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## Classifying drugs in pregnancy

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### Key words

adverse effects, birth  
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Administration

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The thalidomide tragedy changed forever the way in which drug exposures during pregnancy were perceived by patients and their healthcare providers. As a result, in 1963 the Government established the Australian Drug Evaluation Committee to advise on the safety of new drugs being introduced into Australia and to monitor and evaluate potential adverse effects of drugs already in use. The Committee published an Australian categorisation of the risk of drugs in pregnancy (A, B1, B2, B3, C, D, X) (see Box)<sup>1</sup> and the first 'Medicines in pregnancy' booklet in 1989. Because the letter categorisation appears so simple and easy to find in prescribing guides, it is probably the most widely used first-line information about medicines in pregnancy.

Because most women use at least one drug during their pregnancy (average range 1.2–3.2), practitioners will be faced with questions about the safety or otherwise of drugs during pregnancy or breastfeeding.<sup>2,3</sup> It is important to remember that there is a background risk of 3–5% for all couples to have a baby with a major birth defect. Any risks associated with medicine exposures therefore need to be expressed in relation to this background risk – in other words, is the risk increased over the background risk.

To decide if a drug is safe during pregnancy, most doctors (and dispensing pharmacists) depend on the information found in sources such as the Australian Medicines Handbook and medical databases. This information essentially consists of the Australian

Drug Evaluation Committee categorisation and the company product information, in which pregnancy and lactation are almost universally included as special precautions or contraindications.

The biggest problem is the alphabetical nature of the A–X categorisation. It implies (incorrectly) that there is a hierarchy of risk with category C being 'worse' than category B. Unfortunately the apparent simplicity of the categories means that clinicians tend to use it as a gold standard rather than as a guide. This can result in misinterpretation of risk.

The categories also cannot provide clinical context to the risks and do not differentiate between use of medicines for more or less significant conditions – for example, a woman who takes gabapentin (category B1) to treat 'restless legs' syndrome as opposed to someone taking gabapentin to treat a seizure disorder. The time pressures of busy practice coupled with the relative accessibility of the categories mean that practitioners may not consider the complexities involved in balancing the harms and benefits of using a particular drug for a specified indication at a certain stage in pregnancy.

It is reasonable to assume that drugs within the same category carry a similar risk, but this is not true. For example, valproate and paroxetine are both category D, but valproate is associated with a significantly increased risk of birth defects and neurodevelopmental sequelae, while the main concern about paroxetine is a slightly increased risk (in some studies) of heart defects.

The categories also do not consider the stage of pregnancy. For example, tetracyclines cause tooth discoloration only after 14 weeks of pregnancy so being categorised as D is misleading and will cause unnecessary worry for a first-trimester exposure.

Rarely do the categories take dose or route of administration into account. A good example of dose differences is fluconazole (category D). A single dose of 150 mg is not associated with an increased risk of defects, as compared with high-dose intravenous therapy for systemic fungal infections which is associated with an increased risk of craniofacial and skeletal malformations. Topical or inhaled exposures are generally less concerning than oral or parenteral ones. There is less systemic absorption and lower maternal serum concentrations so transplacental passage and risk to the embryo is negligible.

The categories are also not very useful for new drugs as they are assigned before market release and are

## From the Editor



It is now 50 years since the Australian Drug Evaluation Committee was established following the discovery that thalidomide had caused birth defects. Thalidomide was used to manage morning sickness, so there is concern about treating nausea and vomiting in pregnancy. Tricia Taylor tells us about the current guidelines, and Debra Kennedy reviews how the harms of drugs in pregnancy are classified.

Antenatal assessments have advanced since 1963 and Jon Hyett discusses the developments in screening for Down syndrome.

Advances in genetics have led to a better understanding of drug metabolism. Ben Snyder explains why this is important for codeine in his article on the pharmacology of opioids.

While technological advances can result in better treatment, the benefits will be lost if the drugs are taken inappropriately. Rohan Elliott evaluates the evidence for using dose administration aids. This article will be the first subject for *Australian Prescriber's* new continuing professional development activities for pharmacists.

**Box The Australian categories for prescribing medicines in pregnancy<sup>1</sup>**

**Category A**

Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

**Category B1**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have not shown evidence of an increased occurrence of fetal damage.

**Category B2**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

**Category B3**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

**Category C**

Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

**Category D**

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

**Category X**

Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

based only on animal reproductive studies, not human data, due to ethical constraints. Categories are rarely changed despite new, often reassuring, evidence because of a reluctance to advocate the safety of drugs in pregnancy.

Some women may self-medicate with complementary products during pregnancy because they are perceived as natural and therefore safer. There are usually even less safety and efficacy data for these products and the pregnancy categories do not cover them. The pregnancy classifications categorisation also does not apply to breastfeeding, although this is often misunderstood.

Generally, advice given to women by healthcare providers about medicines in pregnancy is cautious and non-evidence-based. This is often compounded by incorrect and potentially frightening information from the internet and other lay sources. Some women even consider terminating otherwise wanted pregnancies because of perceived safety concerns.

Unfortunately, misleading advice based on the Australian Drug Evaluation Committee categorisations can cause significant consequences for both mother and baby. Some women stop the drugs they need because of safety concerns, for example regular asthma medications.<sup>4</sup> They put themselves and their baby at risk of untreated illness which is often higher than the potential risks of the drug.

Other women are switched from a drug which has been beneficial, to a drug which has unknown efficacy (in that particular woman) because of misunderstood grounds of fetal safety. An example of this is switching treatment for depression from citalopram, which is category C, to moclobemide, which is category B3.<sup>5</sup>

Having a discussion with a pregnant woman about the harms versus the benefits of a particular treatment is important. For example, nicotine replacement therapy is classified as pregnancy category D. Nevertheless, it is probably safer than continuing to smoke and may

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be helpful in women who find it hard to stop smoking during pregnancy.

