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EDITORIAL

HIV diagnoses in Australia fall as clinicians embrace pre-exposure prophylaxis

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Keywords
antiretroviral drugs, HIV prevention, human immunodeficiency virus, pre-exposure prophylaxis

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Related article:
Prescribing pre-exposure prophylaxis for HIV

HIV prevention has been revolutionised by pre-exposure prophylaxis (PrEP) with antiretroviral drugs. Since its introduction in Australia, rapidly and at scale, HIV diagnoses have fallen dramatically.

PrEP involves at-risk HIV-negative individuals taking co-formulated tenofovir and emtricitabine. When exposure occurs, high intracellular drug concentrations inhibit viral replication and infection is prevented. PrEP is supported by the strongest possible clinical evidence and is now recommended by Australian guidelines.[1] It is subsidised by the Pharmaceutical Benefits Scheme (PBS) and can be prescribed by GPs using a streamlined authority. The prescription quantity is 30 tablets and two repeats which puts the patient into a three-monthly testing and prescription cycle. Patients with hepatitis B should be referred for specialist care as these drugs are also active against hepatitis B and starting and stopping them may precipitate a flare.

PrEP adherence and efficacy are highly correlated. Daily administration of tenofovir with emtricitabine has been found to be safe and effective for HIV prevention. It is most effective when taken daily and continuously with studies observing close to 100% efficacy in adherent patients.[2] Although efficacy is maintained for sexual exposure in gay and bisexual men who take four or more tablets per week, daily adherence is required for other population groups or types of exposure, including vaginal sex.

PrEP is easy to prescribe. Baseline evaluation (and monitoring) of patients includes establishing eligibility (medium to high HIV risk), testing for HIV and sexually transmitted infection,[3] and determining estimated glomerular filtration rate (eGFR). Australian guidelines recommend that condom use to prevent sexually transmitted infection should be discussed with patients.

Draft Australian guidelines now also recommend on-demand or episodic PrEP in men who have sex with men with less frequent or intermittent sexual exposure.[1] Patients take a loading dose of two tablets between 2 and 24 hours before their sexual contact and continue daily dosing after that for a minimum of two doses, or longer if there is ongoing sex. To date, on-demand PrEP has only been shown to be effective in men who have sex with men[4] and is therefore not recommended in women (including transgender women), or transgender men. It is contraindicated in patients with hepatitis B.

Elimination of HIV transmission will require a high uptake of PrEP in gay and bisexual men. Australia is a global leader in the early, targeted, high-coverage roll-out of PrEP in this population. Demonstration studies were providing prophylaxis to more than 18,000 people nationally at the time of PBS listing in April 2018.[5] In the first 18 months after listing, 29,543 individuals had filled one or more PrEP prescriptions. The effects have been dramatic. In New South Wales, where PrEP has been scaled-up very rapidly, it was associated with a rapid decline in HIV diagnoses, in particular new infections.[5] Declines in newly diagnosed HIV cases have also now been observed nationally, from 1028 in 2015 to 838 in 2018.[6]

Australia's success has occurred because of key enabling factors including:

- early PBS listing
- primary care clinicians ready to prescribe PrEP or keen to learn
- a highly motivated target community
- proactive state and commonwealth governments
- academic institutions ready to lead early PrEP demonstration studies
- robust surveillance systems.

HIV prevention has been revolutionised by PrEP together with the treatment-as-prevention approach. This involves people who test positive for HIV starting antiretroviral therapy so the risk of transmission to others is reduced to zero. While previously HIV prevention was only behavioural (i.e. condoms), PrEP and treatment-as-prevention add complementary clinical interventions.

However, new inequalities are emerging. Nationally over five years, new HIV diagnoses have declined by 44% in Australian-born men who have sex with men. However, diagnoses have not declined in men who have sex with men who were born overseas. This population now makes up approximately 50% of new diagnoses.[6] In NSW, 66% of these men have resided in Australia for four years or less.[7] Most newly arrived men who have sex with men are ineligible for Medicare because of their visa status and this has emerged as a key risk factor for HIV.[8]

Clinicians, and in particular GPs, can help to eliminate HIV transmission in Australia by identifying their patients who are at risk, particularly men who have sex with men. They should encourage them to have three-monthly testing for HIV and sexually transmitted infections and discuss, offer or start PrEP. The at-risk community exists in every town and city in the country. We will only be successful in eliminating HIV if all of these individuals have access to PrEP.

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REFERENCES

1. Australasian Society of HIV Viral Hepatitis and Sexual Health Medicine. PrEP guidelines update. Prevent HIV by prescribing PrEP. Sydney: ASHM; 2019. https://ashm.org.au/resources/hiv-resources-list/prep-guidelines-2019 [cited 2020 Nov 1]
2. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al.; US Preventive Services Task Force. Preexposure prophylaxis for the prevention of HIV infection: US Preventive Services Task Force recommendation statement. JAMA 2019;321:2203-13. https://doi.org/10.1001/jama.2019.6390
3. STIs in Gay Men Action Group. Australian sexually transmitted infection and HIV testing guidelines 2019: for asymptomatic men who have sex with men. Sydney: NSW Government STI Programs Unit; 2019. https://stipu.nsw.gov.au/wp-content/uploads/STIGMA_Guidelines2019_Final-1.pdf [cited 2020 Nov 1]
4. Molina JM, Charreau I, Spire B, Cotte L, Chas J, Capitant C, et al.; ANRS IPERGAY Study Group. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. Lancet HIV 2017;4:e402-10. https://doi.org/10.1016/S2352-3018(17)30089-9
5. Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, et al.; Expanded PrEP Implementation in Communities New South Wales (EPIC-NSW) research group. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. Lancet HIV 2018;5:e629-37. https://doi.org/10.1016/S2352-3018(18)30215-7
6. The Kirby Institute. National HIV notifications: Q1 2014–Q4 2018. Sydney: UNSW; 2019. https://kirby.unsw.edu.au/sites/default/files/kirby/report/National-HIV-Quarterly-Report_2018-Q4.pdf [cited 2020 Nov 1]
7. Health NS. NSW HIV Strategy 2016–2020, Quarter 2 2019, Data Report. https://www.health.nsw.gov.au/endinghiv/Publications/q2-2019-nsw-hiv-data-report.pdf [cited 2020 Nov 1]
8. Medland NA, Chow EP, Read TH, Ong JJ, Chen M, Denham I, et al. Incident HIV infection has fallen rapidly in men who have sex with men in Melbourne, Australia (2013-2017) but not in the newly-arrived Asian-born. BMC Infect Dis 2018;18:410. https://doi.org/10.1186/s12879-018-3325-0

LETTERS

Letters to the Editor

Deprescribing in older people: helpful tools and proton pump inhibitors

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I read the informative article about deprescribing in older people by Michelle Liacos, Amy Page and Christopher Etherton-Beer.[1] While appreciating their efforts, I wish to make the following observations.

Table 3 of the article lists tools to support deprescribing decisions. Explicit tools like the Beers[2] and STOPP criteria[3] can also be applied to detect inappropriate medications in the elderly and would be a useful addition to the article.

Regarding the section on adverse effects, there are some serious concerns about proton pump inhibitors which are worth mentioning. Elderly patients are especially prone to developing osteoporosis-related fractures.[3] Long-term use of proton pump inhibitors (for more than one year) independently increases this risk. Long-term use also increases the risk of vitamin B_{12} deficiency, hypomagnesemia and fundic gland polyps.[4]

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REFERENCES

1. Liacos M, Page AT, Etherton-Beer C. Deprescribing in older people. Aust Prescr 2020;43:114-20. https://doi.org/10.18773/austprescr.2020.033
2. Duke Clinical Research Institute. Beers criteria medication list. https://dcri.org/beers-criteria-medication-list [cited 2020 Nov 1]
3. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age ageing 2015;44:213-8. https://doi.org/10.1093/ageing/afu145
4. Kinoshita Y, Ishimura N, Ishihara S. Advantages and disadvantages of long-term proton pump inhibitor use. J Neurogastroenterol Motil 2018;24:182-96. https://doi.org/10.5056/jnm18001

The authors of the article comment:

We thank Ajay Shukla for his thoughtful input and elaboration on our article. We agree that there are risks associated with the long-term use of proton pump inhibitors. Along with other drugs, they generally pose the greatest potential for absolute benefit but also carry a risk of adverse effects in older adults.

Tools such as the Beers criteria and STOPP will be familiar to many readers, and we have summarised these previously.[1] In our *Australian Prescriber* article we sought to highlight general tools, and specific deprescribing resources, that readers may access to support practice.

REFERENCE

1. Page AT, Potter K, Clifford R, Etherton-Beer C. Deprescribing in older people. Maturitas 2016;91:115-34. https://doi.org/10.1016/j.maturitas.2016.06.006

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ARTICLE

The role of drugs in the treatment of autism

SUMMARY

The prevalence of autism spectrum disorder is increasing. It usually presents in childhood with abnormal behaviour and development.

The diagnosis can be difficult. There are often comorbidities which can cause confusion.

Non-drug treatments are first line. Drug treatment is not effective for the core symptoms of autism spectrum disorder. However, drugs may have a role in managing comorbidities and related symptoms, such as irritability and aggression.

Anxiety is a common comorbidity. Cognitive behaviour therapy can be effective, but in some cases selective serotonin reuptake inhibitors may have a role.

Most patients have problems sleeping, but drugs are not usually used to treat sleep disorders in children.

Antipsychotics, such as risperidone, may be considered for irritability and aggression. Clonidine is first line for children with Tourette syndrome. Patients need regular monitoring because of the adverse effects of these drugs.

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Keywords
antipsychotic drugs, autism spectrum disorder, selective serotonin reuptake inhibitors

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Introduction

The number of people with autism spectrum disorder is growing throughout the western world, partly due to changes in diagnostic methods and criteria.[1] In 2018 there were 205,200 Australians with autism, a 25.1% increase from the 164,000 with the condition in 2015.[2]

The symptoms usually begin in early childhood with the child experiencing problems with social skills, speech and behaviour. Comorbidities are common.

The challenges in managing the disorder are wide and varied. They include:

- communicating with those who have poor speech and language skills
- differentiating the clinical features of autism spectrum disorder from the symptoms of emerging or current mental illness
- determining a treatment plan that addresses very challenging symptoms such as aggression, agitation, impulsivity and obsessions
- avoiding polypharmacy where possible, while also treating a range of mental illnesses.

Many of the drugs prescribed in autism spectrum disorder have limited supporting evidence and some have significant adverse effects so monitoring is required. The impact of drug therapy on the patient and their family must be taken into account.[3]

Pathophysiology

The current hypotheses propose that autism spectrum disorder is caused by, at least in part, dopamine signalling abnormalities in the brain.[4] This impacts on the prefrontal cortex and the mesocorticolimbic circuit[5] which affect behaviour and emotional regulation.

There have been many other postulated neurotransmitter-related causes.[5] These include reduced GABAergic gene expression, increases in glutamate transport proteins, and serotonin transporter gene polymorphisms. Dopamine, glutamate and serotonin have therefore been considered as targets for drug treatment.

Comorbidity

Studies show a high rate of comorbid mental illness in autism spectrum disorder. In one study 74% of young people with autism spectrum disorder had at least five comorbidities.[6] Another study reported comorbidity rates of:

- 28% for attention deficit hyperactivity disorder (ADHD)
- 20% for anxiety disorders
- 13% for sleep–wake disorders
- 12% for disruptive, impulse-control and conduct disorders
- 11% for depressive disorders
- 9% for obsessive compulsive disorder
- 5% for bipolar disorders
- 4% for schizophrenia spectrum disorders.[7]

It is important to remember that a deterioration in behaviour may not be directly related to the disorder. For example, it may be triggered by an underlying physical illness.

Non-drug treatment

Non-drug therapies are first-line interventions, particularly for children under seven or eight years of age, to try and assist with their developmental trajectory. The strategies that are used include psychology-based therapy with cognitive behaviour therapy, narrative therapy, schema therapy and positive behaviour support.[3] Occupational therapy can assist with fine and gross motor skills, interoception skills and social skills.[8]

Drug-treatment strategies

Drugs may be added to augment non-drug therapies or to help with comorbidities. Historically, the most common drugs used for autism spectrum disorder were antipsychotics such as haloperidol.[9] As diagnostic definitions were clarified, modern drugs, including atypical antipsychotics, were studied in children with psychiatric diagnoses.[10]

There have been many small studies, case reports and open-label trials in children with autism spectrum disorder.[11] It is important to focus on a low starting dose and a slow increase to reach the best, but lowest, dose for each patient. The Centre for Interventional Paediatric Psychopharmacology and Rare Diseases in the UK suggests that drug treatment begins with small doses (usually an eighth to a sixth of the typical dose), increasing after about 5–6 half-lives of the drug. For most drugs used in Australia that is an increase every three to seven days. A longer titration time is needed for fluoxetine because its active metabolite, norfluoxetine, has a half-life of 9–14-days.[12]

A large concern for all doctors looking after patients with autism spectrum disorder is the risk of polypharmacy. In one study polypharmacy was seen in 34% of the patients who received drug treatment.[13] However, patients often present with symptoms suggestive of changes in different systems of the brain and it may not be possible to use one drug to treat all the symptoms.

The Table outlines the drugs that may be considered for specific indications.[14-17] Antipsychotic drugs should only be started by a psychiatrist or paediatrician or in consultation with one. For all antipsychotics ongoing monitoring is required. If possible, monitor weight, fasting lipids, blood glucose, prolactin and liver function every six months with more frequent monitoring at the start of treatment at one month and three months.

Anxiety and depression

Anxiety is one of the most common comorbidities with autism. There are links to difficulties with social communication and therefore the internal discomfort that can be experienced when in groups, going to new environments and when experiencing change. Talking-based therapies, in particular cognitive behaviour therapy, have good supporting evidence.[18] These techniques are harder to use in children and adults with a severe autism spectrum disorder who find working in a therapeutic relationship and speaking to a therapist about distressing feelings to be intolerable. Drugs have a role when anxiety is interfering in the functional life of a child, such as avoiding school, losing friendships or ceasing activities that were previously enjoyable.

The first-line drugs are selective serotonin reuptake inhibitors (SSRIs) such as sertraline, fluoxetine and fluvoxamine.[19] The onset adverse effects of fluvoxamine,[20] which include agitation and anxiety, limit its use as a first-line drug. It is often used after a failed trial of sertraline or fluoxetine.

To provide the low doses required for some SSRIs, a compounding chemist may be needed to prepare a low-concentration liquid form.

Sertraline, fluoxetine and fluvoxamine can be used for depressive disorders, however there are less research data from children with autism spectrum disorder and a mood disorder. Treatment is considered on a case-by-case basis after specialist assessment.[3] There is the risk for increased suicidal thinking occurring when using SSRIs. The harm–benefit ratio for each patient needs to be considered as well as monitoring for an increase in suicidal thinking in the first two weeks of treatment.[11]

Mood lability

Children with autism spectrum disorder who present with externalising behaviours, which are behaviours that are targeted toward the external environment when distressed such as physical aggression, threats and destroying property, often have a labile mood. They also often have learning disorders, poor self-regulation and behavioural problems at school.

Sodium valproate can be helpful with aggression and is also used to treat irritability and mood lability.[21] There are insufficient data to indicate the use of other mood stabilisers. Sodium valproate has many adverse effects including nausea, poor attention, skin reactions including Stevens-Johnson syndrome, and liver toxicity. It is best avoided in females because of its teratogenicity and has also been associated with polycystic ovary syndrome.

