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CONTENTS

EDITORIAL

# Guidelines: innovation needed to overcome barriers to use

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clinical decision making, clinical decision support, guidelines

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Medical information continues to increase at an accelerating rate, and there are challenges with keeping up to date with this information which can be conflicting at times. This can be exacerbated in specialities such as general practice, where a GP must have good working knowledge of about 160 conditions to manage 85% of presentations, as shown in an Australian study.[1] Clinical guidelines can be helpful in this context and have the capacity to assist decision making, reduce variation in care and support quality improvement activities.[2] They do not replace clinical judgement. Instead, their application must be individualised to each patient, as they may not be appropriate for all patients.

Despite the stated benefits of guidelines, they are underused. Cardiovascular disease is a clear case in point. Over one million Australians have cardiovascular disease, and 25% of deaths in Australia in 2019 were related to this condition.[3] National clinical guidelines exist to facilitate primary and secondary prevention, yet only about half of all people with established cardiovascular disease are prescribed guideline-recommended treatments.[4] This number is even lower for those at high cardiovascular risk who are yet to have their first cardiac event.[4]

It is evident that the provision of guidelines on their own is not enough to change practice. While significant amounts of time, effort and money often underpin guideline development, these are not always mirrored by an investment in implementation, which is influenced by factors related to patients, politics, health organisations and clinicians.[5] In the Australian general practice setting, some of these factors that make guidelines difficult to use at the point of care include:

- the application of disease-specific clinical guidelines in the context of multimorbidity
- a lack of alignment between guidelines and funding mechanisms, such as the Pharmaceutical Benefits Scheme
- the development of some guidelines relying on health foundations and colleges that may have limited funding for updates and implementation, in contrast to countries like the United Kingdom with centralised, government-funded guidelines
- multiple guidelines for the same condition that have conflicting recommendations
- a lack of trust in guidelines where there are apparent conflicts of interest
- the applicability of guidelines to local primary care settings
- the costs of accessing subscription-based clinical guidelines
- the housing of guidelines and clinical resources on different platforms and websites
- variations in the format and length of guidelines.

Recognising the challenges in applying guidelines into practice has seen the introduction of more user-friendly flow diagrams and primary care-specific abbreviated guidelines by some groups. Some examples include the Kidney Health Australia Chronic Kidney Disease Management Handbook[6] and summaries in the Therapeutic Guidelines.[7] The implementation of these guidelines could be further realised by harnessing innovation to progress from the passive publication of guidelines to active clinical decision support. This is likely to achieve benefits by moving away from the reliance on clinicians making the decision to search for information to the active provision of key information at the point of care.

Australian general practices were early adopters of electronic medical records in the 1990s, with near universal computerisation by 2006.[8] The data recorded can be harnessed to facilitate personalised clinical decision support and translate research and clinical guidelines into practice. Concerns have been raised about limitations associated with the suboptimal quality of data entry in electronic medical records. However, there is an opportunity to develop methods that account for this and to motivate changes in recording behaviour to standardise data entry if the tools have clinical value.[9]

Electronic clinical decision support can assist the performance of health professionals,[10,11] and is more likely to be effective if the advice is provided automatically, on a screen, with patient-specific suggestions, and in combination with other strategies such as the involvement of key opinion leaders and use of educational sessions.[12] This may be facilitated by the development of a community of practice, in which knowledge can cross boundaries between general practices and health services, promoting the standardisation of practice and facilitating innovation.[13]


This article is peer-reviewed

The Royal Australian College of General Practitioners has released a position statement on electronic clinical decision support, identifying opportunities to facilitate the incorporation of treatment guidelines and recommendations, and to improve efficiency through the provision of information that incorporates safety and cost benefits.[14] Clinical decision support features prominently in the government's 10-year primary care plan, with a longer-term aim that 'Clinical decision support tools are supporting best practice in prescribing, point-of-care testing, requests for pathology and diagnostic imaging, safe use of medicines, genomics and virtual care technologies'.[15] The key to achieving this vision is the development of standards and software interoperability.

While standards and interoperability are important to provide a strong foundation, the development and implementation of electronic clinical decision support needs investment that extends beyond technical development and focuses on the needs of end users and implementation. A suboptimal design would lead to alerts being overridden, ignored or misinterpreted and can disrupt workflow, resulting in increases in consultation time, cognitive load and physical fatigue.[16] Successful development and implementation will depend on partnerships between clinicians, researchers, guideline developers and the medical software industry, so that any tools that are developed incorporate guidelines that are endorsed and trusted in a way that optimises usability in practice.

Nearly 85% of Australians consult a GP at least annually.[17] Personalised, evidence-based care can optimise their health outcomes, and GPs may benefit from access to the technology and information that can support them to provide this. Trusted guidelines incorporated into the workflow as part of smart clinical decision support may be one piece of the puzzle to achieve this. It will be important to evaluate the impact of such tools on patient outcomes. The 10-year primary care plan provides an opportunity to transform active, embedded clinical decision support from aspiration to reality. ≺

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LETTERS

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

# Letters to the Editor

## Varenicline and Section 19A products for smoking cessation

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Regarding the article Optimal use of smoking cessation pharmacotherapy by Colin Mendelsohn,[1] it should be noted that, due to nitrosamine contamination, varenicline was recalled by its Australian sponsor in 2021, and the date of return is estimated to be in 2023. There are alternative Section 19A approved products available but, as of the time of writing, these are not listed on the Pharmaceutical Benefits Scheme, leaving patients with a significant out-of-pocket cost. Section 19A products are also by definition temporary supply products and liable to becoming unavailable themselves.

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ARTICLE

# Hormonal contraception and mood disorders


## SUMMARY

Hormonal contraception is known to precipitate or perpetuate depression in some patients. The link between oral contraceptive pills and depression relates to the amount and type of progestogen contained in these pills.

Many of the older oral contraceptive pills, which contain ethinylestradiol, are linked to severe mood problems. Newer oral contraceptive pills containing physiological forms of oestrogen may be better tolerated with a purported weaker link to mood problems.

Clinicians should consider the temporal relationship between the use of hormonal contraception and development of new or worsened depression or mood changes.


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**Keywords**
mood, oestrogen, oral contraceptive pill, progesterone, progestogen

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## Introduction

There are several different forms of contraception available for women. Some of these contain progestogen alone and others contain both oestrogen and progestogen.

There are several forms of long-acting progestogen-only contraception available, including levonorgestrel-releasing intrauterine devices, subdermal implants that release etonogestrel, and medroxyprogesterone acetate intramuscular injections. There are also three different types of progestogen-only pills (Table 1).

Combined contraception is available as a vaginal ring, but combined oral contraceptive pills are the most common form of contraception for women of reproductive age. These contain synthetic analogues of oestrogen and progesterone, which prevent pregnancy by acting locally on reproductive organs and centrally impeding the hypothalamic–pituitary–ovarian axis. Typically, the oestrogen component of oral contraceptive pills contains 20–50 micrograms ethinylestradiol, although newer oral contraceptive pills contain physiological forms of oestrogen such as estradiol and estradiol valerate. The progesterone component is usually a 19-nortestosterone derivative, such as desogestrel, etynodiol diacetate, gestodene, levonorgestrel, lynestronol, norethisterone, norethisterone acetate, norgestimate or norgestrel.

The high efficacy and ease of use of oral contraceptive pills make them very popular. However, there are physical and psychological adverse effects. While the physical risks of the oral contraceptive pill are well established,[1] the psychological adverse effects are not as well described.

## Effects of oestrogen and progesterone on mood

Oestrogen and progesterone influence neurochemistry, brain function and the activity of neurotransmitters gamma-aminobutyric acid, serotonin and dopamine.[2] Oestrogen receptors (ER)-alpha and ER-beta are widely distributed in the brain, with ER-alpha mainly found in the hypothalamus, hippocampus, amygdala and brainstem. Progesterone receptors alpha and beta are most abundant in the amygdala, cerebellum, cortex, hippocampus and hypothalamus.

There is evidence to suggest that oestrogen is neuroprotective in the hypothalamus, hippocampus, amygdala and brainstem, protecting the brain from neurodegenerative disease, cognitive decline and affective disorders.[3-5] Functional brain imaging studies have indicated that oestrogen regulates the activation of brain regions implicated in emotional and cognitive processing such as the amygdala and

*Table 1* **Progestogen-only hormonal contraceptives**

| Progestogen | Progestogen content | Brand name |
|---|---|---|
| Levonorgestrel, oral | 30 micrograms | Microlut |
| Levonorgestrel, intrauterine device | 19.5 mg | Kyleena |
| | 52 mg | Mirena |
| Norethisterone, oral | 350 micrograms | Noriday 28 |
| Drospirenone | 4 mg | Slinda |
| Medroxyprogesterone acetate, intramuscular injection | 150 mg | Depo-Provera |

dorsolateral prefrontal cortex.[6] In animals, oestrogen has been shown to modulate neurotransmitters including serotonin,[7] dopamine[8] and noradrenaline in depression,[9] as well as adrenocorticotropic hormone.[10]

Unlike oestrogen, progesterone is not neuroprotective. Progesterone can worsen mood symptoms.[11-13] Plausible links include progesterone augmentation of GABA-induced inhibition of glutamate transmission,[14] and progesterone increasing the concentrations of monoamine oxidase, resulting in decreased serotonin concentrations.[15]

A large study showed a positive association between the use of a levonorgestrel-containing IUD and depression, anxiety and sleep problems in women who did not have these conditions before use of the IUD.[16] There are two formulations of progestogen-releasing IUDs, containing 19.5 mg and 52 mg of levonorgestrel. The former may be more tolerable in terms of mood, as it releases small amounts of levonorgestrel. However, there are no data yet on the relationship between its use and the development or exacerbation of depression.