The US Food and Drug Administration has been considering removing the letter categorisations and radically revising the product information in pregnancy.<sup>6</sup> This has proven to be extremely time consuming and has not yet been implemented despite years of discussion and planning.

In Australia, thought should be given to improving product information. More narrative style information of fetal risks in the context of background risk could be included, as well as what data the risks are based on, such as animal or human studies. Information about drugs in breastfeeding along the lines of LactMed<sup>7</sup> monographs could also be included in the product information and would help to inform

healthcare providers and women about exposures during pregnancy and breastfeeding.

Sound evidence-based advice regarding pregnancy exposures is currently available to both healthcare professionals and consumers through obstetric drug information services located in most Australian states accessed via the Therapeutics Goods Administration\* and through databases like REPROTOX<sup>†</sup> and The Teratogen Information System<sup>‡</sup>. ◀

*Conflict of interest: none declared*

\* [www.tga.gov.au/hp/medicines-pregnancy-odis.htm](http://www.tga.gov.au/hp/medicines-pregnancy-odis.htm) (see also the table on page 44)

† <http://reprotox.org>

‡ <http://depts.washington.edu/terisweb/teris>

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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. Letters are usually published together with their responses or comments in the same issue. The Committee screens out discourteous, inaccurate or libellous statements and sub-edits letters before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.

## Letters to the Editor

### Topical corticosteroids

Editor, – I enjoyed the article 'Rational use of topical corticosteroids' (*Aust Prescr* 2013;36:158-61). I did, however, find the sentence 'Topical treatment in children should be used with extreme caution' surprising. In general, topical corticosteroid treatment in children is remarkably safe – so safe that some products are available without any prescription. Possibly the authors were referring to more potent corticosteroids such as mometasone or methylprednisolone. Even then, 'extreme' caution is unnecessary given their excellent safety record, even when substantially misused. The article was otherwise excellent and appreciated.

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*Pablo Fernández-Peñas, one of the authors of the article, comments:*



Thank you for your letter. The use of topical corticosteroids may induce atrophy and

other adverse effects. If we consider that kids have a thinner skin, with higher absorption, the use of topical corticosteroids in this population should be more cautious. However, we are not saying that topical corticosteroids should be avoided. As we say in the article, 'Topical corticosteroids are safe and effective drugs. Always establish a clinical diagnosis before prescribing an appropriate topical corticosteroid according to the affected area, patient's age, clinical presentation and predicted responsiveness to treatment'.

One big problem with the 'perceived' effect of topical corticosteroids is adherence to treatment. Patients (and relatives) tend to largely exaggerate their use of topical products. This gives some doctors a false sense of security, and it is probably behind the concept of 'tachyphylaxis'. This is when patients say they are using the topical product when they are not, and suggests the disease is 'resistant' to treatment. Controlled studies have found that atrophy changes appear after seven days of use with moderate potency topical corticosteroids. We should always



keep the risk of atrophy and patients' compliance in mind when prescribing topical corticosteroids, and always give clear guidelines including appropriate treatment duration.

### Chronic non-cancer pain

Editor, – Surely in his reply to Dr Vanlint (Aust Prescr 2013;36:184-5) Dr Cohen who wrote the article on prescribing for persistent non-cancer pain (Aust Prescr 2013;36:113-5) would not be endorsing the long-term use of opioids for chronic non-cancer pain in residential aged-care facilities as the quality use of opioid medicines. Any insinuation that long-term opioids are effective or safe for chronic non-cancer pain lacks evidence<sup>1</sup> outside industry-funded research or guidelines. The practice may increase patient suffering by sentencing our patients to opioid-induced hyperalgesia, tolerance and withdrawal. These latter two problems have recently been determined to be physiological and not contributing towards the definition of dependence.<sup>2</sup>

In a US observational study in the elderly, the all-cause mortality hazard ratio of opioids was 1.87 compared to non-selective non-steroidal anti-inflammatory drugs with increased risk of falls, fractures, cardiovascular events and acute renal injuries.<sup>3</sup>

Those with heroin dependence rarely make it to residential aged-care facilities, but I have had two people on methadone programmes admitted for care through their final illnesses, including one who continued injecting during visiting hours. Nursing staff found illiberal opioid provision challenging.

The current increase of opioid use in residential aged-care facilities puts pharmacists and nursing staff at risk during supply and storage. Even their disposal may lead to 'dumpster diving' or fossicking for discarded opioid patches.


Opioids do not cure chronic non-cancer pain. They frequently usurp quality multimodal care as outlined in Dr Cohen's article which may include psychotherapies and physical therapies such as Tai Chi.<sup>4</sup> Whether or not 'addiction is not an issue in the elderly', long-term opioids should be avoided in chronic non-cancer pain as they are ineffective, may increase pain and cause morbidity and mortality.

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*Milton Cohen, the author of the article, comments:*

 It is clear from Dr Holliday's language – 'insinuation that long-term opioids are effective' and 'sentencing our patients' – that he takes a very strong anti-opioid stance in the management of chronic non-cancer pain. I do not argue that this is unjustified, especially given the great difficulty in actually performing studies to determine the long-term effectiveness of opioids in this context.

However, I would argue for a pragmatic perspective. Chronic non-cancer pain is not 'curable' and a multimodal approach to management is likely to be associated with a better quality of life for the patient compared with a single modality drug-based approach. In my article, the importance of reducing distress by controlling symptoms was emphasised, as was the principle that drug therapy – any drug, including opioids – is an ongoing trial of therapy.