Tics and Tourette syndrome

Clonidine is the first-line treatment for tics and Tourette syndrome. There is evidence that atypical antipsychotics such as aripiprazole can also be used for treatment. Aripiprazole reduces the symptoms of Tourette syndrome, and can be used when there

Table **Drugs that can be considered for comorbidities in children with autism** [14-17,27]

Drug	Dose	Half-life	Best indication	Common adverse effects in young people
Sertraline	Start 0.5 mg/kg, up to 2 mg/kg. Gradual dose increases are recommended. Common dose range is 50–200 mg a day. Alternatively: • over 6 years – start at 25 mg and increase to 50 mg after 1 week then by 25 mg monthly • 6–18 years – maximum dose 200 mg a day.	27 hours	Anxiety disorders, particularly generalised anxiety disorder	In younger children agitation, labile mood. Risk of increased suicidal thinking Withdrawal symptoms if the dose is not tapered off slowly
Fluoxetine	Start 0.5 mg/kg, up to 1 mg/kg. Average dose for 7–12 years – 20–30 mg a day. 12 years and over with eating disorders or obsessive compulsive disorder – up to 60 mg may be needed. The maximum dose for other diagnoses is 40 mg a day. Alternatively: • under 12 years – start at 5 mg and increase by 5 mg monthly to a maximum of 30 mg • 12 years and over – the maximum dose is 40 mg for major depression and 60 mg for obsessive compulsive disorder.	Active metabolite norfluoxetine 9–14 days	Depression, obsessive compulsive disorder, eating disorder symptoms including avoidant restrictive food intake disorder	Nausea, headaches, agitation, insomnia Tablets have a strong aversive flavour Risk of increased suicidal thinking
Fluvoxamine	0.5 mg/kg up to 2 mg/kg. Maximum dose generally 150 mg (divided doses once 100 mg a day is given). Alternatively: • over 8 years – start at 25 mg and increase by 25 mg monthly.	15.6 hours	Obsessive compulsive disorder, significant anxiety disorders	Agitation, restlessness, onset and offset adverse effects when starting and weaning Risk of increased suicidal thinking
Sodium valproate	5 mg/kg once a day for 2 weeks then increase if needed for mood, up to maximum of 20 mg/kg (divided doses once over 200 mg a day).	8–20 hours	Can help with mood lability and aggression particularly in those with comorbid intellectual impairment	Nausea, metallic taste, fatigue, weight gain, poor attention, Stevens-Johnson syndrome, liver toxicity Sevenfold increase in polycystic ovary syndrome Need to monitor blood concentrations, but many children with autism spectrum disorder cannot tolerate venepuncture
Risperidone	Over 5 years and below 20 kg – 0.25 mg once daily for 3 days, then increase to 0.5 mg daily. If necessary, increase by 0.25 mg every 2 weeks. Usual range 0.5–1.5 mg daily. Over 5 years and over 20 kg – 0.5 mg once daily for 3 days, then increase to 1 mg daily. If necessary, increase daily dose by 0.5 mg every 2 weeks. Usual range 1–2.5 mg daily, maximum 3 mg daily.	3–20 hours	Used in autism spectrum disorder, approved by Therapeutic Goods Administration, best for agitation, aggression, impulsivity	Weight gain, increased appetite including hoarding of food at times

Continued over page

Table **Drugs that can be considered for comorbidities in children with autism [14-17,27] (continued)**

Drug	Dose	Half-life	Best indication	Common adverse effects in young people
Aripiprazole	6–18 years – 2.5 mg once daily for 1 week, then 5 mg once daily. If necessary, increase daily dose in 5 mg increments at intervals of at least a week, to a maximum of 15 mg once daily.	75 hours	Agitation, irritability	Less weight gain than risperidone but little sedation and can be an activating drug
Olanzapine	13–18 years if under 40 kg – 2.5 mg at night, maximum dose 5 mg. 13–18 years if over 40 kg – up to 5 mg at night, maximum dose 10 mg.	21–54 hours	Aggression and mood lability when risperidone, aripiprazole and sodium valproate have not been effective	Significant sedation, weight gain and hypersalivation
Quetiapine	Over 13 years old and under 40 kg – 25 mg at night, increase to 25 mg twice a day (or 50 mg long-acting) if tolerated, maximum dose 50 mg a day. Over 13 years old and over 40 kg – 25 mg at night and increase up to maximum dose 100 mg a day if tolerated.	7–12 hours		
Atomoxetine	0.5 mg/kg a day increasing after at least 3 days. Maximum 1.2–1.4 mg/kg a day or 100 mg, whichever is lower.	17 hours	ADHD, slightly better results for inattention	Nausea, fatigue[27]
Methylphenidate	Under 12 years – 5 mg twice a day. Over 12 years – 10 mg twice a day. Maximum 60 mg daily.	Children: 2.5 hours Adults: 3.5 hours	ADHD	Weight loss, poor weight gain, palpitations, agitation
Dexamfetamine	6–12 years – start at 2.5 mg daily and increase at weekly intervals. Usual maximum is 20 mg in 2 divided doses. Over 12 years – 5 mg every morning, daily dose may be increased by 5 mg at weekly intervals until optimal response. Maximum 40 mg a day.	12 hours	ADHD	Weight loss, poor weight gain, palpitations, agitation
Lisdexamfetamine	6–18 years – 30 mg once each morning – if necessary, increase the daily dose by 20 mg at intervals of at least a week. Maximum 70 mg daily.			
Guanfacine	Starting dose of 1 mg. Under 11 years – increase to maximum of 4 mg a day. Over 11 years – increase to maximum of 7 mg a day.	10–30 hours	ADHD	Fatigue, weight gain[27]

ADHD attention deficit hyperactivity disorder

is little response to psychological interventions or when there is a contraindication or no response to clonidine.[22] Aripiprazole may be better tolerated than clonidine.[23]

Irritability and aggression

Aggression is one of the most common sources of concern for parents of children with autism spectrum disorder. It can cause large interruptions in their schooling, relationships, their ability to leave the home and it can greatly disrupt a family.

Often antipsychotics such as aripiprazole and risperidone have been used to help treat irritability and problem behaviours in children and adolescents with autism spectrum disorder.[24,25] In Australia, risperidone is approved by the Therapeutic Goods Administration for irritability and aggression in autism in patients under 18 years of age. However, the risks with risperidone include weight gain, elevated lipids, blood glucose and prolactin, and interruption of puberty. Aripiprazole has been used in other countries, in particular the USA, as it causes less weight gain and has less effect on prolactin. It is not as sedating as risperidone and this can cause difficulties for families if they have been using risperidone to settle night-time aggression and to improve sleep.

Before prescribing, record height, weight, menarche and regularity of menstruation, blood glucose, fasting lipids and prolactin. Monitor these again after one month and then six-monthly. An increase in prolactin or the development of abnormal muscle movements requires the drug dose to be lowered and a review of the antipsychotic therapy.

At present, due to small sample sizes and open-label studies, there is insufficient evidence to show that antipsychotics such as olanzapine, quetiapine, ziprasidone or clozapine are effective in autism spectrum disorder.[10,11] There is also little evidence that older antipsychotics, antiepileptic drugs and glutaminergic modulators (such as ketamine and memantine) are helpful in managing aggression.[25] Sodium valproate can be tried if antipsychotics are not effective or the patient cannot tolerate them.[21]

For some patients with a poor response to risperidone and aripiprazole, off-label use of an alternate antipsychotic can be considered.[26]

Attention deficit hyperactivity disorder

ADHD is a common comorbidity with autism spectrum disorder.[7,27] The drugs used in treatment are the same as those used for ADHD alone, namely methylphenidate, dexamfetamine, guanfacine and atomoxetine.[27] Stimulant treatment improves the symptoms of ADHD in patients with autism spectrum disorder. Atomoxetine can assist with inattentive ADHD and patients with comorbid anxiety symptoms. The adverse effects include nausea and fatigue.[28]

Insomnia

Insomnia and sleep disorders affect close to 80% of people with autism spectrum disorder, and often present as a sleep onset disorder. Behavioural management is the mainstay of treatment.

There are few drugs that are useful for sleep disorders in children. Benzodiazepines are not recommended. Antipsychotics should also be avoided because of their high risk of adverse effects. Melatonin is often used to manage sleep disorders in children, partly because it is available over-the-counter in overseas countries. It has a low risk of adverse effects and dependency.[29] Clonidine in low dose (50–200 microgram at night) has also been used, in particular when the insomnia is secondary to stimulant treatment.[11]

Conclusion

Many patients and families seek medical-based intervention for the core symptoms of autism spectrum disorder including social and emotional skills, rigid thinking and poor theory of mind. For these features of autism spectrum disorder non-drug treatments are first line and are focused on psychology input, social skills groups, peer mentors, and support in education and employment.

Assistance with managing aggression and irritable behaviours may be obtained by using risperidone or aripiprazole, with risperidone having the most research-based data at present. There is little evidence for the use of other antipsychotics or glutaminergic drugs such as ketamine and memantine.

The most common comorbidity is anxiety and SSRIs can be helpful. The possibility of comorbid ADHD is important to consider. Comorbid ADHD can be treated with the same drugs as ADHD alone and for some patients it can be used with an antipsychotic to manage hyperactivity, inattention and aggression.

Polypharmacy should be avoided if possible but comorbid conditions need to be addressed. However, the use of an atypical antipsychotic for aggression and irritability, plus an SSRI for an anxiety disorder or drugs for ADHD, may be needed for patients with these common comorbidities. ◀

Conflict of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Dexamfetamine is the first-choice drug for managing the core symptoms of autism spectrum disorder.
2. Risperidone should not be used in patients with irritability, related to autism spectrum disorder, under the age of 18 years.

Answers on page 225

REFERENCES

1. King M, Bearman P. Diagnostic change and the increased prevalence of autism. Int J Epidemiol 2009;38:1224-34. https://doi.org/10.1093/ije/dyp261
2. Australian Bureau of Statistics. Autism in Australia. In: 4430.0 – Disability, ageing and carers, Australia: summary of findings, 2018. www.abs.gov.au/statistics/health/disability/disability-ageing-and-carers-australia-summary-findings/latest-release [cited 2020 Nov 1]
3. Howes OD, Rogdaki M, Findon JL, Wichers RH, Charman T, King BH, et al. Autism spectrum disorder: consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. J Psychopharmacol 2018;32:3-29. https://doi.org/10.1177/0269881117741766
4. Pavăl D. A dopamine hypothesis of autism spectrum disorder. Dev Neurosci 2017;39:355-60. https://doi.org/10.1159/000478725
5. Eissa N, Al-Houqani M, Sadeq A, Ojha SK, Sasse A, Sadek B. Current enlightenment about etiology and pharmacological treatment of autism spectrum disorder. Front Neurosci 2018;12:304. https://doi.org/10.3389/fnins.2018.00304
6. Joshi G, Petty C, Wozniak J, Henin A, Fried R, Galdo M, et al. The heavy burden of psychiatric comorbidity in youth with autism spectrum disorders: a large comparative study of a psychiatrically referred population. J Autism Dev Disord 2010;40:1361-70. https://doi.org/10.1007/s10803-010-0996-9
7. Lai MC, Kassee C, Besney R, Bonato S, Hull L, Mandy W, et al. Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. Lancet Psychiatry 2019;6:819-29. https://doi.org/10.1016/S2215-0366(19)30289-5
8. National Institute for Health and Care Excellence (NICE). Autism spectrum disorder in under 19s: support and management. Clinical guideline CG170. 2013 Aug 28. http://www.nice.org.uk/guidance/cg170 [cited 2020 Nov 1]
9. Faretra G, Dooher L, Dowling J. Comparison of haloperidol and fluphenazine in disturbed children. Am J Psychiatry 1970;126:1670-3. https://doi.org/10.1176/ajp.126.11.1670
10. Campbell M, Cueva JE. Psychopharmacology in child and adolescent psychiatry: a review of the past seven years. Part I. J Am Acad Child Adolesc Psychiatry 1995;34:1124-32. https://doi.org/10.1097/00004583-199509000-00008
11. Hollander E, Phillips AT, Yeh CC. Targeted treatments for symptom domains in child and adolescent autism. Lancet 2003;362:732-4. https://doi.org/10.1016/S0140-6736(03)14236-5
12. Santosh PJ, Singh J. Drug treatment of autism spectrum disorder and its comorbidities in children and adolescents. BJPsych Adv 2016;22:151-61. https://doi.org/10.1192/apt.bp.115.014597
13. Murray ML, Hsia Y, Glaser K, Simonoff E, Murphy DG, Asherson PJ, et al. Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. Psychopharmacology (Berl) 2014;231:1011-21. https://doi.org/10.1007/s00213-013-3140-7
14. US Food and Drug Administration. Drugs@FDA: FDA-approved drugs. www.accessdata.fda.gov/scripts/cder/daf [cited 2020 Nov 1]
15. Stahl Online. The prescriber's guide. 6th ed. Cambridge: Cambridge University Press; 2020. https://stahlonline.cambridge.org/prescribers_guide.jsf [cited 2020 Nov 1]
16. Shann F. Drug doses. 17th ed. Melbourne: Collective Pty Ltd; 2017.
17. AMH Children's Dosing Companion. Adelaide: Australian Medicines Handbook; 2020. https://childrens.amh.net.au [cited 2020 Nov 1]
18. Wood JJ, Drahota A, Sze K, Har K, Chiu A, Langer DA. Cognitive behavioral therapy for anxiety in children with autism spectrum disorders: a randomized, controlled trial. J Child Psychol Psychiatry 2009;50:224-34. https://doi.org/10.1111/j.1469-7610.2008.01948.x
19. Nadeau J, Sulkowski ML, Ung D, Wood JJ, Lewin AB, Murphy TK, et al. Treatment of comorbid anxiety and autism spectrum disorders. Neuropsychiatry (London) 2011;1:567-78. https://doi.org/10.2217/npy.11.62
20. Reinblatt SP, DosReis S, Walkup JT, Riddle MA. Activation adverse events induced by the selective serotonin reuptake inhibitor fluvoxamine in children and adolescents. J Child Adolesc Psychopharmacol 2009;19:119-26. https://doi.org/10.1089/cap.2008.040
21. Hollander E, Chaplin W, Soorya L, Wasserman S, Novotny S, Rusoff J, et al. Divalproex sodium vs placebo for the treatment of irritability in children and adolescents with autism spectrum disorders. Neuropsychopharmacology 2010;35:990-8. https://doi.org/10.1038/npp.2009.202
22. Quezada J, Coffman KA. Current approaches and new developments in the pharmacological management of Tourettes Syndrome. CNS Drugs 2018;32:33-45. https://doi.org/10.1007/s40263-017-0486-0
23. Hollis C, Pennant M, Cuenca J, Glazebrook C, Kendall T, Whittington C, et al. Clinical effectiveness and patient perspectives of different treatment strategies for tics in children and adolescents with Tourette syndrome: a systematic review and qualitative analysis. Health Technol Assess 2016;20:1-450. https://doi.org/10.3310/hta20040
24. Lake JK, Denton D, Lunsky Y, Shui AM, Veenstra-VanderWeele J, Anagnostou E. Medical conditions and demographic, service and clinical factors associated with atypical antipsychotic medication use among children with an autism spectrum disorder. J Autism Dev Disord 2017;47:1391-402. https://doi.org/10.1007/s10803-017-3058-8
25. Fung LK, Mahajan R, Nozzolillo A, Bernal P, Krasner A, Jo B, et al. Pharmacologic treatment of severe irritability and problem behaviours in autism: a systematic review and meta-analysis. Pediatrics 2016;137 Suppl 2:S124-35. https://doi.org/10.1542/peds.2015-2851K
26. Fitzpatrick SE, Srivorakiat L, Wink LK, Pedapati EV, Erickson CA. Aggression in autism spectrum disorder: presentation and treatment options. Neuropsychiatr Dis Treat 2016;12:1525-38. https://doi.org/10.2147/ndt.s84585
27. Antshel KM, Russo N. Autism spectrum disorders and ADHD: overlapping phenomenology, diagnostic issues, and treatment considerations. Curr Psychiatry Rep 2019;21:34. https://doi.org/10.1007/s11920-019-1020-5
28. Patra S, Nebhinani N, Viswanathan A, Kirubakaran R. Atomoxetine for attention deficit hyperactivity disorder in children and adolescents with autism: a systematic review and meta-analysis. Autism Res 2019;12:542-52. https://doi.org/10.1002/aur.2059
29. Abdelgadir IS, Gordon MA, Akobeng AK. Melatonin for the management of sleep problems in children with neurodevelopmental disorders: a systematic review and meta-analysis. Arch Dis Child 2018;103:1155-62. https://doi.org/10.1136/archdischild-2017-314181

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ARTICLE

Management of postsurgical pain in the community

SUMMARY

Following surgery there is often a need for ongoing pain management after the patient is discharged from hospital. This can be made easier if the patient has an appropriate discussion before leaving hospital about what pain they can expect, and they are given a management plan.

Paracetamol and non-steroidal anti-inflammatory drugs are suitable for most patients. Drugs with a short half-life, such as ibuprofen, may need to be taken regularly.

Short-acting opioids can have a short-term role, providing guidelines are followed. There is a predictable period of time after surgery when the benefit of an opioid is expected to be maximised before harmful adverse effects will dominate.

Gabapentinoids are useful for neuropathic pain, but have a limited role in nociceptive pain. Like opioids, they have a risk of misuse.

The surgeon should be consulted if the patient develops new pain or the postoperative pain becomes more severe.

Most postsurgical pain will resolve within three months. If not, it is deemed persistent pain that may warrant specialist assessment.

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Keywords
gabapentinoids, non-steroidal anti-inflammatory drugs, opioids, postoperative pain

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Introduction

After a patient is discharged from hospital the management of postsurgical pain in the community can be challenging. The degree of difficulty this poses depends on the patient's management before they leave hospital.

On returning home, it is important the patient has realistic expectations of what to expect regarding their pain. This can be facilitated by an appropriate discussion with the surgical or pain management team before discharge. Preferably, the patient is given a written pain management plan that can be followed after leaving hospital, with realistic goals as to when they can return to physical activity or work. Communicating these plans with the patient's local doctor is critical. Patients who still have moderate pain who are discharged with long-acting opioids, without a plan, or any expectation of what to expect in terms of ongoing management, are at a significant disadvantage.

On discharge from hospital the quantity of analgesic drugs should be limited to the equivalent of 2–3 days supply. This encourages the judicious use of the drugs and ensures early contact with their GP to obtain any continuing supply.

Incidence of pain

There have been many well-conducted studies on the incidence of postsurgical pain following discharge from hospital. One major review found the incidence of persistent pain was 13.6% four months after hernia repair, 11.8% after vaginal hysterectomy and 25.1% after abdominal hysterectomy. At one year these figures had fallen to 6.2%, 4.1% and 9.9%.[1]

Other studies enable the likelihood of an increased incidence of persistent pain to be predicted. This is based on both surgical and patient factors (see Boxes 1 and 2).[2,3]

'Red flags'

While some ongoing pain is to be expected after surgery, clinicians should be alert for the appearance of new pain, or pain with increasing severity. This may herald a 'red flag' that might be associated with a complication from the procedure and necessitates referral back to the surgeon. Importantly, ask if the pain has been severe enough to prevent sleep or impede return to some degree of function.

It is important not to miss the emergence of neuropathic pain, which usually responds poorly to conventional analgesics. Pain that occurs within a

circumscribed nerve distribution, exhibits hyperalgesia or allodynia, or is described as 'shooting' or like an 'electric shock' by the patient should arouse suspicion. This is particularly common following certain types of surgery, such as mastectomy or thoracotomy. Neuropathic pain requires a different approach to treatment, so it is crucial that it is detected at an early stage.

A systematic approach

Analgesics are a key component of postsurgical pain management. Using a multimodal approach to analgesia can both maximise the response to medicines and limit the use of opioids.

The prescriber must remember that, with the exception of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), all of the commonly used analgesics can have significant depressant effects on the central nervous system. While tolerance no doubt develops, drowsiness and effects on higher-centre functions may impede the patient's capacity to drive or to return to work.

Paracetamol

Paracetamol is a useful starting point for any analgesic plan. If the pain is persistent, the patient should be encouraged to take paracetamol regularly rather than as needed.

Box 1 **Surgical procedures associated with a high incidence of persistent postoperative pain**[2]

- Amputation
- Coronary artery bypass
- Thoracotomy
- Breast surgery
- Inguinal hernia repair
- Lower segment caesarean section

Box 2 **Patient factors associated with an increased incidence of postoperative pain**[3]

- Young age
- Female
- History of depression or anxiety
- Sleep disturbance
- Increased body-mass index
- Smoking
- Preoperative pain
- Preoperative analgesic use

Non-steroidal anti-inflammatory drugs

For uncomplicated nociceptive pain, NSAIDs are now first line unless contraindicated. Relative contraindications include previous gastrointestinal adverse events, kidney disease, history of cardiovascular disease, older age, and an increased risk of bleeding. The risk of adverse effects needs to be carefully monitored, especially because their incidence appears to be correlated with increases in the dose and duration of treatment.

