

# Australian Prescriber

AN INDEPENDENT REVIEW

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## Rational prescribing: 30 years after

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### Keywords

drug information, drug  
policy, quality use of  
medicines

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Thirty years ago, there was an event that was to have a profound effect on the quality use of medicines in Australia. This was a workshop entitled 'Rational prescribing: the challenge for medical educators'. The workshop was jointly convened by the Consumers Health Forum and the Australasian Society of Clinical and Experimental Pharmacologists (ASCEPT). It was sponsored by the Australian Department of Health. Of importance, and rather revolutionary at the time, the workshop broke new ground by formally bringing together for the first time a consumer organisation and a professional organisation to discuss a topic that had until then been considered solely the province of health professionals. The proceedings of this important workshop were published in a special supplement of *Australian Prescriber*.<sup>1</sup>

The rational prescribing of medicines is just as important today as it was 30 years ago. It is therefore useful to reflect on the successful – and less successful – outcomes of such an important meeting and how our experience since 1991 can help us continue to improve prescribing.

One major concern, which is still very much with us today, was the rise of antibiotic-resistant organisms and the importance of ensuring inappropriate antibiotic prescribing does not exacerbate the problem. Probably the other major concern in 1991 was the rapidly escalating government expenditure on pharmaceutical benefits. This concern is also still with us, but importantly the type of drugs causing the escalating costs has changed completely. Thirty years ago, the major costs arose from drugs still under patent protection and prescribed long term for large numbers of people, for example, statins and ACE inhibitors. Now, the major costs arise from very expensive drugs, nearly all biologicals, which are largely prescribed by specialists for much smaller numbers of patients often with rare diseases.

Probably the biggest success from the meeting was the impetus given to the development of a national drug policy for Australia. This resulted in the National Medicines Policy which includes the quality use of medicines.<sup>2</sup> The meeting also contributed within a few years to the establishment of the Australian Medicines Handbook and the National Prescribing Service (now known as NPS MedicineWise). It reinforced the role of independent information provided through Therapeutic Guidelines and *Australian Prescriber*. Some of these activities which continue to support the quality use of medicines

today might not have come about without the vital initial support gained from the discussions and recommendations at the workshop.

The workshop recommended that all medicines should have consumer product information. This was implemented shortly after the meeting. The recommendation that independent information about therapeutics should continue to be provided to health professionals is evidenced by the longevity of *Australian Prescriber*. The workshop also recommended that drug utilisation reviews should be encouraged as widely as possible.

There were recommendations for the development of undergraduate and postgraduate core curricula in clinical pharmacology and the expansion of clinical pharmacology as both an academic and clinical specialty. These recommendations were also largely implemented over the subsequent few years – although perhaps not quite as successfully as a few of the enthusiasts from ASCEPT might have hoped.

It is clear that the workshop was a great success when judged on how many of the recommendations came to fruition. What might the main topics for discussion be if such a meeting were to be held again today?

One dilemma is how to ensure essential independent drug information and therapeutic advice are available free of charge to all healthcare professionals. This is fundamentally important to enable up-to-date guidelines for antibiotic therapy as part of essential antimicrobial stewardship programs. However, independent information is equally as important for managing many other problems. Examples include minimising the use of opioids in the management of chronic non-cancer pain, ensuring a capped resource such as immunoglobulin is used appropriately, and ensuring that expensive biological drugs for conditions such as macular degeneration, chronic inflammatory diseases and neoplastic conditions are prescribed to only those patients who are likely to benefit.

How to provide information that is independent may be an insoluble dilemma. External funding inevitably compromises independence while self-funding inevitably excludes those unwilling to pay for information. Health professionals often have to look in several different places to find the information they require. It might well be appropriate that *Australian Prescriber*, Therapeutic Guidelines, the Australian Medicines Handbook and NPS MedicineWise all

have different governance and funding models. However, it would seem timely for discussions to occur about whether or not other structures might better support rational prescribing in the future. The Department of Health has recently reviewed the activities of NPS MedicineWise.<sup>3</sup>

One question is whether or not a national formal assessment of medical students' prescribing skills should be a requirement for the accreditation of all medical schools by the Australian Medical Council.<sup>4</sup> Another topic well worth discussion is how best to involve medical specialists and their peak bodies in ensuring the guidelines developed within their

specialties incorporate quality use of medicines. It is important to ensure that the movement towards 'personalised' medicine does not morph into 'idiosyncratic' medicine.

Given these questions, it may be timely for a future workshop to review the quality use of medicines part of the National Medicines Policy.<sup>5</sup> Rational prescribing remains a challenge in the 21<sup>st</sup> century. ◀

*Conflicts of interest: Rob Moulds is a medical advisor to the Partnership Program of Therapeutic Guidelines Ltd and is also a medical advisor to Health Education Australia Ltd.*

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## Letters to the Editor

### Genetic polymorphisms in opioid metabolism

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The article about serotonergic interactions between antidepressants and opioids<sup>1</sup> was a concise depiction of the influence of enzyme inhibitors and inducers of cytochrome P450 (CYP) 2D6 on the extent of the serotonergic, noradrenergic or opioid effects of codeine and tramadol. However, it is not simply drug–drug interactions, but also genetic polymorphisms that dictate the prevalence of serotonergic, noradrenergic, or opioid metabolites.

Equivalent drug doses can produce vastly different degrees of analgesia or serotonergic toxicity if the patient is an ultra-rapid metaboliser of CYP2D6 (the incidence is 1–28% of the worldwide population), or a poor metaboliser.<sup>2,3</sup> Without this caveat, it could be misleading to label codeine and tramadol as ‘weak’ analgesics.<sup>3</sup>

Codeine is a prodrug metabolised to therapeutically active morphine. In ultra-rapid metabolisers it can be a potent analgesic with risks that may not be appreciated if it is considered as a ‘weak’ opioid.<sup>2</sup> In contrast, codeine offers negligible analgesia to poor metabolisers.

Tramadol’s opioid activity is dependent on metabolism to O-desmethyltramadol via CYP2D6. Ultra-rapid metabolisers experience a lower risk of serotonergic and noradrenergic adverse effects yet greater risks of mu-opioid-receptor agonism and respiratory depression.<sup>4</sup>

The table in the article showed the ‘triptan’ class of drugs as being ‘likely’ to increase the risk of serotonin toxicity.<sup>1</sup> They are primarily agonists of 5-HT<sub>1B</sub> and 5-HT<sub>1D</sub> subtypes, while the harms of serotonin toxicity are believed to be primarily mediated through 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> (as the authors note in other work).<sup>5,6</sup> Due to the clinical benefit of having a triptan and opioid analgesic available for the treatment of severe migraine, it may be counterproductive to suggest they should be combined only cautiously.

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# The safety of commonly used vitamins and minerals

## SUMMARY

Dietary supplements are the most common type of complementary medicine in Australia, reportedly used by 47% of the population. Vitamins and minerals are particularly popular.

Like all medicines, supplements can cause potential harms such as adverse reactions, drug interactions, monetary cost, delay of more effective therapy, false hope, and increased medication burden.

Although most vitamins and minerals are available for open sale, many are subject to legal restrictions as scheduled medicines, depending on the dose.

Consumers are at risk of overdose when the same ingredient is present in multiple products.

Health professionals can assist consumers by discussing the potential benefits and harms of vitamins and minerals and assisting them to find authoritative information.

Adverse events with vitamins and minerals should be reported to the Therapeutic Goods Administration.

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## Keywords

adverse effects, complementary medicines, dietary supplements, minerals, safety, vitamins

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## Introduction

Dietary supplements are natural health products used to supplement the diet, such as vitamins, minerals, amino acids, enzymes, plant extracts, algae and macroscopic fungi.<sup>1</sup> Although these products are more commonly referred to as complementary medicines in Australia, particularly for regulatory purposes by the Therapeutic Goods Administration (TGA), the term dietary supplement is frequently used by consumers whose intention is to augment their diet rather than treat disease.

Dietary supplements dominate the complementary medicines industry in Australia. Sales reached AU\$5.6 billion in 2019 after having more than doubled over the preceding 10 years.<sup>2</sup> Complementary medicines are in widespread use in Australia, with a recent national survey showing 63% of people use them regularly. Dietary supplements containing vitamins and minerals were the most popular type of complementary medicine and were reportedly used by 47% of respondents.<sup>3</sup>

## Potential harms of vitamins and minerals

One reason for the persistent popularity of vitamins and minerals is the perception that they are harmless. There are many potential harms (see Box 1 for potential adverse effects of commonly used vitamins and minerals) but, unlike conventional medicines, manufacturers of vitamins and minerals are not required to submit extensive documentation about safety or

effectiveness of their products in order to be included in the Australian Register of Therapeutic Goods.

It is wise to remember that there are several different types of harm that can occur with any medicine other than just adverse drug reactions. See Box 2 for the six potential harms which may be a helpful guide to risk assessment.<sup>4</sup>

Marketing of vitamins and minerals is generally based on their claimed benefits with little, if any, mention of their potential harms. Consumer information leaflets are not provided, and few dietary supplements carry warnings of potential adverse effects on their packaging. Nonetheless, there are well-recognised harms from the ingredients of dietary supplements, especially when taken in high doses. For example, higher dose products of vitamin A and selenium are regulated as Schedule 2, 3 and 4 medicines because of their documented toxicity.