In this area, there is a tension between inappropriate prescriber behaviour and unsanctioned user behaviour.<sup>1</sup> Dr Holliday's example of the latter is indeed distressing and challenging and may well be a consequence of inappropriate prescribing. This is all the more reason for disseminating pragmatic principles for prescribing.<sup>2</sup> In the hands of a conscientious, well-informed prescriber, why should a resident in an aged-care facility be denied a **trial** of opioid under these principles? Given the limited therapeutic options in this population, surely this is an **opportunity** for the quality use of medicines.

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# Treatment of nausea and vomiting in pregnancy

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## Key words

antiemetics, doxylamine,  
hyperemesis gravidarum,  
morning sickness,  
pyridoxine

*Aust Prescr* 2014;37:42-5

## SUMMARY

Most pregnant women will experience some degree of nausea or vomiting during pregnancy.

Dietary and lifestyle interventions, along with appropriate drug treatment, can enable women to continue their everyday life and work with minimal disruption.

Clinical guidelines for therapy are available, and early treatment has been shown to reduce the severity of symptoms.

Pregnant women should be reassured that nausea and vomiting do not usually harm the fetus. Also, medicines used to treat this condition are not associated with an increased risk of birth defects, miscarriage, prematurity or other adverse outcomes in pregnancy.

Severe nausea and vomiting (hyperemesis gravidarum) is associated with weight loss, dehydration and electrolyte abnormalities and may require hospitalisation.

## Introduction

Nausea and vomiting during pregnancy affects up to 90% of women. The symptoms are usually worse in the morning (hence the name 'morning sickness') but can occur at any time of the day, and sometimes continue throughout the day. Nausea and vomiting typically commence around weeks 8 or 9 of pregnancy and subside after 12-14 weeks. However, in 10% of pregnancies symptoms may continue beyond 20 weeks and even until birth.

The cause of nausea and vomiting in pregnancy is unclear and probably has many contributing factors, although it is most likely related to hormonal changes. Before assuming a diagnosis, it is important to rule out other reasons for vomiting in a pregnant woman.

Women who have previously suffered from nausea and vomiting in pregnancy are more likely to have symptoms in a subsequent pregnancy. Symptoms can be more severe in women carrying twins.

Hyperemesis gravidarum is a more severe form of nausea and vomiting which occurs in less than 1% of pregnancies. It is characterised by maternal weight loss greater than 5% of the pre-pregnancy weight, dehydration and electrolyte imbalance, and often requires hospitalisation for intravenous rehydration.

Women can be reassured that mild to moderate nausea and vomiting will not affect their developing baby, and is actually associated with lower rates of miscarriage, stillbirth, premature birth, intrauterine growth restriction and birth defects.<sup>1</sup> However, unrelenting nausea and vomiting is debilitating and

affects a woman's capacity to carry out her normal daily tasks. Some women may choose to terminate an otherwise wanted pregnancy.<sup>2</sup>

## Management

Research has shown that pre-emptive treatment early in pregnancy reduces the severity of symptoms<sup>3</sup> and can have a profound effect on a pregnant woman's health and quality of life. However, studies have shown that many women do not receive appropriate information about lifestyle changes or timely drug treatment.<sup>4</sup>

When symptoms persist despite lifestyle, dietary and non-pharmacological interventions (see Box 1), drug treatment is indicated. Despite the prevalence of nausea and vomiting during pregnancy, there is a lack of high quality evidence to support current treatment guidelines.<sup>5,6</sup> There are ethical issues regarding randomised controlled trials in pregnant women, as well as the difficulty in quantifying levels of nausea and vomiting.

## Pharmacological therapies

In Australia, the Therapeutic Goods Administration determines a drug's pregnancy classification ([tga.gov.au/hp/medicines-pregnancy-categorisation.htm](http://tga.gov.au/hp/medicines-pregnancy-categorisation.htm)) and updates are available on the Prescribing Medicines in Pregnancy Database.<sup>7</sup> Additional information about a drug may be gained by clicking on the drug in the search field.

An evidence-based treatment algorithm developed by the Motherisk teratology information service in Canada<sup>8</sup> has been adapted for use in Australia

(Box 2).<sup>9</sup> Pregnant women can be reassured that there is extensive experience with the drugs included in the guidelines, and that none of them has been shown to increase the risk of adverse outcomes in pregnancy. It is worth emphasising that all women have a background risk of around 3% of giving birth to a baby with a major birth defect and that approximately 15% of known pregnancies end in miscarriage, regardless of any medicines taken by the mother.

### Pyridoxine

Pyridoxine (vitamin B6, uncategorised) is considered first-line therapy and can be taken in conjunction with other antiemetics.<sup>8,9</sup>

### Doxylamine with pyridoxine

A sustained-release tablet combining doxylamine 10 mg and pyridoxine 10 mg has been available for many years in Canada for nausea and vomiting in pregnancy. In 2013, it was also approved in the USA following a randomised, placebo-controlled trial which showed it was effective and well tolerated.<sup>10</sup> A similar product (Debendox) was voluntarily withdrawn in Australia in 1983 after claims that it caused birth defects. Subsequent research has shown that this assertion was unfounded, yet for 30 years Australian women have been denied this safe and effective treatment.<sup>11</sup> However, the two separate medicines can be purchased over the counter in Australia.<sup>12</sup>

#### Box 1 Commonly practised interventions for nausea and vomiting in pregnancy

- identify and avoid known triggers
- avoid having an empty stomach
- eat small amounts of food often
- eat at times when less nauseous
- avoid spicy and fatty foods
- have food and fluids at separate times
- drink small amounts of fluid often, but try to have two litres daily
- cold or frozen drinks and foods are often better tolerated
- keep dry crackers and water by bedside, and eat before getting up in the morning
- get out of bed slowly, and avoid rushing
- herbal teas may help (peppermint, ginger)
- do not brush teeth straight after eating
- excess saliva can be relieved by spitting or using a mouthwash
- rest when possible as fatigue makes nausea worse
- acupuncture

### Prochlorperazine

Prochlorperazine is a pregnancy category C drug. It carries the warning 'when given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the infant'. This is hardly relevant for mothers who take prochlorperazine in early pregnancy.