Although these drugs can be purchased over-the-counter, they are effective analgesics – a fact that often needs to be reinforced with patients. NSAIDs are particularly useful for pain precipitated by movement.[4] While there may be some reticence by surgeons to prescribe these drugs in the very early postoperative period, because of concern about an increased risk of bleeding, this should not be a reason to withhold NSAIDs by the time the patient is rehabilitating.

There seems to be little to differentiate these drugs in terms of efficacy apart from their COX-2 selectivity and pharmacokinetics. Drugs with short half-lives such as ibuprofen or diclofenac need to be taken regularly throughout the day which is a possible disadvantage compared to drugs with long half-lives such as meloxicam. However, drugs with short half-lives have a more rapid onset of action and, should any adverse effects occur, can be quickly discontinued.

COX-2-specific drugs provide a similar level of analgesia, but the incidence of gastrointestinal adverse effects may be lower. While it is a long-held belief that NSAIDs need to be taken with food, recent studies have shown that this does not reduce the rate of gastrointestinal adverse effects. Indeed, taking them on an empty stomach results in higher blood concentrations and improved analgesia.

Opioids

Opioids should have a limited role once the patient is discharged from hospital. If they are used in initial pain management, only immediate-acting products should be prescribed, unless the patient was taking sustained-release drugs before admission for surgery.[5]

The opioid crisis has reinforced the need for more considered prescribing of pure opioid agonists with a clear understanding for both the doctor and the patient of what role the drugs play. While opioids relieve pain they should not be seen as first-line analgesics. They are best viewed as rescue medicines. There are some general considerations that should apply:

1. Opioid use comes at a small risk of significant harm to the patient. Based on recent data, for approximately every 4000 Australians prescribed opioids, there will be one death in the population per year.[6,7]
2. A patient who reports feeling the expected sensations after surgery, who is already taking non-opioid analgesics (e.g. paracetamol plus an NSAID) and who is coping, is unlikely to gain much benefit from the addition of an opioid.
3. When opioids are indicated and a benefit is seen, the dose should be titrated to effect with close monitoring.
4. There is a predictable period of time after an acute injury when the benefit of an opioid is expected to be maximised before harmful adverse effects will dominate. It is helpful if the surgeon can inform the patient's GP what this duration is likely to be. For most types of surgery it is a few days.
5. Opioids are weaned at a rate which matches the resolution of the source of pain. After short-term use of a few days, opioids are commonly weaned rapidly without adverse consequences. Once their use extends into weeks, weaning is generally slower as a compromise between clinical need and patient tolerance. As a rough guide, reduce the dose by approximately 25–40% every few days. The use of drugs with a short half-life, for the shortest possible time, should be the aim.

With regard to the choice of drug, pure opioid agonists have largely replaced the use of the prodrug codeine. Codeine has an unpredictable effect owing to genetically determined variations in metabolism, and when used alone has negligible analgesic properties.

In adults, determining the opioid dose is based more on the age of the patient and presence of debilitating comorbidities, rather than body weight as is often used. Indeed, at the upper extreme of size, owing to the likelihood of obstructive sleep apnoea, weight-based dosing should not be used.

Tapentadol, which is available in immediate-release and sustained-release formulations, is appropriately classified as an opioid, but has a dual mechanism of action which also involves noradrenergic pathways. It has a relatively weak opioid effect and this is reflected in its lower incidence of morphine-like adverse effects.

Tramadol can be useful in the early management of postoperative pain. It acts via opioid receptor stimulation and augmentation of noradrenaline (norepinephrine) and serotonin pathways. Some studies have suggested tramadol may be beneficial in neuropathic pain states. However, the response to tramadol can be mixed, most likely as a result of the complex pharmacokinetic polymorphism associated with its metabolism.[8] This probably explains its failure to elicit a useful response in a subgroup of patients.

Gabapentinoids

While research suggests that pregabalin and gabapentin are useful for neuropathic pain states, reports of their efficacy in postsurgical pain have been mixed.[9,10] Furthermore, there are significant risks associated with long-term prescribing:

- central nervous system depressant effects will be enhanced by concomitant use of opioids
- the incidence of adverse effects, especially somnolence and dizziness, is significant
- there is evidence of dependence.[11]

When to refer

Most pain should resolve within three months. The emergence of red flags after discharge requires prompt consultation with the surgeon.

The International Association for the Study of Pain has defined chronic postsurgical pain as a condition that exists when the pain:

- persists three months after surgery
- was not present before surgery or was of a different character
- originates from the surgical site, or a referred area
- does not have any explainable cause.[12]

When pain persists for more than three months after discharge, or the patient has been unable to return to an expected level of functioning, further assessment either by the treating surgeon or a specialist pain clinic is warranted.

Conclusion

Postsurgical pain is common and a degree of pain can be expected after the patient leaves hospital. Most pain can be managed in the first instance by non-opioid drugs.

It is clearly in the patient's best interest if their ongoing management can be overseen by a single prescriber, who can assess ongoing analgesic requirements and make referrals when appropriate. Good communication between the hospital and primary care is essential. ≺

Ross MacPherson has received payments for educational sessions from Seqirus. Gavin Pattullo has received payments for presentations made from Seqirus and Astra Zeneca.

REFERENCES

1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res 2017;10:2287-98. https://doi.org/10.2147/JPR.S144066
2. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. Anesthesiology 2018;129:590-607. https://doi.org/10.1097/ALN.0000000000002238
3. Yang MM, Hartley RL, Leung AA, Ronksley PE, Jetté N, Casha S, et al. Preoperative predictors of poor acute postoperative pain control: a systematic review and meta-analysis. BMJ Open 2019;9:e025091. https://doi.org/10.1136/bmjopen-2018-025091
4. Zeng AM, Nami NF, Wu CL, Murphy JD. The analgesic efficacy of nonsteroidal anti-inflammatory agents (NSAIDs) in patients undergoing cesarean deliveries: a meta-analysis. Reg Anesth Pain Med 2016;41:763-72. https://doi.org/10.1097/AAP.0000000000000460
5. Australian and New Zealand College of Anaesthetists. Position statement on the use of slow-release opioid preparations in the treatment of acute pain. 2018 Mar. www.anzca.edu.au/resources/professional-documents/statements/sr-opioid-statement-with-disclaimer-20200825 [cited 2020 Nov 1]
6. Australian Bureau of Statistics. 3303.0 Causes of death, Australia, 2018. 2019 Sep 25. www.abs.gov.au/statistics/health/causes-death/causes-death-australia/latest-release [cited 2020 Nov 1]
7. Lalic S, Ilomäki J, Bell JS, Korhonen MJ, Gisev N. Prevalence and incidence of prescription opioid analgesic use in Australia. Br J Clin Pharmacol 2019;85:202-15. https://doi.org/10.1111/bcp.13792
8. Miotto K, Cho AK, Khalil MA, Blanco K, Sasaki JD, Rawson R. Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg 2017;124:44-51. https://doi.org/10.1213/ANE.0000000000001683
9. Fabritius ML, Strøm C, Koyuncu S, Jæger P, Petersen PL, Geisler A, et al. Benefit and harm of pregabalin in acute pain treatment: a systematic review with meta-analyses and trial sequential analyses. Br J Anaesth 2017;119:775-91. https://doi.org/10.1093/bja/aex227
10. Goodman CW, Brett AS. A clinical overview of off-label use of gabapentinoid drugs. JAMA Intern Med 2019;179:695-701. https://doi.org/10.1001/jamainternmed.2019.0086
11. Evoy KE, Morrison MD, Saklad SR. Abuse and misuse of pregabalin and gabapentin. Drugs 2017;77:403-26. https://doi.org/10.1007/s40265-017-0700-x
12. Lavand'homme P, Pogatzki-Zahn E. Chronic postsurgical pain: definition, impact and prevention. Fact Sheet No. 4 on Pain after Surgery. Washington DC: International Association for the Study of Pain; 2017. https://www.iasp-pain.org/GlobalYear/AfterSurgery

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ARTICLE

Treatment of vulvovaginitis

SUMMARY

Vulvovaginitis is a commonly encountered problem in general practice. It usually presents with irritation and vaginal discharge.

A thorough examination is essential in order not to miss the less common causes. Investigations may be needed to confirm the diagnosis.

Candidiasis and bacterial vaginosis are the most common causes. Antifungals and antibiotics are therefore used in management.

Not all causes are infective. Several skin disorders can affect the vulva.

Ongoing or recurrent symptoms require careful evaluation and further investigation.

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bacterial vaginosis, candidiasis, vulvovaginitis

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Introduction

Vulvovaginitis is a common presentation in general practice. Most women will experience at least one episode in their lifetime.[1]

The symptoms of vulvovaginitis include discharge, itch, pain, odour, dysuria and dyspareunia. An accurate diagnosis usually cannot be made on the history alone. An examination is required and investigations may be needed.

The causes can be infective or non-infective. While there are specific treatments, management also includes education about genital skin care.

Infective causes

Most cases are caused by candidiasis or bacterial vaginosis.

Candidiasis

Vulvovaginal candidiasis is usually due to *Candida albicans* which is part of the normal vaginal microbiome of women of reproductive age. This fungus requires an oestrogenised vaginal epithelium so it is seldom a cause of symptoms in postmenopausal women, unless they are taking hormone replacement therapy, or prepubertal girls.

Risk factors for infection include diabetes, pregnancy, recent antibiotics and prolonged corticosteroids. Immunocompromised women are also at risk.

The usual symptoms are itch, with or without a discharge that is classically described as thick and white. Other symptoms include dysuria and dyspareunia.

Examination typically reveals erythema and swelling of the vulva sometimes with splits or fissures. The thick discharge is typically present around the introitus and in the vagina.

The diagnosis of candidiasis is confirmed by microscopy and culture of a high vaginal swab. The presence of budding yeast or hyphae on microscopy is diagnostic.

A microscopy-negative but culture-positive result does not definitively diagnose candidiasis. This is because 10–20% of asymptomatic women will be culture positive. If symptoms are highly suggestive of candidiasis then a positive culture may indicate infection.

Treatment

Candidiasis can be treated with antifungals given by the intravaginal or oral route.[2] Over-the-counter preparations are available including combinations containing a single dose of oral fluconazole 150 mg and an azole cream for external use.

For the treatment of episodic vaginal candidiasis all regimens are at least 80% effective for clinical and mycological outcomes. Treatment guidelines vary internationally. British guidelines list fluconazole 150 mg single dose and clotrimazole 500 mg cream or pessary as first line while Australian guidelines recommend vaginal clotrimazole. Cost and patient preference[3] usually determine the choice of treatment. Topical treatments are generally cheaper.

The choices for intravaginal treatment are:

- clotrimazole – 1% vaginal cream or pessaries at night for six nights
- clotrimazole – 2% cream at night for three nights
- clotrimazole – 10% cream for one night
- nystatin vaginal cream 100,000 units for 14 nights or twice a day for one week.

Clotrimazole and nystatin can be used in pregnancy (category A). Relapses and inadequate resolution of symptoms are more common with short-course treatment.

Oral treatment:

- fluconazole 150 mg can be given as a single dose. This may be repeated in three days if symptoms are severe. Fluconazole is a category D drug in pregnancy.

If vulval symptoms are particularly severe then a combination cream of hydrocortisone 1% with clotrimazole may be applied externally twice a day in the first few days.

Recurrent candida vulvovaginitis

Recurrent candida vulvovaginitis is defined as at least four microbiologically proven infections per year. It can be difficult to prove as many women diagnose and treat themselves, and many doctors do not examine or investigate to confirm the diagnosis.[4] Any recurrent vulval symptoms require examination and investigation.

It is unclear why about 5% of women are susceptible to recurrent vulvovaginal candidiasis. Diabetes and other causes of immunosuppression should be excluded.

Treatment

Treat recurrent infection with suppressive fluconazole with or without initial intravaginal clotrimazole or nystatin. There are numerous regimens of fluconazole in use internationally for recurrent candida vulvovaginitis. Commonly the fluconazole dose is 150 mg weekly for 2–3 months (some groups recommend up to six months), tapering down to fortnightly for two months, then monthly for two months. It may be necessary to resume the weekly regimen for longer should there be a recurrence while the dose is being tapered.

Non-albicans candida vulvovaginitis

Non-albicans species in the vagina are often asymptomatic and for this reason the clinician should take care to exclude other causes of symptoms, for example eczema, before recommending treatment.

The most common non-albicans form of infection is *Candida glabrata*. Azole resistance is common.

Treatment

The choices for intravaginal treatments are:

- nystatin cream 100,000 units twice a day for two weeks (pregnancy category A)
- boric acid pessaries 600 mg at night for two weeks (available from compounding pharmacies). Prescribers should advise patients of the correct route of administration because boric acid is poisonous if taken orally. It is contraindicated in pregnancy.

Relapses may require longer treatment courses and then twice-weekly maintenance therapy for three months.

Bacterial vaginosis

Bacterial vaginosis typically presents with malodorous (often fishy) vaginal discharge. The odour is more marked after intercourse. Discomfort is mild or absent. Risk factors include new sexual partners and vaginal douching. Bacterial vaginosis is more common in women who have sex with women. Despite the association with sexual activity it is not currently recommended practice to treat the partners of women with bacterial vaginosis.

Bacterial vaginosis is a polymicrobial condition with increased numbers of anaerobic organisms and a reduction in lactobacilli. Gardnerella is one of the principle anaerobes identified in bacterial vaginosis but is not the only organism implicated. Recent research has tried to determine potential triggers that alter the vaginal microbiome, but no definitive factor has been identified.

The diagnosis can be made when three out of four Amsel's criteria are present:

- characteristic discharge – thin, greyish white, adherent
- clue cells on Gram stain of a high vaginal swab
- positive 'whiff test' – if the clinician can detect genital malodour during examination
- vaginal pH more than 4.5.

Treatment

Symptomatic women, including pregnant women, should be treated. Asymptomatic women undergoing gynaecological instrumentation (e.g. IUD insertion, hysteroscopy) should also be treated. Treating the male partners of women with bacterial vaginosis is currently not recommended. The female partners of women with bacterial vaginosis should be offered screening and treatment if positive, but there is currently no evidence that this reduces recurrences. Treatment of asymptomatic bacterial vaginosis in pregnancy has not been found to alter pregnancy outcomes.

Treatment may be oral or intravaginal. Studies comparing oral versus topical therapy suggest higher cure rates with seven days of oral metronidazole, however this must be balanced against its higher rate of adverse effects.[5] Cost may also be a factor as the topical therapies are not subsidised by the Pharmaceutical Benefits Scheme. Single doses are associated with higher relapse and recurrence rates.

The options for oral treatment are:

- metronidazole 400 mg twice a day for five to seven days or 2 g single dose
- clindamycin 300 mg twice a day for seven days.

The options for intravaginal treatment are:

- metronidazole gel 0.75% at night for five days
- clindamycin 2% cream at night for seven days.

Metronidazole can cause nausea and should be taken with food. Alcohol should not be consumed with these drugs.

For pregnant women clindamycin is category A. Metronidazole is in category B2 for pregnancy, but has not been proven to be harmful.

Recurrent bacterial vaginosis

Up to 50% of women will have a recurrence within one year. As yet, there are no definitive treatments for recurrent bacterial vaginosis. Some studies have shown suppressive therapy, for example intravaginal metronidazole gel 0.75% twice-weekly for up to six months, to be more effective than placebo. There is currently insufficient evidence to recommend the use of vaginal acidifying agents or probiotics in the treatment of bacterial vaginosis.

Trichomoniasis

Trichomoniasis typically causes mild discomfort and increased vaginal discharge (often frothy yellow or grey), however it is asymptomatic in about 50% of cases. It is a sexually transmitted infection. Trichomoniasis is relatively uncommon in major urban centres[6] with higher rates occurring in rural and remote areas, particularly in indigenous populations. Detection in general practice has been made easier by the advent of a specific PCR test on a vaginal swab or urine sample.

The treatment is either a single 2 g dose of metronidazole or 400 mg twice daily for 5–7 days. The woman's partner should also be treated.

Herpes

Genital herpes simplex virus typically presents with painful vulval irritation. Cervical and vaginal ulceration may also occur. Primary infections present with bilateral ulceration, while recurrences are usually unilateral. Diagnosis is by a herpes simplex virus specific PCR test using a swab from blisters or ulcers.

Treatment

Commence treatment at the earliest symptoms. Contact the obstetric team if the woman is pregnant. Treatment may be episodic or suppressive if there are frequent recurrences.

Initial therapy

Treatment of the initial infection by genital herpes simplex virus should begin within 72 hours of the onset of symptoms – the earlier the better. The options are:

- valaciclovir 500 mg twice a day for five days
- famciclovir 250 mg three times a day for five days.

In severe initial cases it may be appropriate to continue treatment with antivirals for up to 10 days.

Subsequent therapy

For subsequent infections the recommended treatment has usually been for five days:

- valaciclovir 500 mg twice a day for five days
- famciclovir 125 mg twice a day for five days.

There are a number of alternative short-course regimens that are considered to be equally effective:

- famciclovir 500 mg single dose then 250 mg 12-hourly for three doses
- famciclovir 1000 mg twice a day for one day
- valaciclovir 500 mg twice a day for three days.

Immunocompromised patients require higher doses to treat herpes, for example valaciclovir 500 mg twice a day for seven days.

Suppressive therapy

For recurrent infections the decision to use suppressive therapy is dependent on their frequency and severity, as well as the psychological impact of the recurrences. Suppressive therapy reduces the frequency of recurrences by 70–80%. The options are:

- valaciclovir 500 mg daily for 6–12 months, then trial off
- famciclovir 250 mg twice a day for 6–12 months, then trial off.