Vitamins and minerals are generally used safely when prescribed in medical settings for the treatment or prevention of deficiency states and other appropriate conditions. For example, vitamin B<sub>3</sub> is used for hyperlipidaemias and folic acid is used in pregnancy to prevent birth defects (e.g. anencephaly, spina bifida). The key to the safety of vitamins and minerals is the prescribed dose, which is usually derived from research demonstrating that the benefits outweigh the harms. This is often not the case when consumers are self-medicating with products purchased on the open market, as consideration is rarely given to the

**Box 1 Potential adverse effects of commonly used vitamins and minerals****Vitamin A/retinol**

Acute toxicity associated with ingestion >300,000 IU. Chronic toxicity (hypervitaminosis) associated with doses >10,000 IU/day. Symptoms of chronic hypervitaminosis A include skin desquamation, liver impairment, loss of vision and severe intracranial hypertension.

**Vitamin B<sub>3</sub>/niacin/nicotinic acid**

Moderate to high doses of vitamin B<sub>3</sub> are commonly associated with peripheral vasodilation causing skin flushing, burning sensation, pruritus and hypotension. Vasodilation may also occur in the eye resulting in reversible toxic cystoid macular oedema.

**Vitamin B<sub>6</sub>/pyridoxine**

Doses ≥200 mg/day of vitamin B<sub>6</sub> have been associated with severe sensory peripheral neuropathies. Risk often arises from multiple products being taken all containing pyridoxine.

**Vitamin C/ascorbic acid**

Associated with precipitation of cysteine, urate or oxalate kidney stones, especially in people with a predisposition for kidney stones. Vitamin C may reduce effectiveness of antineoplastic drugs such as vincristine, doxorubicin, methotrexate, cisplatin and imatinib.

**Vitamin D/colecalciferol**

Very high doses may cause hypercalcaemia, with symptoms from thirst and polyuria to seizures, coma and death. High intermittent doses of vitamin D have been associated with increased risk of falls and fracture in the elderly.

**Vitamin E/alpha-tocopherol**

Antiplatelet effect and increased risk of haemorrhagic stroke reported.

**Calcium**

Carbonate salt can cause gastric reflux and constipation. High-dose calcium may induce vascular and soft tissue calcification, hypercalciuria, kidney stones and secondary hypoparathyroidism. Interferes with absorption of magnesium, iron and zinc if taken simultaneously, and can reduce absorption of many other drugs e.g. levothyroxine, tetracyclines.

**Magnesium**

High doses often result in diarrhoea, nausea and abdominal cramping due to the osmotic effect. Like other divalent cations, magnesium may chelate and reduce absorption of other minerals or medicines such as tetracyclines.

**Zinc**

Often associated with altered or impaired taste and smell. Intranasal zinc can cause anosmia. Doses ≥80 mg/day in clinical trials were associated with adverse prostate effects.

**Selenium**

Associated with acute and chronic toxicity. Signs of chronic high-dose 'selenosis' are hair and nail loss or brittleness, lesions of the skin and nervous system, nausea, diarrhoea, skin rashes, mottled teeth, fatigue and mood irritability.

**Box 2 Six potential harms of a supplement or medicine****Adverse effects**

Adverse effects should be considered from short- or long-term use, high or low dose, risk during pregnancy or breastfeeding, influence on disease, fertility or malignancy.

**Drug interactions**

Drug-drug or drug-disease interactions, dynamic or kinetic.

Enzyme and transporter interactions, all of which can make other drugs more toxic or less effective.

**Cost**

The cost of dietary supplements can be harmful due to its impact on finances and the ability to afford treatment or other essential items.

**Delay of more effective therapy**

Time spent taking ineffective products may delay more effective interventions, waste valuable time and allow disease progression.

**False hope or fraud**

Falling for fraudulent claims offering false hope can be demoralising and depressing, which for some can make the difference between continuing to manage a health condition and giving up hope.

**Medication burden**

As the number of medicines and supplements increases, so too does the burden of polypharmacy which increases the risk of medication error, interactions and adverse events.

effective or safe dose. Indeed, overdose of ingredients from multiple products, such as pyridoxine or vitamin A, is a much-neglected risk.

For consumers to make balanced and informed decisions about using dietary supplements, details regarding both their benefits and harms should be evidence-based and readily available. Such information can be found, especially on the internet, but consumers have to be motivated to look, know where to look, and know how to critique the information. Health professionals can assist consumers by openly discussing the risks and benefits of dietary supplements, explain why dose is important, and direct them where to go for higher quality information beyond advertising and the manufacturer's label. See Box 3 for links to information resources freely available to both consumers and health professionals regarding dietary supplements and complementary medicines.

When taking a comprehensive history, health professionals should include dietary supplements, detailing the brand, its ingredients and the dose taken in order to assess both the potential benefits and risks, and the potential for cumulative overdose from multiple products. As with all medicines, adverse events associated with dietary supplements should be reported to the TGA ensuring brand names are specified so all ingredients can be identified.

Adapted from reference 4

### Box 3 **Freely available resources regarding dietary supplements and complementary medicines**

#### About Herbs – Memorial Sloane Kettering Cancer Care Centre

<http://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs/search>

#### Drugs.com

[www.drugs.com](http://www.drugs.com)

#### National Institutes of Health, Office of Dietary Supplements

<https://ods.od.nih.gov/HealthInformation/makingdecisions.sec.aspx>

#### National Institutes of Health, National Center for Complementary and Integrative Health

[www.nccih.nih.gov](http://www.nccih.nih.gov)

## Vitamin A

Vitamin A, also known as retinol, is associated with acute and chronic toxicity. Acute toxicity is mostly caused by accidental ingestion of 300,000 IU or more.<sup>5</sup> Signs and symptoms include headache, blurred vision, dizziness, nausea, vomiting and reduced motor coordination secondary to intracranial hypertension.<sup>6</sup>

Vitamin A toxicity can occur with regular ingestion of more than 100,000 IU daily, which may be contributed to by synthetic retinoids. Symptoms of chronic hypervitaminosis A include skin desquamation, liver impairment, loss of vision and severe intracranial hypertension.<sup>6</sup>

Vitamin A taken by pregnant women is associated with birth defects. Ingestion of high-dose vitamin A (>15,000 IU/day from combined sources of food and supplements or >10,000 IU/day from supplements only) has been associated with an increased incidence of craniofacial malformations as well as central nervous system, heart and limb abnormalities.<sup>7</sup>

## Vitamin B<sub>3</sub>

Moderate to high doses of vitamin B<sub>3</sub> (niacin/nicotinic acid) (500 mg/day or more) are commonly associated with peripheral vasodilatation causing skin flushing, burning sensation, generalised pruritus and hypotension, lasting for 20–30 minutes and declining in severity and frequency with time.<sup>8</sup> Niacin-induced vasodilatation also occurs in the eyes. This can result in reversible toxic cystoid macular oedema in 0.67% of patients taking doses of niacin 3–4.5 g daily.<sup>9</sup> Doses of

3 g or more of niacin per day have caused blurred vision, eyelid oedema, toxic amblyopia, proptosis, loss of eyelashes or eyebrows and superficial punctate keratitis.<sup>10</sup>

## Vitamin B<sub>6</sub>

Vitamin B<sub>6</sub> (pyridoxine) has been associated with severe sensory peripheral neuropathies most frequently in doses over 200 mg/day.<sup>6</sup> Because of this potential neurotoxicity, products containing pyridoxine with a daily dose more than 200 mg/day are Schedule 4 prescription-only medicines in Australia and overseas.<sup>11</sup>

## Vitamin C

Urine acidification from supplemental vitamin C (ascorbic acid) in doses as low as 250 mg/day has been associated with precipitation of cysteine, urate or oxalate kidney stones, especially in men and people with a predisposition for kidney stones.<sup>6,12–14</sup> Vitamin C also has many well-known pharmacodynamic drug interactions. One of the more serious interactions is that it may reduce the effectiveness of antineoplastic drugs such as vincristine, doxorubicin, methotrexate, cisplatin and imatinib.<sup>15</sup>

## Vitamin D

Vitamin D (colecalciferol) in doses of 1000–2000 IU/day is well tolerated. However, there are increasing reports of toxicity which appear to relate to manufacturing errors, prescribing errors and the increasing use of high-dose supplements. Toxicity is mediated through hypercalcaemia, with symptoms ranging from thirst and polyuria to seizures, coma and death.<sup>16</sup> High-dose vitamin D in the range of 300,000–500,000 IU administered as an annual intramuscular injection for osteoporosis has been associated with increased risk of fracture.<sup>17,18</sup> Doses of 4000–10,000 IU/day have been associated with diminished bone density.<sup>19</sup>

## Vitamin E

Vitamin E has been associated with an antiplatelet effect and two clinical trials have found an increased risk of haemorrhagic stroke in people taking alpha-tocopherol.<sup>20</sup> Two meta-analyses of randomised trials have also raised questions about the safety of high-dose vitamin E in daily doses of 400 IU or more for over one year, which have linked supplementation with small but statistically significant increases in all-cause mortality.<sup>6,21</sup>

## Calcium

Calcium supplementation, especially in the carbonate salt, can cause gastric reflux and constipation. High-dose calcium may induce vascular and soft

tissue calcification, hypercalciuria, kidney stones and secondary hypoparathyroidism.<sup>22</sup> Calcium also interferes with the absorption of magnesium, iron and zinc if taken simultaneously.<sup>23</sup>

### Magnesium

Magnesium in high doses from dietary supplements or medicines often results in diarrhoea, nausea and abdominal cramping due to the osmotic effect of unabsorbed salts in the intestine.<sup>24</sup> The salts most likely to cause diarrhoea are magnesium carbonate, chloride, gluconate and oxide.<sup>6</sup> Symptoms of hypermagnesaemia usually develop when serum concentrations exceed 1.74–2.61 mmol/L and include hypotension, nausea, vomiting, facial flushing, urine retention, ileus, depression and lethargy. This may progress to muscle weakness, difficulty breathing, extreme hypotension, irregular heartbeat and cardiac arrest.<sup>25</sup>