### Metoclopramide

Metoclopramide is classified as pregnancy category A and is the most commonly prescribed antiemetic in pregnancy. Category A may appear reassuring in terms of safety, but does not give any indication of the drug's efficacy. In fact many pregnant women report that metoclopramide is ineffective for their nausea and vomiting.<sup>4</sup>

### Ondansetron

Although ondansetron has limited safety data in pregnancy, it is often prescribed for women with hyperemesis gravidarum. It is not recommended as first-line therapy, especially in the first trimester of pregnancy.<sup>13</sup> Ondansetron commonly causes constipation, which may already be a problem in pregnancy. Sparing use of ondansetron, and co-administration of laxatives (for example psyllium, docusate, lactulose, polyethylene glycol) is advisable.

#### Box 2 Drug treatments for nausea and vomiting in pregnancy – current guidelines <sup>8, 9</sup> Added May 2014

- Pyridoxine 25–50 mg orally, up to 4 times daily (200 mg/day shown to be safe)
- If symptoms persist, continue pyridoxine and add one of the following antiemetics:
  - doxylamine (category A) 12.5–25 mg orally at night may be increased to 12.5 mg in the morning and early afternoon, and 25 mg at night if drowsiness is not a significant problem
  - promethazine (category C) 10–25 mg orally, 3–4 times a day
  - metoclopramide (category A) 10 mg orally, 3 times a day
  - prochlorperazine (category C) 5–10 mg orally, 3–4 times a day
- If symptoms still persist, continue pyridoxine with a different antiemetic from the list above
- If still no satisfactory response, try ondansetron (category B1) tablet or wafer 4–8 mg, 2–3 times a day
- Patients unable to tolerate tablets or wafers, use one of the following:
  - metoclopramide (category A) 10 mg intramuscular or intravenous, every eight hours
  - ondansetron (category B1) 4–8 mg intravenous, every 8–12 hours
  - prochlorperazine (category C) 25 mg rectally, 1–2 times daily or prochlorperazine (category C) 12.5 mg intramuscular, every 8 hours
  - promethazine (category C) 12.5–25 mg intramuscular, every 4–6 hours
- If vomiting continues, consider treatment in hospital and rehydration with intravenous fluids
- Prednisolone (category A) 50 mg orally daily for 3 days, then 25 mg daily, then reducing by 5 mg daily

### Mirtazapine

Mirtazapine, an antidepressant which blocks 5-HT<sub>3</sub> receptors, may be an alternative when other antiemetics fail to treat hyperemesis. Two small case series<sup>14,15</sup> and three case reports<sup>16-18</sup> describe significant improvement in symptoms of hyperemesis gravidarum which are resistant to other medicines.

### Corticosteroids

Corticosteroid use should be limited to women with intractable nausea and vomiting during pregnancy. Women should have regular medical follow-up to ensure steroids are not taken for lengthy periods. Corticosteroids are best avoided in the first 10 weeks of pregnancy due to a possible association with cleft lip and palate.<sup>9</sup>

### Other treatments

Antacids, ranitidine and proton pump inhibitors are recommended to treat acid reflux or bloating, as

these conditions can exacerbate nausea and vomiting in pregnancy.<sup>8</sup>

Women with prolonged vomiting may be at risk of thiamine deficiency. Thiamine replacement (100 mg daily oral or intravenous) should be considered in these women.

### Conclusion

Nausea and vomiting in pregnancy is very common and there is a wide range of suggested treatments. Dietary and lifestyle changes ought to be implemented first, but pharmacological treatment should not be withheld because of fear of harming the baby. Expert clinical guidelines are available for prescribers who can be assured that early treatment will enhance the quality of life for pregnant women and their families. ◀

*Conflict of interest: none declared*

### Obstetric drug information services in Australia

State	Service	Phone
All states	Medicines Line (NPS MedicineWise)	1300 633 424
Australian Capital Territory	Drug Information Canberra Hospital	02 6244 3333
New South Wales	MotherSafe Royal Hospital for Women Randwick	02 9382 6539 1800 647 848 (toll free NSW)
Queensland (health professionals only)	Queensland Medicines Advice and Information Service Brisbane	07 3646 7098
South Australia	Women's and Children's Hospital Adelaide	08 8161 7222
Victoria	Medicines Information Service Royal Women's Hospital Melbourne	03 8345 3190
	Drug Information Service Monash Medical Centre	03 9594 2361
Western Australia	Women's and Children's Health Services Perth	08 9340 2723

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# Appropriate use of dose administration aids

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## Key words

drug labelling, medication  
errors, medication reviews,  
patient adherence

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## SUMMARY

Dose administration aids can improve medicines management for some people. However, they have a number of limitations and are not suitable for all patients.

Patient assessment is required to identify factors contributing to non-adherence or medication errors. Strategies like simplifying the drug regimen, education and counselling, and a medicines reminder chart or alarm, should be considered before using a dose administration aid.