It is not uncommon for an early recurrence to happen soon after ceasing suppressive therapy. If frequent recurrences occur then restarting suppressive therapy is appropriate, with a further trial off treatment in the future.

Genital infections caused by herpes simplex virus 1 are usually associated with fewer recurrences. The frequency of recurrences with either strain of herpes simplex virus diminishes with time.

Non-infective causes

Non-infective causes of vulvovaginitis are common and often overlooked. There are several types of vulval dermatoses. A careful history should be taken, noting general skin problems and any previous treatments. It is imperative to carefully examine the area especially in any woman who has recurrent symptoms. Biopsy may be needed. Referral to a specialist is recommended.

Lichen simplex

Persistent itching and scratching may lead to the development of lichen simplex. It often presents with excoriation and mild lichenification. Avoid provoking factors such as over-washing, soap and over-wiping during toileting.

Irritant contact dermatitis

An irritant contact dermatitis usually presents with itch and discomfort. It is often caused by application of over-the-counter preparations, lubricants, condoms and alternative therapies. Dermatitis may also result from persisting wetness, for example incontinence.

Seborrhoeic dermatitis

The itch of seborrhoeic dermatitis is generally confined to hair-bearing areas of skin. There is often evidence of seborrhoea elsewhere.

Atopic eczema

In genital eczema, there is often evidence of eczema elsewhere. Areas of excoriation and lichenification are common.

Lichen sclerosus

Lichen sclerosus is a chronic skin disorder that often affects the vulva. It can occur at any age. Itching is the principal symptom, however there may be pain due to skin splits. Lichen sclerosus can be asymptomatic and significant architectural changes may have occurred by the time it is diagnosed. Examination findings vary but include pale thickened plaques, areas of fine crinkling and splits. Lichen sclerosus is usually confined to non-hair-bearing areas and does not extend into the vagina. With progression, there may be resorption of the labia minora and 'burying' of the clitoris under thickened skin. Rarely squamous cell cancer can develop. Referral to a specialist is recommended.

Psoriasis

Psoriasis can present with itch and irritation. On examination there are well-defined erythematous plaques, however the moist environment of the vulva means the classical scale is often absent.

Lichen planus

Lichen planus is an uncommon cause of vulval ulceration, discharge and dyspareunia. Painful well-defined vulval and sometimes vaginal erosions are seen. Referral to a specialist is recommended.

Desquamative vaginitis

A rare form of vaginitis is desquamative inflammatory vaginitis. It presents with discharge and dyspareunia. The cause is unknown.

The vagina appears inflamed with small erosions that may involve the cervix. Microscopy of the discharge shows plentiful polymorphs with parabasal cells (from deeper layers under the erosions). Referral to a specialist is recommended.

Prepubescent girls

The vulva and vagina of a prepubertal girl is not oestrogenised. As a result, the vaginal epithelium is thin, the pH is higher and the external genitals lack the labial bulk that offers some protection from irritants. Girls may complain of itch, discomfort or pain, dysuria and sometimes discharge.

Examination should only be undertaken with a parent or chaperone present and with the consent of the child. Patience and gentle explanation of the process of examination is essential. Much of the time a minimal touch technique can be used. Swabs should only be taken from external skin or from any discharge at the introitus. Check the perianal area for skin changes or worms.

The cause usually relates to toileting and hygiene, irritation from clothing such as wet bathers, and occasionally foreign bodies. Any suspicion of sexual assault or test results consistent with a sexually transmitted infection must be reported to the relevant authorities.

Notable infective causes include:

- threadworm – itching of vulva and perianal area particularly at night
- Group A streptococci – vulval pain with redness and thin discharge visible at introitus
- *Haemophilus*, *Staphylococci* and rarely *Shigella* – may be pathogens
- candida – rarely occurs and if it does clinicians should consider diabetes or immunosuppression.

Management

There is an important role for non-drug management including:

- general measures such as avoiding soap and bubble baths
- toileting and wiping advice – avoid 'holding on', urinate and open bowels regularly, wipe carefully and gently, not excessively
- patting rather than rubbing the vulva with towels
- soaking for 15 minutes in a shallow bath with ½ cup vinegar added
- soothing creams, for example paraffin, emollients.

A short course of a mild topical steroid can be used if excoriation is marked.

Conclusion

Vulvovaginitis is a common problem. It usually presents with itching and vaginal discharge.

The likely causes differ in girls, women and postmenopausal women. Common causes include candidiasis, bacterial vaginosis and skin diseases affecting the vulva. After clinical assessment, investigations may be needed to make the diagnosis.

All patients will benefit from advice on genital skin care. The treatment of vulvovaginitis is guided by the cause. Specialist advice is appropriate if the diagnosis is unclear or if symptoms persist despite following the recommended treatment regimens. ≺

Conflict of interest: none declared

REFERENCES

1. Sobel JD. Vaginitis. N Engl J Med 1997;337:1896-903. https://doi.org/10.1056/NEJM199712253372607
2. Lopez JEM. Candidiasis (vulvovaginal). BMJ Clin Evid 2015;2015:0815.
3. Sobel JD. Factors involved in patient choice of oral or vaginal treatment for vulvovaginal candidiasis. Patient Prefer Adherence 2013;8:31-4. https://doi.org/10.2147/PPA.S38984
4. Foxman B, Muraglia R, Dietz JP, Sobel JD, Wagner J. Prevalence of recurrent vulvovaginal candidiasis in 5 European countries and the United States: results from an internet panel survey. J Low Genit Tract Dis 2013;17:340-5. https://doi.org/10.1097/LGT.0b013e318273e8cf
5. Koumans EH, Markowitz LE, Hogan V; CDC BV Working Group. Indications for therapy and treatment recommendations for bacterial vaginosis in nonpregnant and pregnant women: a synthesis of data. Clin Infect Dis 2002;35 Suppl 2:S152-72. https://doi.org/10.1086/342103
6. Bygott JM, Robson JM. The rarity of Trichomonas vaginalis in urban Australia. Sex Transm Infect 2013;89:509-13. https://doi.org/10.1136/sextrans-2012-050826

FURTHER READING

DermNet NZ. http://www.dermnetnz.org [cited 2020 Nov 1]

Melbourne Sexual Health Centre. www.mshc.org.au [cited 2020 Nov 1]

Royal Children's Hospital Melbourne. Clinical practice guidelines. www.rch.org.au/clinicalguide [cited 2020 Nov 1]

Centers for Disease Control and Prevention. 2015 sexually transmitted diseases treatment guidelines. US Department of Health and Human Services. www.cdc.gov/std/tg2015 [cited 2020 Nov 1]

British Association for Sexual Health and HIV. BASHH guidelines. Cheshire; BASHH; 2020. https://www.bashh.org/guidelines [cited 2020 Nov 1]

ARTICLE

Prescribing pre-exposure prophylaxis for HIV

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emtricitabine, HIV prevention, human immunodeficiency virus, men who have sex with men, pre-exposure prophylaxis, tenofovir

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Related article:
HIV diagnoses in Australia fall as clinicians embrace pre-exposure prophylaxis

SUMMARY

Co-formulated tenofovir disoproxil plus emtricitabine is highly effective as pre-exposure prophylaxis for HIV.

It is suitable for men who have sex with men, for heterosexual sex and for people who use intravenous drugs when there is a risk of HIV infection.

Pre-exposure prophylaxis is one pill per day and can be prescribed by all medical practitioners and nurse practitioners via the Pharmaceutical Benefits Scheme. It is best prescribed in a three-monthly program with regular monitoring for patient adherence, safety, HIV and other sexually transmitted infections.

Prophylaxis is well tolerated but requires monitoring for kidney toxicity and low bone density.

Introduction

In addition to preventing new HIV infection in individuals, and the fears associated with this, pre-exposure prophylaxis (PrEP) has been a major public health development for the community.

HIV is no longer a terminal diagnosis, but can be well managed as a chronic condition with almost normal life expectancy. Nevertheless, there is a burden of comorbidities associated with HIV infection due to increased inflammation even with virus suppression. There are also the lifelong costs of treatment.

With variable use of condoms and in the absence of an HIV vaccine, other measures have been necessary to reduce HIV transmission. Since 2000, there was a gradual increase in new HIV diagnoses in Australia, particularly in men who have sex with men. Since 2012, state health authorities have attempted to tackle the rising incidence more systematically. Initial approaches included increased testing to identify undiagnosed cases, and encouraging treatment of every person with HIV to reduce viral load and transmission in the community (known as treatment as prevention or TasP). This resulted in a plateauing but not a reduction of new diagnoses. Only since the widespread uptake of PrEP in 2016[1] has there been a dramatic fall in new infections (see editorial in this issue). There has been a reduction of up to 50% in men who have sex with men living in inner cities.[1]

Drugs used for prophylaxis

Currently licensed PrEP in Australia consists of co-formulated tenofovir disoproxil 300 mg plus emtricitabine 200 mg. One pill is taken daily, ideally with food which increases drug concentrations by up to 40%. Both compounds inhibit nucleoside reverse transcriptase. This is an essential step for the virus in which single-stranded RNA is converted to double-stranded RNA so the virus can enter the host cell nucleus, integrate, and then replicate.

The intracellular half-lives of tenofovir disoproxil and emtricitabine are long – 150 hours and 39 hours. This enables some leniency in terms of dosing and adherence for men who have sex with men taking PrEP.

The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) updated their PrEP Guidelines, which provide comprehensive guidance for prescribing PrEP in the Australian context.

Who is suitable for PrEP?

PrEP is indicated for people who are at risk of HIV infection, or have fears related to acquiring it. Men who have sex with men account for approximately 70% of HIV diagnoses in Australia. A high risk of HIV infection has been associated with:

- unprotected receptive anal intercourse
- a history of sexually transmitted infections, particularly anorectal gonorrhoea and chlamydia
- use of illicit drugs, particularly crystal methamphetamine because of its effect on behaviour.

Sex workers and people who use intravenous drugs are also at risk of HIV, as are some transgender people and heterosexuals who engage in high-risk behaviour.

While PrEP has been particularly effective in reducing new HIV infections in Australian-born men who have sex with men, there is a need to ensure the provision of PrEP to overseas-born men who have sex with men, heterosexuals at risk, and Aboriginals. These groups have not shown declines in new HIV infections.

PrEP is not recommended in people who already have HIV because dual therapy with tenofovir disoproxil/emtricitabine is insufficient to suppress HIV and there is a risk of drug resistance developing. Additional drugs are needed for HIV treatment regimens.

How to prescribe PrEP

PrEP is available on the Pharmaceutical Benefits Scheme (PBS) via streamlined S85 monthly prescription. Any medical practitioner or qualified nurse practitioner can prescribe up to three months supply. For those who are ineligible through Medicare, the options are via private prescription, or patient importation via online pharmacies (a prescription is required for Customs). PrEPaccessNow is a useful link for reliable online pharmacy sites.

The most effective way to prescribe tenofovir disoproxil/emtricitabine is in a PrEP program. This recommends three-monthly follow-up visits for clinical and laboratory assessment and prescribing of PrEP (see Table). Visits involve regular monitoring for adherence, potential adverse reactions and, with the patient's agreement, for sexually transmitted infections and HIV infection.

At the initial visit, patients should be advised that while PrEP is highly effective in preventing HIV infection, it does not protect against other sexually transmitted infections and condom use is encouraged.

PrEP is not recommended if the estimated glomerular filtration rate (eGFR) is less than 60 mL/min/1.73 m^2 so kidney function should be

Table **Laboratory evaluation and clinical follow-up of individuals who are prescribed pre-exposure prophylaxis**

Test	Baseline (week 0)	1 month after starting PrEP (optional but recommended in some jurisdictions)	3 months after starting PrEP	Every subsequent 3 months on PrEP	Other frequency
HIV testing and assessment for signs or symptoms of acute infection	Y	Y	Y	Y	N
Assess adverse effects	N	Y	Y	Y	N
Hepatitis B serology (vaccinate if non-immune)	Y	N	N	N	Y If patient required hepatitis B vaccine at baseline, confirm immune response 1 month after last vaccine dose
Hepatitis C serology	Y	N	N	N	12 monthly, but more frequently if ongoing risk e.g. non-sterile injection drug use and MSM with sexual practices that pre-dispose to anal trauma
STI (i.e. syphilis, gonorrhoea, chlamydia) as per Australian STI Management Guidelines	Y	N	Y	Y	N
eGFR	Y	N	Y	N	At least every 6 months or according to risk of chronic kidney disease
Urine protein:creatinine ratio	Y	N	Y	N	Every 6 months
Pregnancy test (for women of child-bearing age)	Y	Y	Y	Y	N

Y Yes
N No
MSM Men who have sex with men
STI sexually transmissible infection
eGFR estimated glomerular filtration rate
Source: ASHM PrEP Guidelines September 2019 update

measured at baseline. Patients with an eGFR below 60 mL/min/1.73 m^2 should be referred to a specialist for management. Other potential issues such as low bone density should also be assessed. The use of concomitant drugs that could potentiate toxicity such as non-steroidal anti-inflammatory drugs should be avoided, as well as pre-existing HIV infection (by fourth generation HIV antibody/antigen blood testing) and other sexually transmitted infections.

Some practitioners may elect to review the patient after one month to assess any issues related to PrEP adherence, toxicity, and re-test for HIV infection.

How effective is PrEP?

PrEP taken daily reduces HIV infection via sexual transmission by 99%.[2] Lower adherence reduces PrEP effectiveness – if four pills are taken per week, effectiveness is reduced to 96% and falls rapidly after that as adherence drops. Transmission via intravenous drug use was reduced by 74% in those with detectable tenofovir levels.[3]

Tenofovir disoproxil/emtricitabine is highly effective as PrEP because high drug concentrations are rapidly achieved in rectal tissue. This is less so in vaginal tissue and to maintain optimal drug concentrations in women, daily adherence should be emphasised. Steady state drug concentrations of tenofovir disoproxil are achieved in genital and rectal tissues by one week, and in blood by 20 days.

For men who have sex with men, a loading dose of two pills with subsequent daily dosing will enable effectiveness of PrEP from two hours after first administration. For men and women practising at-risk heterosexual sex and for those who are transgender, PrEP is effective after seven days of daily dosing.

Adherence

Illicit drug use may affect adherence to PrEP, and drug and alcohol issues may need to be addressed. Adherence can be supported with increased knowledge about PrEP and its effectiveness as well as dealing with adverse effects and concerns about toxicity.

Patients may take PrEP for periods of time at risk and then stop if they enter into a monogamous relationship. For men who have sex with men, stopping PrEP is safe after they have taken a 24- and 48-hour dose following the last sexual exposure. For men and women engaging in heterosexual sex and people who use intravenous drugs, it is recommended to continue PrEP for 28 days after their last exposure.

Adolescents and young adults taking PrEP are more likely to discontinue PrEP so may require more frequent monitoring to support adherence.

Adverse effects, drug interactions and monitoring

It is rare for PrEP to be stopped because of adverse events. Initial adverse effects tend to be transient and include gastrointestinal (e.g. nausea and diarrhoea) and central nervous system events (e.g. headache lasting a week or slightly longer).

Kidney and liver toxicity are rare but regular monitoring is required. Patients aged over 40 years with eGFR less than 90 mL/min/1.73 m^2, hypertension or diabetes or taking concomitant nephrotoxic drugs should have three-monthly renal assessment (see Table).

Tenofovir disoproxil and emtricitabine are renally excreted via glomerular filtration and tubular secretion. There are potential drug–drug interactions that can adversely affect renal function. These can occur with concomitant use of renally excreted drugs such as non-steroidal anti-inflammatory drugs, aminoglycosides, aciclovir and valaciclovir. Characteristically, renal complications involve proximal tubular damage, leading to acute kidney injury, Fanconi syndrome or chronic kidney disease. There can also be a milder 'creatinine creep' with gradually increasing creatinine and decreasing eGFR over time.

Tenofovir disoproxil is associated with reduced bone density of 3–4% in the first year of treatment. This plateaus out to normal bone density loss of 1% per year (after the age of 30 years). For the majority of PrEP users, this bone density reduction is not clinically significant. However, for those over 40 years of age who are at risk of low bone density, bone density can be assessed using the FRAX fracture risk assessment score, or dual-energy X-ray absorptiometry (DXA) scanning. This is Medicare reimbursable under certain criteria, as outlined in Osteoporosis Australia's bone density testing brochure for general practice.

PrEP can be used in patients with hepatitis B infection. However, interrupting PrEP can lead to a symptomatic flare of hepatitis B or drug resistance so these patients should be monitored closely.

On-demand PrEP

On-demand or intermittent use of PrEP has demonstrated effectiveness for men who have sex with men.[4] Two pills of tenofovir disoproxil/emtricitabine are taken 2–24 hours before sex, followed by a single pill 24 hours and 48 hours after the initial dose. If there is further sexual activity, PrEP can continue to be taken daily for two subsequent days following the last sexual activity. On-demand PrEP is potentially suitable for those who have sexual contact on an occasional or intermittent basis and

are able to plan for these episodes. This method is endorsed in the ASHM guidelines as an alternative to daily PrEP for men who have sex with men, but is not recommended for those with hepatitis B infection, women, heterosexual men, and for those who are transgender.

Other PrEP medicines

The DISCOVER study demonstrated the effectiveness of tenofovir alafenamide co-formulated with emtricitabine as PrEP.[5] This combination has reduced kidney and bone toxicity and is currently licensed in Australia only for HIV treatment.

There are currently studies of longer acting PrEP drugs such as injectable cabotegravir, an integrase strand transfer inhibitor given every second month, which has been found to be effective in treatment of HIV infection.[6]

Conclusion

PrEP provides a valuable, safe and effective method for medical practitioners to assist their patients in preventing HIV transmission. It can be prescribed in the community with regular monitoring every three months. <

Mark Bloch has participated on medical advisory boards for Gilead Sciences, VIV Healthcare and Abbvie. He has received support to attend scientific conferences from Gilead Sciences and has given lectures for Gilead Sciences, VIV Healthcare and Abbvie. His institution has received payments for clinical research from Gilead Sciences, VIV Healthcare, Abbvie, MSD, GSK, Eli-Lilly, Amgen and Pfizer.

