online resources.

We also recommend going directly to the NSW Cannabis Medicines Advisory Service which provides expert clinical guidance and support for NSW doctors (and pharmacists) when considering the potential use of a cannabis medicine in an individual patient. This is a very valuable resource for this sometimes challenging area of clinical practice.

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Evolving evidence for immunosuppressants in COVID-19

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I read with great interest the informative article on the role of immunosuppression in the treatment of COVID-19.[1] While appreciating their efforts, I wish to make a few observations.

In the section where the authors have stated the role of systemic corticosteroids, there are two more findings that are worth mentioning. First, a study found that SARS patients treated with high-dose pulse therapy of methylprednisolone had systemic damage along with metabolic alterations at 12-years follow-up.[2] Second, in the RECOVERY trial, treatment with a daily dose of dexamethasone for up to 10 days was associated with reduced 28-day mortality in COVID-19 patients with respiratory support.[3]

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The authors of the article comment:

Evidence in COVID-19 continues to evolve at a rapid pace. While the promise of certain therapeutic options has not materialised, other medicines have emerged from clinical trials with proven clinical efficacy.

While early observational data were promising, tocilizumab failed to improve clinical status and reduce mortality in the COVACTA trial[1] or prevent intubation in the BACC Bay trial.[2] Dexamethasone, in contrast, has demonstrated some clinical and mortality benefit in advanced disease in the RECOVERY trial.[3] As Ajay Shukla points out, the adverse effects of corticosteroids are broad and potentially long-term and should be closely monitored.[4,5] Despite dexamethasone, mortality rates remain high. Successful strategies potentially hinge on strategic selection of the mode and timing of immunomodulation in appropriate clinical settings. Refining this treatment paradigm may only be achieved through rigorous clinical trial evaluation.

Trials evaluating the efficacy and safety of multiple immunosuppressive therapies, including tumour necrosis factor inhibitors[6] and tyrosine kinase inhibitors,[7] continue as we still grapple with this evolving global health crisis. Resources such as the Australian National COVID-19 Clinical Evidence Taskforce's Living Guidelines[8] provide a useful reference point, with important clinical information and summation of emerging evidence for healthcare workers.

While evidence evolves, therapies will either be discounted as unsafe or ineffective or be validated and approved as standard of care. As therapeutic validation occurs, it is important to remember that prescribing outside of clinical trials remains off label and should be conducted in an ethical and considered manner.[9]

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ARTICLE

Limiting antipsychotic drugs in dementia

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antipsychotic drugs, behavioural symptoms, dementia, deprescribing, psychotropic drugs, risperidone

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SUMMARY

Most patients with dementia have behavioural and psychological symptoms. The first-line treatments for these symptoms are not drugs, but behavioural and psychological interventions.

Antipsychotic drugs are widely prescribed for people living with dementia. This is despite a high adverse effect burden and limited evidence of efficacy.

Most behavioural and psychological symptoms will subside spontaneously within six months. Trials of deprescribing are therefore recommended.

Behaviours should be seen as symptoms that have an underlying cause. Treatment should target these causes, rather than the resultant behaviours.

Introduction

Older people are prescribed psychotropic drugs at a rate that dwarfs that of younger cohorts (Fig. 1).[1,2] Much of this prescribing occurs in residential care settings. The prevalence of antipsychotic use may be up to 44% in this population.[3] A large proportion of antipsychotic prescribing occurs in the three months before someone enters aged care. It then increases markedly in the three months after admission.[4] These drugs are often prescribed for the management of the behavioural and psychological symptoms of dementia. This is despite a lack of efficacy and high rates of adverse effects.[5] It has been estimated that only 10% of psychotropic prescribing for those living with dementia is appropriate.[6]

Antipsychotic effectiveness

Many behaviours that can occur in dementia are unlikely to respond to pharmacotherapy at all. For example, there is no drug treatment for wandering, or calling out. A drug cannot be expected to modify behaviours such as shadowing staff, exit-seeking, disrobing or inappropriate voiding. In such cases, the only means by which an antipsychotic may have efficacy is by sedating the person to the point where they are no longer able to engage in such behaviours. This constitutes chemical restraint.

Placebo response rates in randomised controlled trials of antipsychotics for behavioural and psychological symptoms of dementia are high. This reflects the high rate of spontaneous remission of all these types of symptoms within three months.[7] When an antipsychotic has been prescribed and a behaviour subsequently resolves, it may be tempting to conclude that this is because of the drug, however the behaviour may well have settled without the drug.

The behaviours for which antipsychotics may have some benefit are limited to psychosis, agitation and aggression. However, apart from psychosis, the mechanism of action is unclear, so the effects may also represent non-specific sedation.

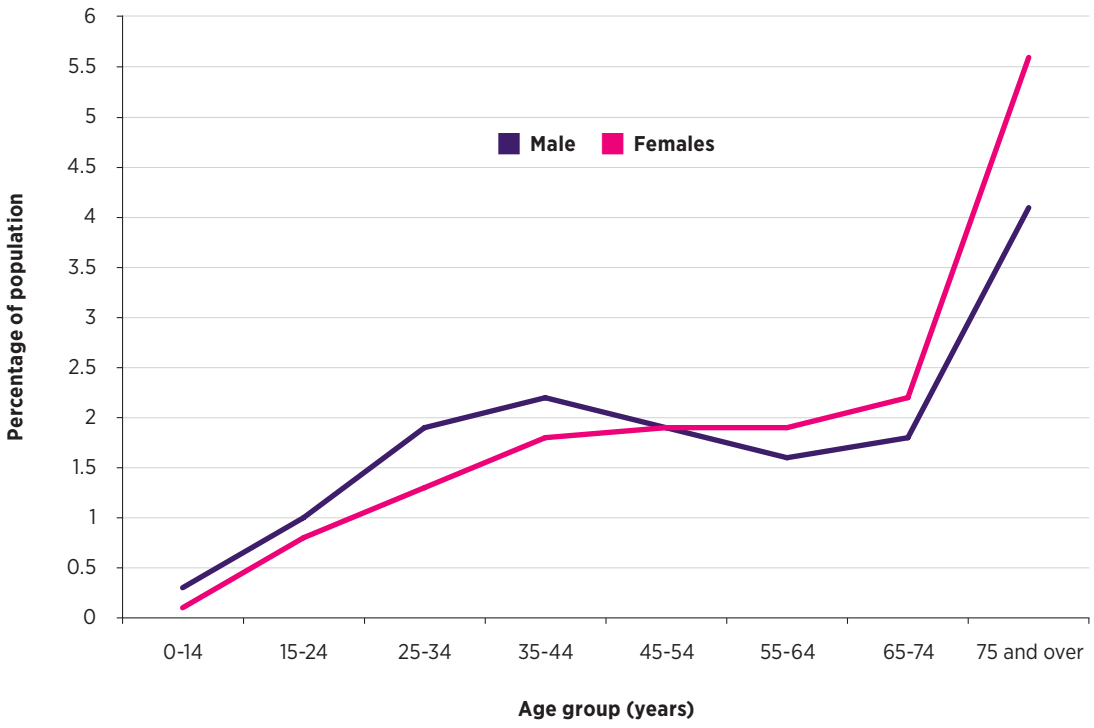
In Australia, risperidone is the only antipsychotic approved for the treatment of behavioural and psychological symptoms of dementia. However, there are data that other antipsychotics are frequently prescribed off label for the behavioural and psychological symptoms of dementia.[8] The Pharmaceutical Benefits Scheme restricts the use of risperidone to behavioural symptoms characterised by psychosis and aggression in those with Alzheimer's disease, for a 12-week period, and only after non-pharmacological interventions have failed. While there is evidence that risperidone can benefit the specific behavioural and psychological symptoms of agitation and aggression, the effect sizes are small.[9]

The adverse effect burden of antipsychotic drugs is significant and includes falls, sedation, extrapyramidal adverse effects and death. These problems are often treatment-emergent and related not only to dose, but duration of exposure, underlining the need for frequent monitoring for adverse effects. The limited efficacy of antipsychotics, combined with their poor tolerability and safety profile, makes the obtaining of consent vital before starting any treatment. An assessment of an individual's capacity to refuse treatment must always be made before seeking proxy consent from an authorised decision maker.

Deprescribing

A deprescribing plan should be provided when starting an antipsychotic drug in a patient with dementia. If an antipsychotic has been prescribed and the symptoms settle, a trial of deprescribing is warranted. Figure 2

Fig. 1 **Proportion of population accessing subsidised antipsychotic drugs in 2011** [2]



shows an algorithm as to how deprescribing might be approached.[10] It is important to involve other members of the multidisciplinary team such as nurses and a pharmacist in the development of a deprescribing plan. Deprescribing provides an ideal opportunity to try specific non-drug strategies for any behaviours that might re-emerge as the drug is withdrawn.