The patient's preferences and attitude to medicine-taking, and their suitability for a dose administration aid, should also be explored.

When dose administration aids are packed by a third party such as a community pharmacy, interdisciplinary communication and teamwork, patient education, monitoring and regular medicines reconciliation and review are vital to minimise the risk of problems.

## Introduction

Dose administration aids organise doses of tablets and capsules according to when they should be taken (Table 1). The devices may be filled by the patient, or by a third party such as a community pharmacy.

Dosing aids may improve medicines management for some people, but they are not without limitations and problems (Table 2)<sup>1–13</sup> and are not suitable for all patients. Careful patient selection and awareness of the limitations of dosing aids are vital for ensuring appropriate and safe use.

## The evidence for using dose administration aids

There have been few well-designed controlled trials evaluating the impact of dosing aids on medication adherence and clinical outcomes. Most studies have had methodological flaws (for example inadequate randomisation, short duration, high loss to follow-up, and variations in concurrent adherence strategies provided with the device).<sup>14,15</sup> Most trials have focused on a single health problem, for example hypertension, limiting their generalisability to typical users of dose administration aids (older people with multiple comorbidities).

A recent Cochrane review<sup>15</sup> pooled data from several studies (none focusing on older people) and found that dose administration aids modestly increased the percentage of pills taken (mean difference of 11%, 95% confidence interval 6–17%). Meta-analyses of studies that focused on patients with hypertension or diabetes suggested some improvements in diastolic blood pressure and HbA1c in users of dose administration aids, but with low certainty.<sup>15</sup> Only one

small study focusing on older people met the criteria for inclusion. This study reported a non-significant effect on the mean number of missed doses and clinical outcomes.<sup>16</sup>

The UK National Institute for Health and Clinical Excellence reviewed the use of dosing aids. It concluded that the evidence for their benefits was not strong enough to recommend widespread use and they should only be used to overcome practical problems if there is a specific need.<sup>17</sup>

There has been limited evaluation of sachet dosing aids and automated medication dispensing devices.<sup>15</sup> A qualitative study of Danish patients using a sachet system found that it did not eliminate non-adherence, especially conscious non-adherence, or stockpiling of medicines in the home.<sup>18</sup> A large, non-randomised, retrospective cohort study in the USA reported that a sachet dosing system combined with regular telephone follow-up improved medication refill adherence, but did not reduce health service use or costs in a middle-aged population with multiple comorbidities.<sup>19</sup> Two low quality studies reported that automated dispensing devices led to fewer missed doses compared with manually operated dosing aids,<sup>16,20</sup> but the differences were unlikely to be clinically important.

Few trials on dose administration aids have been conducted in Australia. However, unpublished Australian studies and clinical experience suggest that dosing aids provided as part of a medicines management service by community pharmacies may benefit appropriately selected patients (Box 1).<sup>5,10,21</sup> These studies have led to government-subsidised dosing aid programs in Australia and professional practice standards to support this service.<sup>3</sup>

## When should a dose administration aid be considered?

Australian guidelines recommend that dispensed medicines should be retained in their original packaging unless a dose administration aid could help to overcome specific problems.<sup>4</sup> Practical aids or strategies such as simplifying the regimen, reminder charts, calendars and alarms should be considered before trying a dosing aid filled by a third party.<sup>1,17,22</sup> Assessing the patient is vital to identify the type of medicines management problem and whether it is likely to be resolved by using a dosing aid.

A dose administration aid may be considered when a person is struggling to manage a complex medicine regimen that cannot be simplified and primarily consists of regularly scheduled, solid oral dose forms that are suitable for packing. They may also be considered for a person who sometimes forgets whether or not they have taken their medicines (leading to risk of double dosing) and requires a visual cue, or a patient whose medicine-taking is being monitored by a carer. Ideally the medicine regimen should be stable and unlikely to change frequently.

Dosing aids are most effective in people who are motivated and willing to take their medicines and possess adequate vision, cognition and dexterity to use the device. Although they may be helpful in people with mild cognitive impairment, there has to be an adequate level of cognition. For example, the patient needs to be able to understand how to use the device, orientated to the day and time, and be able to remember when medicines need to be taken or respond to a reminder.

Dose administration aids are not effective for addressing deliberate non-adherence, poor motivation and errors due to more severe cognitive impairment.

### Box 1 Potential benefits of dose administration aids<sup>5,10,15,21</sup>

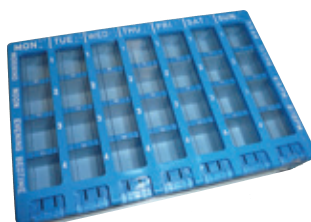
Benefits of dose administration aids packed by community pharmacies, in appropriately selected patients as part of a co-ordinated multidisciplinary approach to medicines management, may include:

- fewer medicines stored in the home
- fewer doses missed or taken incorrectly
- reduced patient and/or carer stress
- better disease control
- increased communication and collaboration between community pharmacy and the GP
- improved access to the patient's (oral) medicines profile, potentially facilitating medicines review and identification of drug interactions

## What do patients think of dose administration aids?

Studies assessing patients' opinions report that some users like the fact that the device simplifies their medicine-taking and reduces stress associated with managing multiple medicines.<sup>2,5,18,23</sup> Other users prefer to manage their medicines from original packs or experience difficulties using the devices.<sup>2,5,6,8,15,18</sup> Some users feel that the decision to issue a dose administration aid reflects a paternalistic or ageist attitude by health professionals.<sup>2</sup> A small study assessing user acceptability of several automated dispensing and

Table 1 Types of dose administration aids



Picture courtesy of the author

### Compartmentalised plastic boxes (e.g. Dosette)

Reusable devices that are usually filled by the user, sometimes filled by health professionals. Many varieties, with one, two or four compartments for each day of the week. Some devices have the days and times labelled in Braille for people with vision impairment. Some contain a built-in alarm that can be set to remind the user when it is time to take their medicines. Usually not tamper-evident.