REFERENCES

1. Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, et al.; Expanded PrEP Implementation in Communities New South Wales (EPIC-NSW) research group. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. Lancet HIV 2018;5:e629-37. https://doi.org/10.1016/S2352-3018(18)30215-7
2. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, et al.; iPrEx Study Team. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med 2012;4:151ra125. https://doi.org/10.1126/scitranslmed.3004006
3. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med 2011;3:112re4. https://doi.org/10.1126/scitranslmed.3003174
4. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, et al.; ANRS IPERGAY Study Group. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med 2015;373:2237-46. https://doi.org/10.1056/NEJMoa1506273
5. Hare CB, Coll J, Ruane P, Molina JM, Mayer KH, Jessen H, et al. The phase 3 discover study: Daily F/TAF or F/TDF for HIV preexposure prophylaxis. Abstract 104. Conference on Retroviruses and Opportunistic Infections (CROI); 2019 Mar 4–7, Seattle, USA. https://www.croiconference.org/abstract/phase-3-discover-study-daily-ftaf-or-ftdf-hiv-preexposure-prophylaxis [cited 2020 Nov 1]
6. Overton ET, Richmond GJ, Rizzardini G, Jaeger H, Orrell C, Nagimova F, et al. Cabotegravir + rilpiverine every 2 months is noninferior to monthly: ATLAS-2M study. Abstract 34. Conference on Retroviruses and Opportunistic Infections (CROI); 2020 Mar 8–11, Boston, USA. https://www.croiconference.org/abstract/cabotegravir-rilpivirine-every-2-months-is-noninferior-to-monthly-atlas-2m-study [cited 2020 Nov 1]

DIAGNOSTIC TESTS

Testing for COVID-19

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SUMMARY

Accurate diagnostic tests that provide results in a timely manner are essential for the clinical and public health management of COVID-19 disease.

The choice as to which test to use will depend on the clinical presentation and the stage of the illness.

Nucleic acid tests, using real-time reverse transcriptase-polymerase chain reaction, are the most appropriate for diagnosing acute infection. Combined deep nasal (or nasopharyngeal) and throat swabs are the preferred sample.

Serology can be used to diagnose previous infection, more than 14 days after the onset of symptoms.

Antigen tests are in development and their role is not yet defined.

Interpretation of results must take into account the pre-test probability of the patient having the disease. This is based on their clinical presentation and epidemiological risk.

Introduction

COVID-19 is caused by the SARS-CoV-2 virus and was first identified after an outbreak of pneumonia in Wuhan, China in December 2019. Since then, no country has escaped the ensuing pandemic that continues on an upward trajectory. Access to accurate and reliable diagnostic testing is key to the public health response. Identifying infected individuals, tracing their contacts, and quarantine and isolation measures are an essential part of reducing the transmission, morbidity and mortality from COVID-19.

There are a number of different diagnostic tests for COVID-19: nucleic acid tests, serological tests for antibody detection, and antigen tests. These can be laboratory-based and point-of-care tests (see Table). It is important to be aware of what the different tests are, when they should be used, what samples should be collected and how to interpret test results.

The virus

SARS-CoV-2 is a member of the coronavirus family. This is a diverse group of enveloped, single-stranded, positive-sense RNA viruses. Four important structural proteins are the most common targets for diagnostic tests (see Fig. 1):

- spike protein that allows entry into the cell
- nucleocapsid protein that surrounds the genomic RNA
- membrane protein
- envelope protein.[1]

Clinical disease and transmission

The mean incubation period for infection with SARS-CoV-2 is five days, with a range of 2–14 days reported. The most common symptoms are fever, dry cough and fatigue, with sore throat, rhinorrhoea, dysgeusia and anosmia also described. Reported fatality rates vary from 0.7% to approximately 5%.[2]

Transmission is primarily via respiratory droplets or fomites. Viral shedding is thought to peak on or just before the onset of symptoms, with viral loads decreasing thereafter.[3]

Prolonged detection of viral RNA is not uncommon, with reports of detection by PCR up to 12 weeks after symptoms have resolved.[4] However, this does not necessarily mean there is infectious virus present. Transmission of the virus is thought to be unlikely 10 or more days after the onset of symptoms based on viral culture and epidemiological studies (Fig. 2).[5] Asymptomatic infections are increasingly recognised as important in the ongoing transmission of the virus. However, testing should continue to be targeted and avoid non-clinically indicated asymptomatic testing to preserve reagents and testing capacity.[6]

Who should be tested

Testing should be performed on patients who have a compatible clinical illness, or as part of enhanced surveillance of asymptomatic individuals in high-risk settings such as returned travellers, healthcare workers, contacts of confirmed cases and in outbreak situations. Individuals in enclosed environments with

Table **Diagnostic tests for SARS-CoV-2 infection**

Test	Purpose of test	When to order this test	Sample type
Point-of-care nucleic acid tests	Diagnosis of current infection (when a rapid turnaround is required)	Symptomatic patients early in their illness	Combined nasopharyngeal or deep nasal with throat swab, or sputum or BAL if lower respiratory symptoms
Laboratory-based nucleic acid tests: many commercial and in-house laboratory developed assays	Routine diagnosis of current infection	Symptomatic patients early in their illness	Combined nasopharyngeal or deep nasal with throat swab, or sputum or BAL if lower respiratory symptoms
Laboratory-based testing for antibodies to various antigens including nucleocapsid and spike proteins	Diagnosis of past infection	At least 14 days since the onset of symptoms. Repeat testing out to 28 days is recommended when there is a high pre-test probability	Serum from blood sample
Point-of-care antibody tests	Detection of IgG and IgM antibodies	Should not be used until at least 2 weeks post symptom onset.	Venous or finger prick blood tests
Antigen tests	Rapid diagnosis	Usually symptomatic patients within 5 days of symptom onset. Role for these assays not yet defined	Respiratory specimens as for RT-PCR. Repeat testing may be required as reduced sensitivity compared to RT-PCR

RT-PCR reverse transcriptase-polymerase chain reaction
BAL broncho-alveolar lavage
Ig immunoglobulin

an increased risk of transmission, such as aged-care facilities, abattoirs and prisons, may also be tested. Testing guidelines should be checked as they are regularly updated.[7,8]

Nucleic acid tests and their interpretation

Real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assays are the cornerstone of acute diagnosis for COVID-19 and work by detecting SARS-CoV-2 RNA in respiratory tract specimens.[7] At least one, but often two or more RNA target sequences are generally used. While the analytical sensitivity of these tests is excellent, their clinical interpretation depends on the prevalence of SARS-CoV-2 in the population tested. Other factors contributing to this variability include the adequacy of the sample collected and the timing of sample collection in relation to the likelihood of viral shedding and stage of the illness (Fig. 2). A single negative result is generally sufficient to exclude disease in most cases, but in patients with a clinically compatible illness and a high index of suspicion, repeat testing should be performed. Overall, the likelihood of false positives and false negatives occurring is very low.[9]

Fig. 1 **Structure of the SARS-CoV-2 virus**

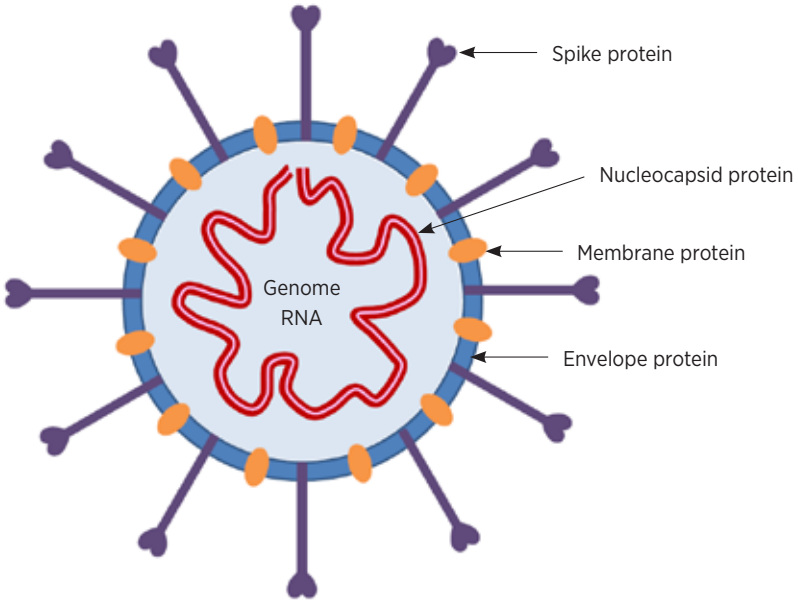
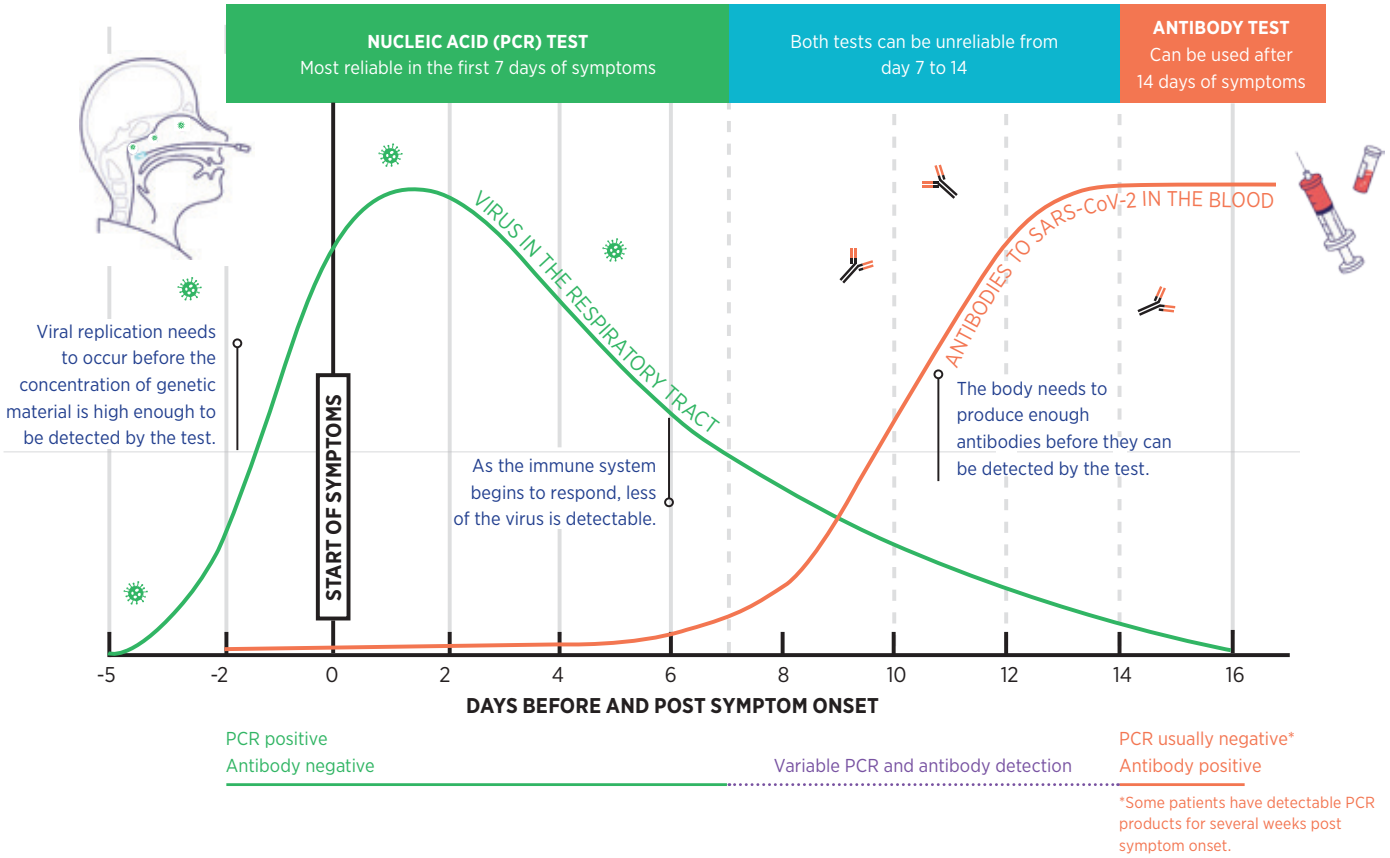


Fig. 2 **Correlation between viral load, antibody production, diagnostic windows and clinical course of SARS-CoV-2 infection**



Collecting samples for nucleic acid testing

To maximise the chance of virus detection, sampling the oropharyngeal (throat) and bilateral deep nasal (or nasopharyngeal) sites is recommended.[10] Using the same flocked or foam swab for both is preferred. This is more sensitive than throat-only swabs. For those with lower respiratory tract symptoms, sputum or broncho-alveolar lavage specimens (on intubated patients) are preferred.[7]

Self-collected nasal and throat swabs have been shown to be as sensitive as samples collected by healthcare workers and are an appropriate alternative.[11] The option of self-collection can be offered by a medical practitioner or under public health direction. Where possible, it should be supervised.

Saliva may be another alternative sample type, albeit slightly less sensitive. However, there is insufficient evidence at present to recommend its use.[12] Although SARS-CoV-2 RNA has been detected in faecal samples, these specimens are not recommended for routine testing. They can be considered when there is a high suspicion of SARS-CoV-2 in patients with a negative PCR result on respiratory samples.

For nucleic acid testing, swabs should ideally be placed in suitable validated liquid media and transported at ambient temperature to the laboratory.

Point-of-care nucleic acid tests

A point-of-care RT-PCR test, the Xpert Xpress SARS-CoV-2 (Cepheid, USA), is currently in use in Australia (performed on the GeneXpert system).[13] The advantage of this test is the short time for a result to be available (approximately 45 minutes from the time the sample arrives), as there is no separate extraction step. However, this system is not suitable for simultaneous testing of large numbers of samples and reagent cartridges are of limited availability nationally. Similar rapid assays that include multiplexed additional respiratory virus targets are becoming available, such as QIAstat-Dx Respiratory SARS-CoV-2 Panel (QIAGEN GmbH) and the cobas SARS-CoV-2 and Influenza A/B nucleic acid test (Roche Molecular Systems). The ID NOW COVID-19 assay (Abbott) is in use in some point-of-care settings such as hospital emergency departments. It uses isothermal nucleic acid amplification technology. Analytical sensitivity is reduced compared to other sample-to-answer platforms.[14]

Laboratory-based nucleic acid tests

There are many available commercial and in-house-developed nucleic acid tests in use in Australian laboratories. Extraction of the RNA from samples before amplification is required and so the total test time is approximately six hours. However, due to transport time and the need to batch samples together, the actual turnaround time is closer to 24–48 hours. The advantage of these tests is the ability to perform a large volume of tests at the same time.

New fully integrated sample-to-answer molecular diagnostic platforms are now available. Examples include Hologic's Panther Fusion and Aptima SARS-CoV-2 assays and Roche's cobas SARS-CoV-2 test, which offer high throughput, and DiaSorin Molecular's Simplexa COVID-19 Direct kit, which in addition offers improved turnaround times.

Antibody assays

Serological testing detects antibody responses (IgM, IgA and IgG) to SARS-CoV-2 in patient sera. Due to the delay in antibody production, serology is not recommended for the diagnosis of acute infections. Sero-positivity increases from day seven of the illness, with most patients seroconverting by day 14, although some can take up to 28 days (Fig. 2). It is thought that 5–10% of patients may never seroconvert following infection with SARS-CoV-2.

Assays most commonly are designed to detect antibodies to the spike protein, or the nucleocapsid protein, with the choice of antigen designed to minimise cross-reaction against other human coronaviruses.[15]

Serology is recommended for:

- patients who have had symptoms consistent with COVID-19 but had a negative PCR result or were not tested
- patients with unexpected positive or inconclusive PCR results
- assisting with outbreak investigations and epidemiological surveys
- identifying convalescent patients for plasma donation.

Duration of antibody response and correlation with protection and immunity to COVID-19 are both unknown at this time. There is early evidence to suggest that while antibodies may decline over a few months, protection from reinfection may be more durable.[16]

Serum should be collected from patients with a compatible clinical illness at least 14 days after the onset of symptoms. Consideration can be given to taking an earlier sample that can be stored and used for parallel testing.

Laboratory-based antibody tests

COVID-19 serology is currently performed in the laboratory using either in-house methodology or, more commonly, commercially manufactured kits. Most laboratories are using an enzyme-linked immunosorbent assay (ELISA), either as manual ELISAs that need to be batched, or as high-throughput immunoassays that allow samples to be tested as they arrive. Some reference laboratories are also using neutralisation assays, microsphere immunoassays or immunofluorescent assays.[7] The real-world sensitivity of these commercial assays has been reported as 80–100% depending on the assay, with specificities of 98–100%.[17] In the Australian setting where the prevalence of infection is still very low (0.1%), the predictive value of a positive test even with this high specificity is low and of the order of 10%.

To improve the positive predictive value of serological results and reduce false-positive results, some laboratories are screening with one assay, then performing a second independent assay detecting antibodies to a different antigen on all positive results. The results of both assays will be considered when interpreting the final result.

Interpreting antibody results

Consultation with the laboratory regarding the interpretation of SARS-CoV-2 serological results is recommended. Definitive laboratory evidence of SARS-CoV-2 infection is seroconversion or a significant (e.g. at least fourfold) rise in either neutralising or IgG antibody concentrations. Detection of IgG in a single specimen from a person with a compatible clinical illness and with one or more defined epidemiological criteria for COVID-19 is suggestive evidence of SARS-CoV-2 infection. Detection of IgM, IgA or both without IgG is not sufficient evidence of infection, and a follow-up sample should be requested.[15]

Lateral flow point-of-care antibody assays

A number of lateral flow point-of-care assays have been developed to detect SARS-CoV-2-specific IgM, IgG and total antibody. Blood samples are taken from a vein or by finger prick providing a rapid turnaround time. These tests are not recommended for acute diagnosis because of the delayed antibody response. An independent evaluation of eight of these antibody tests found that they generally have not met manufacturer claims for diagnostic sensitivity.[18] Whether there is a role for these tests in determining immunity for return-to-work purposes or population surveillance remains to be determined.