## Common effects of oral contraceptive pills on mood

There is evidence to suggest that both oestrogen and progesterone influence brain function, which may be responsible for the negative mood changes and depression commonly reported in women taking oral contraceptive pills.[17-19] One of the most common reasons given for the discontinuation of oral contraceptive pills is changes in mood or an increase in depressive symptoms.[20,21] Currently, all oral contraceptive pills may cause mood changes, but the newer oral contraceptive pills containing estradiol or estradiol valerate may be less likely to cause mood changes.

The mechanism underlying how oral contraceptive pills influence mood remains controversial. Nonetheless, there is mounting evidence suggesting a significant relationship between taking oral contraceptive pills and lowered mood and mood disorders such as depression.[20,22-25] A comprehensive review published in 2002 included 13 controlled studies investigating the relationship between mood and oral contraceptive pill use.[26] All but one study found differences in affect between oral contraceptive pill users and non-users. Another pilot study involving 58 women found that current oral contraceptive pill users or recent users had higher subjective and objective depression rates than those of non-users.[27] Moreover, a large Danish study involving more than one million women found an increased risk for first use of an antidepressant and first diagnosis of depression among users of different types of oral contraceptive pills, with the highest rates among adolescents.[11] Furthermore, users of medroxyprogesterone acetate, an injectable progestogen contraceptive, reportedly have greater depressive symptoms than those in non-users.[17] The link between taking oral contraceptive pills and depression may be attributed to the amount and type of progestogen contained in oral contraceptive pills (Table 2).

Given that there is a link between hormonal contraception and negative mood or depression, caution must be taken in women who have a personal or family history of depression. However, oral contraceptive pills may provide relief from depressive symptoms in women with premenstrual dysphoric disorder by stabilising the fluctuations in hypothalamic–pituitary–gonadal steroid production.[28,29] In this disorder, the regular use of an active oral contraceptive pill (without seven days of placebo pills) has an antidepressant effect.

## Emerging research: nomegestrol acetate with 17-beta estradiol

Currently, all available oral contraceptive pills affect mood. We have shown that nomegestrol acetate (1.5 mg) with 17-beta estradiol (2.5 mg) is better tolerated by women with mood disorders.[30] Our pilot study was a single-site clinical follow-up study that assessed the tolerability and subjective mood response to nomegestrol acetate 17-beta estradiol. Based on a sample of 49 women, we showed that women report a positive mood response and reduced self-reported overall DASS-21 score after taking nomegestrol acetate with 17-beta estradiol compared to previously used oral contraceptive pills.[30] Future research with a larger sample is required.

Nomegestrol acetate with 17-beta estradiol is a monophasic preparation with an extended regimen of 24 active pills followed by four placebo pills. The drug can cross the blood–brain barrier, interact with serotonin receptors and regulate cerebral blood flow to the amygdala, dorsolateral prefrontal cortex and many other areas of the brain involved in depression.[31] Women who develop depression soon (usually between 4 and 12 weeks) after taking other oral contraceptive pills (especially older oral contraceptive pills) may better tolerate nomegestrol acetate with 17-beta estradiol. This is consistent with its successful use in clinical practice for the off-label treatment of mood symptoms associated with premenstrual dysphoric disorder.[30]

*Table 2* **Progestogen and oestrogen content of oral contraceptive pills**

| Progestogen | Oestrogen | Quantity* | Brand names |
|---|---|---|---|
| **Levonorgestrel (micrograms)** | **Ethinylestradiol (micrograms)** | | |
| 100 | 20 | | Femme-Tab ED 20/100, Microgynon 20 ED, Microlevlen ED, Loette, Lenest 20 ED, Micronelle 20 ED |
| 150 | 30 | | Femme-Tab ED 30/150, Levlen ED, Microgynon 30 ED, Monofeme, Nordette, Evelyn 150/30 ED, Eleanor 150/30 ED, Micronelle 30 ED, Lenest 30 ED |
| 125 | 50 | | Microgynon 50 ED |
| 50 | 30 | 6 tablets | Logynon ED, Trifeme, Triphasil, Triquilar ED |
| 75 | 40 | 5 tablets | |
| 125 | 30 | 10 tablets | |
| **Norethisterone (micrograms)** | **Ethinylestradiol (micrograms)** | | |
| 500 | 35 | | Brevinor, Norimin |
| 1000 | 35 | | Brevinor-1, Norimin-1 |
| 500 | 35 | 7 tablets | Improvil 28 Day, Synphasic 28 |
| 1000 | 35 | 9 tablets | |
| 500 | 35 | 5 tablets | |
| **Desogestrel (micrograms)** | **Ethinylestradiol (micrograms)** | | |
| 150 | 30 | | Marvelon 28, Madeline |
| **Gestodene (micrograms)** | **Ethinylestradiol (micrograms)** | | |
| 75 | 30 | | Minulet |
| **Drospirenone (mg)** | **Ethinylestradiol (micrograms)** | | |
| 3 | 20 | | Yaz, Yaz Flex |
| 3 | 30 | | Isabelle, Petibelle, Yasmin |
| **Cyproterone acetate (mg)** | **Ethinylestradiol (micrograms)** | | |
| 2 | 35 | | Brenda-35 ED, Carolyn-35 ED, Diane-35 ED, Estelle-35 ED, Jene-35 ED, Juliet-35 ED, Laila-35 ED |
| **Dienogest (mg)** | **Ethinylestradiol (micrograms)** | | |
| 2 | 30 | | Valette |
| **Dienogest (mg)** | **Estradiol valerate (mg)** | | |
| 0 | 3 | 2 tablets | Qlaira |
| 2 | 2 | 5 tablets | |
| 3 | 2 | 17 tablets | |
| 0 | 1 | 1 tablet | |
| 0 | 0 | 2 tablets | |
| **Nomegestrol acetate (mg)** | **Estradiol (mg)** | | |
| 2.5 | 1.5 | | Zoely |

* For products with multiple phases of active ingredients

## Suggestions for prescribing hormonal contraceptives

The initial decision for prescribing involves a discussion with a woman to determine her preference. The woman's age, general health, past contraceptive use and experience, and reliability in terms of daily pill adherence are usually discussed. The woman's mental health should be discussed in detail in view of links between depression and some contraceptives. This is often ignored and unfortunately can lead to poor outcomes in women.[32] Any history of premenstrual depression or depression related to previous contraception should be carefully noted.

Progestogen-only contraceptives should be used with caution in women with current or past depression.[11] However, if there is a major contraindication for oestrogen-containing contraceptives, a low-dose progestogen IUD or barrier contraceptives may be options.

Healthcare practitioners must recognise the impact of gonadal hormones on mental health and validate their patients' observations, thus promoting a good therapeutic relationship. Weight gain and depression appear to be the main issues that drive changing oral contraceptives. Outcomes are likely to improve with shared decision making for the trial of a particular contraceptive, noting that a change may need to be made after approximately three months. Poor outcomes can occur when practitioners deny a woman's observed relationship between depression, anxiety symptoms and the oral contraceptive.

## Conclusion

General community education and better information are urgently needed for primary healthcare practitioners regarding the relationship between oral contraceptive pills and depression. Progestogen-only contraception (Table 1) seems to create a greater propensity for depressive disorders in vulnerable women. Further research is required to determine why some women experience hormone contraceptive-precipitated depression and anxiety, while many women taking hormone contraceptives do not experience mental health issues. It is critical for clinicians to consider the history given by many women of a clear temporal relationship between starting or using a hormone contraceptive and the development of new or worsened depression. In such cases, exploring different types of contraceptives, including barrier methods, is an important patient-validating and therapeutic discussion. ◀

*Conflicts of interest: none declared*

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ARTICLE

# Prescribing for patients taking antiretroviral therapy

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## SUMMARY

Current first-line antiretroviral therapy comprises a combination of drugs that are generally well tolerated. Adverse effects include hypersensitivity reactions, renal and liver toxicity, rhabdomyolysis, hyperlipidaemia, weight gain and neuropsychiatric disorders.

Most drug–drug interactions related to antiretroviral therapy involve drug absorption, metabolism or elimination. Some interactions may increase toxicity or reduce the effectiveness of antiretroviral therapy potentially resulting in treatment failure.

Routinely checking for adverse drug effects and potential drug–drug interactions is an important part of the care of people taking antiretroviral therapy. This includes asking about the patient's use of over-the-counter and complementary medicines.

## Introduction

Antiretroviral therapy is recommended for everyone living with human immunodeficiency virus (HIV) starting from the time of diagnosis. The aim is to suppress the viral load and maintain immune function. A suppressed viral load also prevents HIV transmission.

In Australia, antiretroviral therapy is prescribed by accredited S100 prescribers. GPs may see patients taking antiretroviral therapy and should be aware of the implications for prescribing. These include encouraging adherence to therapy and being alert for adverse effects and drug interactions.

## Antiretroviral therapy

The six main classes of antiretroviral drugs (Table) target various steps in the HIV replication cycle (Fig.) If drugs are used individually, resistance rapidly develops, so antiretroviral therapy is given as a combination of drugs. Most commonly the combination includes a 'backbone' of two nucleoside/nucleotide reverse transcriptase inhibitors plus an integrase strand inhibitor (the preferred initial third drug for most people with HIV), a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor. Entry inhibitors and fusion inhibitors are reserved for when standard treatments have failed.

Two-drug regimens (e.g. dolutegravir/lamivudine or rilpivirine/dolutegravir) are increasingly being used when certain criteria are met. The first long-acting injectable antiretroviral therapy (cabotegravir/rilpivirine) is now available on the Pharmaceutical Benefits Scheme.