### Blister or bubble packs

(e.g. MedicoPak, Webster-Pak)

Plastic or disposable cardboard device with four compartments for each day of the week. Provided by pharmacies. Usually filled manually, although some pharmacies use an automated packing method. Some brands may be easier to use than others. Blister packs for people with low vision or who cannot read English are available from some suppliers.



Picture by Australian Prescriber

### Sachet systems

(e.g. APHS medication sachets, MPS Packettes)

Tablets and capsules for a particular date and dose time packed in an individual sachet, labelled with the date and time, the medicine details and the patient's name. Sachets are rolled up in chronological date and time order and usually provided in a container. Sachets are prepared using automated packing technology. Community pharmacies usually outsource sachet packing to a large-scale packing facility, although some pharmacies have installed technology to enable onsite packing.



Picture by Australian Prescriber

### Automated medication dispensing devices

(e.g. Medido, TabTimer)

Devices that dispense the medicines for a particular dose-time after the user has responded to a built-in reminder alarm that activates when medicines are due to be taken. The device may need to be manually filled or it may dispense pre-filled medication sachets. Some devices have a monitoring function which can send a text message or email to a designated person if the user does not respond to the reminder within a set time.



Picture with permission from TabTimer

reminder devices found that most patients would be unlikely to want to use one.<sup>24</sup> Cost and the need for technical support are also barriers to their use.<sup>20,24</sup>

### Inappropriate use

Dosing aids are sometimes used by patients who could potentially manage their medicines from original packs with appropriately targeted information, counselling and simple adherence strategies or aids, and would prefer to do so.<sup>1,2,5,6,8,18</sup> In these circumstances, using a dose administration aid may lead to unnecessary patient disempowerment and de-skilling.<sup>2,5,6,8</sup>

Often other strategies to improve medicine-taking are not tried before implementing a dosing aid.<sup>1,8,25</sup> Patient suitability is not always assessed,<sup>5,6,8,26</sup> and initiation and subsequent choice of device sometimes focuses on the needs of health professionals and carers rather than the patient.<sup>8,18,25</sup>

Results of a recent NPS MedicineWise hypothetical case study for health professionals suggested that there are misunderstandings about when it is appropriate to use a dose administration aid. In response to the case, 77% of GPs and 76% of pharmacists recommended a dose administration aid for a 65-year-old woman with heart failure despite the fact that her non-adherence appeared to be a result of uncertainty about why she needed to take the medicines rather than her inability to manage them.<sup>27</sup> Providing information and education to the patient was suggested by only 44% of GPs and 62% of pharmacists. Practical aids or strategies – for example reminder charts, alarms, placing medicines in a prominent place, simplifying dose times or linking them to meals – were recommended by just 21% of GPs and 27% of pharmacists.<sup>27</sup>

Table 2 The limitations of dose administration aids

Limitations	Implications
<b>They do not address all medicines management problems</b> (intentional non-adherence, poor motivation, forgetfulness) <sup>1,2</sup>	Other adherence strategies may be more effective for some patients
<b>Many medicines cannot be packed in a dosing aid</b> (see Box 2) <sup>3,4</sup>	Most users will need to maintain two medicines management systems – packed oral medicines and non-packed oral medicines or non-oral medicines
<b>When filled by a third party, they may reduce the user's medicines knowledge and autonomy</b> <sup>2,5-7</sup>	Users often do not know what they are taking or why they are taking it. Removal from the original packaging means the user cannot check that the correct drug has been dispensed. Inability to identify individual tablets prevents reasoned decisions to not take a medicine (e.g. a laxative when bowels are loose). A medicines list with tablet images may be helpful.
<b>When home delivered, the opportunity for pharmacist review and counselling may be reduced</b> <sup>2,5</sup>	Regular review and counselling should be provided such as home visit, phone call, Home Medicines Review or MedsCheck
<b>People with impaired dexterity, eyesight or cognition often have difficulty using them</b> <sup>4,5,8</sup>	Ability to manage the dosing aid should be assessed before implementation. For people who have difficulty extracting medicines from blister packs, assistive devices are available (e.g. Pil-Bob, Pak-Popper)
<b>Doses may be missed if tablets are spilled during removal from the dosing aid</b> (patient may have no 'spare' medicines at home) <sup>5</sup>	Compartmentalised boxes may be more likely than other devices to result in medication spillage
<b>Risk of double dosing if the patient also maintains a supply of non-packed medicines</b> <sup>9</sup>	Ensure the user knows which medicines are packed. A medicines list with generic and trade names, and images may help.
<b>Medication changes and care transitions such as hospital discharge are more complex with a dosing aid</b> <sup>5,6,10,11</sup>	Delays or errors in implementation of changes to medication regimens sometimes occur. Outsourcing of packing by community pharmacies may increase delays.
<b>Unintended discrepancies in the contents occur in more than 10% of patients</b> (failure to communicate medication changes, dispensing or packing errors) <sup>8,12,13</sup>	Regular medication reconciliation is required
<b>They increase the cost of medication management</b> (set-up costs, weekly charges, wastage when there are medicine changes) <sup>4,5,10</sup>	Cost may be a barrier to their use, or could increase the risk of non-adherence*
<b>Implementation of a dosing aid may increase dose-related adverse effects if it leads to a sudden increase in adherence</b>	Increased monitoring for adverse reactions is required after implementation

\* Indigenous patients may be eligible for subsidised dose administration aids through the Quality Use of Medicines Maximised in Aboriginal and Torres Strait Islander Peoples (QUMAX) Program

## The suitability of medicines

Despite the widespread use of dosing devices, there are few data regarding the stability (and therefore efficacy and safety) of medicines during packing and storage.<sup>3,28</sup> Some medicines may not be suitable for use in a dosing aid (see Box 2)<sup>3,4,28,29</sup> or may have reduced shelf-life when re-packed (for example thyroxine is only stable for 14 days in a sealed, light protected dosing aid stored below 25°C). In warm and humid climates, stability of medicines in dosing aids may be further reduced.