### Zinc

Zinc, even in small doses, is associated with adverse effects on taste and smell. Anosmia is associated with intranasal use.<sup>6</sup> Acute high-dose zinc (>40 mg/day) can cause nausea, vomiting, abdominal cramps, diarrhoea and headaches.<sup>26</sup> It is well established that long-term high-dose zinc can induce copper deficiency.<sup>6</sup> In the Age-Related Eye Disease study (AREDS), 80 mg/day of zinc oxide for an average of 6.3 years was associated with a significant increase in hospitalisations for genitourinary causes. This raises the possibility that chronic high-dose zinc adversely affects prostate health.<sup>27</sup>

### Selenium

Selenium toxicity can occur with acute or chronic high-dose ingestion.<sup>6</sup> Early indicators of excess intake are 'garlic breath' and a metallic taste in the mouth. Signs of chronic high selenium intake or 'selenosis' are hair and nail loss or brittleness, lesions of the skin and nervous system, nausea, diarrhoea, skin rashes, mottled teeth, fatigue and mood irritability. Oral selenium products with a daily dose of 300 micrograms or more are regulated as Schedule 4 medicines because of their potential toxicity.<sup>11</sup>

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### Iron salts

Adverse effects of oral iron supplements are dose related, so a key predictor of harm is assessing how much elemental iron is being taken. Some commercial iron supplements only contain tiny doses, that is 10–20 mg iron per unit, which reduces the risk of adverse effects but also the chance of benefit.

Typical adverse effects of therapeutic iron doses, such as 100–200 mg/day include abdominal pain, nausea, vomiting, constipation, diarrhoea and black discoloration of faeces. Black discoloration of teeth is associated with liquid iron preparations.

### Folic acid

Folic acid is well tolerated in fortified foods and supplemental doses used for medical indications up to 1 mg daily.<sup>6</sup> Doses from 5–15 mg/day have been associated with a range of gastrointestinal adverse effects including abdominal cramps, diarrhoea, nausea, flatulence and a bitter taste in the mouth.<sup>6</sup>

Due to its antagonistic effects, folic acid reduces the adverse effects of methotrexate used in management of rheumatoid arthritis. However, it may decrease the efficacy of methotrexate in the treatment of acute lymphoblastic leukemia<sup>28</sup> and psoriasis.<sup>29</sup> Excess folate or folic acid may mask vitamin B<sub>12</sub> deficiency.<sup>30</sup>

### Conclusion

Dietary supplements have a range of potential risks and few benefits. Consumers should be aware that there is no case for vitamin or other supplements in normal healthy people, who are not pregnant or breastfeeding and are consuming a healthy diet.<sup>31</sup>

In order to make informed decisions about dietary supplement use, consumers require information on both their benefits and harms. As the risks of dietary supplements are not well known, manufacturers should be required to make this information more readily available. Health professionals and consumers should report adverse events associated with dietary supplements to the TGA. ◀

*Conflicts of interest: none declared*



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# Management of insomnia in primary care

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## Keywords

benzodiazepines, cognitive behavioural therapy, hypnotics, insomnia, sleep disturbance, sleep-wake disorders

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## SUMMARY

Insomnia can have significant health and economic impacts. In contrast, sleep disturbance is common but does not usually affect daytime activity.

Short-term approaches for acute insomnia are often appropriate. These include dealing with precipitating factors such as stress.

Chronic insomnia has a high relapse and recurrence rate. It is best managed with cognitive behavioural therapy which includes sleep hygiene, stimulus control and sleep restriction.

In primary care, brief behavioural therapy for insomnia is an accessible and effective management strategy. If there is no response, referral should be considered.

Adjuvant use of drugs in insomnia may be appropriate in some cases. Prescription should be for a limited duration.

## Introduction

Insomnia is a common sleep disorder involving difficulty initiating or maintaining sleep and results in daytime consequences (see Box).<sup>1</sup> Chronic insomnia is the most prevalent sleep disorder and affects 12.2% of Australian adults. It is often under-recognised with only 7.5% reporting that they have had a diagnosis by a medical professional.<sup>2</sup> Inadequate sleep and chronic insomnia are associated with a high burden

of disease with an increased risk of depression, cardiovascular disease and death.<sup>3–5</sup> People suffering from insomnia have greater work absenteeism, reduced productivity and are more likely to access healthcare with increased presentations to general practice and hospital.<sup>6,7</sup>

The cost of insufficient sleep in Australia is significant. The associated healthcare costs are \$1.24 billion with an estimated \$12.19 billion in lost productivity.<sup>8</sup>

## Evaluation and diagnosis

It is important to take a thorough history to distinguish between insomnia and sleep disturbance. While sleep disturbance, with difficulty initiating and maintaining sleep, is a common complaint, many people continue to function well throughout the day. In contrast, insomnia has an impact on daytime functioning.<sup>1</sup> Presentations with sleep disturbance stem from a belief that sleep is failing to meet expectations rather than having any true negative consequences. This belief is often perpetuated by society's emphasis on the importance of obtaining perfect sleep for optimal health and well-being.

## Acute insomnia

Short-term insomnia with sleep disturbance and daytime impacts for less than three months will often occur in response to a precipitating stressor which results in a predictable change in sleep quality.<sup>1</sup> Acute insomnia is at risk of evolving into chronic insomnia if individuals develop changed thinking and maladaptive behaviours around sleep.<sup>9</sup> For example, if people are not sleeping well, it is common for them to retire to bed earlier wishing to get to sleep, which leads to spending longer in bed getting frustrated about not

### Box Diagnostic criteria of insomnia<sup>1</sup>

Dissatisfaction with sleep quality or quantity associated with one or more of the following:

- difficulty initiating sleep
- difficulty maintaining sleep (frequent awakenings or problems returning to sleep after awakening)
- early morning awakening with inability to return to sleep.

Disturbance causes clinically significant distress or impairment (social, occupational, educational, academic, behavioural or other important areas of functioning).

Frequency of at least three nights per week.

Duration more than three months.

Occurs despite adequate opportunity for sleep.

Is not better explained by, and does not occur exclusively during, the course of another sleep-wake disorder (e.g. narcolepsy, breathing-related sleep disorder, a circadian rhythm sleep-wake disorder, parasomnia).

Coexisting mental disorders and medical conditions do not adequately explain the predominant complaint of insomnia.

Insomnia is not attributable to the physiological effects of a substance (e.g. drug of abuse or medicine).

sleeping. People can also start using countermeasures like caffeine to reduce tiredness during the day, which can negatively impact on sleep on subsequent nights.

### Chronic insomnia

Chronic insomnia or insomnia disorder is defined as a sleep disturbance occurring on three or more nights per week, over a three-month period, which results in significant distress or impacts on daytime functioning.<sup>1</sup>

There is a high rate of recurrence so a previous history of insomnia is a significant predictor of the future development of insomnia disorder.<sup>10</sup> In a longitudinal study of 388 patients with chronic insomnia, 46% of patients had persistent symptoms at three years and 14% had a relapse following remission of their insomnia.<sup>11</sup>

### Comorbidities

Comorbid disorders such as depression, anxiety and chronic medical conditions are common.<sup>12</sup> As insomnia and comorbidities can impact on each other, comprehensive assessment and management of all contributing conditions is essential.

Insomnia may also present in conjunction with a comorbid sleep disorder. Up to 50% of people with obstructive sleep apnoea will report symptoms of insomnia and may have difficulty in adhering to continuous positive airway pressure (CPAP) therapy.<sup>13</sup> While tiredness and fatigue are common symptoms of insomnia, excessive daytime sleepiness is uncommon and warrants further investigation and exclusion of sleep disordered breathing. Other sleep disorders such as restless legs syndrome and circadian rhythm disorders can also present as insomnia.

### Initial management

In patients with acute insomnia, a short-term approach to improve sleep quality is appropriate. This may involve strategies to reduce acute distress and possibly a short course of a hypnotic drug. Given the poorer prognosis with chronic insomnia, longer term management strategies are required to improve outcomes.

The key principles in the management of insomnia include reducing sleep-related anxiety and maladaptive behaviours around sleep, in addition to addressing comorbidities and precipitating factors. Education about sleep is an important component, addressing unrealistic or misinformed expectations about sleep which often perpetuate symptoms of insomnia. A stepped-care approach to insomnia in primary care may be appropriate given the high prevalence of insomnia and limited numbers of specialist sleep medicine and sleep psychology practitioners.<sup>14,15</sup>

### Cognitive behavioural therapy

Cognitive behavioural therapy for insomnia is recommended as first-line therapy. It has five components (see Table):<sup>16</sup>

- sleep hygiene
- sleep restriction
- stimulus control
- relaxation strategies
- cognitive therapy.

Sleep hygiene aims to promote healthy behaviours and a conducive environment to improve sleep quality. However, there is limited evidence supporting sleep hygiene as a sole behavioural strategy and patients are at risk of developing maladaptive behaviours around sleep.<sup>17</sup>

Sleep restriction is a behavioural strategy that aims to reduce the time spent awake in bed by matching total time in bed with estimated sleep duration. A randomised trial involving 45 patients with chronic insomnia reported an improvement in symptoms in 73% of those receiving sleep restriction therapy and sleep hygiene compared with 35% of a control group receiving sleep hygiene alone.<sup>18</sup>

Stimulus control strategies aim to improve sleep quality by implementing a consistent sleep-wake schedule and strengthening cues that promote sleep. Strategies include directing patients to only go to bed when sleepy and leaving the bedroom to engage in another activity if they fail to fall asleep or wake during the night. These strategies attempt to reduce sleep-related anxiety and a conditioned response around sleep.