Assessing the patient

It is important to identify what may be causing the behavioural and psychological symptoms in someone with dementia. Agitation and aggression are symptoms, not diagnoses. Just because a drug may have efficacy in treating agitation does not mean that the drug is indicated in response to the symptom. The key to developing effective non-pharmacological interventions is an accurate assessment of the cause of the behavioural symptoms. Appropriate management cannot occur in the absence of adequate assessment.

Common causes of symptoms include unrecognised or undertreated pain, depression, and delirium. Expert consensus for the pharmacotherapy of behavioural and psychological symptoms of dementia emphasises trials of analgesia and antidepressants before considering antipsychotic use.[11] If an antipsychotic is going to be used, the need for continuing analgesics and antidepressants should be reviewed.

Multidisciplinary approach

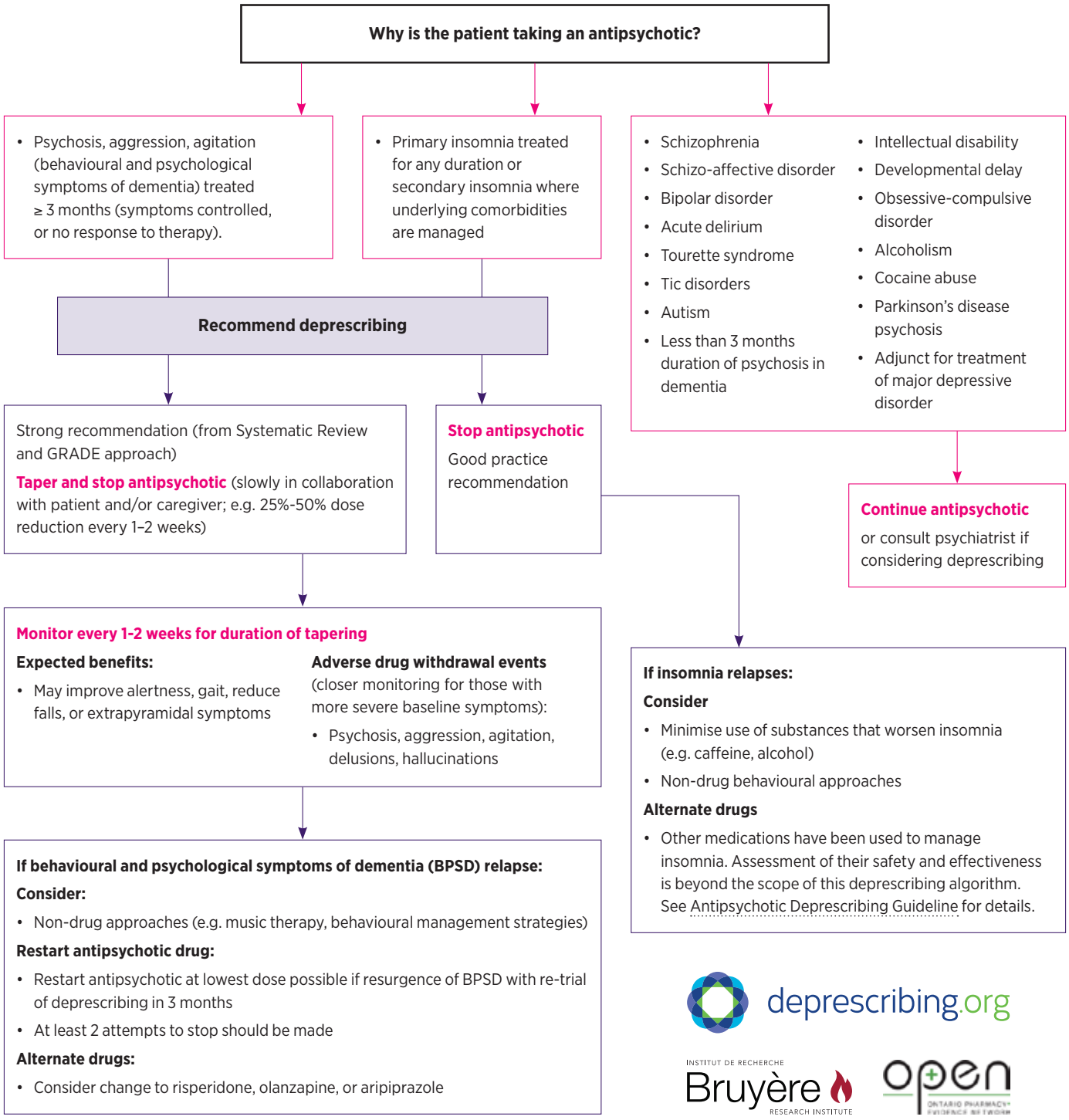
The Commonwealth Government has funded free, national dementia behaviour-management services since 2007. The various state and territory-based services were united under a single provider, Dementia Support Australia, in 2016. This has a multidisciplinary workforce with expertise in the assessment and non-pharmacological management of the behavioural and psychological symptoms of dementia. It is backed by a national team of geriatricians and old-age psychiatrists. Referrals can be made via 1800 699 799 or online.

Conclusion

The evidence for the efficacy of antipsychotic drugs in the treatment of behavioural and psychological symptoms of dementia is unconvincing. However, the drugs cause definite harm including an increased risk of death.

The common medical causes of altered behaviour in someone with dementia should be identified. More detailed evaluation and the subsequent development of individualised behaviour-management plans can involve referral to a multidisciplinary team with experience in the area. <

Fig. 2 **Antipsychotic deprescribing algorithm** [10]



Bjerre LM, Farrell B, Hogel M, Graham L, Lemay G, McCarthy L, et al. Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Can Fam Physician 2018;64:17-27 (Eng), e1-e12 (Fr).

November 2020: Algorithm (Aug 2018) modified by *Australian Prescriber* in accordance with the Bruyère Deprescribing Guidelines Research Team's Modification Policy. Acronyms spelled out. Spelling modified for Australian audience. Second page removed. Original materials available at https://deprescribing.org/wp-content/uploads/2018/08/AP-deprescribing-algorithm-2018-English.pdf

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ARTICLE

Choosing an antidepressant

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depression, selective serotonin reuptake inhibitors, tricyclic antidepressants

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SUMMARY

A biopsychosocial and lifestyle approach should be used when managing depression. Many patients seen in primary care do not require drug therapy.

Evidence-based treatments such as psychological therapies and antidepressant drugs are effective for depression. All patients should receive education about depression.

Shared decision making with the patient is critical if an antidepressant is prescribed. The choice of antidepressant depends on its efficacy and tolerability, the depressive presentation, patient preference and drug interactions.

Introduction

Major depression is best conceptualised using a biopsychosocial and lifestyle model.[1] All those factors need to be considered when formulating a management plan. Lifestyle factors (such as alcohol or substance misuse, lack of exercise or poor sleep habits) that may be contributing to the onset and maintenance of the depressive episode need to be dealt with concurrently (see Table 1). There is a need to be mindful of any psychosocial factors, such as unemployment or interpersonal stress, that maintain the depression.

All patients should receive psychoeducation with a discussion about the symptoms of depression, contributing factors and management options. When appropriate this education can involve other people close to the patient.

Table 1 **Lifestyle factors and interventions for depression**

Potential lifestyle risk factors	Interventions
Poor sleep pattern	Encourage good sleep hygiene – regular bedtime and wake up time, bed is for sleep and not for other activities (TV, social media). There are useful apps that provide basic psychoeducation and a sleep diary.
Alcohol misuse	Encourage safe drinking. If there is heavy use and the patient is seeking treatment, refer to an addiction medicine service. If they are not seeking treatment, do a brief intervention.
Substance misuse	Provide psychoeducation about the harmful effects of substances, advise abstinence, formal counselling or refer to addiction medicine services.
Smoking	Encourage smoking cessation, and consider motivational interviewing and nicotine replacement therapy.
Unhealthy diet	Psychoeducation about healthy diet and the harms associated with processed food. Encourage Mediterranean diet and increased intake of fruit and vegetables.
Lack of exercise	Encourage regular exercise (e.g. daily walks), emphasising a graded approach to exercise.

Specific treatments

While attending to lifestyle factors and providing psychoeducation may be helpful for some patients, others need more specific treatments. These are formulation-based psychological treatment and antidepressant drugs. The efficacy of psychological treatment, such as cognitive behavioural therapy, is equivalent to drug therapy in mild–moderate disease. Ideally, psychological treatment should be offered first, unless the patient refuses or is unable to access or afford psychological treatment, or expresses a strong preference for drug treatment. Sometimes there is a clear indication for prescribing an antidepressant drug.