## Avoiding problems with dose administration aids

The risk of problems with dose administration aids may be minimised in a number of ways.<sup>3,4,28</sup> These are best achieved through active collaboration between the general practitioner, pharmacist and patient or carer:

- assess the patient's suitability (see Box 3)
- consider whether the potential benefits outweigh the potential problems (Table 2)
- determine the most suitable type of device in consultation with the patient, and provide education and counselling about its use
- provide education and counselling about the medicines packed in the device, including a printed medicine list\*, preferably with images of the medicines
- document the patient's current medicine regimen, type of device, which medicines are to be packed, packing interval and harm-benefit assessment. This document should be shared between the packing pharmacy, prescriber(s), the patient (and their carer if applicable), and updated whenever there are changes to the medicines or packing arrangements<sup>3</sup>
- put in place a system to ensure good reciprocal communication between prescriber(s), the packing pharmacy and the patient or carer to ensure medicine changes are implemented accurately and in a timely fashion
- consider delaying non-urgent medication changes until the next packing cycle to minimise wastage and costs
- avoid prescribing medicines that are not suitable for packing in a dosing aid
- ensure the device is packed as close as possible to the date that it will be used, and protect from direct light and heat during storage and use to minimise risks of drug degradation

- provide regular patient follow-up and monitoring to ensure that the patient is successfully managing the device and that it has addressed their medication management problem. Make sure that better adherence has not led to increased adverse effects, and that ongoing information and education needs are met
- conduct regular medication reconciliation to ensure that the medicines packed in the device match the prescriber's intended regimen.

A Home Medicines Review can help to identify factors contributing to medication errors or non-adherence, and assess the patient's suitability for a dose administration aid or other strategies to improve

### Box 2 Not all medicines can be used in a dose administration aid<sup>3,4,28,29</sup>

Medicines may not be suitable if they:

- deteriorate when removed from the manufacturer's packaging e.g. effervescent, dispersible, buccal and sublingual preparations
- degrade when exposed to light e.g. frusemide, nifedipine
- absorb moisture from the air when removed from packaging e.g. sodium valproate, (es)omeprazole
- have special administration instructions e.g. alendronate
- have special handling requirements e.g. cytotoxic medicines, finasteride
- are taken 'when required' or in variable doses e.g. warfarin
- are not available in a solid oral dose form

### Box 3 Assessing a patient's suitability for a dose administration aid

If the answer to any of these questions is 'no', then a dose administration aid may not be suitable:

- Has a specific medicines management problem been identified that may be resolved with a dosing aid? (e.g. unintentional non-adherence or errors due to a complex regimen, double dosing due to short-term memory loss)
- Is the person motivated to take their medicines?
- Has a medicines review and regimen simplification occurred?
- Have other strategies been considered and discussed with the person? (e.g. linking dose times to meals or other regular activities, medication list or chart with dose times, medication calendar or diary, multi-alarm reminder device)
- Are a majority of the person's medicines suitable for packing in a dosing aid?
- Has the person been shown the dosing aid and agreed to use it?
- Has the person demonstrated that they can use the dosing aid (able to identify correct compartment and remove medications) or do they have a carer who is able to assist?
- Will the person be able to manage dual medication management systems, if applicable? (for packed and non-packed medicines)
- Can the person afford the fees associated with packing?

\* [www.nps.org.au/conditions-and-topics/topics/how-to-be-medicinewise/managing-your-medicines/medicines-list](http://www.nps.org.au/conditions-and-topics/topics/how-to-be-medicinewise/managing-your-medicines/medicines-list)



## ARTICLE

## Dose administration aids

SELF-TEST  
QUESTIONS

## True or false?

1. Dose administration aids improve adherence in patients who are poorly motivated to take their medicines.
2. Patients need to have an adequate level of cognition for a dose administration aid to be useful.

Answers on page 71

medicines management. A pharmacy MedsCheck<sup>†</sup> or Home Medicines Review can also provide education and medication reconciliation for users.

## Conclusion

Dose administration aids are not a panacea for all medicines management problems. They only benefit appropriately selected patients when a specific medicines management problem has been identified and less complex adherence strategies have been tried. In such patients a dosing aid, as part of a coordinated multidisciplinary approach to

medicines management, may support the person to remain independent with medicine-taking and reduce the risk of medication administration errors. Healthcare providers need to be aware of the benefits and limitations of dosing aids, and carefully assess patients to determine whether potential benefits outweigh risks and costs. ◀

*Conflict of interest: none declared*

<sup>†</sup> <http://5cpa.com.au/programs/medication-management-initiatives/medscheck-diabetes-medscheck/>

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For more information see page 45

# Non-invasive prenatal testing for Down syndrome

## SUMMARY

Fetal DNA can be detected in maternal plasma. This can be used to identify chromosomal and genetic abnormalities.

The concentration of free fetal DNA increases with advancing gestation. Non-invasive prenatal testing should not be performed before 10 weeks.