Brief behavioural therapy for insomnia combines sleep restriction and stimulus control strategies. In a randomised controlled trial of 82 patients there was remission in 36% and a response in 60% of patients after six months of follow-up.<sup>19</sup> The therapy consists of two face-to-face sessions, with an assessment and intervention session for 45–60 minutes and a 30-minute follow-up session after two weeks. As it does not require specialist training and can be delivered in an efficient manner, the Royal Australian College of General Practitioners supports its use by GPs and practice nurses.<sup>20</sup>

In patients who do not respond to brief behavioural therapy, cognitive therapies for insomnia may be required. Referral to a sleep psychologist should be considered.

Cognitive behavioural therapy is an effective long-term intervention, with a meta-analysis reporting significant improvement in sleep onset latency and sleep efficiency extending to 12 months.<sup>21</sup> It is generally delivered weekly for two to eight sessions by a psychologist or trained health professional. However, there can be a significant barrier to access in primary care given the shortage of specialist sleep medicine and sleep psychology practitioners.

Table Components of cognitive behavioural therapy for insomnia

| Components                    | Rationale   | Directions  |
|-------------------------------|---|---|
| Sleep hygiene                 | Promotes healthy bedtime behaviours and an ideal environment for sleep  | Behaviours: <ul style="list-style-type: none"> <li>• Avoid caffeine and nicotine before bedtime</li> <li>• Maintain a regular bed and wake time</li> <li>• Take regular daytime exercise</li> </ul> Environment: <ul style="list-style-type: none"> <li>• Maintain bedroom as a place to sleep</li> <li>• Reduce noise and light</li> <li>• Control temperature</li> <li>• Avoid bedroom clutter</li> </ul>   |
| Sleep/time in bed restriction | Aims to balance estimated total sleep time with opportunity to sleep. This reduces the unnecessary amount of time spent in bed awake and increases sleep drive and sleep debt to consolidate sleep on subsequent nights | Assess patient's natural time of feeling sleepy and estimated total sleep time overnight (a sleep diary is often helpful in this setting).<br>Schedule a fixed bed and wake time based on estimated total sleep time, with at least six hours of opportunity for sleep, aiming for no longer than 30 minutes of wakefulness.<br>Maintain a consistent sleep-wake schedule regardless of how much sleep is obtained overnight<br>Lengthen sleep window in 30-minute increments on subsequent reviews depending on progress |
| Stimulus control              | Promotes a consistent sleep-wake schedule and reduces conditioned response around sleep   | Avoid naps during the day to increase natural homeostatic sleep drive<br>Only go to bed when sleepy<br>If unable to fall asleep or waking for prolonged periods during the night, engage in another activity<br>Only return to sleeping position or bed when sleepy   |
| Relaxation strategies         | Aim to reduce hyperarousal that often underpins insomnia and to improve stress management   | Meditation<br>Breathing exercises<br>Progressive muscle relaxation<br>Guided visualisation practices<br>Implement short relaxation periods at various times during the day  |
| Cognitive therapy             | Encourages thought restructuring around sleep and promotes mindfulness  | Challenge unhelpful beliefs and attitudes around sleep including the requirement for a certain number of hours of sleep, the health impacts of insomnia and attributional biases attached to inadequate sleep   |

### Drug management

Up to 40% of patients with insomnia will have ongoing symptoms despite cognitive behavioural therapy.<sup>22,23</sup> If drug therapy is considered, it is important to evaluate the underlying nature of the patient's insomnia and what the intended outcome of prescribing is.

#### Acute insomnia

Short-term drug therapy may be appropriate in acute insomnia with an identifiable precipitating stressor, illness or circumstances, in order to prevent progression to chronic insomnia. This would generally be of short duration, up to four weeks, while in parallel working on addressing the acute precipitating circumstances.

### Chronic insomnia

In patients with chronic insomnia and high levels of distress, using a drug as an adjunct to cognitive behavioural therapy can be helpful to provide predictability with sleep and prevent escalation of sleep-related anxiety. In a trial of 160 adults with chronic insomnia, patients were randomised to receive cognitive behavioural therapy alone, or in conjunction with zolpidem for the first six weeks. The group that had combined therapy for six weeks, then cognitive behavioural therapy alone during six months of extended therapy, had the best outcomes with remission rates of 68% at six months.<sup>22</sup> This study demonstrated the importance of addressing distress associated with insomnia early in treatment

(first six weeks in this study), while people are working through cognitive behavioural therapy and increasing their skills and confidence in the cognitive and behavioural strategies. However, when prescribing any medicine in chronic insomnia it should be discussed with patients that the medicine is only intended as being short term as effects generally reduce over time.

Melatonin (2 mg extended-release formulation) is effective in treating insomnia in adults over the age of 55 over a 13-week period.<sup>24</sup> It may also be useful in patients with a circadian rhythm disturbance, resulting in sleep onset insomnia or early morning awakening.<sup>24,25</sup> However, there is little evidence to guide formulation, dose and duration of therapy when used outside of melatonin's registered indication of insomnia in adults over the age of 55 years.

Suvorexant, a dual orexin receptor antagonist, can be an effective treatment in sleep maintenance insomnia due to hyperarousal. It can improve sleep latency, sleep maintenance and total sleep time compared to placebo.<sup>23,26</sup>

Benzodiazepines and benzodiazepine receptor agonists, including zolpidem and zopiclone, are effective short-term therapies for sleep onset and sleep maintenance insomnia. Data on long-term efficacy are limited.<sup>23,27</sup>

There is a risk of drug dependency, tolerance and abuse, but limiting dose escalation and regular monitoring are likely to mitigate this risk.<sup>23</sup> When prescribing these drugs for insomnia, a harm-benefit assessment should be undertaken, with particular care in the elderly population. Sleep-promoting medicines can interact with other drugs that cause sedation, including alcohol, and should be used cautiously in these circumstances. Hypnotic drugs may increase the risk of falls, but so does a lack of sleep.

Despite a lack of evidence, antidepressants, sedating antipsychotics and antihistamines are often prescribed for the treatment of insomnia despite having significant potential adverse effects.<sup>28-30</sup> These drugs are not recommended because of this limited evidence and their adverse effects.<sup>23</sup>

## Stopping drugs

Benzodiazepines and benzodiazepine receptor agonists are only recommended for short-term use, up to four weeks, so a strategy for their safe withdrawal is required. In a systematic review and meta-analysis, combining cognitive behavioural therapy with gradual tapering of the drugs over three months was more effective for stopping the drugs than gradual tapering alone. The combination was associated with short-term improvement in the symptoms of insomnia.<sup>31</sup>

## Referral

Referral to a sleep specialist for further evaluation should be considered in patients with insomnia who have a possible comorbid sleep disorder, do not respond to brief behavioural therapy or have persistent and distressing symptoms. The Australasian Sleep Association Sleep Services Directory is a useful resource to assist with referrals.<sup>32</sup> When it is suspected that insomnia is related to other comorbidities such as depression or anxiety, referral to a psychiatrist should be considered.

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## Conclusion

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Chronic insomnia disorder is a common condition that presents many challenges in its evaluation and management in primary care due to limited resources and support. Brief behavioural therapy for insomnia is an efficient management strategy that does not require specialised training and can be used effectively as first-line therapy in general practice.

Drugs may be useful as a short-term approach during episodes of acute insomnia, as an adjuvant to behavioural therapy or when there is a high level of distress. The nature of the patient's insomnia and the intended effect should be taken into consideration when prescribing. There should be a harm-benefit assessment before starting drug therapy and a plan for stopping it. Referral to specialised sleep services for complex patients is recommended. ◀

*Conflicts of interest: none declared*

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# The ocular adverse effects of oral drugs

## SUMMARY

Some commonly prescribed drugs have ocular adverse effects. Many parts of the eye can be affected by oral drugs. Some ocular adverse effects may be reversed with medical or surgical intervention whereas other drugs may cause irreversible loss of vision.

The risk of visual loss can be reduced by a number of approaches, including monitoring for ocular toxicity, reducing the drug dose, or stopping the drug and looking for an alternative. This can be supported by good communication between the prescribing clinician and ophthalmologist.

Infrequent or delayed ocular adverse effects may not be identified in clinical trials of new drugs. Reporting adverse events is therefore important.

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## Keywords

eye, ocular toxicity

## Introduction

Drugs that are taken orally are systemically absorbed, with the potential to affect all parts of the body including the eye. Its rich blood supply and relatively small mass increase the susceptibility of the eye to drug-related adverse effects.<sup>1</sup> Many parts of the eye can be affected by oral drugs. Patients presenting with unexplained ocular symptoms should be asked which drugs they are taking. Table 1 shows some of the ocular adverse effects to consider with common orally administered drug classes.<sup>2-35</sup>

## Structures of the eye affected by oral drugs

Drugs may cause symptoms characteristic of specific eye diseases (Table 2). Some drugs, such as those with anticholinergic activity, affect several parts of the eye (see Fig.).

### Anterior chamber and cornea

Anticholinergic drugs cause the relaxation of the ciliary muscle, leading to temporary blurred vision.<sup>7</sup> They can contribute to dry-eye symptoms by suppressing normal parasympathetic activity. Anticholinergic drugs can also cause the severe adverse effect of angle-closure glaucoma.<sup>7</sup> This usually occurs in long-sighted patients with narrow drainage angles. Angle closure is highly unlikely in patients who have had cataract surgery because removing the lens deepens the anterior chamber.