Indications for drug therapy

Antidepressant drugs are indicated for patients with:

- major depression (characterised by marked symptoms and functional impairment)
- melancholia (characterised by significant psychomotor symptoms – agitation or retardation)
- psychotic depression (depression with delusions or hallucinations).

Antidepressants are also indicated for patients who have had a previous good response to them and for when psychological therapies are not accessible or have been ineffective. Even if a drug is indicated, psychoeducation along with basic counselling is still required.

Drug selection

The choice of antidepressant for a particular patient should be based on four major considerations:

- finding the right balance between efficacy and tolerability
- matching the antidepressant to the type of depression and its presenting features

- safety – risk of overdose, interactions with other drugs or medical disorders (some groups need special consideration, such as older patients and women during pregnancy and lactation, as the baby will be exposed to the antidepressant)[2]
- patient preference.

There is not yet sufficient evidence confirming that the choice of antidepressant should routinely be made using pharmacogenetic data. Patients, particularly those vulnerable to marketing messages, can be advised that, except in some very special cases, genetic testing is not essential. They can save money by not paying for genetic tests.

Balancing efficacy with tolerability

The efficacy of antidepressant drugs has been confirmed in a network meta-analysis.[3] Each antidepressant was compared with other antidepressants using data from randomised placebo-controlled trials. 'Dual-acting' antidepressants that target more than one neurotransmitter system, such as the serotonin noradrenaline reuptake inhibitors (SNRIs) and tricyclics, are more efficacious than 'single-action' drugs, such as the selective serotonin reuptake inhibitors (SSRIs) like sertraline and escitalopram, based on the odds ratio of achieving a 50% response (see Table 2).[3] This meta-analysis also examined the acceptability of the various antidepressants by comparing the drop-out rates in clinical trials. While this is a useful metric of acceptability, the rates of adverse effects for each antidepressant are more useful in clinical practice.

Table 3 summarises the common adverse effects ranked according to a 'limitation' score for each of the antidepressant classes. The frequency of adverse effects can vary greatly between antidepressant classes, due to having different mechanisms of action. There are fewer differences between drugs in the same antidepressant class, although there are some exceptions.

In general, for an uncomplicated mild–moderate depression, the first choice of antidepressant should be a drug that will be well tolerated and has good efficacy. The ease of switching treatment[4] should be considered because the first antidepressant may not lead to full remission, requiring the patient to change to a different antidepressant.[5]

For patients with a severe depression or melancholia (characterised by significant psychomotor change), the prime consideration is efficacy rather than tolerability. The first choice will then be one of the more potent antidepressants, generally a dual mode-of-action drug, such as an SNRI or a tricyclic antidepressant.

Table 2 **Efficacy of antidepressants compared to placebo**

Antidepressant	Odds ratio	95% confidence interval
Amitriptyline	2.13	1.89–2.41
Mirtazapine	1.89	1.64–2.20
Duloxetine	1.85	1.66–2.07
Venlafaxine	1.78	1.61–1.96
Paroxetine	1.75	1.61–1.90
Fluvoxamine	1.69	1.41–2.02
Escitalopram	1.68	1.50–1.87
Sertraline	1.67	1.49–1.87
Vortioxetine	1.66	1.45–1.92
Agomelatine	1.65	1.44–1.88
Fluoxetine	1.52	1.40–1.66
Citalopram	1.52	1.33–1.74
Clomipramine	1.49	1.21–1.85
Desvenlafaxine	1.49	1.24–1.79
Reboxetine	1.37	1.16–1.63

Efficacy is given as the odds ratio of achieving a response (>50% reduction in severity). These studies generally used the typical dose to treat depression (although some of the studies were 'dose finding' studies in which lower doses were used).
Source: adapted from reference 3

Matching the antidepressant to the clinical presentation

Antidepressants differ in the specific symptoms that they target, so it is possible to choose an antidepressant according to the patient's clinical presentation. It is also possible to use the adverse effects to target specific symptoms. For example, mirtazapine is sedating, so it is an option for patients with significant insomnia. Mirtazapine is also associated with weight gain so it may be useful for major depression accompanied by significant weight loss.[6] In short-term trials, the serotonin modulator vortioxetine benefited patients who had major depression with marked cognitive deficits.[7]

The choice of an antidepressant also depends, to some degree, on the symptom profile of the patient or a specific subtype of depression.[8] Table 4 lists the antidepressants that are preferred for different depressive symptom profiles. Many patients with major depression in primary care also have significant symptoms of anxiety or have a comorbid anxiety disorder. The antidepressant of choice

Table 3 **Antidepressant adverse effects and their limitations on use**

Class	Major adverse effects				Ease of switching (half-life)
	Weight gain	CNS effects – sedation/agitation	Sexual	Withdrawal syndrome	
Selective serotonin reuptake inhibitors (SSRIs)	•	••	•••	••†	••
Serotonin noradrenaline reuptake inhibitors (SNRIs)	•	••	•••	•••	••
Serotonin modulator (vortioxetine)	•	•	••	••	•••
Noradrenaline reuptake inhibitor (reboxetine)	•	•	••	•	••
Tricyclic antidepressants (TCAs)	•••	•••	•••	•••	•••
Reversible inhibitor of monoamine oxidase A (moclobemide)	•	••	•	•	•••
Tetracyclic (mianserin)	••	••	•	••	•
Noradrenergic and specific serotonergic (mirtazapine)	•••	•••	••	••	•
Monoamine oxidase inhibitors (MAOIs)	••	•••	••	••	•••
Melatonergic (agomelatine)	•	•	•	•	•

• Minimal limitation
•• Some limitation
••• Marked limitation
† There is little variation in the severity of adverse effects within classes of antidepressants (but patients may differ in the adverse effects they experience). One exception is the withdrawal symptoms following discontinuation of SSRIs. There is an absence of withdrawal symptoms for fluoxetine but very severe withdrawal symptoms for paroxetine.

Table 4 **Symptoms and initial antidepressant choice**

Symptoms	Preferred antidepressant
Anxiety	Selective serotonin reuptake inhibitors Moclobemide
Weight loss, reduced appetite	Mirtazapine Mianserin
Sleep disturbance, insomnia	Agomelatine Mirtazapine Mianserin Tricyclic antidepressants
Sexual dysfunction	Agomelatine
Blunting, anhedonia, demotivation	Selective serotonin reuptake inhibitors Serotonin noradrenaline reuptake inhibitors Agomelatine Monoamine oxidase inhibitors Reboxetine
Melancholia, severe depression	Serotonin noradrenaline reuptake inhibitors Tricyclic antidepressants Vortioxetine Monoamine oxidase inhibitors
Pain	Duloxetine Tricyclic antidepressants
Cognitive difficulties	Vortioxetine

here is an SSRI.[9] For patients with a melancholic depression, which has a clear biological underpinning characterised by vegetative symptoms and psychomotor change such as agitation or retardation, a dual-action antidepressant should be the first option. The tricyclic antidepressants or duloxetine may be used in certain neuropathic pain conditions. While they can be prescribed for patients with pain and associated depression, the doses of a tricyclic used to treat major depression need to be higher than those used for adjunctive therapy in pain management.

Safety considerations

Patients with depression can often have suicidal thoughts and may try to commit suicide. This needs to be considered when prescribing an antidepressant. A suicidal patient should not be given quantities of a drug that could be fatal in an overdose. The SSRIs have a much lower potential lethality than the tricyclic antidepressants.

Ask about any other drugs the patient may be taking to avoid potential interactions. For example, there is an increased risk of serotonin toxicity when taking SSRIs in combination with tramadol, St John's wort or monoamine oxidase inhibitors (MAOIs). SSRIs are also associated with increased bleeding due to changes in platelet function. Caution is therefore needed if they are taken with anticoagulants or non-steroidal anti-inflammatory drugs (NSAIDs). With the

increased risk of bleeding, there is a need to consider any comorbid conditions that may add to this risk. In order to limit potential drug and disease interactions, it is recommended that prescribers only use a few antidepressants that they know and understand well.[10]

Patient preference

A key consideration is patient preference. Adherence to antidepressants is essential to ensure remission of the depression. A significant proportion of patients will stop their antidepressant.[11] Adherence is improved if the patient is involved in the decision about which treatment to take. This involves a discussion about the expected benefits of the antidepressant and its potential adverse effects. Some adverse effects, such as sedation, may be more acceptable to patients, but others such as weight gain may be less acceptable. Be aware that patients might have misinformation from the internet or through word of mouth that the adverse effects of an antidepressant are 'dreadful and nobody should ever take it'. In such situations, it is essential to listen to the patient's concerns and present them with clear and accurate information about the drug, including providing them with consumer fact sheets. This approach will improve adherence.