Antigen assays

Antigen assays detect virus proteins, usually the nucleocapsid protein in respiratory samples and are used for acute diagnosis. Their availability in Australia is currently limited. While most require laboratory equipment for reading of results, some are applicable for point-of-care testing.

There is increasing interest in these tests because of their lower relative cost to RT-PCR and rapid turnaround time, and can be scaled up to test large numbers of patients. However, concerns remain around their sensitivity to detect virus compared to RT-PCR tests. Rigorous postmarket evaluation of these tests is essential. A discussion around their future role in the Australian context has recently been published.[19] The widespread availability of RT-PCR testing, generally with good turnaround times, reduces the need for antigen assays in Australia. However, there may be a role in certain particularly high-risk settings.

Personal protection during sample collection

Personal protective equipment consisting of gloves, surgical mask and eye protection should be used when collecting respiratory samples in symptomatic patients suspected of having SARS-CoV-2 infection. The need for a gown or apron should be based on a risk assessment.[20] This should also be the case when collecting blood for serological testing if the patient is symptomatic, otherwise standard precautions are appropriate. The Infection Control Expert Group, together with the National COVID-19 Evidence Task Force, is currently analysing the high rates of infection that have been seen in some types of healthcare workers and updated recommendations are anticipated. Specimen collection has not specifically been identified as high risk.

Conclusion

Prompt identification of patients with SARS-CoV-2 infection using laboratory diagnostic tests is essential, for both the clinical monitoring and treatment of the patient and to inform subsequent quarantining and isolation. The appropriate choice of diagnostic test and sample type will maximise the chance of identifying positive cases, and minimise the unnecessary anxiety and expense of tests with little clinical use. <

Conflict of interest: none declared

REFERENCES

1. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020;12:372. https://doi.org/10.3390/v12040372
2. Park SE. Epidemiology, virology, and clinical features of severe acute respiratory syndrome – coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). Clin Exp Pediatr 2020;63:119-24. https://doi.org/10.3345/cep.2020.00493
3. He X, Lau EH, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26:672-5. https://doi.org/10.1038/s41591-020-0869-5
4. Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: not a rare phenomenon. J Med Virol 2020;92:2286-7. https://doi.org/10.1002/jmv.25952
5. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. Clin Infect Dis. Epub 2020 May 22. https://doi.org/10.1093/cid/ciaa638
6. Australian Government Department of Health. Public Health Laboratory Network statement on asymptomatic testing for SARS-CoV-2. 2020 Aug 6. Updated 2020 Aug 7. www.health.gov.au/resources/publications/phln-statement-on-asymptomatic-testing-for-sars-cov-2 [cited 2020 Sep 30]
7. Australian Government Department of Health. Public Health Laboratory Network guidance on laboratory testing for SARS-CoV-2 (the virus that causes COVID-19). 2020 Mar 14. Updated 2020 Sep 30. www.health.gov.au/resources/publications/phln-guidance-on-laboratory-testing-for-sars-cov-2-the-virus-that-causes-covid-19 [cited 2020 Sep 30]
8. Australian Government Department of Health. Coronavirus disease 2019 (COVID-19): CDNA national guidelines for public health units. 2020 Aug 24. www1.health.gov.au/internet/main/publishing.nsf/Content/cdna-song-novel-coronavirus.htm [cited 2020 Sep 30]
9. Australian Government Department of Health. Public Health Laboratory Network guidance on nucleic acid test result interpretation for SARS-CoV-2. 2020 Jun 11. Updated Sep 17. https://www.health.gov.au/resources/publications/phln-guidance-on-nucleic-acid-test-result-interpretation-for-sars-cov-2 [cited 2020 Sep 30]
10. Australian Government Department of Health. Public Health Laboratory Network guidance: COVID-19 swab collection – upper respiratory specimen. 2020 Jun 3. www.health.gov.au/resources/publications/phln-guidance-covid-19-swab-collection-upper-respiratory-specimen [cited 2020 Sep 30]
11. Wehrhahn MC, Robson J, Brown S, Bursle E, Byrne S, New D, et al. Self-collection: an appropriate alternative during the SARS-CoV-2 pandemic. J Clin Virol 2020;128:104417. https://doi.org/10.1016/j.jcv.2020.104417
12. Australian Government Department of Health. Public Health Laboratory Network statement on the use of saliva as an alternative specimen for the diagnosis of SARS-CoV-2. 2020 May 21. www.health.gov.au/resources/publications/phln-statement-on-use-of-saliva-as-an-alternative-specimen-for-the-diagnosis-of-sars-cov-2 [cited 2020 Sep 30]
13. Wolters F, van de Bovenkamp J, van den Bosch B, van den Brink S, Broeders M, Chung NH, et al. Multi-center evaluation of cepheid xpert® xpress SARS-CoV-2 point-of-care test during the SARS-CoV-2 pandemic. J Clin Virol 2020;128:104426. https://doi.org/10.1016/j.jcv.2020.104426
14. Smithgall MC, Scherberkova I, Whittier S, Green DA. Comparison of Cepheid Xpert Xpress and Abbott ID NOW to Roche cobas for the rapid detection of SARS-CoV-2. J Clin Virol 2020;128:104428. https://doi.org/10.1016/j.jcv.2020.104428
15. Australian Government Department of Health. Public Health Laboratory Network guidance for serological testing in COVID-19. 2020 Jun 29. Updated 2020 Sep 3. www.health.gov.au/resources/publications/phln-guidance-for-serological-testing-in-covid-19 [cited 2020 Sep 30]
16. Patel R, Babady E, Theel ES, Storch GA, Pinsky BA, St George K, et al. Report from the American Society for Microbiology COVID-19 International Summit, 23 March 2020: value of diagnostic testing for SARS-CoV-2/COVID-19. MBio 2020;11:e00722-20. https://doi.org/10.1128/mBio.00722-20
17. Caini S, Bellerba F, Corso F, Díaz-Basabe A, Natoli G, Paget J, et al. Meta-analysis of diagnostic performance of serological tests for SARS-CoV-2 antibodies up to 25 April 2020 and public health implications. Euro Surveill 2020;25: 2000980. https://doi.org/10.2807/1560-7917.ES.2020.25.23.2000980
18. Therapeutic Goods Administration, Australian Government Department of Health. Post-market evaluation of serology-based point of care tests. 2020 Sep 29. www.tga.gov.au/post-market-evaluation-serology-based-point-care-tests [cited 2020 Sep 30]
19. Australian Government Department of Health. PHLN and CDNA joint statements on SARS-CoV-2 rapid antigen tests. 2020 Oct 9. https://www.health.gov.au/resources/publications/phln-and-cdna-joint-statement-on-sars-cov-2-rapid-antigen-tests [cited 2020 Oct 10]
20. Australian Government Department of Health. Coronavirus (COVID-19) guidance on the use of personal protective equipment (PPE) in non-inpatient health care settings, during the COVID-19 outbreak. 2020 May 11. Updated 2020 Jul 31. www.health.gov.au/resources/publications/coronavirus-covid-19-guidance-on-use-of-personal-protective-equipment-ppe-in-non-inpatient-health-care-settings-during-the-covid-19-outbreak [cited 2020 Sep 30]

FEATURE

Top 10 drugs 2019–20

Aust Prescr 2020;43:209
https://doi.org/10.18773/austprescr.2020.075

Tables 1–3 show the top 10 drugs for the year July 2019 – June 2020. The figures are based on PBS and RPBS prescriptions from the date of supply. The figures include prescriptions under the co-payment (non-subsidised).

Table 1 **Top 10 PBS/RPBS drugs by DDD/1000 population/day**

	Drug	DDD/1000 pop/day*
1.	atorvastatin	72.93
2.	rosuvastatin	61.03
3.	perindopril	52.34
4.	amlodipine	50.15
5.	candesartan	33.52
6.	telmisartan	32.19
7.	irbesartan	29.87
8.	ramipril	26.44
9.	sertraline	25.67
10.	metformin	25.51

Table 2 **Top 10 PBS/RPBS drugs by prescription counts**

	Drug	Prescriptions
1.	rosuvastatin	12,968,693
2.	atorvastatin	11,241,737
3.	pantoprazole	8,283,205
4.	esomeprazole	8,171,291
5.	perindopril	6,688,735
6.	cefalexin	5,347,062
7.	metformin	5,183,224
8.	escitalopram	4,983,887
9.	amoxicillin	4,777,911
10.	sertraline	4,714,321

Table 3 **Top 10 PBS/RPBS drugs by cost to government (does not include rebates)**

	Drug	Cost to government	DDD/1000 pop/day*	Prescriptions
1.	aflibercept	$392,045,570	‡	315,200
2.	nivolumab	$344,751,398	‡	51,882
3.	pembrolizumab	$342,875,272	‡	38,860
4.	adalimumab	$320,969,041	0.76	257,328
5.	denosumab	$244,407,111	18.44	884,413
6.	sofosbuvir + velpatasvir†	$223,484,429	‡	17,733
7.	ranibizumab	$218,085,968	‡	190,126
8.	ustekinumab	$211,250,971	0.49	29,603
9.	apixaban	$210,022,698	6.81	2,580,428
10.	glecaprevir + pibrentasvir†	$186,730,613	‡	9,956

DDD defined daily dose

PBS Pharmaceutical Benefits Scheme

RPBS Repatriation Pharmaceutical Benefits Scheme

* DDD/thousand population/day is a more useful measure of drug utilisation than prescription counts. It shows how many people in every thousand Australians are taking the standard dose of a drug every day. DDD includes use in combination products. The calculation is based on ABS 3101.0 – Australian Demographic Statistics for December 2019.

† DDDs for combination products are accounted for in constituent drugs

‡ The World Health Organization has not allocated a DDD for this drug

Source: Department of Health, December 2020. ©Commonwealth of Australia

FEATURE

Medicines Australia Code of Conduct: breaches 2019–20

Keywords
Medicines Australia, codes of conduct, drug industry

Aust Prescr 2020;43:210
https://doi.org.au/10.18773/austprescr.2020.071

The Medicines Australia Code of Conduct guides the promotion of prescription products by pharmaceutical companies.[1] Each year Medicines Australia publishes a report, from its Code of Conduct Committee, which details all the complaints that have been received about advertising and other promotional activities.

In 2019–20 the Code of Conduct Committee finalised five complaints (see Table). These were dealt with under the 18th edition of the Code of Conduct.[1] The current 19th edition was introduced in March 2020.[2]

Four of the five complaints were made by pharmaceutical companies. Two of them involved rival companies complaining about their competitor's influenza vaccine. The one complaint from a health professional related to being featured in a video. While the health professional had been paid for assisting in the production, they had not given written consent for the release of the video.

In four cases there was an appeal against the decisions of the Code of Conduct Committee. One of the appeals was by a company which had made a successful complaint. This appeal resulted in a doubling of the fine that had been imposed as a sanction.

More details about the complaints can be found in the full report on the website of Medicines Australia.[3]

Table **Breaches of the Medicines Australia Code of Conduct July 2019 – June 2020**

Company	Brand (generic) name	Material or activity	Sanction
Sanofi-aventis	Fluzone High-Dose (influenza vaccine)	Product-specific consumer media release	$100,000 fine Claims not to be used again
Seqirus	Fluad (influenza vaccine)	Promotional material	$40,000 fine increased to $80,000 on appeal. Corrective letter to health professionals
Pfizer	Xeljanz (tofacitinib citrate)	Promotional banner at trade display	$25,000 fine Materials not to be used again
Bayer	Xarelto (rivaroxaban)	Promotional material	$150,000 fine Clinical Paper Carrier not to be used again Corrective letter to health professionals
Eli Lilly	Taltz (ixekizumab)	Professional conduct	$15,000 fine

REFERENCES

1. Medicines Australia. Code of Conduct. 18th ed. 2015. https://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-current-edition [cited 2020 Nov 1]
2. Medicines Australia. Code of Conduct. 19th ed. 2019. https://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-current-edition [cited 2020 Nov 1]
3. Medicines Australia. Code of Conduct Annual Report 2019–2020. https://medicinesaustralia.com.au/code-of-conduct/code-of-conduct-reports [cited 2020 Nov 26]

New label advice for antibiotics

Aust Prescr 2020;43:211
https://doi.org/10.18773/austprescr.2020.072

The label attached by pharmacists to antibiotic packaging has previously advised patients to continue taking the antibiotics until they are all finished. This advice has been in line with the approved product information. However, this advice may have contributed to the excessive use of antibiotics and antibiotic resistance. There is now awareness that the required duration of treatment may need a smaller quantity of antibiotic than the pack that is supplied to the patient.[1,2]

In consultation with other organisations, the Pharmaceutical Society of Australia has revised the cautionary advisory label used by pharmacists for antibiotics. It will now state, 'Take for the number of days advised by your prescriber.'

As a consequence of this change there are several important messages for prescribers and pharmacists:

- Prescribers should include the expected duration of therapy on the prescription and communicate the duration of therapy to the patient at the time of prescribing.
- Including a repeat for an antibiotic on the prescription by default is generally not appropriate.
- Pharmacists should confirm that the patient understands the prescribed duration of therapy. If the duration of therapy is not communicated on the prescription, and the patient does not know, the pharmacist should contact the prescriber to confirm the duration of therapy.
- Pharmacists should not dispense a repeat prescription for an antibiotic without first clarifying clinical appropriateness.
- Prescribers and pharmacists should make patients aware that the advice to take the antibiotics for the prescribed duration of therapy may be inconsistent with the advice that is currently in Consumer Medicine Information for the antibiotic.
- Patients should be advised to take any 'leftover' antibiotics back to the pharmacy for disposal.

The new label is expected to be used from January 2021.

REFERENCES

1. McGuire TM. Does size matter? Addressing pack size and antibiotic duration. Aust Prescr 2019;42:2–3. https://doi.org/10.18773/austprescr.2019.005
2. Wilson HL, Daveson K, Del Mar CB. Optimal antimicrobial duration for common bacterial infections. Aust Prescr 2019;42:5–9. https://doi.org/10.18773/austprescr.2019.001

NEW DRUGS

New drugs

Dinutuximab beta

Aust Prescr 2020;43:212–3
https://doi.org/10.18773/austprescr.2020.068
First published 22 October 2020

Approved indication: neuroblastoma

Qarziba (EUSA Pharma)
vials containing 20 mg as concentrate

Neuroblastoma is an extracranial childhood cancer. While it accounts for about 12% of cancer deaths in children, some neuroblastomas regress spontaneously. Cases are classified according to prognostic factors such as age and the stage of the disease. Children with high-risk neuroblastomas have a poor prognosis. Treatment can include surgery, radiotherapy, high-dose chemotherapy and stem-cell transplants. For children who survive, isotretinoin has been used as a maintenance therapy.

Neuroblastomas express an antigen called disialoganglioside 2 (GD2). This prompted research into whether immunotherapy could have a role in treatment. An antibody called ch14.18 was found to have a cytotoxic effect against cells expressing GD2. This antibody can be produced by different methods. Dinutuximab beta is a form of ch14.18 recloned using Chinese hamster ovary cells.

The antibody is given in five consecutive cycles of 35 days duration. Dinutuximab beta is diluted in a solution of sodium chloride and albumin. It can be infused over eight hours on the first five days of each treatment cycle or given as a continuous infusion for the first 10 days. The maximum plasma concentration is reached on the last day of the infusions. Dinutuximab beta is then broken down like other antibodies. It has a half-life of eight days. Liver and kidney function, and a full blood count should be checked before each infusion.

An analysis of early non-randomised studies of ch14.18, after initial treatment of metastatic neuroblastoma, assessed the outcomes for 166 children who received the antibody. They were compared with 99 given maintenance therapy and 69 children given no additional therapy. This univariate analysis found that overall survival after three years was 68.5% in the antibody group, 56.6% in the maintenance group and 46.8% in the untreated group. However, there was uncertainty about the difference between these therapies depending on which statistical analysis was used.[1]

A phase III trial randomised 226 children with high-risk neuroblastoma which had responded to induction therapy and stem cell transplantation.[2] A group of 113 then received an immunotherapy regimen of the ch14.18 antibody with interleukin 2, granulocyte-macrophage colony-stimulating factor (GM-CSF) and isotretinoin. The other 113 patients were treated with isotretinoin alone. After a median follow-up of 2.1 years the trial was stopped early because of emerging differences in survival. Event-free survival at two years was estimated to be 66% with immunotherapy and 46% with isotretinoin alone. The estimated rates of overall survival were 86% and 75%.[2]

It was uncertain which components of the immunotherapy regimen were effective. Another phase III trial of 406 patients therefore compared treatment with dinutuximab beta, interleukin 2 and isotretinoin to treatment with dinutuximab beta and isotretinoin. In effect, this trial was assessing whether including interleukin 2 in the regimen improved outcomes for patients with high-risk neuroblastoma.[3] The patients in the trial had received chemotherapy, stem cell transplant and radiotherapy. Their median age was around three years. The median follow-up was 4.7 years during which the children were monitored for events such as relapse, progressive disease or death. When assessed at three years, the event-free survival was 60% for the 206 children treated with dinutuximab beta and interleukin 2 compared with 56% for the 200 treated with dinutuximab beta alone. Three-year overall survival was 70% with interleukin 2 and 69% without it. At five years the overall survival was 62% versus 63%.[3]

Children with neuroblastoma have to endure many harmful treatments and dinutuximab beta is no exception. Infusing an antibody can cause severe reactions including anaphylaxis and cytokine-release syndrome. Patients require premedication with antihistamines before each infusion. Premedication is also required for the very common problem of pain. In addition to other analgesics, morphine infusions are required while dinutuximab beta is being delivered. Gabapentin is started three days before each infusion of dinutuximab beta. Pain still occurs in most patients despite giving analgesics. Other very common adverse events include capillary leak syndrome, haematological toxicity, infections, fever and neurological disorders of the eye. Such adverse reactions may require treatment to be interrupted.