Bisphosphonates can cause inflammation leading to conjunctivitis, episcleritis, scleritis, keratitis and uveitis. The exact mechanism of this ocular inflammation is not yet known.<sup>14</sup> Symptoms usually emerge more slowly (usually 6–8 weeks) with oral versus intravenous dosing. Unilateral and bilateral ocular presentations have been reported.<sup>14</sup> Bisphosphonates

may also cause corneal or scleral melting which requires urgent ophthalmology referral.

Amiodarone, and other drugs such as hydroxychloroquine, can deposit on the basal epithelial layer of the cornea causing the formation of whirl-like corneal microdeposits called vortex keratopathy.<sup>3</sup> This is usually asymptomatic and does not require stopping the treatment. However, advanced corneal deposits can cause visual symptoms, hence patients should be referred for an ophthalmic review if the keratopathy affects their vision.

Phenothiazines can cause the development of corneal epithelial changes that can eventually result in corneal oedema. The changes of corneal oedema can become permanent if the drug is not stopped promptly.<sup>25</sup>

The long-term use of corticosteroids via any route of administration may increase intraocular pressure by interfering with the outflow from the trabecular meshwork. This is a significant risk factor for the development of glaucoma.<sup>19</sup>

### Iris and lens

Corticosteroids can accelerate cataract progression. Classically, they cause posterior subcapsular cataracts which develop more rapidly than typical age-related nuclear sclerotic cataracts.<sup>19</sup> This may relate to corticosteroid-induced changes to gene transcription in the epithelial cells of the lens.<sup>19</sup> The long-term use of allopurinol has also been linked to cataract formation.<sup>5</sup>

The use of alpha<sub>1</sub> adrenergic receptor antagonists, such as tamsulosin, may lead to the iris becoming mobile during cataract surgery, a phenomenon called intraoperative floppy iris syndrome.<sup>2</sup> The mechanism is probably related to the blockade of alpha<sub>1</sub> adrenergic receptors within the dilator muscle of the iris. Floppy iris syndrome may increase the likelihood of iris or posterior

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Table 1 Common or serious ocular adverse effects of selected oral drugs

| Oral drug  | Ocular adverse effects  | Management  | Action required   |
|--|---|---|---|
| Alpha <sub>1</sub> adrenergic receptor antagonists <ul style="list-style-type: none"> <li>tamsulosin</li> <li>dutasteride</li> <li>finasteride</li> </ul>                                      | Intraoperative floppy iris syndrome resulting in the iris becoming mobile during cataract surgery. <sup>2</sup> This increases the risk of iris damage with greater chance of postoperative blurred vision, sensitivity to light and difficulty driving at night.<br><br>Floppy iris syndrome can also increase the risk of damage to the posterior lens capsule – a poor prognostic factor for cataract surgery. | Usually there is no need to stop the drug as stopping it does not necessarily prevent floppy iris syndrome.<br><br>The ophthalmic surgeon can take precautions during cataract surgery if aware the patient is on this class of drug.   | Inform ophthalmic surgeon of present or past drug use if patient is referred for cataract surgery.  |
| Antiarrhythmics <ul style="list-style-type: none"> <li>amiodarone</li> </ul>   | Corneal microdeposits called vortex keratopathy have been reported in most patients.<br><br>Amiodarone can rarely cause optic neuropathy which may result in permanent visual loss. <sup>3</sup>  | Most are asymptomatic and do not require intervention but advanced corneal deposits can cause visual symptoms. <sup>3</sup><br><br>Consider discussing this potential ocular adverse event when prescribing or dispensing.  | Routine ophthalmology referral only if patient is symptomatic.<br><br>Immediate ophthalmology referral if patient has symptoms of optic neuropathy.   |
| <ul style="list-style-type: none"> <li>digoxin</li> </ul>  | Ocular symptoms include yellowing of vision, scintillating scotoma and blurred vision. These changes are likely due to direct photoreceptor toxicity. <sup>4</sup>  | The visual symptoms usually reverse when digoxin is stopped.  | Routine ophthalmology referral if patient is symptomatic.   |
| Allopurinol  | Long-term use of allopurinol has been associated with the development of cortical and subcapsular cataract formation. <sup>5</sup>  | Consider discussing this potential ocular adverse event when prescribing or dispensing.   | Routine ophthalmology referral if patient is symptomatic.   |
| Anticholinergics including: <ul style="list-style-type: none"> <li>antihistamines</li> <li>antipsychotics</li> <li>antispasmodics, e.g. oxybutynin<sup>6</sup></li> </ul>                      | Reduced tear production (dry eyes).<br>Dilated pupils. <sup>7</sup><br>Decreased accommodation. <sup>7</sup><br>Risk of acute angle-closure glaucoma in patients with narrow angles – this is unlikely to occur if the patient had previous cataract surgery. <sup>7</sup>  | Consider discussing angle-closure glaucoma when prescribing or dispensing.  | Immediate ophthalmology referral if angle-closure glaucoma is suspected.<br><br>Otherwise, routine ophthalmology referral if ocular symptoms persist after stopping the anticholinergic drug or if it has to continue. <sup>7</sup>                   |
| Anticoagulants <ul style="list-style-type: none"> <li>aspirin</li> <li>clopidogrel</li> <li>warfarin</li> <li>apixaban</li> <li>dabigatran</li> <li>rivaroxaban</li> <li>ticagrelor</li> </ul> | Potential haemorrhagic complications during peri-ocular surgery. <sup>8</sup>   | Discussion of possible cessation before certain types of surgery such as eyelid surgery. <sup>8</sup><br><br>Anticoagulants do not always need to be stopped before cataract surgery, especially if it is performed under topical anaesthesia. The ophthalmic surgeon should provide guidance.<br><br>Anticoagulants are not routinely stopped before intravitreal therapy. | Immediate ophthalmology referral if there is bleeding in the eye.<br><br>Subconjunctival haemorrhage on the surface of the eye will usually resolve within 3 weeks and does not require ophthalmology referral if there are no other ocular symptoms. |

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**Table 1 Common or serious ocular adverse effects of selected oral drugs (continued)**

| Oral drug   | Ocular adverse effects   | Management  | Action required   |
|---|--|---|---|
| Antiepileptics<br>• topiramate  | Topiramate can cause secondary angle-closure glaucoma hence onset can sometimes be delayed. Most cases present in the first few weeks of treatment although some cases are reported within hours of treatment. <sup>9-11</sup><br>Visual field defects. <sup>9</sup><br>Oculogyric crisis – a dystonic reaction characterised by prolonged involuntary upward deviation of the eyes. <sup>9,10</sup><br>Uveitis. <sup>9</sup>      | Bilateral angle closure should raise suspicions of a secondary angle-closure mechanism. Topical or systemic aqueous suppressants and topical cycloplegics (e.g. tropicamide, cyclopentolate or atropine) are initially used to manage secondary angle closure.<br>The initial management of primary angle closure is different where, in addition to aqueous suppression, the pupils are constricted with pilocarpine.  | Immediate ophthalmology referral for symptomatic patients. <sup>9</sup>   |
| • gabapentin  | Cases of nystagmus, diplopia and visual field defects have been reported. <sup>12</sup>  | The incidence of visual field defects is low and therefore routine eye screening is not widely recommended. An annual computerised visual field test as part of the patient's routine eye check with an optometrist or ophthalmologist is reasonable.   | Immediate ophthalmology referral is recommended for symptomatic patients.   |
| • vigabatrin  | Patients can develop visual field constriction attributable to vigabatrin. Patients may not notice visual field loss until the central field is affected. <sup>13</sup><br>Patients can also develop optic atrophy with pallor of the optic nerve head. <sup>13</sup>  | A baseline visual field should be obtained before treatment.<br>Computerised visual field assessment should be repeated every 6 months for 5 years and can be extended to annually thereafter in patients who have no visual field defects.<br>The visual field defects may not reverse on cessation of the drug but would likely worsen with continued use. <sup>13</sup>  | Ensure patients on vigabatrin are referred for ophthalmology screening.   |
| Bisphosphonates<br>• alendronate sodium<br>• risedronate<br>• zoledronic acid | These drugs can cause inflammation in the eye leading to conjunctivitis, episcleritis, scleritis, keratitis or uveitis. <sup>14</sup><br>Corneal and scleral melting have been reported.<br>Symptoms usually emerge more slowly (usually 6–8 weeks) with oral versus intravenous dosing. <sup>14</sup>   | Ocular signs usually abate after stopping the bisphosphonate but might require topical or oral corticosteroids. <sup>14</sup><br>Symptoms generally recur upon bisphosphonate rechallenge.  | Corneal and scleral melting require urgent ophthalmology referral.<br>Conjunctivitis and episcleritis can be referred routinely to ophthalmology. |
| Chloroquine-based drugs<br>• chloroquine<br>• hydroxychloroquine              | Patients are usually asymptomatic early on but advanced maculopathy or peripheral retinopathy can result in irreversible visual loss. <sup>15-17</sup><br>Patients who have been taking hydroxychloroquine for a period longer than 5 years or have been taking doses greater than 5 mg/kg/day are at an increased risk of maculopathy. Renal or liver impairment or concomitant tamoxifen use increase the risk. <sup>15-17</sup> | Ocular screening consists of structural imaging such as optical coherence tomography or fundus autofluorescence, and functional tests such as computerised visual fields or less widely available multifocal electroretinograms. <sup>15-17</sup><br>Baseline ocular assessment is recommended up to 12 months after starting hydroxychloroquine treatment. Repeat assessment should occur annually after 5 years of treatment or after 12 months in high-risk groups. <sup>15-18</sup><br>Chloroquine has a worse adverse effect profile than hydroxychloroquine and all patients on chloroquine require baseline and at least annual ocular monitoring. | Ensure patients on chloroquine-based drugs are referred for ophthalmology screening.  |