Conclusion

After deciding that a patient needs to take an antidepressant, the choice of drug depends on the severity and symptom pattern of the depressive episode. There has to be a balance between efficacy and tolerability, which also considers patient safety and preference.

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ARTICLE

Is it time to stop using statistical significance?

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bias, confidence interval, statistical data analysis, statistics

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SUMMARY

The important first step in the critical appraisal of a randomised trial is not an evaluation of the statistical analyses. The most important aspect to consider when reviewing a study of a new drug is the appropriateness and quality of the trial design and methods.

The next most important aspect is the effect size of different treatments and its clinical significance. Rather than reporting statistical significance, studies should report the difference between treatments and its precision.

Over-reliance on statistical significance and p values may lead to incorrect conclusions. Trial reports about drugs should therefore avoid the term statistical significance and quote p values with caution.

Introduction

Criticisms of the misuse and misinterpretations of statistical significance testing (and of p values) were made throughout the last century.[1] William Rozeboom, an eminent philosopher of science, once asserted that it was 'surely the most bone-headedly misguided procedure ever institutionalised in the rote training of science students'.[2] This criticism reached a zenith in 2019, when the American Statistical Association, an international peak body of professional statisticians, formally recommended against statistical significance testing – both its use and in the reporting of results.[3]

There are many examples of how the term 'significant' can be open to interpretation. A review of fremanezumab for migraine in *Australian Prescriber*[4] stated:

> 'At the end of the trial, monthly injections had reduced the number of headache days by 4.6 days and the number of migraine days by 5.0 days. With quarterly injection the reductions were 4.3 days for headache and 4.9 days for migraine. Both regimens were significantly better than the reductions of 2.5 days and 3.2 days seen in the placebo group.'

For most readers of *Australian Prescriber*, that statement might seem eminently reasonable. However, the routine use of the word 'significantly' is misleading.[3]

Statistical significance

To understand why the term statistical significance is problematic, it is necessary to consider the context in which statistical significance testing occurs. Empirical research is about discovering and constructing knowledge about the world, for instance, whether a new drug works from the perspective of causation and predicting patient outcomes. This research often involves describing the empirical world using numbers (quantitative methods). Statistical inferential testing can be a useful tool whose results can inform us about the real world. However, discomfort with uncertainty promotes overconfidence in statistical rituals,[5] and contributes to the belief that statistical testing is always necessary.

Clinicians commonly misinterpret statistical significance and its conceptual twin, the p value.[6] This potentially results in gross overestimation of the strength of evidence.[7] Importantly, neither the validity of the study nor the truth of its findings can be inferred from p values and statistical significance alone.

Two simple heuristics to reduce misinterpretation of p values and statistical significance are:[6]

- They do not numerically refer to the probability of a phenomenon or event occurring in the real world. For instance, the claims that one or both show the likelihood of the experimental result being true, or due to chance, are incorrect.[8]
- They should not be interpreted using thresholds. Any cut-off value (such as p=0.05) is arbitrary. Making binary empirical conclusions based on which side of the threshold the test statistic falls is unsound reasoning.

Null hypothesis

Statistical significance is fundamentally a mathematical concept that should be understood only in the context of null hypothesis statistical testing. This involves creating a statistical model, a simplified and artificial 'mathematical world' where the researcher can define all the rules. In this model,

one of the rules is that drugs or procedures have zero effectiveness – hence the term null hypothesis.

Seen from within the mathematical world, using the assumptions of this 'zero-effectiveness' statistical model, the unusualness of the real-world data collected in the study can be calculated. The p value can be considered a measure of how compatible the data are with this statistical model. Larger p values are more compatible with the null hypothesis and small p values less so.

Statistical significance only means that the data reached an arbitrarily defined level of incompatibility with the statistical model. However, this zero-effectiveness statistical model might be incompatible with the data for many reasons. For instance, the data collected might have been biased, or one or more assumptions used in the statistical model were unsound or violated. Statistical significance does not indicate on its own that the result is true or that the null hypothesis is false. Moreover, statistical significance does not indicate or imply that a result is clinically important.

Clinical significance

Clinical significance pertains to patient care. Deciding whether or not a study result is clinically significant cannot be determined by an algorithm. Rather it requires judgement, clinical expertise and a respect for context.

The important first step in the critical appraisal of a clinical trial is not an evaluation of the statistical analyses. Analysing the patients, intervention, comparison and outcomes in the methods section of the report, and being satisfied with the reasonableness of the question asked by the researchers, is important in deciding whether or not to read more of the report.

Next is an appraisal of the internal validity of the trial, which can be framed as a series of questions. For a randomised trial:[9]

- was the assignment of patients to treatments randomised?
- were the groups similar at the start of the trial?
- aside from the allocated treatment, were the groups treated equally?
- were all patients who entered the trial accounted for?
- were measures objective and were the patients and clinicians kept blind to which treatment was being received?

Threats to the internal validity of a study's methodology reduce the confidence that the results usefully represent what the study sought to investigate. Simply, if the study has major methodological biases, the results will need to be taken with a grain of salt. The results might even be uninterpretable.

Effect size

When looking at trial results, the focus should be on the primary outcome, its effect size, and the precision with which that effect has been able to be estimated. This precision is often described as a confidence interval. If the differences in outcomes between groups are small, there is likely to be little clinical benefit from using a trial treatment instead of a comparator. However, it is important to remember that the reported effect size is the average for the sample of people in the study and it is likely that many participants (half of the sample, assuming normal distribution) benefited more while others benefited less (again half, assuming normal distribution). Whether an effect size is clinically significant depends on the nature of the condition, the effect and the context. Synthesising these together requires clinical judgement. Fortunately, investigators often include a discussion of clinical significance when describing the power and sample size calculations in the methods section of their reports.

A useful concept to consider is the minimum clinically important difference, especially when there may not be a good intuitive grasp of the outcome measure. For example, the six-item headache impact test (HIT-6) has a range from 36 (no impact) to 78 (very severe). The minimum clinically important difference is considered to be 2.5 points.[10] In the trial described in *Australian Prescriber*, fremanezumab reduced the HIT-6 score compared with placebo by 1.9 when given quarterly and by 2.4 when given monthly.[11] Both changes are statistically significant, but are less than the minimum clinically important difference. It is important to note that only about 20% of participants in the trial were using any migraine-preventing medicine. When balancing the modest average therapeutic effect of fremanezumab with the need for it to be injected and its high cost compared to established drugs for migraine prophylaxis, it seems hard to justify it as a first-line treatment.

Confidence intervals

The confidence interval, typically reported at 95%, can be interpreted as the (im)precision of the effect-size estimate. This is the range of values that are mathematically compatible with the effect-size estimate.

If the confidence interval is wide, the lower and upper limits indicate very different clinical effects ranging from a tiny effect size to a substantial effect. The effect-size estimate is therefore imprecise and

it would be misleading for it to be quoted without caution and appropriate context.

If the confidence interval is subjectively narrow, the lower and upper limits would give roughly the same clinical interpretation. It could then be claimed that the estimate of effect size is precise.

Judgement and care are required regardless of the confidence interval. A large drug trial undertaken in men could conceivably yield a very precise effect-size estimate, that would be incorrect in women.

It is time to stop using statistical significance

As an exercise to develop insight, try replacing instances of the term statistically significant with the synonym 'mathematically unusual'. Paraphrasing the original quoted *Australian Prescriber* new drug comment as 'both regimens were [statistically] significantly better than the placebo group' becomes 'both regimens were mathematically unusually better than the placebo group'. The apparent meaninglessness of the second sentence is what is meant by the first.

The hidden absurdity of commonly seen statements in reports such as 'the results approached [statistical] significance' is revealed when they are transformed into 'the results approached mathematical unusualness'.

Conclusion

Significance is still a useful word that should not be abandoned. However, for too long statistical significance has co-opted the use of the word. The medical literature commonly conflates statistical significance with the everyday meaning of significance. In line with the recommendation of the American Statistical Association, it is time to move on. Its executive director wrote in unambiguous terms 'statistically significant – don't say it and don't use it'.[3] Rather, we should focus on the effect-size estimate and its precision and interpret these through the lens of clinical significance. <

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ARTICLE

COVID-19 vaccines – are we there yet?

SUMMARY

The novel coronavirus SARS-CoV-2, the cause of the COVID-19 pandemic, is a highly infectious human respiratory pathogen to which the global population had no prior immunity. The virus will likely continue to cause significant morbidity until there is a broadly effective vaccine.

As of mid-December 2020, more than 200 COVID-19 vaccine candidates are in development and 11 have entered phase III clinical trials globally. All generate immunity to the viral spike glycoprotein.