Antiretroviral drugs are also used to prevent HIV infection. A regimen for pre-exposure prophylaxis (PrEP) is tenofovir disoproxil fumarate/emtricitabine. For post-exposure prophylaxis tenofovir disoproxil fumarate/emtricitabine can be used with the addition of dolutegravir, raltegravir or rilpivirine for higher risk exposures.

### *Booster drugs*

Some antiretroviral drug combinations include ritonavir or cobicistat to inhibit the cytochrome P450 (CYP) liver enzymes that metabolise protease inhibitors and elvitegravir. This inhibition boosts the plasma concentrations of these antiretroviral drugs, allowing lower doses to be used. As many drugs are metabolised by the CYP system, the pharmacokinetic boosters are particularly prone to cause drug–drug interactions. Before prescribing a new drug for a patient taking antiretroviral therapy, drug interactions should be checked via the University of Liverpool's HIV Drug Interactions website. If there is any doubt, it is best to contact the prescribing doctor or a specialist in HIV medicine as certain drug interactions may lead to a failure of antiretroviral therapy.

## Adverse effects of antiretroviral drugs

The current regimens are generally well tolerated. This is important because adherence to treatment is essential. Some patients may have an increased risk of adverse effects because of comorbidities such as reduced renal function.

### *Nucleoside and nucleotide reverse transcriptase inhibitors*

Nucleoside and nucleotide reverse transcriptase inhibitors are the backbone of today's antiretroviral therapy. They inhibit the reverse transcription of viral RNA to double-stranded DNA (Fig.). The usual


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*Table* **Classes of antiretroviral therapy**

| Antiretroviral class | Comments |
|---|---|
| **Entry inhibitors** | |
| Maraviroc (CCR5 antagonist) | • Not routinely used.<br>• Only indicated for CCR5-tropic strains of HIV. |
| **Fusion inhibitors** | |
| Enfuviritide | • Not routinely used.<br>• Twice daily subcutaneous injections, high rate of injection-site reactions. |
| **Nucleoside and nucleotide reverse transcriptase inhibitors** | |
| Abacavir | • Hypersensitivity reaction, check for HLA-B*5701 allele before prescribing.<br>• Potential increased cardiovascular risk, avoid if cardiovascular risk factors. |
| Lamivudine<br>Emtricitabine | • Also used to treat hepatitis B in combination with tenofovir to avoid the development of hepatitis B virus resistance.<br>• Generally well tolerated. |
| Tenofovir alafenamide | • Can cause renal toxicity – avoid if eGFR <30 mL/min.<br>• Potential weight gain and raised lipids.<br>• Drug interactions with rifampicin, rifabutin, phenytoin and phenobarbital (may reduce exposure to tenofovir).<br>• Used with another drug to treat hepatitis B co-infection. |
| Tenofovir disoproxil fumarate | • Reduced renal function – avoid if eGFR <60 mL/min. Associated with renal tubulopathy and urine phosphate wasting. Monitor renal function.<br>• Avoid nephrotoxic drugs e.g. NSAIDs.<br>• Associated with decreases in bone mineral density and osteomalacia. Avoid in osteoporosis.<br>• Used with another drug to treat hepatitis B co-infection. |
| Zidovudine | • Rarely used now.<br>• Can cause anaemia. |
| **Non-nucleoside reverse transcriptase inhibitors** | |
| Rilpivirine | • Take with a meal for optimal absorption.<br>• Contraindicated with proton pump inhibitors (cause virological failure), $H_2$-receptor antagonists and antacids. Should be dosed separately to rilpivirine.<br>• Adverse effects include raised serum creatinine concentration without an effect on renal function, skin rash, QT prolongation on the ECG, exacerbation of psychiatric symptoms.<br>• Drug interactions with carbamazepine, rifampicin, dexamethasone and St John's wort. Avoid with other drugs that can increase risk of torsades de pointes. |
| Efavirenz | • Rarely used now.<br>• Neuropsychiatric adverse effects are common, e.g. vivid dreams. Avoid if the patient has a history of psychiatric illness. Take on an empty stomach to reduce adverse effects.<br>• Causes raised lipids.<br>• Drug interactions with oral contraception, direct-acting oral anticoagulants (apixiban and rivaroxaban), rendering them ineffective. Avoid with other drugs that can increase risk of torsades de pointes. Reduces methadone concentrations, so may lead to withdrawal symptoms. |
| Nevirapine<br>Etravirine | • Rarely used now.<br>• Nevirapine causes serious and potentially fatal toxicity (hepatotoxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis). Reduces plasma concentrations of direct-acting oral anticoagulants (apixiban and rivaroxaban), rendering them ineffective. |

*Continued over page*

*Table* **Classes of antiretroviral therapy *(continued)***

| Antiretroviral class | Comments |
|---|---|
| **Integrase strand inhibitors** | |
| Bictegravir | • Raised serum creatinine concentration, nil effect on renal function.<br>• Raised creatine kinase.<br>• Concentration decreased by products containing polyvalent cations.*<br>• CYP3A4 and UGT1A1 substrate, potential for drug–drug interactions e.g. with rifampicin. |
| Dolutegravir | • Raised serum creatinine concentration, nil effect on renal function. Hepatotoxicity, raised creatine kinase.<br>• Neuropsychiatric adverse effects.<br>• Concentration decreased by products containing polyvalent cations.*<br>• Interaction with metformin – do not exceed metformin 1 g daily.<br>• Interactions with phenytoin, phenobarbital, rifampicin, St John's wort, carbamazepine. |
| Elvitegravir/cobicistat | • Take with food.<br>• Lots of potential drug interactions due to cobicistat.<br>• Raised lipids.<br>• Raised serum creatine kinase concentration, monitor for myopathy and rhabdomyolysis. |
| Raltegravir | • Depression, suicidal ideation (rare – usually if pre-existing psychiatric conditions). Concentration decreased by products containing polyvalent cations.*<br>• Statins – increased risk of rhabdomyolysis.<br>• Rare cases of severe hypersensitivity reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis). |
| **Protease inhibitors†** | |
| Darunavir | • Absorption is improved with food.<br>• Skin rash, raised serum transaminases, raised lipids, potential cardiovascular risk. |
| Atazanavir | • Absorption depends on food and a low gastric pH. Absorption reduced with proton pump inhibitors which should be avoided. $H_2$-receptor antagonists and antacids should be avoided or dosed apart. Adverse effects include jaundice, indirect hyperbilirubinaemia, cholethiasis, nephrolithiasis and prolongation of the PR interval on the ECG. |
| Indinavir | • Raised lipids. |
| Lopinovir | • Raised lipids. |

* Polyvalent cations include aluminium, calcium, iron, magnesium and zinc.

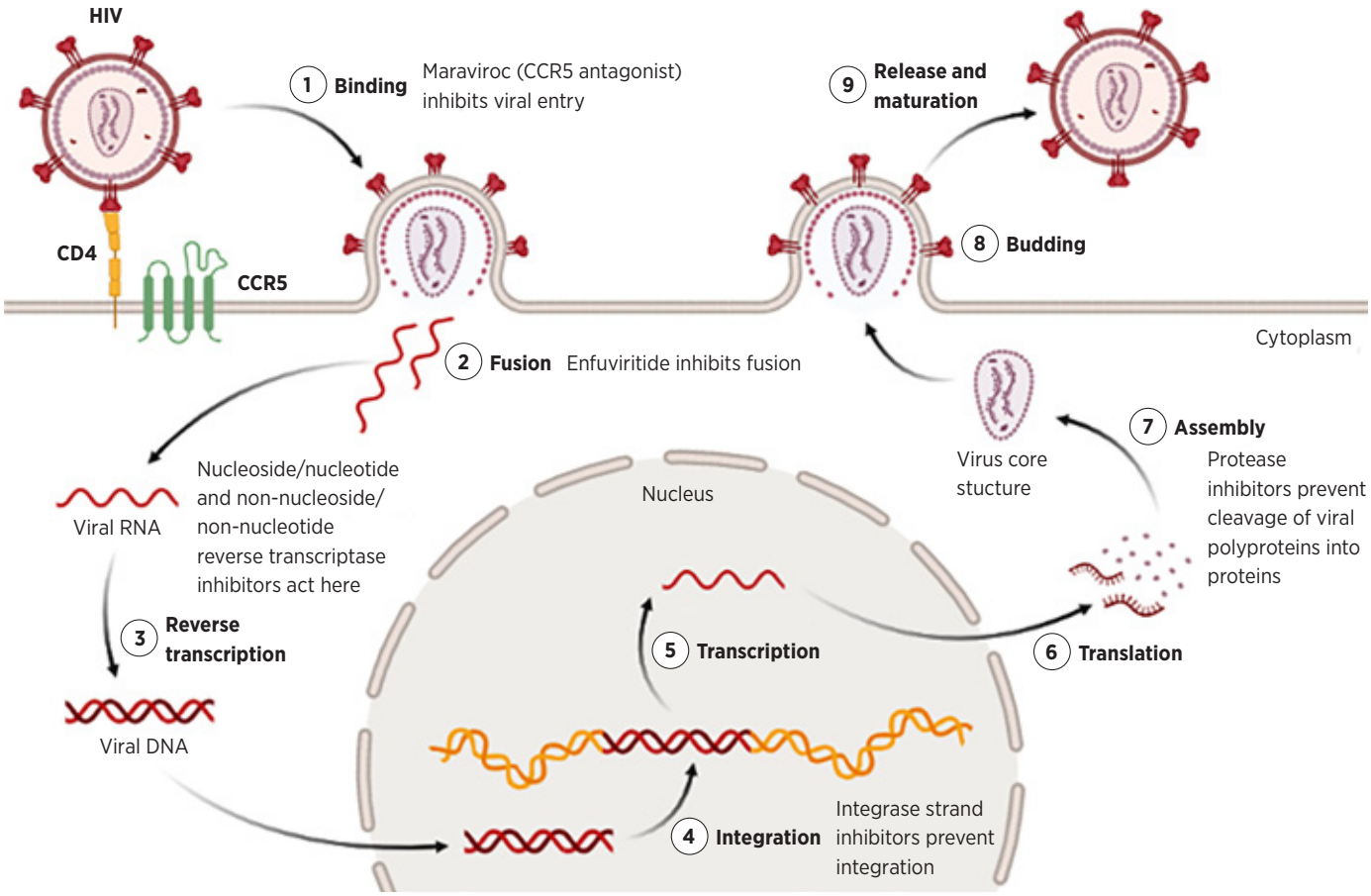
† All protease inhibitors are 'boosted' with either cobicistat or ritonavir which are inhibitors of CYP3A, increasing the concentrations of drugs metabolised through the same pathway. This interaction is seen with statins, phosphodiesterase 5 inhibitors, direct-acting oral anticoagulants, calcium channel blockers, beta blockers and some antiarrhythmic drugs (amiodarone and flecainide). Cushing's syndrome has been reported in patients taking cobicistat or ritonavir with fluticasone, budesonide or mometasone, which are predominantly metabolised by CYP3A enzymes (inhaled, intranasal, intra-articular, topical, and intraocular corticosteroids). Beclomethasone is not metabolised by CYP3A4 and so is suitable to use.