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Table 1 Common or serious ocular adverse effects of selected oral drugs (continued)

| Oral drug   | Ocular adverse effects  | Management  | Action required  |
|---|---|---|--|
| Corticosteroids <ul style="list-style-type: none"> <li>• prednisolone</li> <li>• dexamethasone</li> </ul> | <p>Corticosteroid-induced raised intraocular pressure can lead to glaucoma.<sup>19</sup> Open-angle glaucoma is asymptomatic until advanced.</p> <p>Corticosteroids can accelerate cataract progression and cause posterior subcapsular cataracts.</p>  | <p>Open-angle glaucoma is usually managed with drops or laser. However, more complicated cases may require surgery.</p> <p>Intraocular pressure should be monitored by an optometrist with referral to an ophthalmologist if it is raised. Intraocular pressure often returns to normal following cessation of corticosteroids.</p>   | Routine ophthalmology referral if patient is symptomatic with cataract or noted to have raised intraocular pressure. If the intraocular pressure is greater than 30 mmHg the referral should be expedited. |
| Ethambutol  | <p>Ethambutol can cause optic neuropathy characterised by bilateral central visual loss, decreased colour vision, central visual field defects and eventually optic atrophy.<sup>20</sup></p> <p>Toxicity is dose-related with an incidence of 18% above 35 mg/kg/day and under 1% at 15 mg/kg/day or less.</p>   | <p>Between 30% and 64% of patients will show some visual recovery if the optic neuropathy is detected early and the ethambutol is stopped.<sup>20</sup></p> <p>Baseline ophthalmology assessment is required. Re-assessment every 3 months while the patient remains on low-dose treatment or every month if the dose is above 15 mg/kg/day.</p>  | Ensure patients on ethambutol are referred for ophthalmology screening.  |
| Fingolimod  | <p>Fingolimod-associated macular oedema has been reported in approximately 0.4% of patients. It usually develops within 4 months of starting treatment.<sup>21</sup></p> <p>Patients can report blurred vision, distortion and impaired reading vision.</p>   | <p>Ophthalmic assessment including optical coherence tomography imaging at baseline and then 3–4 months after starting treatment. Ocular surveillance can be annual thereafter or earlier if the patient becomes symptomatic.</p> <p>Fingolimod should ideally not be started within 3 months of intraocular surgery as it can make differentiating postoperative macula oedema from drug toxicity challenging.</p> <p>Patients with fingolimod-associated macular oedema do not always have to stop the treatment. Stopping may cause a rebound of multiple sclerosis. The macular oedema can often be treated with local therapy.</p> | Ensure patients on fingolimod are referred for ophthalmology screening.  |
| Isotretinoin and vitamin A  | <p>Ocular surface signs:<sup>22</sup></p> <ul style="list-style-type: none"> <li>• blepharconjunctivitis</li> <li>• chalazia</li> <li>• corneal opacities</li> <li>• dry eyes.</li> </ul> <p>Retinopathy:<sup>22</sup></p> <ul style="list-style-type: none"> <li>• excess vitamin A may worsen certain retinal dystrophies.</li> </ul>   | Visual symptoms should stop with drug cessation if not too advanced. <sup>22</sup>  | Routine ophthalmology referral if symptomatic.   |
| MEK inhibitors e.g. crizotinib  | <p>Visual disturbances have been reported in patients taking oral MEK inhibitors. Reported ocular adverse effects include:</p> <ul style="list-style-type: none"> <li>• decreased visual acuity</li> <li>• visual field defects</li> <li>• dry-eye symptoms</li> <li>• eyelid abnormalities<sup>23</sup></li> <li>• retinal vein occlusion</li> <li>• MEK-associated retinopathy.<sup>23</sup></li> </ul> | MEK-associated retinopathy has been reported to improve after drug cessation. <sup>23</sup>   | Routine ophthalmology referral if symptomatic.   |

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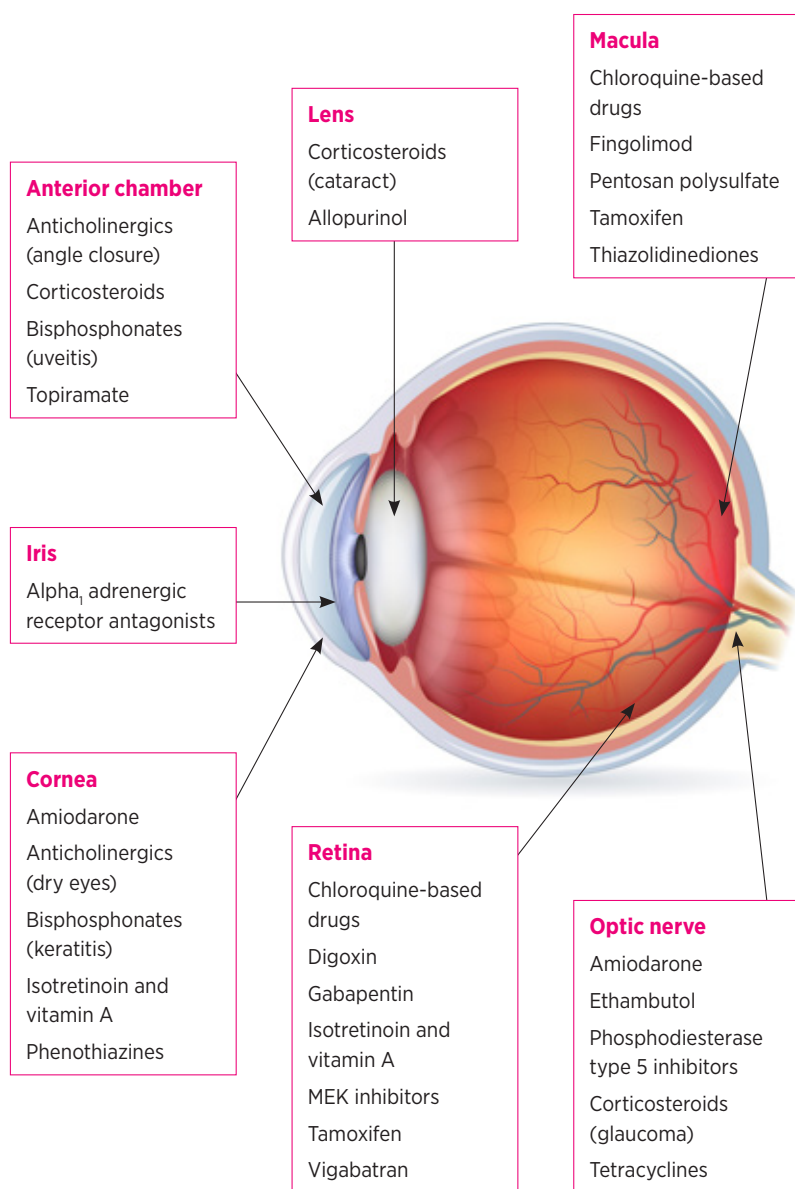
**Table 1 Common or serious ocular adverse effects of selected oral drugs (continued)**

| Oral drug  | Ocular adverse effects   | Management  | Action required  |
|--|--|---|--|
| Pentosan polysulfate   | Pentosan polysulfate maculopathy has been reported to have an incidence of 16%. Retinal pigment epithelial lesions are more common with prolonged use and higher daily and cumulative doses. <sup>24</sup>   | Multimodal retinal imaging can identify pentosan polysulfate maculopathy before irreversible macular damage has developed.<br><br>Patients with cumulative dosages over 500 g should receive annual ophthalmology assessment and those with cumulative dosages over 1000 g, especially over 1500 g, should be monitored for macular toxicity even more regularly.   | Ensure patients on pentosan polysulfate with a cumulative dose over 500 g are referred for ophthalmology screening.                            |
| Phenothiazines   | High doses result in abnormal pigmentation of the eyelids, conjunctiva and cornea. <sup>25</sup><br><br>High doses have been reported to cause corneal epithelial changes. <sup>25</sup><br><br>A rare but serious adverse effect is development of corneal oedema.                | Epithelial keratopathy does not usually cause any visual impairment and normally clears after stopping the drug.<br><br>Corneal oedema may result in irreversible visual impairment if the drug is not stopped promptly. <sup>25</sup>  | Immediate ophthalmology referral in symptomatic patients.  |
| Phosphodiesterase type 5 inhibitors<br>• sildenafil<br>• tadalafil   | A bluish discoloration of vision may occur 1–2 hours after ingestion. <sup>26</sup><br><br>Persistent blurred vision has been reported secondary to non-arteritic ischaemic optic neuropathy, cilioretinal artery occlusion, or central serous chorioretinopathy. <sup>27,28</sup> | Consider discussing this potential ocular adverse event when prescribing or dispensing.   | Routine ophthalmology referral if any persisting visual symptoms. <sup>27,28</sup>   |
| Tamoxifen  | Intraretinal crystalline deposits, macular oedema and punctate retinal pigmentary changes have been reported. <sup>29–32</sup><br><br>The degree of toxicity is related to the dose and duration of tamoxifen use. <sup>30</sup>   | Systematic screening of all symptom-free patients taking the lower dose (20–40 mg a day) for metastatic breast cancer has not been shown to be of high yield in detecting ocular toxicity. <sup>31</sup> However, routine ophthalmological assessment is reasonable in asymptomatic patients on higher doses, treatment for more than 5 years or pre-existing macular disease. <sup>32</sup><br><br>Early crystalline maculopathy without visual symptoms does not always require stopping the drug. Alternative oncological therapies are available if serious ocular complications arise. | Baseline ophthalmology assessment and regular monitoring in high-risk groups.<br><br>Immediate ophthalmology referral in symptomatic patients. |
| Tetracyclines<br>• doxycycline<br>• tetracycline                     | Nausea, vomiting and morning headaches may be symptoms of idiopathic intracranial hypertension which can lead to permanent loss of vision. <sup>33</sup>   | Consider discussing the symptoms of idiopathic intracranial hypertension when prescribing or dispensing this medication.  | Urgent ophthalmology referral if patient is symptomatic.   |
| Thiazolidinediones (glitazones)<br>• pioglitazone<br>• rosiglitazone | May result in development of macular oedema. <sup>34,35</sup>  | Consider an alternative drug in patients with diabetic retinopathy. <sup>34,35</sup>  | Diabetic retinopathy screening as per national guidelines and immediate ophthalmic referral in symptomatic patients.                           |