Three vaccine candidates have agreements for procurement and use in Australia if efficacy and safety requirements are met – one protein-based vaccine, one vaccine using a simian-derived adenovirus vector and one messenger RNA vaccine. The latter two vaccines have published interim analyses and efficacy results of their phase III trials. The messenger RNA vaccine is being rolled out in the UK, USA and Canada.

Significant uncertainties remain. How well will some of those at highest risk of severe disease (such as older people aged >75 years and those with immunocompromising conditions) be protected by a vaccine, and for how long? Also, to what extent will vaccination protect against infection? This will determine the degree of indirect 'herd' protection needed through broad vaccine coverage of younger age groups.

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Introduction

Like influenza, coronaviruses are RNA viruses. The SARS-CoV-2 virus which causes COVID-19 belongs to the betacoronavirus family. This also includes the SARS-CoV-1 virus which causes Severe Acute Respiratory Syndrome (SARS) and MERS-CoV which causes Middle East Respiratory Syndrome (MERS). Another four seasonal human coronaviruses circulate annually, mostly causing mild upper respiratory tract infections.

SARS (2003) and MERS (2014) caused short-lived epidemics with a high case fatality. MERS still occurs sporadically, but SARS-CoV-1 has not been in circulation since 2008.[1]

COVID-19 is most severe in the elderly and those with significant comorbidities. SARS-CoV-2 also results in asymptomatic infection. Unlike SARS-CoV-1, SARS-CoV-2 can be very contagious before and shortly after symptom onset, which has helped drive rapid global spread. Although estimates of the degree of immunity in the population required to control the COVID-19 pandemic vary, most centre around 60–70%.[2] High coverage with effective vaccines is the only ethically acceptable path to achieving this level of immunity. The effectiveness of the various COVID-19 vaccine candidates will depend on their ability to reduce infectiousness versus their ability to prevent serious disease if someone gets infected.

Pandemic preparedness

Experience of disease outbreaks over the past two decades, including SARS and MERS, influenza in 2009, Ebola[3] in 2014 and the emergence of Zika virus, has underpinned rapid progress towards vaccines for COVID-19. This has been enabled by remarkable innovations in fundamental vaccine research and development.[4] Establishing the Coalition for Epidemic Preparedness and Innovations in 2017 was very timely and has helped to identify and give financial support to candidate vaccines against diseases with pandemic potential, including MERS.

Vaccine development

Vaccination is only successful if vaccine development results in a product approved for use and delivered to the target population. The vaccine development process is stepwise, pyramidal and selective.[5] If initial studies in the laboratory (in cell lines and experimental animals) are favourable, human vaccine trials enter the phase I stage which assesses safety, dosage and immunogenicity in small numbers of healthy people. Typically, only a small proportion of vaccine candidates progress to phase II trials, which are designed to identify optimal formulations, numbers of doses and dosing intervals. These trials require hundreds to around a thousand participants. Phase III vaccine trials evaluate protective efficacy against clinical disease as well as safety. Their study size depends on the expected number of cases but is usually many thousands.

Progress through all trial stages usually takes at least 10 years. However, the magnitude of the COVID-19 pandemic has led to funding for the development of 'vaccines at pandemic speed' by running some processes in parallel (see Fig. 1).[4] Many studies have combined phase I and II trials and a few have combined phase II and III trials to compress time frames. This has not compromised scientific rigour as safety, immunogenicity and efficacy outcomes are strictly assessed and safety monitoring will continue even after registration.

As of mid-December 2020, four COVID-19 vaccines have reported estimates of efficacy from their phase III trials in press releases.[6] However, only two of these, one adenovirus-vectored vaccine (University of Oxford/AstraZeneca) and one messenger RNA vaccine (BioNTech/Pfizer), have published interim efficacy results.[7,8] Although vaccines produced in China and Russia have been approved for use in those countries (Table 1), detailed efficacy and safety data at the level required by regulatory bodies in most countries, including Australia, are not currently publicly accessible.

COVID-19 vaccine candidates have been developed using conventional and novel approaches to vaccine development (see Fig. 2). All of them generate immunity to the viral spike glycoprotein, which is required for the virus to enter host cells. The aim of vaccine-generated antibodies against the spike glycoprotein is to prevent viral replication, or 'neutralise' the virus, and stop it from infecting cells.

Conventional approaches

Conventional approaches to vaccine development have the advantage of being familiar and well-studied, but these vaccines may take longer to manufacture. COVID-19 vaccine candidates developed by conventional approaches and currently in clinical trials include:

- inactivated viral vaccines (like the influenza (split virus) and inactivated polio (whole virus) vaccines)
- protein or protein subunit vaccines (like the diphtheria and tetanus protein (toxoid) vaccines, hepatitis B and herpes zoster adjuvanted vaccine)
- virus-like particles (like the human papillomavirus vaccine)
- live-attenuated viral vaccines

Only one live-attenuated COVID-19 vaccine is currently being progressed to human studies (NCT04619628).

Novel vaccine approaches

Novel approaches have potential advantages in the strength of immune responses and rapidity of manufacture but are less well studied. These newer technologies for COVID-19 include viral vectored vaccines and mRNA and DNA vaccines. Vectored vaccines currently in phase III trial use adenoviruses of human or non-human primate origin. These are harmless, non-replicating viruses which are able to enter cells and deliver the genetic code for SARS-CoV-2 spike protein antigen. DNA-based vaccines may require specific devices to deliver the DNA into cells (e.g. by electroporation), and from the cytoplasm to the nucleus once in the cell. Conversely, mRNA vaccines are often encapsulated into lipid nanoparticles which allow mRNA to fuse into the cytoplasm without being degraded (Moderna and BioNTech/Pfizer's vaccines use this technology). Both DNA and mRNA vaccines induce the recipient's own cells to produce SARS-CoV-2 spike protein.

COVID-19 vaccines in clinical trials

Table 1 lists the characteristics of the 11 vaccine candidates in phase III trials as of mid-December 2020.[7-17] Table 2 lists vaccines in phase I or II trials in Australia.

Australia currently has one agreement to locally manufacture a vaccine – ChAdOx1 nCoV-19/AZD1222 (University of Oxford/AstraZeneca). This is a viral vectored vaccine in phase III trials, with interim efficacy results.[7] Previously the University of Queensland/CSL had an agreement for local manufacture of the v451 clamp vaccine. However a decision has been made to not proceed into phase III clinical trials as antibodies to the vaccine interfere with HIV screening tests.[18,19]

Vaccine registration

All COVID-19 vaccines used in Australia will require approval by the Therapeutic Goods Administration (TGA). The TGA has recently determined that three vaccines in phase III trials are eligible to apply for provisional registration in the Australian Register of Therapeutic Goods. These are:

- BNT162b2 (mRNA vaccine)
- ChAdOx1 nCoV-19/AZD1222 (viral vectored vaccine)
- Ad26.CoV2.S (viral vectored vaccine).

Provisional TGA registration of medicines or vaccines is on the basis of preliminary clinical data on quality, safety and effectiveness of the vaccine, and the sponsor's plan to submit comprehensive clinical and stability data before the provisional registration ends.[20]

The status of other vaccine candidates is available through the World Health Organization website which is regularly updated.[21] As of mid-December, the BNT162b2 vaccine has been granted Emergency Use Authorisation in at least three countries, including the UK, Canada and the USA, where it is being rolled out in COVID-19 vaccination programs.

Fig. 1 **Timeline of COVID-19 vaccine development and approval compared to conventional vaccine pathway**