eGFR estimated glomerular filtration rate

NSAIDs non-steroidal anti-inflammatory drugs

CYP cytochrome P450

*Fig.* **Viral replication cycle and sites of antiretroviral therapy action**




HIV primarily infects host immune cells, mainly CD4 T-cell lymphocytes. After successful binding and fusion with the CD4 cell (1,2), the virion's single-stranded RNA is transported to the cell's interior. Here it is reverse transcribed (3) by the viral reverse transcriptase enzyme into double-stranded DNA. This is integrated into the host DNA by viral integrase (4), and then transcribed into RNA (5), which is then translated into viral polyproteins (6) which are cleaved by viral protease. The viral proteins (reverse transcriptase, integrase and protease) are combined with viral genomic RNA and assembled into viral packages (7) which bud from the host cell (8), forming new virions which are released (9) and which then infect other host CD4 cells.

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Adapted from 'HIV Replication Cycle', by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates/t-5f32d8b236677100ac51c32e-hiv-replication-cycle

combinations are abacavir/lamivudine, tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine. Emtricitabine and lamivudine have had fewer reported adverse effects than other nucleotide reverse transcriptase inhibitors.[1-3]

### *Abacavir*

Abacavir can cause a potentially lethal, multisystem hypersensitivity reaction within six weeks of starting treatment.[4] Patients who have the HLA-B*5701 genotype are especially susceptible, so genotypic screening is needed before prescribing abacavir.

Abacavir has been associated with an increased risk of ischaemic cardiovascular events in some cohort studies.[5-8] However, other studies and meta-analyses concluded that abacavir does not confer a higher risk of cardiovascular events compared to regimens without abacavir.[9] While the data remain conflicting and no plausible biological mechanism explains the increased risk, most experts and international guidelines recommend avoiding abacavir in patients with cardiovascular risk factors.[10-12]

### *Tenofovir formulations*

Tenofovir disoproxil fumarate is primarily eliminated by the kidneys. It has been associated with renal toxicity, including Fanconi syndrome manifesting as type 2 renal tubular acidosis and phosphate wasting.[13-15] The drug is not recommended for patients with an estimated glomerular filtration rate (eGFR) below 60 mL/minute. Monitoring of renal function is essential and includes the eGFR, urinalysis for glucose

and protein, and the protein:creatinine ratio. Renal monitoring (six-monthly eGFR) is also recommended in PrEP users, although the risk of toxicity in this group is much lower than in people living with HIV.[16-18] Reduced bone mineral density has been reported so tenofovir disoproxil fumarate should be avoided in patients with osteoporosis.[19-20]

Renal and bone effects occur to a lesser extent with tenofovir alafenamide as serum drug concentrations are lower, however this formulation should be avoided in patients with an eGFR below 30 mL/minute. Tenofovir alafenamide has previously been reported to cause greater weight gain, especially when combined with dolutegravir, compared to tenofovir disoproxil fumarate. Whether this is an effect of weight gain with tenofovir alafenamide, weight loss with tenofovir disoproxil, or simply represents better gastrointestinal tolerability and improved health is uncertain.[21-22]

Tenofovir disoproxil fumarate and tenofovir alafenamide are first-line drugs for hepatitis B management. In patients co-infected with HIV and hepatitis B, dual therapy with tenofovir disoproxil fumarate or tenofovir alafenamide in combination with either lamivudine or emtricitabine is used to avoid the development of hepatitis B virus drug resistance. These patients also require a third drug with activity against HIV, for example bictegravir/tenofovir alafenamide/emtricitabine. Patients with hepatitis B should be advised on the importance of adherence as stopping their hepatitis B antiviral therapy can result in a flare of hepatitis.

### *Integrase strand inhibitors*

Integrase strand inhibitors are highly effective with few adverse effects and are recommended for most patients in combination with nucleotide reverse transcriptase inhibitors. Possible adverse effects include headache, nausea and diarrhoea. Several studies have concluded that integrase strand inhibitors, particularly dolutegravir, lead to greater weight gain than other classes of antiretroviral therapy, but the mechanism and clinical significance are unclear.[23-26]

Bictegravir, dolutegravir and raltegravir can increase serum creatine kinase and there are case reports of rhabdomyolysis with raltegravir.[27-29] Serum creatine kinase should be checked in those presenting with myalgia and specialist advice sought as the patient may require switching to a different regimen.

Bictegravir, dolutegravir and certain other drugs (e.g. rilpivirine, cobicistat) inhibit creatinine excretion in the proximal renal tubule. This causes a physiological, but clinically unimportant 10–20% increase in serum creatinine within the first eight weeks of treatment. Aside from measuring serum creatinine to establish a new baseline when starting therapy, no further action is required.

Integrase inhibitors have rarely been associated with central nervous system effects, such as insomnia and headache. A meta-analysis reported no significant effect of dolutegravir on the risk of suicide-related adverse events.[30]

### *Non-nucleoside and non-nucleotide reverse transcriptase inhibitors*

The most prescribed drug in this class is rilpivirine which is generally well tolerated, however it needs to be taken with a meal to facilitate its absorption. An important adverse effect is prolongation of the QT interval on the ECG which also has implications for drug–drug interactions. Rilpivirine may also exacerbate existing psychiatric conditions, but has fewer neuropsychiatric adverse effects than efavirenz.

Efavirenz, although rarely used nowadays, can cause dizziness and vivid dreams. Taking it at bedtime on an empty stomach reduces insomnia and dizziness. It can also cause or worsen depression and increase the risk of suicidal ideation.[31]

### *Protease inhibitors*

Gastrointestinal adverse effects may occur with any antiretroviral therapy, but are most common with protease inhibitors, especially when in combination with a booster drug (cobicistat or ritonavir). Troublesome diarrhoea may be managed with loperamide after exclusion of other causes.

Hyperlipidaemia is a common adverse effect of protease inhibitors, especially ritonavir-boosted regimens. This may require drug treatment in addition to optimising diet and exercise.[32] Simvastatin is contraindicated with boosted regimens as there is an increased risk of rhabdomyolysis. Atorvastatin, rosuvastatin and pravastatin should be started at low doses with careful dose titration to the lowest effective dose with measurement of creatine kinase if indicated. The maximum dose of these statins is reduced when they are taken with boosted regimens.

## Common and serious drug–drug interactions

It is crucial to regularly review treatments, including over-the-counter or complementary medicines, in patients taking antiretroviral therapy and to check for potential interactions using the University of Liverpool HIV Drug Interactions website. Drug interactions may not be specific within antiviral classes and may not be easily recognised. If there is any doubt, seek specialist advice as drug interactions can result in antiretroviral therapy failing to suppress

viral replication or can lead to serious and potentially fatal toxicity.

There are specific drug interactions that need to be highlighted to minimise the risk of toxicity or failure of antiretroviral treatment.

### *Nephrotoxic drugs and tenofovir*

The concentrations of renally eliminated drugs such as aciclovir, valaciclovir, aminoglycosides and non-steroidal anti-inflammatory drugs (NSAIDs) may be increased when taken with tenofovir disoproxil fumarate. Acute renal failure after starting high-dose NSAIDs has occurred in patients taking tenofovir disoproxil fumarate.[33] Patients taking tenofovir-based regimens, including PrEP, should be advised not to take NSAIDs and to check with a pharmacist before using over-the-counter medicines.

### *Metformin and integrase inhibitors*

The organic cation transporter 2 is involved in the renal excretion of drugs including metformin. Dolutegravir inhibits this transporter so co-administration doubles the concentration of metformin.[34] The US prescribing information advises that the daily dose of metformin should not exceed 1 g when starting metformin or dolutegravir.