Table 2 Symptoms associated with disease of different parts of the eye

| Disease                                  | Symptoms   |
|--|--|
| Angle-closure glaucoma                   | Ocular pain, haloes around lights, nausea and vomiting                     |
| Corneal disease                          | Photophobia, grittiness, ocular pain, blurred vision                       |
| Ocular inflammation (uveitis, scleritis) | Photophobia, blurred vision, ocular pain, floaters                         |
| Cataract                                 | Constant clouded, blurred and dim vision, glare (for example when driving) |
| Macular disease                          | Distortion, central scotoma, blurred vision, difficulty reading            |
| Optic neuropathy                         | Impaired colour vision, red desaturation, blurred vision, field defect     |

Fig. Examples of drugs affecting different parts of the eye



capsule damage during intraocular surgery. Usually there is no need to stop the drug as stopping it does not necessarily prevent floppy iris syndrome. Instead, the ophthalmic surgeon should be informed so they can take appropriate precautions during cataract surgery.

**Retina**

Chloroquine and hydroxychloroquine can cause degeneration of the retina and retinal pigment epithelium.<sup>15-17,36</sup> The risk of toxicity is increased with higher doses and a longer duration of treatment. Additional risk factors are renal or liver impairment or concomitant tamoxifen use. Toxicity can lead to reduced visual acuity, paracentral scotomas and bull's eye (parafoveal) maculopathy. Retinopathy does not always develop in a bull's eye pattern as a more peripheral paracentral pattern of damage can be observed in patients of Asian backgrounds. As a result, screening practices need to be adjusted to recognise both paracentral and parafoveal retinopathy. The damage may be irreversible. Ocular screening during treatment is therefore recommended (Table 1).<sup>15-17,36,37</sup>

Tamoxifen retinal toxicity can cause symptoms of decreased visual acuity and colour vision with signs of intraretinal crystalline deposits, macular oedema and punctate retinal pigment epithelial changes. These adverse effects usually occur with higher doses of the tamoxifen (Table 1).<sup>29-32</sup>

Digoxin can cause ocular symptoms including yellowing of vision, scintillating scotoma and blurred vision. These changes are likely to be due to direct photoreceptor toxicity.<sup>4</sup> The visual symptoms usually reverse when digoxin is discontinued.

Fingolimod, used in the management of multiple sclerosis, has secondary effects on the function of the vascular-endothelial barrier, thereby potentially compromising the blood-retina barrier. Fingolimod-associated macular oedema can cause blurred vision, distortion and impaired reading vision.<sup>21</sup> Patients with fingolimod-associated macular oedema do not always have to stop treatment because of the risk of a flare-up of the multiple sclerosis. The macular oedema can often be treated with ocular therapy.

New ocular adverse effects are being identified with the increased use of oral immune-based therapies such as kinase inhibitors. These include visual disturbances, visual field defects as well as retinal vein occlusion and MEK-associated retinopathy. Communication between the physician and ophthalmologist is important if ocular adverse effects are suspected.<sup>23</sup>

Thiazolidinediones, such as pioglitazone, have been associated with systemic fluid retention. These drugs can worsen diabetic macular oedema, especially in patients with pre-existing diabetic retinopathy.<sup>6,34,35</sup>

Drugs for erectile dysfunction, such as sildenafil, can inhibit photoreceptor function. This may cause transient blurring of vision or altered colour perception. There have also been reports of non-arteritic ischaemic optic neuropathy, cilioretinal artery occlusion and central serous chorioretinopathy.<sup>26-28</sup> Routine referral to an ophthalmologist is required if there are persisting visual symptoms.

Central serous chorioretinopathy is characterised by the accumulation of fluid in the central vision of patients. Symptoms include blurred central vision, distortion and washing out of colours. Central serous chorioretinopathy is associated with systemic steroid use and has been reported with sildenafil.

Vigabatrin has been associated with the development of visual field constriction. Patients may not notice any visual field loss until the central field is affected. The visual field defects do not reverse when the drug is stopped and may worsen with continued use. Hence, a computerised visual field assessment is usually obtained before treatment and is repeated every six months for five years. This can then be extended to an annual review if the patient does not have any visual field defects.<sup>13</sup>

### Optic nerve

Amiodarone may rarely induce optic neuropathy.<sup>3</sup> This is characterised by swelling of the optic discs in addition to the typical symptoms of optic neuropathy (Table 2). The main differential diagnosis is non-arteritic anterior ischaemic optic neuropathy, which is more common in patients with vasculopathy and is associated with an altitudinal monocular visual field defect (superior or inferior half of the vision is affected). Tetracyclines have been reported to cause idiopathic intracranial hypertension which in some instances can lead to permanent loss of vision.<sup>33</sup> Nausea, vomiting and morning headaches, as well as the symptoms of optic neuropathy (Table 2), can be suggestive of idiopathic intracranial hypertension.

Ethambutol can cause optic neuropathy. Animal studies have suggested retinal ganglion cells are

predominantly affected.<sup>32</sup> Risk factors include higher doses, prolonged use, poor renal function and concurrent antiretroviral therapy.

### Management of ocular adverse effects

Consultation with an ophthalmologist is recommended if a drug is suspected to be affecting a patient's vision. Interventions can include screening before treatment, monitoring for ocular toxicity, reducing drug doses, or stopping the drug and looking for an alternative. Some ocular adverse effects such as raised intraocular pressure can be managed with medical or laser therapy. Cataracts can be managed with surgical intervention. However, some ocular adverse events such as macular atrophy can cause irreversible visual loss, hence the need to screen for damage at an early stage.

### Pharmacovigilance

Medicine is a constantly evolving field with new drugs being developed all the time. Many ocular adverse effects are reported during the clinical trials of drug development but others emerge later. Postmarketing surveillance, such as the [Black Triangle Scheme](#), has proved to be valuable in the identification of rare and otherwise not previously reported adverse effects. It is important to keep an open mind when prescribing new drugs and be vigilant in assessing any possible ocular adverse effects. [Adverse events should be reported to the Therapeutic Goods Administration.](#)

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### Conclusion

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Commonly used oral drugs can cause ocular adverse effects. As well as retinal toxicity, oral drugs can affect other parts of the eye including the cornea, lens and optic nerve. Consider drugs as a possible cause of unexplained ocular symptoms. Communication between the prescribing clinician and ophthalmologist will facilitate the best possible patient care. ◀

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## New drugs

### Elexacaftor/tezacaftor/ivacaftor

#### Approved indication: cystic fibrosis

#### Trikafta (Vertex)

#### 100 mg/75 mg/50 mg film-coated tablets

Cystic fibrosis is an autosomal recessive disorder caused by mutations in the genes encoding the cystic fibrosis transmembrane conductance regulator (CFTR). There are many possible mutations affecting the formation and function of the CFTR protein. The most common is the F508del mutation. These mutations result in defects in the transport of chloride ions. This leads to the formation of thick mucus which affects the lungs, pancreas and gut.

In the past decade several drugs have been developed to enhance the structure and activity of the CFTR protein. The first was *ivacaftor* and this is now available in combination with *lumacaftor* or *tezacaftor*. Elexacaftor is a new drug that acts at a different site on the CFTR protein. This increases the amount of CFTR protein delivered to the cell surface. The new combination of elexacaftor, tezacaftor and ivacaftor is intended to enhance the quantity and function of the protein. Patients will take two tablets of the combination in the morning and a separate dose of ivacaftor 150 mg in the evening.

The combination should be taken with a moderately fatty meal as this will increase the absorption of elexacaftor. As the drugs in the combination are extensively metabolised by cytochrome P450 (CYP) 3A4/5, there are many potential interactions including with grapefruit juice. Strong inducers such as carbamazepine, and inhibitors such as azole antifungals, of CYP3A should be avoided. The combination is also not recommended for patients with moderate or severe liver disease. Little drug is excreted in the urine so no dose adjustment is recommended in kidney disease, although there are no studies in patients with severe renal impairment. The pharmacokinetics of the combination in children aged 12 years and over are similar to adults. Treatment is not currently approved in younger children. Animal studies show the drugs in the combination cross the placenta and are excreted in breast milk.