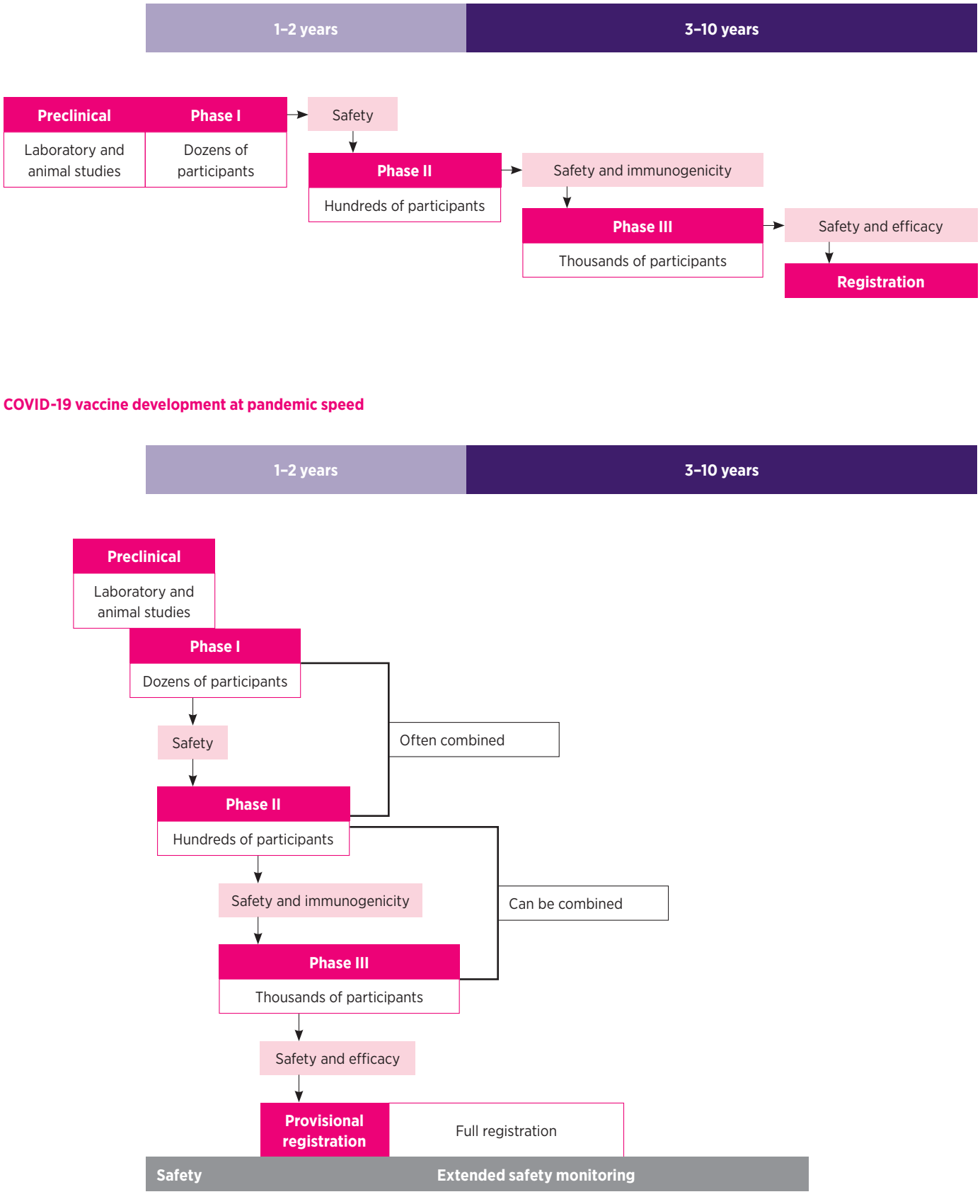

Table 1 **COVID-19 vaccine candidates in phase III clinical trials worldwide (as of mid-December 2020)**

Vaccine	Developer (country)	Platform technology	Dose schedule	Published results	Published Phase III efficacy
ChAdOx1 nCoV-19/ AZD1222*	University of Oxford/ AstraZeneca (UK)	Viral vector (chimpanzee adenovirus vector)	2 doses	Phase I/II[9] Phase II/III[10] Phase I/II and III[7]	Half dose and then full dose: 90% (95% CI: 67.4–97%) Two full doses: 62.1% (95% CI: 41–75.7%)[7]
mRNA-1273	Moderna/NIAID (USA)	mRNA (lipid nanoparticle)	2 doses	Phase I (18–55 years)[11] Phase I (≥56 years)[12]	
CoronaVac	Sinovac Biotech (China)	Inactivated virus	2 doses		
Unnamed	Beijing Institute of Biological Products/Sinopharm (China)	Inactivated virus	2 doses		
Unnamed	Wuhan Institute of Biological Products/Sinopharm (China)	Inactivated virus	2 doses		
BNT162b2*	BioNTech/Pfizer (Germany, USA)	mRNA (lipid nanoparticle)	2 doses	Phase I/II[13] Phase II/III[8]	Two doses: 95% (95% CI: 90.3–97.6%)[8]
Gam-COVID-Vac	Gamaleya Research Institute (Russia)	Viral vector (human adenovirus type 26 and 5, sequentially administered)	2 doses in total	Phase I/II[14]	
Ad5-nCoV	CanSino Biologics (China)	Viral vector (human adenovirus type 5)	2 doses	Phase I[15] Phase II[16]	
NVX-CoV2373*	Novavax (USA)	Protein lipid nanoparticle with Matrix M adjuvant	2 doses	Phase I[17]	
Ad26.CoV2.S	Janssen/Johnson & Johnson (USA)	Viral vector (human adenovirus type 26)	1 dose		
BBV152B/ Covaxin	Bharat Biotech International (India)	Inactivated virus	2 doses		

* Australian Government has advance purchase agreements for ChAdOx1 nCoV-19/AZD1222, BNT162b2 and NVX-CoV2373 subject to registration requirements

Vaccine safety

Safety is paramount at all stages of the clinical development process. It is built into vaccine development by guidelines from the earliest stages (Good Laboratory Practice) to clinical trials (Good Clinical Practice). For each vaccine, safety is assessed by Data Safety Monitoring Boards, independent of the manufacturer, during the trial. Safety is also assessed after trial completion by the regulator when it reviews the vaccine for approval.[22]

In Australia, enhanced reporting of adverse events following immunisation (AEFI) at national and state and territory levels is designed to ensure that the safety of any COVID-19 vaccines used in the National Immunisation Program is comprehensively monitored. This is supplemented by near real-time active vaccine safety surveillance, such as through AusVaxSafety.[23] All these mechanisms will be outlined in detail in the Australian national COVID-19 vaccine pharmacovigilance plan.

Some potential safety concerns were identified early on for COVID-19 vaccine candidates based on previous experience with coronavirus vaccine candidates. In experimental animals given vaccines for SARS and MERS, some studies showed evidence of lung immunopathology after challenge with wild virus (termed disease enhancement).[24] However, this proved not to be an issue for COVID-19

vaccines in animal studies, as high concentrations of neutralising antibody were produced. These antibodies not only bind to viral antigen, they also prevent the virus from infecting cells. In addition, the T-cell responses seen were not associated with allergy (i.e. T helper 1 biased rather than T helper 2).[24] It is a requirement that vaccine candidates satisfy these criteria before entering phase I human trials. To date, no COVID-19 candidate vaccines have generated safety signals of concern.

How will we use COVID-19 vaccines?

There is general agreement that front-line workers, such as healthcare staff, and individuals at the highest risk of severe disease, particularly the elderly, should be prioritised to receive COVID-19 vaccines once available.[25-27] A key question is how well vaccines that show protection in young, healthy individuals will work in people who have chronic medical conditions or are immunocompromised, and in older people, particularly those who are frail or living in residential care. Up until 2020, the only vaccine with high levels of protection in older people (>70 years) is a recombinant shingles vaccine which uses a novel adjuvant.[28] This vaccine is available in the USA, but not Australia. Such novel adjuvants may prove important for COVID-19 vaccines in older people and other groups likely to have reduced vaccine responses.

Fig. 2 **Approaches being used to develop SARS-CoV-2 vaccines to protect against COVID-19**

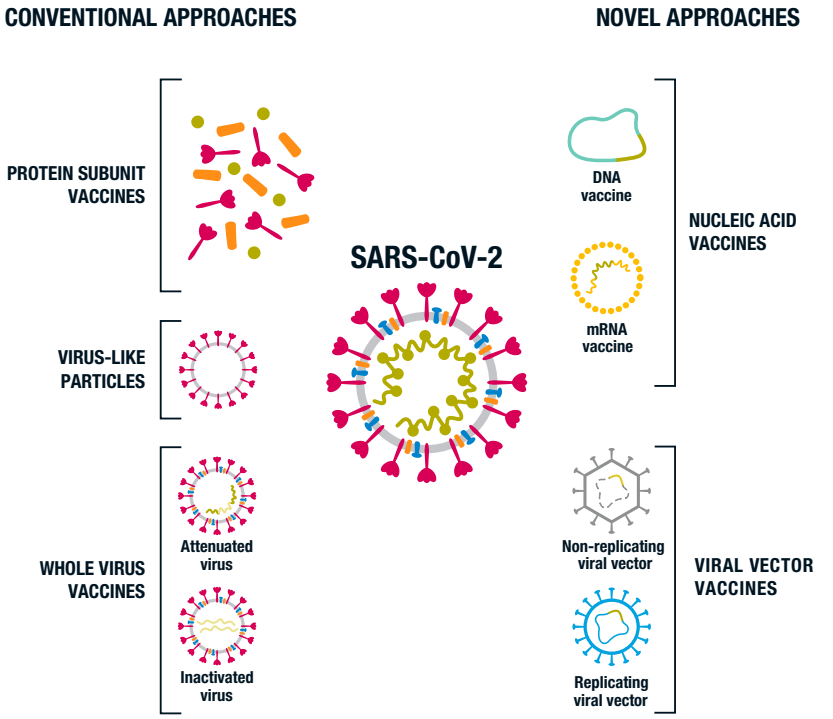

Table 2 **COVID-19 vaccines in human clinical trials in Australia (as of mid-December 2020)**