While dinutuximab beta is toxic, using it alone results in less toxicity than combining it with interleukin 2. In that trial, serious adverse events which were less frequent

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.

with dinutuximab alone included hypersensitivity, infection, fever and pain.[3] As there was no difference in efficacy, this suggests dinutuximab beta should be used without interleukin 2 in the treatment of high-risk neuroblastoma after chemotherapy. Future research should investigate the optimum stage of the disease to use dinutuximab beta, the most effective regimens and how to reduce toxicity.

TT manufacturer provided additional useful information

REFERENCES

1. Simon T, Hero B, Faldum A, Handgretinger R, Schrappe M, Niethammer D, et al. Consolidation treatment with chimeric anti-GD2-antibody ch14.18 in children older than 1 year with metastatic neuroblastoma. J Clin Oncol 2004;22:3549-57. https://doi.org/10.1200/jco.2004.08.143
2. Yu AL, Gilman AL, Fevzi Ozkaynak M, London WB, Kreissman SG, Chen HX, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010;363:1324-34. https://doi.org/10.1056/nejmoa0911123
3. Ladenstein R, Pötschger U, Valteau-Couanet D, Luksch R, Castel V, Yaniv I, et al. Interleukin 2 with anti-GD2 antibody ch14.18/CHO (dinutuximab beta) in patients with high-risk neuroblastoma (HR-NBL1/SIOPEN): a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1617-29. https://doi.org/10.1016/s1470-2045(18)30578-3

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.

NEW DRUGS

Entrectinib

Aust Prescr 2020;43:214–5
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First published 22 October 2020

Approved indications: non-small cell lung cancer and solid tumours

Rozlytrek (Roche)
100 mg and 200 mg hard capsules

Like crizotinib, entrectinib is an oral tyrosine kinase inhibitor for non-small cell lung cancer. It inhibits the proto-oncogene tyrosine-protein kinase ROS1, tropomyosin receptor kinases (TRK) and anaplastic lymphoma kinase (ALK). These kinases are associated with unconstrained cell proliferation so inhibiting them aims to slow tumour growth. Unlike crizotinib, entrectinib can cross the blood–brain barrier and so has activity at intracranial sites.

Entrectinib is specifically indicated for:

- adults with ROS1-positive advanced non-small cell lung cancer
- adults and children over 12 years with metastatic or inoperable solid tumours, with a neurotrophic tyrosine kinase (NTRK) gene fusion, that have progressed after treatment or have no alternative therapy (provisional approval only).

The approval of entrectinib for both indications is based on prospective subgroup analyses of three phase I–II, single-arm, open-label trials called ALKA, STARTRK-1 and STARTRK-2. These studies enrolled patients with solid tumours (e.g. sarcoma, non-small cell lung cancer, breast). In a pooled analysis of participants with ROS1-positive advanced non-small cell lung cancer, 77% (41/53) responded to once-daily entrectinib (100–1600 mg) – three had a complete response and 38 had a partial response. Overall, the median duration of response was 24.6 months and median progression-free survival was 19 months. In a subgroup of 23 patients who had central nervous system metastases at baseline, 17 had a partial response.[1]

In a pooled analysis of participants with NTRK-positive tumours, 57% (31/54) responded to entrectinib 600 mg once a day – four had a complete response and 27 had a partial response. The median duration of response was 10 months. In a subgroup of 12 patients who had central nervous system disease at baseline, six had a partial response.[2]

In a safety cohort of 355 patients, the most common grade 3 or 4 adverse events included lung infection (5%), weight gain (7%), dyspnoea (6%), fatigue (5%), cognitive disorders (4.5%), syncope (2.5%), pulmonary embolism (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), sepsis (2.5%), diarrhoea (2%) and urinary tract infection (2.5%). In terms of grade 3 or 4 laboratory abnormalities, the most common were lymphopenia (12%), hyperuricaemia (10%), increased lipase (10%), anaemia (9%), neutropenia (7%), hypophosphataemia (7%) and increased amylase (5.4%). Dose interruptions because of an adverse event occurred in 46% of patients and 9% of patients discontinued treatment because of an event.

The recommended dose of entrectinib is 600 mg once a day. A reduced dose is recommended for paediatric patients depending on their body surface area. Capsules can be taken with or without food. Maximum plasma concentrations are reached 4–6 hours after administration and most of the dose is excreted in the faeces. Lowering the dose or permanently discontinuing entrectinib is recommended for certain adverse events depending on their severity. These include congestive heart failure, central nervous system effects, hepatotoxicity, hyperuricaemia, prolonged QT interval, anaemia or neutropenia and vision disorders.

Dose adjustment is not likely to be required in renal impairment as elimination via the kidneys is negligible. It is also not required in hepatic dysfunction, although patients with severe impairment have not been studied.

Entrectinib is mainly metabolised by cytochrome P450 (CYP) 3A4. Concomitant use of strong or moderate inhibitors of this enzyme (e.g. cannabidiol) can increase entrectinib exposure and are not recommended. If they cannot be avoided, the entrectinib dose should be reduced. CYP3A4 inducers (e.g. rifampicin) should also be avoided as concomitant use can decrease entrectinib concentrations. Drugs that increase gastric pH (e.g. lansoprazole) can also have this effect.

Entrectinib can increase the concentrations of other drugs that are substrates of CYP enzymes (e.g. midazolam) or P-glycoprotein (e.g. digoxin). Medicines that prolong the QT interval are not recommended with entrectinib.

The majority of patients with ROS1- or NTRK-positive tumours seemed to respond to entrectinib. However, it is difficult to quantify this benefit as patient numbers in the trial were low, particularly the paediatric population, and there were no comparators. Overall survival with entrectinib therapy is currently unknown.

Entrectinib is subsidised on the Pharmaceutical Benefits Scheme for patients with ROS1-positive non-small cell lung cancer who have not previously received crizotinib or could not tolerate it.[3] It is important to note that the approval of entrectinib for patients with NTRK-positive tumours is provisional until the Therapeutic Goods Administration receives more data from the sponsor.

T manufacturer provided the product information

REFERENCES

1. Drilon A, Siena S, Dziadziuszko R, Barlesi F, Krebs MG, Shaw AT, et al. Entrectinib in ROS1 fusion-positive non-small-cell lung cancer: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:261-70. https://doi.org/10.1016/s1470-2045(19)30690-4
2. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-82. https://doi.org/10.1016/s1470-2045(19)30691-6
3. Australian Government Department of Health. The Pharmaceutical Benefits Scheme. Entrectinib: capsule 200 mg; Rozlytrek. Public summary document. March 2020 PBAC meeting. www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2020-03/entrectinib-capsule-200-mg-rozlytrek [cited 2020 Sep 29]

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

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

NEW DRUGS

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https://doi.org/10.18773/austprescr.2020.065
First published 22 October 2020

Lorlatinib

Approved indication: non-small cell lung cancer

Lorviqua (Pfizer)
25 mg and 100 mg tablets

The outcomes for patients with non-small cell lung cancer have improved with increased understanding of the genetics of the disease. Genetic rearrangements and mutations result in abnormal kinases. Examples include the c-ros oncogene (ROS1) and anaplastic lymphoma kinase (ALK). About 3–5% of non-small cell lung cancers are ALK-positive. These genetic discoveries led to tyrosine kinase inhibitors being used in treatment. Crizotinib was approved in 2014 for ALK-positive advanced non-small cell lung cancer. It was followed by so-called 'second-generation' drugs such as alectinib and ceritinib. Lorlatinib is a 'third-generation' drug that inhibits the ALK and ROS1 tyrosine kinases.

Lorlatinib can be given orally. It does not need to be swallowed with food but should be taken at the same time each day. The half-life is 24 hours with most of the dose being metabolised by cytochrome (CYP) P450 3A4 and UGT 1A4. Severe hepatotoxity can occur if lorlatinib is taken with strong inducers of CYP3A, such as rifampicin, so these drugs are contraindicated. The risk with moderate inducers is unknown so they should be avoided if possible. Strong inhibitors of CYP3A, such as itraconazole, should also be avoided. The effect of moderate–severe liver disease or severe kidney impairment on the concentrations of lorlatinib is unknown.

A range of doses was tested in an open-label trial. In phase I of the trial lorlatinib was given to 54 patients with locally advanced or metastatic non-small cell lung cancer. Brain metastases were present in 39 patients and 28 patients had already been treated with two or more tyrosine kinase inhibitors. Although tolerability was the main focus of the trial, 42% (11/26) of the previously treated patients with ALK-positive cancer responded to lorlatinib. A single daily dose of 100 mg was chosen for subsequent studies.[1]

In phase II of the trial, 275 patients with metastatic non-small cell lung cancer received lorlatinib. The 228 patients with ALK-positive cancer were divided into groups according to their previous treatment regimens, including 30 patients who had not been previously treated. There was also a group of 47 with ROS1-positive cancer. Across all the groups, 60% of the patients had brain metastases. In the untreated group 90% had an objective tumour response (complete or partial) to lorlatinib. For the 198 patients who had been treated with at least one tyrosine kinase inhibitor, 47% had an objective response. Intracranial responses were seen in 63% (51/81) previously treated patients with measurable lesions in the central nervous system. For all the patients with previously treated ALK-positive cancer, the median progression-free survival was 7.3 months.[2]

A separate analysis of the patients with ROS1-positive cancer reported an objective response to lorlatinib in 41% (28/69). An intracranial response was seen in 12 of the 24 patients with metastases who had been previously treated with crizotinib. Overall, the median progression-free survival was 8.5 months in previously treated patients.[3]

Adverse reactions are common and may require treatment to be reduced or stopped. In the phase II trial, 57% of the patients were able to continue taking lorlatinib for a median of 8.3 months.[2] The most frequent adverse effect is hyperlipidaemia and in many cases this has to be managed with lipid-lowering drugs. Oedema and peripheral neuropathy are also common. Less frequent but serious adverse reactions include interstitial lung disease and atrioventricular block. The most common reason for permanently stopping treatment in the phase II trial was cognitive effects.[2] Patients may also experience altered speech, hallucinations, mood changes and seizures.

As the clinical trials of lorlatinib are ongoing, lorlatinib has been granted a provisional approval in Australia. It is approved for patients with ALK-positive advanced non-small cell lung cancer that has progressed despite treatment. The approval specifies patients who have been treated with alectinib, ceritinib, or crizotinib and at least one other tyrosine kinase inhibitor. Lorlatinib is not approved for ROS1-positive cancer.

With several tyrosine kinase inhibitors now available, future research will need to determine what order to use them in. As 90% of previously untreated patients in the phase II trial had an objective response,[2] it is possible that lorlatinib may come to be used earlier in treatment. However, the response rate is a surrogate outcome and the effect of lorlatinib on overall survival is unknown.

T manufacturer provided the AusPAR and the product information

REFERENCES

1. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. Lancet Oncol 2017;18:1590-9. https://doi.org/10.1016/s1470-2045(17)30680-0

2. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19:1654-67. https://doi.org/10.1016/s1470-2045(18)30649-1
3. Shaw AT, Solomon BJ, Chiari R, Riely GJ, Besse B, Soo RA, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol 2019;20:1691-1701. https://doi.org/10.1016/s1470-2045(19)30655-2

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.

NEW DRUGS

Aust Prescr 2020;43:218–9
https://doi.org/10.18773/austprescr.2020.069
First published 22 October 2020

Polatuzumab vedotin

Approved indication: B-cell lymphoma

Polivy (Roche)
vials containing 140 mg as powder for reconstitution

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma. It can be treated with a combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone, but up to 40% of patients relapse or do not respond. They may then be considered for a stem cell transplant. For patients who are unable to have a transplant, polatuzumab vedotin adds to the options for treatment, such as gemcitabine, rituximab and bendamustine.

Polatuzumab vedotin is a combination of a monoclonal antibody and the cytotoxic drug monomethyl auristatin E (MMAE). The monoclonal antibody is aimed at a component of B-cell receptors called CD79b. This is found on the surface of normal and malignant B-cells. After the antibody binds to CD79b, the linkage with MMAE is cleaved and the cytotoxic drug is released inside the B-cell. MMAE has an antimitotic action and induces apoptosis. A similar combination, brentuximab vedotin, has been approved for Hodgkin lymphoma.

Polatuzumab vedotin has to be given intravenously. After it is reconstituted the drug is diluted and infused. The first infusion is given over 90 minutes. If this is well tolerated, subsequent infusions can be given over 30 minutes. Most of the MMAE in the circulation is conjugated to the antibody. This conjugated form has a half-life of about 12 days. The antibody is expected to be catabolised like other proteins with most of the dose probably being eliminated in the faeces. Unconjugated MMAE is a substrate for cytochrome P450 3A4 so inhibitors and inducers of this enzyme could change the concentrations of MMAE. There are limited data about the effect of liver or kidney disease on the pharmacokinetics of polatuzumab vedotin.

There is also limited information about the effectiveness of polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. The main study of patients who were ineligible for a transplant was an open-label, phase II trial of 80 people.[1] Forty patients were randomised to treatment with polatuzumab vedotin plus bendamustine and rituximab, while the other 40 received bendamustine and rituximab. The polatuzumab vedotin regimen was an infusion every 21 days for up to six cycles. Positron emission tomography identified a complete response in 16 patients compared with seven patients who responded to bendamustine and rituximab. After a median follow-up of 22.3 months, the progression-free survival for the three-drug regimen was 9.5 months versus 3.7 months for bendamustine and rituximab. Adding polatuzumab vedotin reduced the risk of death – median overall survival was 12.4 months compared with 4.7 months for bendamustine and rituximab.[1]

As CD79b is not limited to cancer cells, adding polatuzumab vedotin to bendamustine and rituximab increases toxicity. Myelosuppression is very common and may require treatment to be reduced or stopped. Patients can develop febrile neutropenia, and infections, such as pneumonia, are very common. These infections may be fatal. Peripheral neuropathy is a frequent adverse effect possibly because of the action of unconjugated MMAE in the circulation. This can be another reason to reduce or stop treatment.

Other adverse events that are more frequent when polatuzumab vedotin is added to bendamustine and rituximab include diarrhoea, fever, reduced appetite, hypokalaemia, hypoalbuminaemia and hypocalcaemia. In addition to monitoring the patient's blood count, liver function should be checked as there is a risk of hepatotoxicity. Approximately one third of patients will have an infusion-related reaction. Every patient should be given an antihistamine and an antipyretic before each infusion.

The median survival for patients who have refractory disease or have relapsed and cannot have a stem cell transplant is approximately six months. On the evidence available survival is improved if polatuzumab vedotin is added to bendamustine and rituximab. However, this needs to be confirmed in a larger trial. There have been concerns that the 40 patients given polatuzumab vedotin in the phase II trial had more favourable prognostic factors at baseline than patients in the other group. Treatment will inevitably include managing the serious adverse effects. In the phase II trial 33% of the patients discontinued treatment because of adverse events, compared with 10% of those treated with bendamustine and rituximab. The adverse events were fatal for approximately 23% of the patients taking polatuzumab vedotin with bendamustine and rituximab versus 28% of those taking bendamustine and rituximab.[1]

T manufacturer provided the product information

REFERENCES

1. Sehn LH, Herrera AF, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol 2020;38:155-65. https://doi.org/10.1200/jco.19.00172

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ARTICLE

Updated Australian guidelines for mild asthma: what's changed and why?

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Keywords
asthma, budesonide–formoterol, corticosteroids

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SUMMARY

The Australian asthma guidelines have recently been updated and include additional treatment options for adults and adolescents with mild asthma.

Mild asthma is not necessarily a benign condition and patients are still at risk of severe flare-ups, particularly if they overuse short-acting beta$_2$ agonists such as a salbutamol inhaler.

For adults and adolescents with mild asthma, the updated guidelines include as-needed inhaled low-dose budesonide–formoterol as an alternative to daily low-dose inhaled corticosteroid plus as-needed short-acting beta$_2$ agonist.

The budesonide–formoterol combination should be taken as needed to provide symptom relief and reduce the risk of severe exacerbations.

Introduction

A recent update to Australian asthma guidelines was launched in September 2020 (version 2.1).[1] It provides evidence-based, practical online guidance for health professionals, particularly in primary care. The 2020 updates focus on expanded options for the treatment of mild asthma in adults and adolescents. Key changes have been made around the rationale and evidence for management options, and the factors to consider in shared decision making.

Many adults and adolescents with asthma (50–70%) have mild disease, that is an estimated 1.1–1.6 million Australians. Asthma is classified as mild if it can be well controlled with a short-acting beta$_2$ agonist (SABA) such as salbutamol, or a low-dose inhaled corticosteroid (ICS). From the perspective of patients and clinicians, asthma is usually regarded as mild if symptoms are infrequent or quickly relieved by a salbutamol inhaler, with little interference on their day-to-day life. These patients may not even seek medical advice since in Australia salbutamol inhalers can be purchased over-the-counter. In a large Australian population survey, 39% of asthma patients (aged ≥16 years) had not used a preventer inhaler in the previous year. Almost half of these usually bought relievers over-the-counter.[2]

Mild asthma is not necessarily benign

In the past, it was thought that mild asthma was of little concern, and that treating it with as-needed SABAs for symptom relief and an occasional course of oral corticosteroids was a simple and inexpensive therapeutic strategy. However, patients with mild asthma are still at risk of severe exacerbations, particularly if they overuse SABAs. Overuse is generally defined as dispensing of three or more canisters of salbutamol in a year (an average of 1.6 or more puffs per day). This is associated with a doubling of the risk of emergency department presentation[3] and an increased risk of asthma death.[4] Approximately 15% of asthma deaths occur in patients with apparently mild asthma.[5]

The risk of a severe flare-up can be reduced by half (or more) with daily low-dose ICS, for example fluticasone propionate ≤200 microgram/day or budesonide ≤400 microgram/day. There is no evidence of adverse effects at these doses. However, patients are rarely adherent with this therapy, and poor adherence is associated with an increased risk of severe flare-ups requiring oral corticosteroids.[6]

In the past, an occasional course of oral corticosteroids was considered acceptable, but as few as four or five lifetime courses of oral corticosteroids are associated with an increased risk of adverse effects such as osteoporosis, pneumonia, cataracts and diabetes.[7] To mitigate these risks, clinicians from the Global Initiative for Asthma (GINA) initiated clinical trials that have culminated in evidence-based changes to global, and now Australian, treatment options for mild asthma.[8]

Low-dose budesonide–formoterol

Australian asthma guidelines now include as-needed inhaled low-dose budesonide–formoterol (eformoterol) for patients with mild asthma. Budesonide is an ICS and formoterol is a quick-onset long-acting beta$_2$ agonist (LABA). This combination gives rapid symptom relief and also reduces the risk of severe exacerbations. It provides an alternative to regular daily low-dose ICS plus an as-needed SABA (see Level 2 of treatment in Fig.)