### *Antacids, multivitamins and integrase inhibitors*

The absorption of integrase strand inhibitors is impaired by co-administration of antacids and mineral supplements containing polyvalent cations such as aluminium, magnesium, calcium and iron. These bind and chelate integrase strand inhibitors, impairing their ability to bind to the active site of the HIV integrase enzyme.[35,36] To avoid this interaction, antacids and supplements containing polyvalent cations should be taken separately from the integrase strand inhibitor. For example, dolutegravir should be taken two hours before or six hours after products containing polyvalent cations.[37]

### *Acid-suppressing drugs and rilpivirine and atazanavir*

The absorption of rilpivirine and atazanavir requires an acidic pH so drugs such as proton pump inhibitors and $H_2$-receptor antagonists reduce absorption.[38] Proton pump inhibitors are contraindicated with rilpivirine as they can cause a failure of therapy. If a patient is taking a proton pump inhibitor with rilpivirine, seek immediate specialist advice. $H_2$-receptor antagonists should only be taken 12 hours before or at least four hours after rilpivirine.

### *Steroids and regimens containing ritonavir or cobicistat (boosted protease inhibitors or elvitegravir)*

Ritonavir and cobicistat are potent CYP3A inhibitors so they increase the concentration of drugs metabolised through the same pathway including some steroids. Iatrogenic Cushing's syndrome and adrenal suppression can occur in patients taking ritonavir or cobicistat with steroids such as fluticasone, budesonide or mometasone.[39] This interaction has been observed with inhaled, intranasal, intra-articular, topical, and intraocular corticosteroids.[40-42] Seek expert advice if this drug interaction is suspected. As beclomethasone is not metabolised by CYP3A4, it is suitable to use with ritonavir or cobicistat-boosted regimens.

### *Phosphodiesterase 5 inhibitors and regimens containing ritonavir or cobicistat*

The concentrations of phosphodiesterase 5 inhibitors such as sildenafil are increased by boosters (ritonavir and cobicistat), increasing the risk of adverse effects such as priapism and hypotension. A reduced dose (e.g. sildenafil 25 mg) and no repeat dosing within 48 hours is advised.

## Vaccination

HIV primarily affects CD4 T-cell numbers and function but also impacts other parts of the immune system, increasing the risk of some infections, many of which are vaccine-preventable. However, patients older than five years with CD4 T-cell counts below 200/microlitre should not be given live attenuated vaccines, such as measles, mumps and rubella vaccine.[43] In addition, responses to certain vaccinations, for example hepatitis B vaccine, may be reduced and so increased doses are recommended. The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine provides excellent guidance on vaccination.

Vaccination against COVID-19 is advised for people living with HIV. No safety or efficacy data have emerged to cause concern that they are at any greater risk of adverse effects from COVID-19 vaccination.[44] There are no interactions between COVID-19 vaccines and antiretroviral drugs.[45] The Australian Technical Advisory Group recommends that a third primary dose of COVID-19 vaccine should be offered to those with advanced HIV (CD4 counts <250/microlitre) or those with a higher CD4 count unable to be established on effective antiretroviral therapy.[46]

## Conclusion

Most current first-line antiretroviral drugs are well tolerated by patients. However, there are important drug interactions and adverse effects that prescribers should be aware of. The safest approach is to check for drug interactions each time using the University of Liverpool HIV Drug Interactions website.

People living with HIV have an increased risk of poorer outcomes from some vaccine-preventable conditions. Immunisation is recommended when possible. ≺

*Conflicts of interest: Louise Tomlins has received speaker fees for Gilead Sciences. She is a member of advisory boards for Gilead Sciences and Viiv Healthcare.*

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DIAGNOSTIC TESTS

# Imaging in headache disorders

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## SUMMARY

Patients with a suspected change in intracranial pressure or a trigeminal autonomic cephalgia require MRI.

The need for investigation for other headache disorders is guided by the clinical evaluation of the patient. Particular care should be taken to identify any 'red flags'.

Incidental findings on MRI occur in approximately 2% of patients. Patients with migraine have an increased rate of white matter lesions, but these are of uncertain clinical significance.

## Introduction

Headache disorders are a leading cause of disability. Worldwide, migraine is the second leading cause of years lived with disability and, in Australia, it is among the top 20 reasons for consulting a GP.[1,2] While migraine is the most common disabling headache disorder, patients and clinicians are often concerned a headache could be a symptom of secondary pathology.

In a Norwegian population study, the one-year prevalence of secondary headaches was 2.14%. In 80% of these, the cause of the secondary headache could be diagnosed on the patient's history.[3]

In a UK tertiary referral headache service, 3655 consecutive patients were screened using 'red flags' to identify the need for imaging. Over a five-year period, 14.5% underwent imaging, with 11 patients having a significant finding. This represents 2.1% of patients scanned or 0.3% of the clinic population.[4]

There are several evidence-based guidelines that recommend that imaging of patients with headaches should not be routine. The need for imaging should be guided by clinical evaluation.[5-7]

## Clinical evaluation

A thorough clinical assessment is essential for evaluating a patient who presents with headache and for determining the need for imaging. The key features of a headache history can be summarised by 'the 5Ps':

- patient
- pattern
- phenotype
- precipitants
- pharmacology.[8]

A thorough headache history, considering potential red flags (Table 1)[8] and 'green flags' (Table 2),[9] coupled with a detailed neurological examination is required. This not only determines the need for imaging, but also guides which imaging modality to use.

The recognition of red flags is useful for identifying which patients need further evaluation, however the specific differential diagnosis should be considered. This guides the choice of investigation and its urgency. For example, a patient with suspected stroke or meningitis requires urgent evaluation, while a patient with a recent change in the pattern of their headache is likely to be suitable for outpatient evaluation.

Green flags are reassuring features in a headache history (Table 2). They suggest a secondary cause of headache is unlikely. The green flags were determined by an expert group of the International Headache Society,[9] but have not been validated in a prospective study.

### *Patient*

When deciding on the need for investigation, patient factors such as age and general health are the most critical consideration. A patient with new headaches late in life, or in the setting of malignancy or immunosuppression, always requires further evaluation, regardless of other factors. The presence of neurological or systemic signs in relation to the headache also requires further evaluation. Conversely, the presence of a strong family history of similar headaches is a reassuring factor.

### *Pattern*

The temporal pattern of a patient's headache can help distinguish primary and secondary causes. A headache that has been present and unchanged from childhood, or is consistently related to menstruation, is less likely to have a secondary cause.[9] Conversely, a recent onset or new pattern is suspicious for a secondary cause of headache. The timing of the change in pattern can give a clue as to the cause, such as in the case of medication-overuse headache.


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*Table 1* **The SNOOP4 list of 'red flags' for secondary headaches**[8]

| | Mnemonic | Examples of red flags | Possible secondary headache |
|---|---|---|---|
| **S** | Systemic symptoms | Fever, weight loss | Meningitis, encephalitis, giant cell arteritis |
| | Secondary risk factor | Malignancy, immunosuppression | Metastasis, leptomeningeal carcinomatosis |
| **N** | Neurological deficit | Focal neurological sign, altered conscious state | Stroke, space-occupying lesion, hydrocephalus |
| **O** | Onset | Thunderclap, abrupt onset | Includes subarachnoid haemorrhage, pituitary apoplexy, cerebral venous sinus thrombosis |
| **O** | Older age | New or progressive headache (>50 years) | Mass lesion, giant cell arteritis |
| **P4** | Positional | Changes with change in posture | Intracranial hypotension or hypertension |
| | Pattern change | Change in character from baseline | Mass lesion |
| | Precipitated by | Valsalva, coughing, sneezing | Posterior fossa lesion |
| | Papilloedema | Visual obscuration | Idiopathic intracranial hypertension |

*Table 2* **Potential 'green flags' for primary headaches**[9]

| Green flag | Rationale |
|---|---|
| The current headache was present during childhood | Secondary headaches are uncommon in childhood and common secondary causes in childhood (viral, post-trauma) do not usually persist. |
| The headache is temporally related to the menstrual cycle | Menstrually related migraine is common, and the probability of a migraine during the first three days of the menstrual cycle is elevated. |
| The patient has headache-free days | Most primary headache disorders are intermittent, whereas secondary causes (excepting brain tumours) are less commonly so, and secondary causes are less commonly associated with an identifiable trigger. |
| Close family members have the same headache type | Migraine and cluster headache can be inherited, and so the presence of a family history is supportive of the diagnosis. |

### *Phenotype*

The characteristics of a headache in an individual are called the phenotype. Accurate evaluation of the phenotype is key to determining the headache disorder. In the setting of an established, recurrent phenotype, the presence of a new phenotype requires increased clinical vigilance. However, the presence of a phenotype with features of a primary headache disorder, such as tension-type headache or migraine, should not provide false reassurance if there are red flags. For example, in one study of patients who were found to have primary or metastatic brain tumours, 77% presented with headaches phenotypically in keeping with tension-type headache.[10] Some phenotypes always require further evaluation. These include the 'thunderclap' headache and trigeminal autonomic cephalgias, such as cluster headache.

### *Precipitating factors*

The relationship of the headache to precipitating or provoking factors can provide a further clue to the underlying aetiology. A trigger, for example alcohol, may suggest a primary headache disorder such as migraine or cluster headache, whereas eating tyramine-containing food while taking a monoamine oxidase inhibitor suggests a secondary cause. Precipitating factors such as the valsalva manoeuvre or a change with posture are concerning because they may be due to posterior fossa pathology or raised intracranial pressure. Headaches can occur solely in 'task-specific' settings, such as exertion, intercourse or sleep, and the clinician should be alert to these factors in the patient's history. Finally, new headaches that are 'precipitated' in the setting of pregnancy, postpartum, or ischaemic heart disease (cardiac cephalgia) may be suspicious for a secondary cause, and require specific consideration.