Vaccine	Developer (country)	Platform technology	Phase	Clinical trial location	Age of participants	Clinical trial registration
SCB-2019	Clover Biopharmaceuticals (China)	Protein	I	Perth	18–75 years	NCT04405908
NVX-CoV2373	Novavax (USA)	Protein lipid nanoparticle with Matrix M adjuvant	I/II	Melbourne and Brisbane (phase I) 10 locations in ACT, NSW, QLD and VIC and 8 in the USA (phase II)	18–59 years	NCT04368988
Covax-19	Vaxine (Australia)	Protein	I	Adelaide	18–84 years	NCT04453852
v451*	University of Queensland (Australia)	Protein	I	Brisbane	18–65 years	NCT04495933
RBD-SARS-CoV-2 HBsAg VLP	SpyBiotech (UK)	Virus-like particle	I/II	Melbourne	18–79 years	ACTRN12620000817943
bacTRL-Spike	Symvivo (Canada)	DNA (oral administration)	I	Melbourne	≥18 years	NCT04334980

* The Australian Government had an advance purchase agreement for v451 vaccine subject to registration requirements. However, further trials of this candidate vaccine have been cancelled due to the vaccine causing false positive HIV tests in those who receive it.[18,19] (This is related to a protein fragment contained in the vaccine formulation.)

Another key uncertainty is whether COVID-19 vaccination will reduce transmission of SARS-CoV-2 and produce indirect 'herd' immunity which could protect people who are unable to respond to vaccines. It will take time for data to emerge on this and on the duration of protection and need for repeated doses.[29]

More detailed priorities for specific target groups will vary with the availability of vaccines and their specific characteristics. Vaccine recommendations, along with other control recommendations are evolving as our experience with COVID-19 grows.

Conclusion

Ensuring public confidence in both the safety and effectiveness of COVID-19 vaccines will be critical to achieving high vaccine uptake among target populations during vaccine roll out in Australia from 2021.[30] As COVID-19 vaccines become available for use, immunisation service providers can take early steps to prepare for vaccine introduction, such as ensuring connectivity to the Australian Immunisation Register and engagement with other systems such as adverse events following immunisation reporting.

Much needs to be done to ensure that the unprecedented scientific effort which has allowed rapid development of COVID-19 vaccines translates into the high vaccine uptake needed to rapidly overcome the most significant global pandemic seen in over a century. ◅

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LATEST NEWS

Valediction: Darren Roberts

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For many years the Editorial Executive Committee of *Australian Prescriber* has provided the opportunity for advanced trainees in clinical pharmacology to participate in editorial meetings. In 2009 the editorial registrar was Dr Darren Roberts. During that year Darren took on the task of preparing an article on the challenging topic of renal bone disease.

In 2014 (now) Associate Professor Roberts was invited to join the Editorial Executive Committee as a full member. Since then he has contributed several editorials and articles to *Australian Prescriber* and has again been willing to tackle challenging topics such as the rescheduling of codeine and, more recently, the impact of COVID-19 on the quality use of medicines.

Associate Professor Roberts became the Chair of the Editorial Executive Committee in 2017. During his tenure Darren has used his experience of the process to help the recent registrars complete their own papers for publication.

The Editorial Executive Committee thanks Associate Professor Roberts for his long-term commitment to *Australian Prescriber*.

New drugs

Cannabidiol

Approved indication: epilepsy (Lennox-Gastaut syndrome, Dravet syndrome)

Epidyolex (Emerge Health)
oral solution containing 100 mg/mL

Cannabidiol is indicated for adjunctive therapy for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients aged two years and older. It is a constituent of the marijuana plant *Cannabis sativa* but unlike tetrahydrocannabinol (THC) cannabidiol does not have psychoactive effects like euphoria.

It is not clear how exactly cannabidiol works to reduce seizures, but it is thought to affect the transmission of electrical signals by modulating the movement of calcium in neurones. Cannabidiol also affects signalling mediated by adenosine which has an important role in seizure suppression.

Adding cannabidiol to other epilepsy medicines has been investigated in four randomised, placebo-controlled trials – two in patients with Lennox-Gastaut syndrome[1,2] and two in patients with Dravet syndrome[3,4] (see Table). The majority of participants in the trials were children with uncontrolled seizures who were already taking at least two antiepileptics. The most commonly used were clobazam and valproate.

Following a four-week baseline period, an oral solution of cannabidiol (titrated to a dose of 10 mg/kg or 20 mg/kg) or placebo was added twice a day to the patient's usual antiepileptic therapy for 14 weeks. In the Lennox-Gastaut syndrome trials, patients were having at least eight drop seizures a month at baseline. These were defined as atonic, tonic or tonic-clonic seizures that could cause a sudden fall. By the end of the treatment, cannabidiol had lowered the frequency of drop seizures per month more than placebo (by 37–44% vs 17–22%).[1,2] In the Dravet syndrome trials, patients were having at least four convulsive seizures a month at baseline. By the end of the treatment, cannabidiol had lowered the seizure frequency per month more than placebo (by 39–49% vs 13–27%) (see Table).[3,4] This effect seemed to be maintained in a 48-week open-label extension study of all four trials.[5,6]

Table **Efficacy of cannabidiol in severe epilepsy**

Study	Treatment group (participants)	Reduction in the frequency of seizures per month from baseline	Improvement in overall condition from baseline on the patient's or caregiver's GIC scale*
Lennox-Gastaut syndrome trials (mean age 15 years)†			
Devinsky 2018[1]	Cannabidiol 10 mg/kg/day	37.2%	66% (48 of 73 patients)
	Cannabidiol 20 mg/kg/day	41.9%	57% (43 of 75 patients)
	Placebo	17.2%	44% (33 of 75 patients)
Thiele 2018[2]	Cannabidiol 20 mg/kg/day	43.9% (from a median of 71.4 to 31.4)	58% (49 of 84 patients)
	Placebo	21.8% (from a median of 74.7 to 56.3)	34% (29 of 85 patients)
Dravet syndrome trials (mean age 9 years)‡			
Devinsky 2017[3]	Cannabidiol 20 mg/kg/day	38.9% (from a median of 12.4 to 5.9)	61.6% (37 of 60 patients)
	Placebo	13.3% (from a median of 14.9 to 14.1)	34.4% (20 of 58 patients)
Miller 2020[4]	Cannabidiol 10 mg/kg/day	48.7%	68.1% (45 of 66 patients)
	Cannabidiol 20 mg/kg/day	45.7%	60.6% (40 of 66 patients)
	Placebo	26.9%	41.5% (27 of 65 patients)

* GIC global impression of change at last visit
† efficacy was defined as median percent reduction in the frequency of drop seizures per month from baseline
‡ efficacy was defined as median percent reduction in frequency of convulsive seizures per month from baseline

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

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The proportion of patients (or their caregivers) who reported improvement on a global impression of change (GIC) scale at last visit was higher in the cannabidiol groups than in the placebo groups (see Table). However, trials that assessed quality of life[1,3,4] did not find a statistically significant difference between cannabidiol and placebo.

The most common adverse events with cannabidiol (affecting at least 10% of patients) were somnolence and sedation, decreased appetite, diarrhoea, fever, fatigue, vomiting and weight loss. These effects appeared to be dose related.[2,3]

Cannabidiol also causes dose-related increases in liver transaminases and is contraindicated when transaminase concentrations are greater than three times the upper limit of normal and bilirubin concentrations are greater than two times the upper limit of normal. Overall, 13% of patients receiving cannabidiol had elevated alanine aminotransferase (>3 times the upper limit of normal) compared to 1% of those who received placebo. The incidence was higher in those taking concomitant valproate (17%) or concomitant valproate and clobazam (23%). Serum transaminases should be tested before cannabidiol is started and regularly during treatment. The cannabidiol dose (or other antiepileptic) may need to be reduced, interrupted or discontinued if signs of hepatic dysfunction develop.

Cannabidiol increases concentrations of co-administered clobazam by 3–4-fold, probably through inhibition of cytochrome P450 (CYP) 2C19. Increases in the active cannabidiol metabolite (7-hydroxy-cannabidiol) are also observed. As a consequence, somnolence and sedation are increased with this combination and the clobazam (or cannabidiol) dose may need to be reduced. Cannabidiol may also increase co-administered stiripentol, phenytoin and lamotrigine so patients should be carefully monitored for adverse reactions.