A phase II trial studied the effect of different daily doses of elexacaftor in combination with tezacaftor and ivacaftor in 123 patients with cystic fibrosis who had F508del genotypes. After four weeks all doses had resulted in improvements in the percentage of

predicted forced expiratory volume in one second (FEV<sub>1</sub>). There was no change in the patients given a placebo. Treatment with the combination also reduced the chloride concentration in sweat.<sup>1</sup>

The triple combination therapy, containing elexacaftor 200 mg, was compared to placebo in a 24-week phase III trial. The 403 patients in the trial had an F508del mutation on one allele and a minimal function mutation on the other. At baseline their mean percentage of predicted FEV<sub>1</sub> was approximately 61%. By four weeks this had improved by an average of 13.6 percentage points in the 200 patients who took the combination. This change was sustained at week 24 while the FEV<sub>1</sub> of patients in the placebo group declined slightly. There were 41 pulmonary exacerbations in the treatment group compared with 113 in the placebo group. Treatment also reduced the sweat chloride concentration.<sup>2</sup>

Another phase III trial studied the combination in patients who were homozygous for the F508del mutation. This randomised 55 patients to take the combination and 52 to take ivacaftor and tezacaftor. The mean percentage of predicted FEV<sub>1</sub> was approximately 61% at the start of the study. After four weeks of treatment this had increased by 10.4 percentage points with the combination, but only by 0.4 percentage points with ivacaftor and tezacaftor. The combination also reduced the sweat chloride concentration.<sup>3</sup>

Most patients with cystic fibrosis will experience adverse events which may be unrelated to drug therapy. In the placebo-controlled phase III trial the most common adverse events were exacerbations of cystic fibrosis and increased sputum. Only two of the 202 patients in that trial discontinued the combination because of adverse effects.<sup>2</sup> Adverse events that have been reported more frequently with the combination than with placebo include headache, diarrhoea and rashes. Patients taking elexacaftor, tezacaftor and ivacaftor may develop increases in liver transaminases and creatine phosphokinase.

The three-drug combination is indicated for patients, aged 12 years and above, who have at least one F508del mutation. This increases the proportion of patients with cystic fibrosis who may benefit from therapy with CFTR modulators, but the combination is not a cure and it will be unsuitable for treating patients with different mutations. There is still a need

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## NEW DRUGS

for standard management such as airway clearance. Most of the trials were short term, but cystic fibrosis is lifelong so it will be important for the patients to adhere to treatment. Adding elexacaftor to tezacaftor and ivacaftor further improves FEV<sub>1</sub>,<sup>3</sup> but continuing follow-up is going to be needed to confirm that this leads to long-term clinical benefits.

**T** manufacturer provided the product information

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

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



## Tafamidis

**Vyndamax (Pfizer)**

**61 mg soft gelatin capsules**

## Tafamidis meglumine

**Vyndaqel (Pfizer)**

**20 mg soft gelatin capsules**

### Approved indication: amyloid cardiomyopathy

Transthyretin is a plasma protein, produced in the liver. It is involved in the transport of thyroxine. In some people genetic mutations result in the protein dissociating into monomers. These monomers can aggregate into amyloid fibrils which deposit into the tissues. In the heart, the amyloid fibrils cause thickening of the ventricular walls. This restrictive cardiomyopathy reduces life expectancy to 2–6 years from diagnosis. The mutations may be inherited (familial amyloidotic cardiomyopathy) or be a wild type (senile systemic amyloidosis).

Tafamidis reduces the formation of monomers by attaching to the thyroxine-binding sites to stabilise the transthyretin molecule. Tafamidis meglumine is a salt formulation. An 80 mg dose of this formulation produces similar concentrations to the recommended daily dose of 61 mg tafamidis.

The capsules can be taken with or without food. Most of the dose is excreted unchanged in the faeces, with metabolites being excreted in the urine. The half-life of tafamidis is around 49 hours. No dose adjustment is recommended in patients with kidney disease or mild–moderate liver disease. Tafamidis does not induce or inhibit the cytochrome P450 system.

A phase II open-label trial tested the effect of daily doses of tafamidis meglumine 20 mg in patients with amyloid cardiomyopathy. The outcomes of treatment were assessed in 31 patients with wild-type mutations treated for up to a year. By six weeks transthyretin had been stabilised in 30 of these patients. At 12 months transthyretin was still stable in 25 of the 28 patients who remained in the study.<sup>1</sup>

To investigate the clinical impact of the stabilisation of transthyretin, a phase III trial studied 441 patients with amyloid cardiomyopathy and a history of heart failure. These patients were randomised to take tafamidis meglumine 80 mg (176), 20 mg (88) or a placebo (177) for 30 months. During the trial 52.3% of the patients taking tafamidis were admitted to hospital with a cardiovascular problem compared with 60.5% of the placebo group. All-cause mortality was

also lower with tafamidis as 29.5% of the patients died compared with 42.9% of the placebo group. Tafamidis also reduced the decline in the distance patients could walk in six minutes.<sup>2</sup>

During the phase III trial the frequency of adverse events was similar with the two doses of tafamidis and placebo. Many adverse events, such as atrial fibrillation and heart failure, could have been related to the underlying disease. Adverse events thought to be related to treatment which were more frequent with tafamidis than placebo included asthenia, balance disorders, cataracts and cystitis.<sup>2</sup> As tafamidis reduces thyroxine binding, thyroid function tests may be altered. In the clinical trials, hypothyroidism was reported in 6.8% of the patients taking tafamidis meglumine 80 mg, compared with 5.6% of those taking placebo. Tafamidis may also alter liver function tests and reduce the neutrophil count in a few patients.

Although most patients are elderly, any women who could become pregnant are advised to use contraception during treatment and for one month afterwards. Tafamidis may cause harm in pregnancy.

The two formulations of tafamidis have been approved for the treatment of patients with wild-type or hereditary transthyretin amyloid cardiomyopathy. Ongoing trials should help to determine which patients will get the most benefit from treatment. For example, the benefit of tafamidis meglumine over placebo was less clear in patients with New York Heart Association class III heart failure, and patients in class IV were excluded from the phase III trial.<sup>2</sup>

**T** manufacturer provided the AusPAR and the product information

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## Trifarotene

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### Approved indication: acne

#### Alkief (Galderma) cream containing 50 microgram/gram

Acne vulgaris is a common skin condition of adolescents, which is mild and self-limiting in many cases. However, it sometimes persists into the 30s and 40s age groups and the more severe forms at any age may lead to lowering of self-esteem and mood disorders. Permanent scarring can also occur. Acne is thought to develop due to abnormal follicular keratinocyte hyperproliferation causing follicular plugs and increased sebum production with subsequent overgrowth of bacteria such as *Cutibacterium acnes*. Clinical manifestations range from comedones to painful cysts.

Management is guided by the severity of the skin lesions. Topical retinoid monotherapy is preferred for the treatment of mild comedonal acne. For moderate to severe acne, a combination of topical therapies, or oral drugs such as antibiotics, is recommended. Other treatments include oral isotretinoin for refractory acne and combined oral contraceptives when appropriate.

Trifarotene is a terphenyl acid derivative with retinoid-like activity. Retinoids work by binding to retinoic acid receptors (RAR), of which there are three isoforms (alpha, beta and gamma). RAR-gamma is the most widely distributed in the skin and is thought to be the most relevant in the development of acne. Trifarotene is the only topical retinoid that is a selective RAR-gamma agonist.<sup>1</sup> It has anti-inflammatory and comedolytic properties.

There were two identical phase III randomised placebo (vehicle)-controlled multi-site trials (PERFECT 1 and PERFECT 2).<sup>2,3</sup> These trials included patients of nine years of age and older, with moderate facial and truncal acne, but no cysts or nodules. PERFECT 1 had 1208 participants and PERFECT 2 had 1212. The investigators' assessments found that over 12 weeks trifarotene applied once daily reduced inflammatory and non-inflammatory lesions on the face and trunk more than placebo. Lesions on the trunk took longer to start improving than on the face.<sup>3</sup>


In the PERFECT trials, most adverse events were mild with transient local irritation consistent with other topical retinoids, with mild-moderate erythema, scaling, dryness and burning, worse on the face than the trunk. Nine patients had severe symptoms such as sunburn and allergic dermatitis.<sup>3</sup> A longer term, non-comparative, multi-site trial studied the efficacy and safety of trifarotene over 52 weeks.<sup>4</sup> A total of 453 patients aged nine years and over with moderate

acne were enrolled and 348 completed the study. Thirteen (2.9%) patients discontinued treatment because of adverse events related to trifarotene. Overall, 218 (48.1%) patients experienced adverse events, mostly during the first three months, with 57 (12.6%) participants having cutaneous symptoms. The most common effects were pruritus (4.6% patients), irritation (4.2%) and sunburn (1.8%). Three patients had severe cutaneous adverse effects.<sup>4</sup>

While global trials included patients from nine years of age, trifarotene is approved in Australia for patients aged 12 years and above for the topical treatment of acne of the face and the trunk when many comedones, papules or pustules are present. However, safety and efficacy have not been evaluated in people aged 65 years and over, nor in those with renal and hepatic impairment. Trifarotene is contraindicated during pregnancy and for women planning to become pregnant. A discussion about contraception may be appropriate. Systemic exposure is low and it is estimated that most of the drug will be eliminated within four days of the last application of the cream.

Treatment should be assessed after three months and may be continued if necessary and for maintenance. In the long-term trial, lesions improved over time with 57.9% of patients having their face and trunk clear or almost clear at week 52.<sup>4</sup>

Trifarotene potentially is a useful addition to the topical treatments for acne. Due to its targeting of the RAR-gamma receptor, it may improve acne compared to other topical retinoids, although it has not been directly compared to them in trials. As with other topical retinoids, patients should be warned about erythema, scaling and dryness, and advised to use a moisturiser during treatment, as well as sunscreen to help avoid sunburn.

 manufacturer provided additional useful information.

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## Update

### Antipsychotic switching tool [Update 3]

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The online tool by Nicholas Keks et al has been updated. [View updated tool \(v4\).](#)

It includes a clarification that the paliperidone depot-to-depot advice applies to the once-monthly long-acting injection.

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