### *Pharmacology*

Prescription and non-prescription medicines may precipitate or perpetuate headaches. As such, a detailed history noting the timing of new drugs and the pattern of headaches is required. The overuse of acute analgesia is a critical issue to be addressed in patients with a primary headache disorder. Medication-overuse headache may occur in over 70% of patients with a chronic daily headache.[11] Patients who regularly use opioid or triptan analgesia for more than 10 days/month or simple analgesia for more than 15 days/month are at risk of increased neuronal hyperexcitability, peripheral and central sensitisation, and further potentiation of their headaches.[11]

Headache may also be an adverse reaction to a prescribed drug. The product information of many medicines lists headache as a possible adverse effect. Careful attention should therefore be paid to the temporal relationship when evaluating the relationship between a new drug and headaches. There are several classes of drugs that are well known to precipitate headaches. These include tacrolimus, interferon-beta, nitric oxide donors, phosphodiesterase inhibitors, some antidepressants and ciclosporin.[12] Other drugs such as tetracyclines and vitamin A analogues may raise intracranial pressure, increasing the risk of idiopathic intracranial hypertension.[13]

## Imaging of primary headaches

If imaging is indicated, MRI provides the most useful information. However, incidental findings are common and often result in patient anxiety, referral, and more imaging. Incidental findings on MRI occur in 2% of the general population.[14] These findings include neoplasia in 0.7%, aneurysm in 0.35%, arachnoid cysts in 0.5%, Chiari I malformations in 0.24% and demyelination in 0.06%.[14]

In patients without red flags, there is not an absolute need for imaging in every patient. The decision to proceed to imaging should be made with consideration of the possibility of incidental findings and the overall clinical picture.

In selected scenarios, CT may be considered, depending on the question to be addressed by the imaging. It may be adequate at identifying subdural or epidural haematoma, skull fracture, sinus infection or subarachnoid haemorrhage (depending on the timing of the scan following the index event).

### *Migraine*

Migraine, as the most common disabling primary headache disorder, is frequently investigated to exclude secondary pathology. In population studies, women with migraine are at an increased risk of white matter lesions (odds ratio 2.1, 95% CI 1.0–4.1) and hyperintense lesions in the brainstem (4.4% vs 0.7%).[15] These findings are more common in patients with migraine aura, longer disease duration and higher attack frequency.[15] The clinical significance of these lesions is still a matter of ongoing research, however they are not believed to be associated with cognitive changes.[16,17] They can generally be differentiated from demyelination by an experienced reviewer, however serial imaging may be required.

### *Trigeminal autonomic cephalgias*

The trigeminal autonomic cephalgias are a group of primary headache disorders characterised by unilateral (side-locked) headaches and ipsilateral cranial autonomic symptoms. All patients with a trigeminal autonomic cephalgia are required to have MRI primarily to exclude pathology in the pituitary region.

Ideally, the MRI would be of the brain and pituitary region, however it is not uncommon that just the brain is imaged. A review has now recommended that further dedicated pituitary imaging is only required if there are atypical features (older age, prolonged duration, higher frequency of attacks, bilateral attacks (rare, and should precipitate specialist review) or the absence of autonomic symptoms), pituitary-related symptoms, an abnormal examination or a poor response to treatment.[18,19] Among 376 patients with cluster headache, the rate of pituitary adenomas was similar to the rate in the general population. Only patients with suggestive symptoms therefore require an additional MRI of the pituitary.[19]

### *Other primary headache disorders*

Several primary headache disorders specifically require imaging to evaluate the patient for a possible secondary cause. Primary headache associated with sexual activity should be considered as attributed to reversible cerebral vasoconstriction syndrome until proven otherwise by angiographic study.[20] Similarly, the diagnosis of primary exertional headache first requires evaluation for other causes of thunderclap headache.[20] Primary cough headache should be evaluated with MRI particularly to check for posterior fossa pathology or structural malformations such as the Chiari I malformation.[20,21]

## Imaging of secondary headaches

When investigating for a secondary headache, the clinical situation needs to be considered.

### *Thunderclap headache*

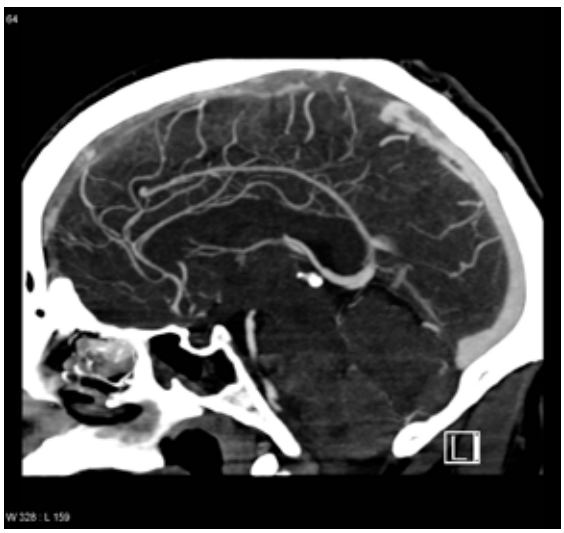
Thunderclap headaches are sudden and severe. They are often due to cerebrovascular disorders, such as

subarachnoid haemorrhage (see Box[22-24] and Fig. 1[25]). A non-contrast CT is frequently ordered for a patient presenting with a thunderclap headache. If performed within six hours of onset, CT has a sensitivity of 98.7% (CI 97.1–99.4%),[26] however this drops considerably after six hours.[27] A negative CT scan therefore may be falsely reassuring for ruling out subarachnoid haemorrhage, depending on the timing. CT is also likely to miss differential diagnoses that may be clinically relevant, including cerebral venous sinus thrombosis (see Fig. 2[28]), reversible cerebral vasoconstriction syndrome, pituitary apoplexy or arterial dissection.

*Box* **Selected possible causes of thunderclap headache in order of frequency**[22-24]

- Subarachnoid haemorrhage
- Reversible cerebral vasoconstriction syndrome
- Cerebral venous thrombosis
- Other primary headache: primary thunderclap, cough, sexual and exertional headaches
- Cervical artery dissection
- Infection (e.g. sinusitis, meningitis, encephalitis)
- Spontaneous intracranial hypotension
- Stroke (haemorrhagic or ischaemic)
- Posterior reversible encephalopathy syndrome
- Pituitary apoplexy
- Third ventricular colloid cyst
- Sentinel headache (preceding a subarachnoid haemorrhage)
- Retroclival haematoma

*Fig. 1* **Diffuse subarachnoid haemorrhage on a CT scan**[25]



Full evaluation for a patient with a thunderclap headache therefore includes non-contrast CT, with a lumbar puncture if the onset was more than six hours before, or the image is technically inadequate.[27] When subarachnoid haemorrhage is excluded, there are many alternative diagnoses to consider (see Box).[22] MRI with venography and angiography is recommended for investigating these causes.[23]

### *Disorders of intracranial pressure*

Patients with a history or clinical examination suggestive of raised intracranial pressure always require further investigation. This is to exclude hydrocephalus, a space-occupying lesion and cerebral venous sinus thrombosis. Ideally, MRI of the brain and orbits and venography are performed.[13] MRI features in keeping with raised intracranial pressure include flattening of the globe, optic nerve distension or tortuosity, empty sella, posterior displacement of the pituitary stalk, slit-like ventricles and an inferior position of the cerebellar tonsils (see Fig. 3[29]).[30] However, MRI findings are not pathognomonic, nor does their absence completely exclude idiopathic intracranial hypertension, so all patients with papilloedema should be referred for expert opinion. Conversely in patients with spontaneous intracranial hypotension, MRI may reveal diffuse pachymeningeal enhancement, descent of the tonsils (mimicking the Chiari I malformation), hygromas, or engorgement of the pituitary and the cerebral venous sinuses.[31] These patients generally require expert evaluation and management.

*Fig. 2* **CT venogram showing extensive venous thrombosis in the superior sagittal sinus**[28]

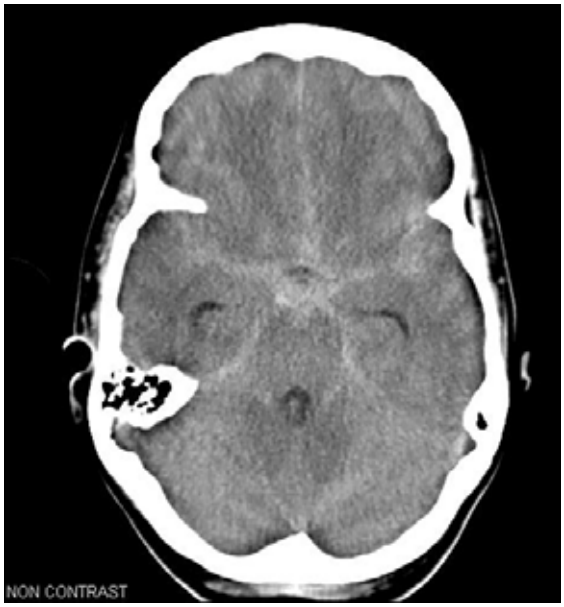
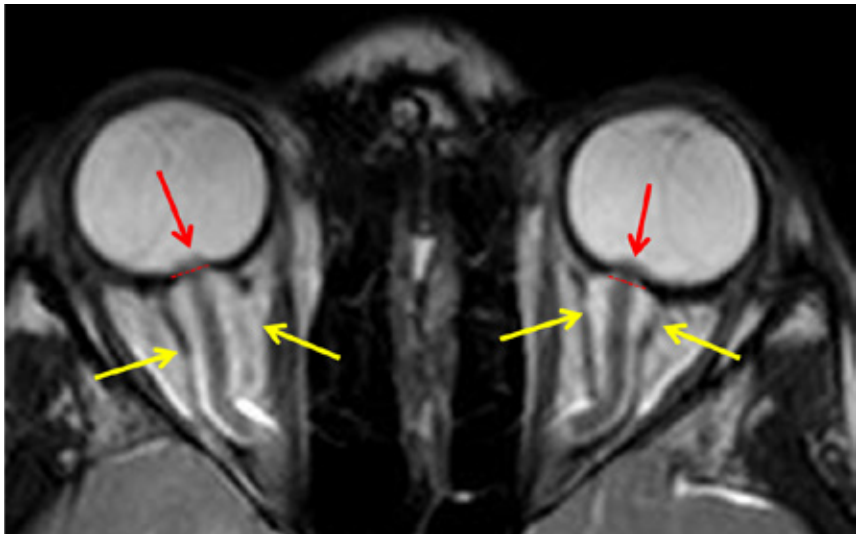


*Fig. 3* **A case of idiopathic intracranial hypertension**[29]



MRI shows flattening of the posterior sclera, intraocular protrusion of the optic nerve head (red arrows) and tortuous optic nerves with prominent subarachnoid space (yellow arrows).