Cannabidiol is extensively metabolised in the liver by CYP2C19 and 3A4 and uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A7, 1A9 and 2B7 so there is a potential for many drug interactions. Concurrent use of moderate and strong inducers of CYP2C19 (e.g. rifampicin) and CYP3A4 (e.g. carbamazepine, enzalutamide, St John's wort) may decrease cannabidiol concentrations and reduce its effectiveness. Conversely inhibitors of CYP2C19, CYP3A4, UGT1A7, UGT1A9 and UGT2B7 enzymes may increase cannabidiol exposure and increase the risk of adverse effects. If these combinations are used, the dose of cannabidiol or the interacting drug may need to be reduced.

Following oral administration of cannabidiol, maximum plasma concentrations are reached within 2.5–5 hours. Its half-life is 56–61 hours and, following metabolism in the liver, most of the dose is excreted in the faeces. The recommended starting dose is 2.5 mg/kg taken twice a day for a week. After that, the dose should be titrated to a maintenance dose of 5 mg/kg twice daily based on therapeutic effect and patient tolerance. The maximum recommended dose is 10 mg/kg taken twice a day.

As food can increase the absorption of cannabidiol, the dose should be taken consistently with or without food each day. Dose adjustments are not needed in renal impairment, but lower doses are recommended in patients with moderate–severe hepatic impairment.

Cannabidiol reduces the frequency of treatment-resistant drop seizures in patients with Lennox-Gastaut and convulsive seizures in Dravet syndrome when added to usual antiepileptic therapy. However, cannabidiol has many potential drug interactions, particularly with other antiepileptic medicines. Somnolence and elevations in liver transaminases are common and patients need to be closely monitored.

T manufacturer provided the product information

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

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

Caplacizumab

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Approved indication: thrombotic thrombocytopenic purpura

Cablivi (Sanofi-Aventis)
vials containing 10 mg as powder for reconstitution

The von Willebrand factor is a glycoprotein involved in coagulation. In acquired thrombotic thrombocytopenic purpura there is an autoantibody that prevents the cleaving of multimers of von Willebrand factor. These multimers then accumulate resulting in excessive platelet aggregation. This leads to thrombosis, haemolytic anaemia and thrombocytopenia. Patients may present with cerebrovascular or cardiovascular events, kidney injury or gut ischaemia. The mortality rate was high, but has been greatly reduced by plasma exchange therapy and immunosuppression.

Caplacizumab is an antibody fragment that has been genetically engineered to bind with von Willebrand factor. This blocks the interaction between the multimers and platelets so should reduce platelet aggregation.

The first dose of caplacizumab is given intravenously before plasma exchange. Patients are then given daily subcutaneous injections of caplacizumab after each plasma exchange. They continue these daily injections into the abdomen for 30 days after plasma exchange therapy is stopped. The antibody reaches a peak concentration 6–7 hours after injection and markers of platelet aggregation decrease rapidly. The pharmacokinetics of caplacizumab are influenced by the concentration of von Willebrand factor. The half-life will therefore vary depending on how much antibody is bound to the factor. Bound antibody will be catabolised while unbound caplacizumab is thought to be excreted in the urine. No dose adjustments have been advised for patients with liver or kidney disease.

The efficacy of caplacizumab was initially assessed in a phase II trial involving patients requiring plasma exchange for acquired thrombotic thrombocytopenic purpura. In addition to standard care, 36 patients were given caplacizumab and 39 received injections of placebo. The primary end point of this trial was the normalisation of the platelet count. This took a median of three days with caplacizumab and 4.9 days with placebo. There was complete remission, with no subsequent exacerbations, in 81% of the caplacizumab group and 46% of the placebo group. Two patients died in the placebo group.[1]

To confirm the effect of treatment, a double-blind phase III trial studied patients who had already received a single plasma exchange. There were 72 patients in the caplacizumab group and 73 in the placebo group. Compared to the standard of care, patients given caplacizumab were 1.55 times more likely to have normalisation of their platelet count. The composite end point of death, thromboembolism or a recurrence of thrombotic thrombocytopenic purpura during treatment occurred in 12% of the caplacizumab group and 49% of the placebo group. The three deaths during treatment were all in the placebo group. Markers of organ damage, such as cardiac troponin I, returned to normal in a median of 2.86 days with caplacizumab and 3.36 days with placebo.[2]

As von Willebrand factor has a key role in haemostasis, bleeding is an adverse effect of caplacizumab. In the phase III trial 65% of the caplacizumab group had bleeding compared with 48% of the placebo group. Epistaxis, haematuria, vaginal haemorrhage and gingival bleeding are common. In severe cases it may be necessary to consider giving von Willebrand factor if it is available. Bleeding can also occur at the injection sites and some patients will develop a haematoma in the wall of the abdomen. Consecutive injections should not be given into the same quadrant of the abdomen. Other very common adverse events in patients injecting caplacizumab include headache, urticaria, fever and fatigue.[2]

It is important to note that caplacizumab is not aimed at the autoantibody that causes thrombotic thrombocytopenic purpura. Ongoing autoimmune activity can lead to recurrences. Continuing treatment after plasma exchange could be where the main benefit of caplacizumab is. In the phase III trial the median time to normalisation of the platelet count was 2.69 days with caplacizumab and 2.88 days with placebo. However, during the treatment period there was an exacerbation in 38% of the placebo group versus 4% of the caplacizumab group. The patients given caplacizumab also needed less plasma exchange and fewer days of intensive care. Their average hospital stay was 9.9 days versus 14.4 days for the placebo group.[2]

T manufacturer provided the product information

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

Midodrine

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Approved indication: orthostatic hypotension

Vasodrine (Southern Cross Pharma)
2.5 mg and 5 mg tablets

In conditions affecting the autonomic nervous system, such as Parkinson's disease, patients may be unable to maintain their blood pressure when standing. The drop in blood pressure can result in light-headedness or syncope. Although education and non-drug therapy such as venous compression may help, some patients still have severe symptomatic orthostatic hypotension. One pharmacological approach to management is to use a sympathomimetic to raise venous tone.

Midodrine is a prodrug of desglymidodrine which stimulates alpha 1 adrenergic receptors. This results in venous vasoconstriction and consequently a rise in blood pressure, however the clinical effect is uncertain. Midodrine was given an accelerated approval in the USA in 1996, but in 2010 the drug was almost withdrawn from the market because its benefit had not been confirmed.[1]

The conversion of midodrine to desglymidodrine is rapid with peak plasma concentrations within an hour of an oral dose. Desglymidodrine is metabolised and has a half-life of about three hours. It is mainly excreted with its metabolites in the urine. Midodrine is contraindicated if the creatinine clearance is below 30 mL/minute.

The main phase III study of midodrine was a six-week, placebo-controlled trial involving patients who had symptomatic neurogenic orthostatic hypotension with a drop of at least 15 mmHg in systolic blood pressure. A group of 82 patients took midodrine 10 mg three times a day. This regimen resulted in an average rise of 22 mmHg in standing systolic blood pressure. There was little change in the blood pressure of the 89 patients in the placebo group.[2]

The effect of midodrine on symptoms was assessed in a double-blind postmarketing study. This recruited 19 patients who had been taking the drug for at least three months to manage severe symptomatic orthostatic hypotension. The study had a crossover design with patients taking either midodrine or a placebo, then swapping over the next day. They were subjected to a tilt-table test, one hour after the dose, to see how quickly they felt faint. The mean time to the onset of symptoms was approximately 18 minutes with placebo and 27 minutes with midodrine.[3]

Although the phase III trial was relatively short, only 59 of the 82 patients taking midodrine completed the study.[2] Fifteen patients dropped out because of adverse effects such as hypertension and urinary frequency or urgency. Other common adverse effects in that trial included pilomotor reactions, pruritus, paraesthesia and urinary retention. Midodrine should be used with caution in men with disorders of the prostate gland. Caution is also advised in patients with atherosclerotic disease and those at risk of QT prolongation.

Patients should begin midodrine at a low dose. This can be increased weekly according to the response. To reduce the risk of supine hypertension the evening dose of midodrine should be taken at least four hours before bedtime. Only eight patients need to be treated for one to develop supine hypertension. If this is not resolved by a dose reduction, midodrine should be stopped.

Orthostatic hypotension can be difficult to treat, but it is unclear how effective midodrine is. While the phase III trial showed a statistically significant advantage for midodrine in improving the symptom of light-headedness, the mean difference was less than one point on a 10-point visual analogue scale.[2] A systematic review found that midodrine improves standing systolic blood pressure, but the change in blood pressure when moving from a supine to standing position did not differ from control groups. The reviewers concluded that there was insufficient evidence to recommend midodrine for orthostatic hypotension.[4] Its approval in Australia is limited to patients with severe symptomatic hypotension due to autonomic dysfunction after exacerbating factors have been addressed and other treatments have been inadequate.

T T T manufacturer provided clinical evaluation

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