What does 'as-needed' mean?

Patients should use the low-dose budesonide–formoterol inhaler in the same way as a salbutamol inhaler. This means they should use it as needed to relieve asthma symptoms, or when they are going to encounter a known trigger (e.g. allergen, exercise). If their asthma symptoms increase, they should take more doses to relieve the symptoms. It is extremely important to explain the meaning of 'as-needed' with this new approach as it is different from the way patients typically use a preventer inhaler.

Which inhalers can be used and how often?

For mild asthma, as-needed budesonide–formoterol can only be prescribed with the following inhalers:

- Dry powder inhaler (Symbicort Turbuhaler 200/6 or DuoResp Spiromax 200/6 containing budesonide–formoterol 200/6 micrograms). The patient should take one inhalation when needed for symptom relief, or before exposure to known triggers. If symptoms persist after a few minutes, they can take an additional inhalation. No more than six inhalations should be used on any single occasion, and no more than 12 in a day.
- Pressurised metered dose inhaler (Symbicort Rapihaler 100/3 containing budesonide–formoterol 100/3 micrograms). The patient should take two separate puffs when needed, as described above, with no more than 12 puffs on a single occasion, and no more than 24 in a day.

The choice of inhaler will depend on patient preference and confirmation that they are able to use the inhaler correctly. However, of the two dry powder inhalers, Symbicort Turbuhaler 200/6 is approved for adults and adolescents aged 12 years and over, whereas the DuoResp Spiromax 200/6 is only approved for adults 18 years and over. The Symbicort Rapihaler 100/3 is approved for adults and adolescents.

Before prescribing one of these inhalers, always check that the patient can use the inhaler correctly. Videos on how to use inhalers are available.

Patients should be advised that they do not need to rinse and spit out after taking as-needed doses of budesonide–formoterol. This recommendation is supported by safety data from studies in more than 30,000 patients, with no increase in risk of candidiasis or hoarse voice. However, patients prescribed maintenance ICS only or ICS–SABA are still advised to rinse and spit out after their maintenance doses.

Budesonide–formoterol 400/12 dry powder inhaler and 200/6 pressurised metered dose inhaler should not be used as reliever inhalers because the dose of formoterol would escalate too quickly when extra doses were taken.

Other ICS–LABA combinations also cannot be used for symptom relief, either because the onset of action of the LABA is too slow (e.g. fluticasone propionate–salmeterol), or the inhaler is approved only for once-daily use (e.g. fluticasone furoate–vilanterol).

How does as-needed budesonide–formoterol work?

First, although formoterol is a LABA, it has a rapid onset of action, and the combination of an ICS and formoterol reduces symptoms and bronchoconstriction as quickly and as effectively as a SABA alone, so it can be used for symptom relief. This has been recommended for more than 10 years as the reliever in 'maintenance and reliever therapy' (MART) at Levels 3–4 of asthma treatment (see Fig.).[9]

Second, a rapid increase in doses of both budesonide and formoterol as soon as symptoms increase, even on a single day, reduces the risk of progression to a severe flare-up over the following days or weeks compared to using a salbutamol inhaler alone.[10,11]

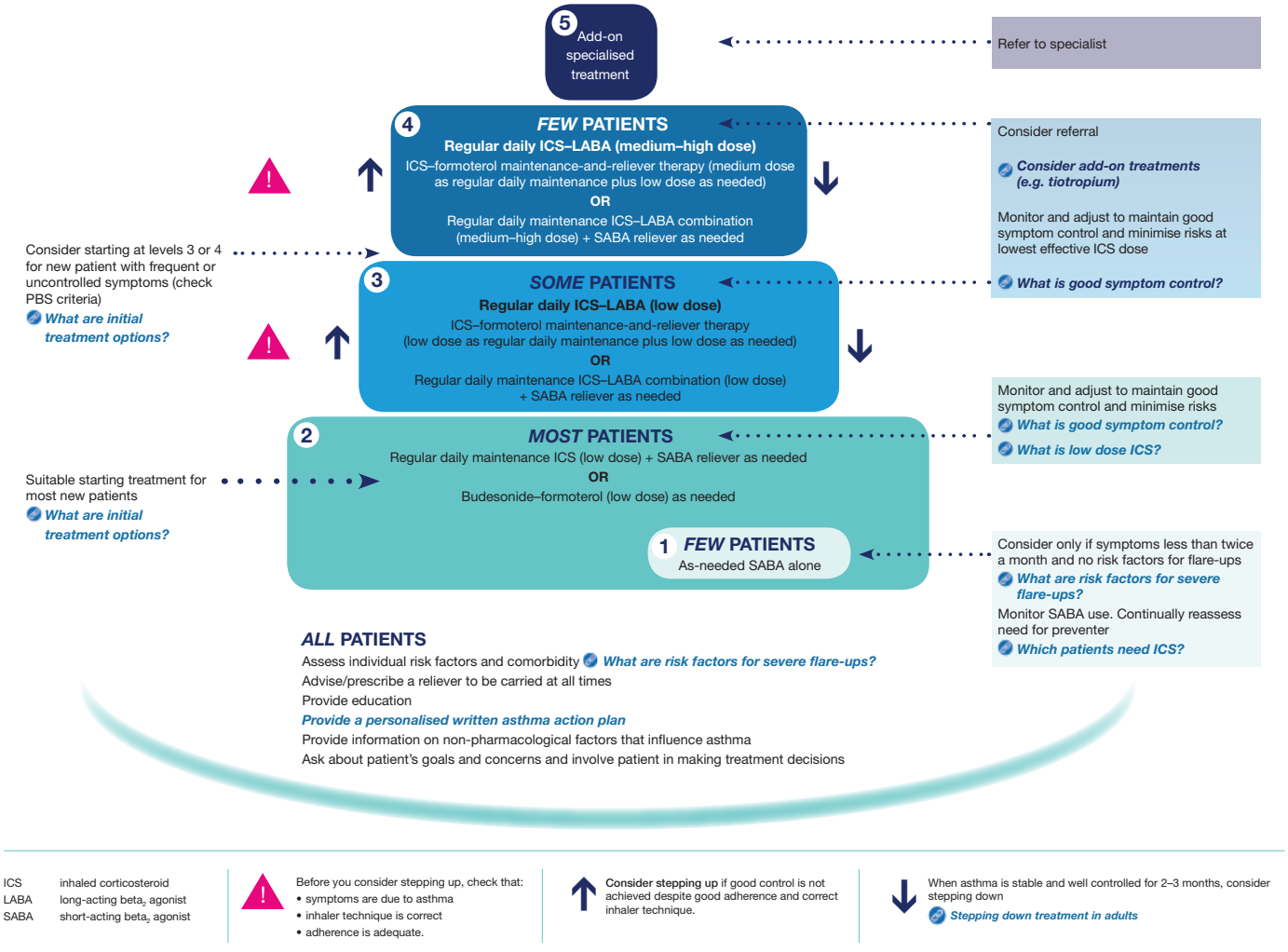
Third, not all exacerbations are inflammatory, so using an inhaler providing both an ICS and more stable bronchodilatation treats both types of flare-ups.

How strong is the evidence for the new recommendations?

The new recommendations are supported by high-quality evidence from five clinical trials totalling approximately 10,000 patients. Participants had mild asthma and were eligible for Level 2 treatment, either by taking a SABA alone, or with well- or partly controlled asthma on Level 2 treatment (low-dose ICS, or montelukast). Patients with very poorly controlled asthma were not included as they should receive Level 3 treatment (see Fig.). Two 12-month studies in participants aged ≥12 years were double-blind regulatory studies in patients previously taking either SABA alone or ICS or montelukast.[12,13] A further two 12-month studies in adults were more pragmatic open-label studies with patients using the as-needed inhaler as they would in real life.[14,15] In one of these studies all patients were previously using SABA alone[14] and in the other, 70% were previously using low–medium-dose ICS.[15]

The main focus of the studies was on the risk of severe flare-ups, since symptoms are not burdensome for most patients with mild asthma. Importantly, as-needed low-dose budesonide–formoterol reduced the risk of severe flare-ups requiring oral corticosteroids or emergency care by 64–65% compared with SABAs alone.[12,14] This effect was the same,[12,13] or better,[14,15] than regular ICS plus an

Fig. **Selecting and adjusting asthma medication for adults and adolescents**



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as-needed SABA. A recent meta-analysis of all four studies found that as-needed budesonide–formoterol reduced the risk of emergency department visits for asthma by 35% compared with regular ICS plus as-needed SABA.[16]

Symptom control, lung function and asthma-related quality of life were slightly better with daily ICS than with budesonide–formoterol in three studies. However, these differences were not large enough to be felt by the patients and did not become cumulatively worse over 12 months.[12-14] With budesonide–formoterol use averaging 3–4 times a week, airway inflammation (measured by exhaled nitric oxide) was significantly reduced and did not worsen over 12 months.[14,15] These benefits were achieved with a very low budesonide dose (median approximately 60–100 microgram/day).

Another study in patients with mild asthma found that as-needed budesonide–formoterol taken for symptom relief, and before exercise, reduced exercise-induced bronchoconstriction to the same extent as daily ICS with an as-needed SABA.[17] This means that patients prescribed as-needed budesonide–formoterol do not need to be prescribed a SABA for pre-exercise use.

Established options for mild asthma treatment remain

Regular ICS plus an as-needed SABA is still a very effective and safe treatment for mild asthma. It reduces severe flare-ups by more than half, even in patients with infrequent symptoms. However, before prescribing this, explain the importance of taking the ICS every day as patients who do not are at greater risk of severe flare-ups.

Which treatment for which patient?

Adults and adolescents with a diagnosis of asthma who are currently using a salbutamol inhaler alone are suitable for as-needed low-dose budesonide–formoterol or a regular ICS plus as-needed SABA (Level 2 treatment). This is unless their asthma is very poorly controlled (e.g. they need their reliever inhaler more than twice a day) or they have low lung function.

As-needed low-dose budesonide–formoterol is also suitable for patients whose asthma is well controlled with regular low-dose ICS. This is much safer than stepping down to a SABA alone.

In mild asthma, unlike in severe asthma, patients do not need to be 'phenotyped'. As-needed budesonide–formoterol reduces severe exacerbations compared with regular ICS or SABA alone, and with similar symptom control. This is regardless of whether the patient does or does not have 'type 2' inflammation (blood eosinophils or exhaled nitric oxide).[14,15]

Treatment with a salbutamol inhaler alone should only be considered if patients have symptoms less than twice a month and have no risk factors for exacerbations (e.g. smoking) or have not had an exacerbation in the previous year. There have been no studies of any asthma treatment in patients with symptoms less than twice a month.

Cost to the patient is often important. For as-needed budesonide–formoterol, with the usage seen in clinical trials (median 3–4 doses/week), the average monthly cost to the patient can be as little as one-sixth of that for a daily low-dose preventer, depending on the specific ICS.[18]

Other updates in the 2020 Australian asthma guidelines

More asthma medicines have been added to the 2020 guidelines including:

- once-daily fluticasone furoate 50 microgram for children aged ≥5 years and for adults and adolescents whose ICS dose can be tapered
- beclomethasone–formoterol 100/6 microgram inhaler for maintenance therapy in moderate–severe asthma. This medicine is not yet listed on the Pharmaceutical Benefits Schedule
- dupilumab (anti-interleukin-4-receptor) injectable add-on therapy for severe type 2 asthma. This adds to the three existing monoclonal antibodies (benralizumab, mepolizumab and omalizumab) approved for severe asthma in Australia. Their use requires specialist referral. Dupilumab is not yet listed on the Pharmaceutical Benefits Schedule.

Conclusion and recommendations

When considering the new asthma guidelines, it is important to remember the basics of asthma management:

- Confirm the diagnosis of asthma.
- Involve patients in shared decision-making and self-management education.
- Prescribe an ICS-containing treatment for almost all patients with asthma to control symptoms and reduce the risk of severe flare-ups. Consider treatment with SABA alone only if patients have asthma symptoms less than twice a month and no history of a flare-up in the past year.
- For patients with mild asthma, a new treatment option is as-needed low-dose budesonide–formoterol. This is much safer than SABA-only treatment and is as effective as maintenance ICS without the need to take daily treatment.
- Avoid over-reliance and overuse of salbutamol inhalers.
- Review and adjust treatment periodically – do not 'set and forget'.
- Check and correct inhaler technique and adherence at every opportunity.
- Provide a written asthma action plan for every patient. The National Asthma Council action plan library includes simple fillable Australian-designed action plans for patients prescribed budesonide–formoterol maintenance and reliever therapy or reliever-only therapy (including Turbuhaler action plan and Rapihaler action plan). It also provides conventional action plans. ◀

Helen Reddel or her institute have received honoraria for providing independent advice in advisory boards/steering committees for – AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and Novartis; for an international data safety monitoring board for AstraZeneca, GlaxoSmithKline, Merck, and Novartis; consulting for AstraZeneca and GlaxoSmithKline; and for providing independent medical education at symposia funded by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mundipharma, Novartis and Teva. Helen Reddel's institute has received unrestricted research grants from AstraZeneca, GlaxoSmithKline and Novartis.

Helen Reddel was one of four members of the Global Initiative for Asthma (GINA) who, from 2007 onwards, made multiple applications to industry and to government agencies for randomised controlled trials of as-needed inhaled corticosteroids–formoterol to reduce the risk of severe exacerbations in mild asthma. When

AstraZeneca eventually agreed to conduct two such studies, she was a member of the steering committee for these studies. Helen Reddel was also a member of the steering committee for two additional randomised controlled trials of this regimen, sponsored by the Health Research Council of New Zealand.

Helen Reddel is Chair of the GINA Science Committee, and a member of the National Asthma Council Guidelines Committee. As all members of the GINA Science Committee and several members of the Australian Asthma Handbook Guidelines Committee are active asthma researchers, the corresponding Boards of Directors conducted a detailed review of processes for handling of potential conflicts of interest, before the above studies were reviewed by the relevant committees.

REFERENCES

1. National Asthma Council Australia. Australian Asthma Handbook. Version 2.1. Melbourne: National Asthma Council Australia; 2020. http://www.asthmahandbook.org.au [cited 2020 Oct 27]
2. Reddel HK, Ampon RD, Sawyer SM, Peters MJ. Risks associated with managing asthma without a preventer: urgent healthcare, poor asthma control and over-the-counter reliever use in a cross-sectional population survey. BMJ Open 2017;7:e016688. https://doi.org/10.1136/bmjopen-2017-016688
3. Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol 2012;109:403-7. https://doi.org/10.1016/j.anai.2012.08.014
4. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J 2020;55:1901872. https://doi.org/10.1183/13993003.01872-2019
5. Dusser D, Montani D, Chanez P, de Blic J, Delacourt C, Deschildre A, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. Allergy 2007;62:591-604. https://doi.org/10.1111/j.1398-9995.2007.01394.x
6. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J 2015;45:396-407. https://doi.org/10.1183/09031936.00075614
7. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. J Asthma Allergy 2018;11:193-204. https://doi.org/10.2147/JAA.S176026
8. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management: treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J 2019;53:1901046. https://doi.org/10.1183/13993003.01046-2019
9. Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and long-acting beta-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. JAMA 2018;319:1485-96. https://doi.org/10.1001/jama.2018.2769
10. Buhl R, Kuna P, Peters MJ, Andersson TL, Naya IP, Peterson S, et al. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. Respir Res 2012;13:59. https://doi.org/10.1186/1465-9921-13-59
11. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zheng J, Gustafson P, et al. Effect of a single day of increased as-needed budesonide-formoterol use on short-term risk of severe exacerbations in patients with mild asthma: a post-hoc analysis of the SYGMA 1 study. Lancet Respir Med. Epub 2020 Oct 1. https://doi.org/10.1016/s2213-2600(20)30416-1
12. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med 2018;378:1865-76. https://doi.org/10.1056/NEJMoa1715274
13. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. N Engl J Med 2018;378:1877-87. https://doi.org/10.1056/NEJMoa1715275
14. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al.; Novel START Study Team. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med 2019;380:2020-30. https://doi.org/10.1056/NEJMoa1901963
15. Hardy J, Baggott C, Fingleton J, Reddel HK, Hancox RJ, Harwood M, et al.; PRACTICAL study team. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet 2019;394:919-28. https://doi.org/10.1016/S0140-6736(19)31948-8
16. Hatter L, Bruce P, Braithwaite I, Holliday M, Fingleton J, Weatherall M, et al. ICS-formoterol reliever versus ICS and SABA reliever in asthma: a systematic review and meta-analysis. ERJ Open Research 2020; in press. https://doi.org/10.1183/23120541.00701-2020
17. Lazarinis N, Jørgensen L, Ekström T, Bjermer L, Dahlén B, Pullerits T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. Thorax 2014;69:130-6. https://doi.org/10.1136/thoraxjnl-2013-203557
18. Reddel HK, Lembke K, Zwar NJ. The cost of asthma medicines. Aust Prescr 2018;41:34-6. https://doi.org/10.18773/austprescr.2018.011

Correction

Prescribing medicinal cannabis [Correction]

Aust Prescr 2020;43:225
First published 9 October 2020
https://doi.org/10.18773/austprescr.2020.073

The Table in the medicinal cannabis article by Jonathon Arnold et al. (Aust Prescr 2020;43:152-9) has been amended to clarify Queensland's requirements for prescribing Schedule 8 medicinal cannabis products. View corrected article.

In the 'Documents required' section of the Table, the QLD State Health application cell should have read "No – unless a drug-dependent person" (not "Done simultaneously via TGA online portal").

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 False

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