## Conclusion

The overall rate of significant pathology found on MRI is relatively low, with incidental findings in approximately 2% of people. Investigation should therefore be guided by a thorough clinical assessment, to ensure the appropriate type and speed of investigation. ≺

*Conflicts of interest: Jason Ray has received compensation from the Pharmaceutical Society of Australia, sponsored by Viatris for educational material.*

*Elspeth Hutton has served on advisory boards for Sanofi-Genzyme, Novartis, Teva, Eli Lilly, Allergan, Lundbeck, been involved in clinical trials sponsored by Novartis, Teva, Xalud, Daewong and Novotech, and received payment for educational presentations from Allergan, Teva, Eli Lilly and Novartis.*

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MEDICINAL MISHAP

# Chronic lithium toxicity

## Case

A 66-year-old man presented to hospital following two weeks of diarrhoea and worsening confusion, unsteady gait and muscle twitching. His oral intake and urine output were markedly reduced. The medical history included bipolar disorder, class III obesity, type 2 diabetes, hypertension and dyslipidaemia. He was being treated with venlafaxine, mirtazapine, lithium, aripiprazole, metformin, empagliflozin, olmesartan and rosuvastatin, which he continued while unwell. He had been on lithium for nearly 20 years with no recent change of dose. Serum trough concentrations of lithium were maintained around 0.6 mmol/L (target range 0.6–0.8 mmol/L). Renal function was normal when measured three months earlier.

On examination, the man was lethargic and not orientated to time or place. His blood pressure was 100/65 mmHg with otherwise normal vital signs. He had a coarse tremor, myoclonic jerks and generalised hyperreflexia, but no focal neurological deficit.

Investigations revealed normal serum sodium, potassium and glucose concentrations, but urea was 25 mmol/L and creatinine was 1130 micromol/L. Serum lithium had increased to 2.7 mmol/L. There was a moderately severe anion gap metabolic acidosis but a normal lactate. An ECG showed a normal sinus rhythm. CT of the abdomen excluded structural abnormalities that may have accounted for impaired kidney function or diarrhoea.

The patient was diagnosed with severe acute kidney injury precipitated by hypovolaemia and subsequent neurotoxicity from lithium accumulation. All drugs were temporarily ceased, intravenous fluids were given and he was admitted to intensive care. Continuous renal replacement therapy was provided under vasopressor support until serum lithium concentrations approached 1 mmol/L and renal function improved. The diarrhoea settled, but the man's neurological recovery was slow and complicated by hypernatraemia, ileus and hospital-acquired pneumonia.

After four weeks, the patient was transferred to a rehabilitation facility and lithium recommenced at half the usual dose. His daily urine output remained greater than 3 L which was consistent with nephrogenic diabetes insipidus.

## Comment

Lithium is an effective mood-stabilising drug that requires monitoring to avoid toxicity.[1] Long-term treatment can cause nephrogenic diabetes insipidus, where resistance to antidiuretic hormone produces polyuria. Patients usually compensate by increasing their water intake, but an inability to maintain hydration can lead to acute kidney injury.

Lithium shares characteristics with sodium. Both are monovalent cations distributed through total body water and eliminated by the kidneys. Lithium's usual half-life of 12 hours can be much longer in renal impairment.[2] Drugs that reduce glomerular filtration, such as ACE inhibitors, angiotensin receptor blockers and non-steroidal anti-inflammatory drugs, as well as dehydration caused by diuretics and diabetes insipidus, can therefore lead to accumulation of lithium. The patient's venlafaxine, metformin and olmesartan are also renally excreted.

Exposure to elevated lithium concentrations over days to weeks, known as chronic lithium toxicity, can manifest as worsening tremor, lethargy, confusion, ataxia, myoclonic jerks and seizures.[3] Elderly patients are particularly susceptible due to reductions in renal function, body water and cognitive reserve. Treatment includes lithium elimination, through restoration or replacement of renal function, and supportive care. Resolution of neurotoxic effects may take weeks and can be incomplete.[4]

## Conclusion

To prevent chronic lithium toxicity, drug concentrations and kidney function should be checked during intercurrent illness. Patients with diabetes insipidus and the elderly require particularly close monitoring. In renal impairment, exposure to lithium and other nephrotoxic drugs must be reduced or avoided. A sick-day plan should direct patients to seek medical attention if symptoms of chronic lithium toxicity develop.

Physicians experienced in pharmacology or a Poisons Information Centre can advise on the management of chronic lithium toxicity. In mild cases, lithium is stopped until clinical resolution and then reintroduced at a lower dose, while patients with severe toxicity require admission to hospital.

*Conflicts of interest: none declared*

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lithium, nephrogenic diabetes insipidus, neurotoxicity, renal impairment, renal replacement therapy

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 This article is peer-reviewed

# New drugs

## Alpelisib

**Approved indication: breast cancer**

**Piqray (Novartis)**

**50 mg, 150 mg and 200 mg tablets**

The medical management of breast cancer is guided by the histopathological subtype of the tumour. Most cancers are positive for hormone receptors and negative for human epidermal growth factor receptor 2 (HER2). Treatment options for patients with this tumour type include endocrine therapies such as tamoxifen (an estrogen receptor modulator), fulvestrant (an estrogen receptor antagonist) or anastrozole (an aromatase inhibitor). However, endocrine therapy eventually fails to halt the progression of advanced breast cancer. Resistance to endocrine therapy can be related to mutations in the PIK3CA gene. These mutations result in overactivity of a kinase (PI3K) which results in cell proliferation. Inhibiting this kinase may therefore slow tumour growth.

Alpelisib is an inhibitor of PI3K. Preliminary studies confirmed that alpelisib had antitumour activity, particularly if given in combination with fulvestrant.

The once-daily dose is taken immediately after a meal as food improves absorption. Most of the dose is metabolised. As cytochrome P450 (CYP) 3A4 is responsible for only a small part of this metabolism, clinically significant interactions with CYP3A4 inducers or inhibitors are unlikely. Although data are limited, no dose adjustments are recommended for patients with liver or kidney impairment. Most of the dose is excreted from the gut.

The approval of alpelisib is mainly based on the phase III SOLAR-1 trial.[1] This randomised 571 postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer that had relapsed or progressed despite treatment with an aromatase inhibitor. Most of the patients had metastases. The patients were divided into two cohorts according to the presence of the PIK3CA mutation. They were treated with either oral alpelisib 300 mg daily and injections of fulvestrant, or fulvestrant and a placebo.

The 341 patients with PIK3CA mutations were followed up for a median of 20 months. There was a response to treatment in 26.6% (45/169) of the patients given alpelisib and fulvestrant, and 12.8% (22/172) of those given fulvestrant alone. The median progression-free survival was 11 months with alpelisib and fulvestrant, and 5.7 months with fulvestrant. In the 231 women without a PIK3CA mutation there was no advantage for alpelisib treatment. Median progression-free survival was 7.4 months compared with 5.6 months for fulvestrant alone.[1]

Adverse events led to 25% of the patients receiving alpelisib and fulvestrant stopping treatment. This compares with 4.2% of the patients given fulvestrant and a placebo. Adverse events that were more frequent in patients given alpelisib included hyperglycaemia, diarrhoea, nausea, vomiting, reduced appetite, weight loss, rashes and alopecia. Patients with type 1 or uncontrolled type 2 diabetes were excluded from the SOLAR-1 trial, but many patients needed antidiabetic drugs as 63.7% of those taking alpelisib developed hyperglycaemia.[1] Fatal ketoacidosis has been reported. The skin rashes associated with alpelisib include severe cutaneous reactions such as Stevens-Johnson syndrome. Toxicities such as rashes, diarrhoea or hyperglycaemia require treatment to be reduced or stopped.

Like most new anticancer drugs, it is going to take time to determine where alpelisib fits in therapy. It is clearly of no benefit to the majority of women as they do not have the PIK3CA mutation. In recent years, inhibitors of cyclin-dependent kinases 4 and 6 (CDK4/6), such as palbociclib, have become available for the treatment of hormone receptor-positive and HER2-negative advanced breast cancer. Only 20 of the patients with PIK3CA mutations in the SOLAR-1 trial had been treated with these drugs. A phase II trial has studied a cohort of 127 women who had previously been treated with an aromatase inhibitor and a CDK4/6 inhibitor. They were treated with alpelisib and fulvestrant, with a median follow-up of 11.7 months. Their median progression-free survival was 7.3 months with a median overall survival of 17.3 months.[2] An analysis of overall survival in the SOLAR-1 trial showed no statistical advantage for alpelisib and fulvestrant. Median overall survival was 39.3 months with the combination and 31.4 months with fulvestrant alone.[3]

In addition to postmenopausal women, alpelisib with fulvestrant has also been approved for the

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treatment of men with hormone receptor-positive, HER2-negative advanced or metastatic breast cancer containing the PIK3CA mutation. However, only one man was involved in the SOLAR-1 trial.[1]

T manufacturer provided the product information

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

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

## Eptinezumab

**Approved indication: migraine**

**Vyepti (Lundbeck)**
**vials containing 100 mg/mL concentrated solution for dilution**

Drugs aimed at the calcitonin gene-related peptide (CGRP) are recent additions to the options for the prevention of migraine attacks.[1] This peptide is involved in vasodilation and high concentrations are associated with migraine. Like the previously approved drugs, erenumab, fremanezumab and galcanezumab, eptinezumab is a monoclonal antibody. It binds to CGRP to stop the peptide binding to its receptors.

While the other drugs are given by subcutaneous injection, eptinezumab is given intravenously. The concentrate must be diluted then infused over 30 minutes and subsequent doses are only required 12 weeks apart. The half-life of eptinezumab is 27 days. It is metabolised like other antibodies, so no dose adjustments are recommended in renal or hepatic impairment and pharmacokinetic drug interactions are unlikely.

PROMISE–1 was a placebo-controlled trial of eptinezumab in episodic migraine. The 888 patients in the trial were having up to 14 days of headaches each month including at least four days of migraine. Infusions were given every 12 weeks with the patients randomised to eptinezumab receiving 30 mg, 100 mg or 300 mg doses. When efficacy was assessed after 12 weeks, treatment had reduced the mean number of migraine days per month by approximately four from a baseline of 8.6 days. The reduction in the placebo group was approximately three days (see Table).[2] After a year the reductions from baseline were 4.5 days with eptinezumab 100 mg and 5.3 days with 300 mg. The reduction in the placebo group was 4.1 days.[3]

The PROMISE–2 trial studied 1072 patients with chronic migraine. In a 28-day period, these patients had an average of 20.5 days of headache with 16.1 days of migraine. The patients were randomised to receive eptinezumab 100 mg, 300 mg or an infusion of placebo. After 12 weeks the mean number of migraine days each month reduced by 7.7 days with eptinezumab 100 mg, 8.2 days with 300 mg and 5.6 days with placebo.[4] After 24 weeks the respective reductions were 8.2, 8.8 and 6.2 days (see Table).[5]

Patients with chronic migraine were also studied in the open-label PREVAIL trial. They were given an infusion of eptinezumab 300 mg every 12 weeks for up to eight doses. There were 118 patients who were treated for 48 weeks and 101 who continued treatment to week 84 of the trial. The majority of the 100 patients who completed the study felt improved and found their migraine less disabling when they were reviewed at 104 weeks.[6]

During the PREVAIL trial 7.8% of the patients stopped eptinezumab because of an adverse reaction. The most common of these problems was extravasation at the infusion site.[6] Infusing an antibody can also cause allergic reactions including anaphylaxis. In the

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*Table* **Short-term efficacy of eptinezumab for migraine prophylaxis**

| Trial regimen | Numbers of patients assessed for efficacy | Assessment | Mean days of migraine per month | | Proportion of patients with 75% or greater response |
|---|---|---|---|---|---|
| | | | Baseline | Change with prophylaxis | |
| **PROMISE-1[2] (episodic migraine)** | | | | | |
| Eptinezumab | | | | | |
| 30 mg | 223 | 12 weeks | 8.7 | –4.0 | 24.7% |
| 100 mg | 221 | | 8.7 | –3.9 | 22.2% |
| 300 mg | 222 | | 8.6 | –4.3 | 29.7% |
| Placebo | 222 | | 8.4 | –3.2 | 16.2% |
| **PROMISE-2[4,5] (chronic migraine)** | | | | | |
| Eptinezumab | | | | | |
| 100 mg | 356 | 12 weeks (24 weeks) | 16.1 | –7.7 (–8.2) | 26.7% (39.3%) |
| 300 mg | 350 | | 16.1 | –8.2 (–8.8) | 33.1% (43.1%) |
| Placebo | 366 | | 16.2 | –5.6 (–6.2) | 15% (23.8%) |

NEW DRUGS

PREVAIL trial 7% of the patients developed potentially neutralising antibodies to eptinezumab, but their effect is unclear.[6] Symptoms related to the upper respiratory tract, such as nasopharyngitis, were the most frequent adverse events reported in PROMISE-1[2] and PROMISE-2.[4]

The main trials of eptinezumab excluded patients with cardiovascular disease, diabetes and obesity. Data about using the drug in children and pregnant or lactating women are also lacking.

The evidence shows that infusions of eptinezumab have greater efficacy than placebo at preventing migraine. While the main difference over placebo in episodic migraine may only be about one less day of migraine each month,[2] this may be of benefit to some patients. If a patient has migraine that is severe enough to warrant prophylaxis with a CGRP antagonist, it is unclear which of the class is most effective and whether someone who has not responded to one drug will respond to another drug in the class. Unlike the other formulations, eptinezumab cannot be self-administered. One factor that may influence the future use of eptinezumab is the finding that the infusion can bring rapid relief during an acute attack.[7] For now, its indication is limited to the prevention of migraine in adults.

T manufacturer provided information regarding availability

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

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

# Larotrectinib

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**Approved indication: solid tumours**

**Vitrakvi (Bayer)**
**25 mg and 100 mg capsules**
**oral solution containing 20 mg/mL**

Genomic research has found that in some rare cases apparently different cancers can share the same genetic abnormality. An example involves the genes that encode for the tropomyosin receptor kinases TRKA, TRKB and TRKC. Rearrangement of these genes results in gene fusion and the production of TRK fusion proteins. These abnormal proteins stimulate cell proliferation which can become cancerous. Inhibition of these effects may therefore be an approach to treating TRK fusion cancers. While these gene fusions have been found in cases of colorectal, lung and thyroid cancer, they are uncommon. They are more frequently found in rare cancers such as infantile fibrosarcoma and congenital mesoblastic nephroma.

Larotrectinib is a selective inhibitor of TRKA, TRKB and TRKC. In animal studies it significantly reduced tumour growth.

The drug is taken by mouth twice a day. A steady state is reached in about a week. Larotrectinib is thought to be metabolised by cytochrome P450 (CYP) 3A4/5, but about 30% of the dose is excreted unchanged in the urine. Although no adjustment is required in renal disease, the dose needs to be reduced if there is moderate or severe liver impairment. Adjustments are also needed if strong inhibitors or inducers of CYP3A4 cannot be avoided.

Conducting randomised trials in rare diseases is difficult and, in the case of TRK fusion cancers, there is more than one type of tumour to study. The approval of larotrectinib is therefore mainly based on three open-label phase I and phase II trials.[1] These trials enrolled a total of 159 patients, ranging from babies to someone 84 years old. Most had already received standard therapy for locally advanced or metastatic tumours including soft tissue sarcoma, non-small cell lung cancer and thyroid cancer. Treatment with larotrectinib ranged from a day to over 47 months. In a pooled analysis 79% (121/153) of the patients had an objective response, such as a reduction in tumour size. There was a complete response in 16% of the patients. Overall, the median duration of the response was 35.2 months. The median overall survival was 44.4 months.[1]

Only two patients discontinued larotrectinib because of adverse effects, although 8% (13/159) required a dose reduction. Adverse events were similar in adults and children. They included fatigue, myalgia, constipation, nausea and vomiting. Some patients experience neurological symptoms, such as dizziness, particularly at the start of treatment. Liver function should be monitored as aminotransferase concentrations can increase. Some patients develop anaemia.[1]

Long-term safety is currently unclear. There is a potential for the tumours to develop resistance to larotrectinib.

In view of the rarity of TRK fusion cancers, there are limited data about the efficacy, safety and outcomes for larotrectinib. It is therefore appropriate that larotrectinib has only been provisionally approved for when no alternatives are available to treat advanced or metastatic solid tumours, or when surgery is likely to cause severe morbidity in patients with TRK fusion cancers.

T manufacturer provided the AusPAR and the product information

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UPDATE

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# Update

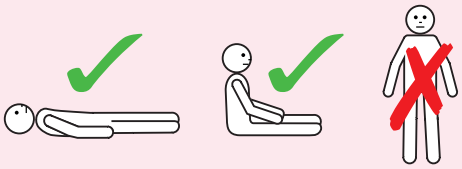
## Anaphylaxis: emergency management for health professionals [Update 1]

The Anaphylaxis Wallchart has been updated to reflect the latest advice on positioning of patients, and use of different-sized autoinjectors. View updated wallchart (v2).

### *Step 1, second point*

*Original version:*

- Lay patient flat – do not allow them to stand or walk.
  If unconscious place in recovery position and maintain airway.
  If breathing is difficult allow the patient to sit (as illustrated).



*Updated version:*

- Lay patient flat – do not allow them to stand or walk.
  If breathing is difficult, allow the patient to sit with legs outstretched.
  Hold young children flat, not upright.

### *Step 2, Autoinjector box*

*Original version:*

An adrenaline autoinjector, e.g. EpiPen, may be used instead of an adrenaline ampoule and syringe.

For children 10–20 kg (aged ~1–5 years) a 0.15 mg device, e.g. EpiPen Jr, should be used.

Instructions are on device labels.

*Updated version:*

An adrenaline autoinjector, e.g. EpiPen or Anapen, may be used instead of an adrenaline ampoule and syringe.

- 150 microgram (0.15 mg) device for children 7.5–20 kg (aged ~1–5 years)
- 300 microgram (0.3 mg) device for children over 20 kg (aged ~5–12 years) and adults
- 300 microgram (0.3 mg) or 500 microgram (0.5 mg) device for children over 50 kg (aged ~>12 years) and adults

Instructions are on device labels and ASCIA Action Plans.

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