Non-invasive prenatal testing has more than 99% sensitivity and specificity for trisomy 21. It can also be used to identify trisomy 18, trisomy 13 and 45X.

Non-invasive prenatal testing will not detect all chromosomal abnormalities found by amniocentesis.

## Introduction

The identification of cell-free fetal DNA in maternal plasma<sup>1</sup> has enabled identification of genetic differences between mother and fetus. This allows fetal sex or rhesus D blood group to be determined without recourse to invasive prenatal diagnosis.<sup>2,3</sup> A highly sensitive and specific screening test for Down syndrome, called non-invasive prenatal testing, has been developed.<sup>4-14</sup> The test is likely to improve prenatal care.

## Fetal DNA

Fetal DNA is thought to be derived from the placenta, which undergoes continual remodelling throughout pregnancy.<sup>15</sup> Once a mother delivers, fetal DNA is rapidly cleared. This means that any fetal DNA present originates from the current rather than previous pregnancies.<sup>16</sup>

Most cell-free DNA in plasma (85–90%) is maternal. Tests designed to identify fetal fragments have to focus on parts of the genome that are unique to the fetus. An example would be to look for the male sex determining region Y gene, which, if present, must be fetal rather than maternal.<sup>2</sup> This is the basis of testing designed to identify genetic differences or disorders in the fetus, but it is not readily applied to identification of chromosomal abnormalities.

## Non-invasive prenatal testing

'Next generation' sequencing generates masses of DNA sequence data at relatively low cost. It is the most common method used to identify numeric chromosomal abnormalities. This relatively new technology is used to define the relative proportion of DNA fragments originating from different chromosomes. If a fetus is trisomic, then the

proportion of DNA fragments related to that specific chromosome will be increased relative to other chromosomes.

A positive result is reported when the number of fragments of an individual chromosome is more than three standard deviations from the mean of reference chromosomes. The absolute difference in the proportion of fragments is very small as the abnormal fetal genome is diluted by normal maternal genome. However, the advantage of sequencing technology is that millions of fragments are counted, allowing these small differences to be resolved. After sequencing, bioinformatic analysis determines whether there is evidence of a numeric chromosomal abnormality.

Non-invasive prenatal testing does not necessarily differentiate between fragments of maternal and fetal DNA, although at least 4% of cell-free DNA needs to be fetal in origin to be able to resolve differences between euploid and trisomic samples.<sup>17</sup> Approximately 2–5% of samples will have lower levels of fetal DNA and in these circumstances it is not possible to report a result.

## What does the test screen for?

As well as trisomy 21, non-invasive prenatal testing can report trisomies 13 and 18 and 45X (Turner syndrome). This means that the test covers about 80–90% of anomalies that would be detected using traditional cytogenetic karyotyping. The test does not pick up all chromosomal abnormalities that would be reported by amniocentesis.

It is possible to sequence the fetal genome in more detail (described as deep sequencing). In the future non-invasive prenatal testing may be used to screen the whole genome in higher resolution.<sup>18</sup>

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## Key words

aneuploidy, genetic testing,  
trisomy, Turner syndrome

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DIAGNOSTIC TESTS

Non-invasive prenatal testing for Down syndrome

Currently, non-invasive prenatal testing cannot detect single gene disorders such as cystic fibrosis, beta-thalassaemia and sickle cell anaemia, which can only be identified by invasive testing. The test will not detect triploidy or molar placenta.

### How accurate is the test?

It is important to recognise that non-invasive prenatal testing is not a diagnostic test, but a very effective screening test. A number of studies have shown that it is highly sensitive (99.6%) and specific (99.9%) as a screening tool for trisomy 21 (Table).<sup>4-14</sup> Most studies were performed in 'high-risk' populations (advanced maternal age, previous history, abnormal ultrasound, increased risk after routine screening) but there are also data that support testing in an unselected population.<sup>10,11</sup> Based on sensitivity and specificity results, likelihood ratios can be calculated – a positive result effectively increases a patient's a priori risk of having an affected pregnancy almost 1000-fold and a negative test reduces a patient's risk 250-fold.

The sensitivity and specificity for trisomies 18 and 13 appears to be lower as sequencing is less accurate for fragments of these chromosomes. There are, however, recent datasets that report 98.4% sensitivity for trisomy 18 and 85% sensitivity for trisomy 13 (Table).<sup>6-9,12-14</sup> An alternative approach, based on single nucleotide polymorphism analysis rather than just counting DNA fragments, may improve the efficacy of

non-invasive prenatal testing for trisomies 18 and 13 and for sex chromosome aneuploidy.<sup>9</sup>

Although most commercial laboratories are able to report fetal sex with this technology and offer non-invasive prenatal testing for sex chromosome aneuploidy (often 45X), there is little published data describing its effectiveness.<sup>9,13</sup> Sensitivity for 45X currently appears to be 90.5% (Table).

### Current screening for Down syndrome

The current 'gold standard' for Down syndrome screening is combined first trimester screening. This is performed between 11 weeks and 13 weeks 6 days of pregnancy and involves risk assessment based on:

- maternal age (Fig. 1)<sup>19</sup>
- ultrasound measurement of nuchal translucency thickness
- maternal serum analytes – free beta human chorionic gonadotrophin and pregnancy-associated plasma protein A.

This assessment has 90% sensitivity and 95% specificity for Down syndrome.

### How will the test fit into practice?

When the new test is compared to combined first trimester screening purely on sensitivity and specificity results, non-invasive prenatal testing appears to be better.<sup>20</sup> Combined first trimester

**Table Studies reporting the effectiveness of non-invasive prenatal testing for trisomy 21 in high-risk populations†**

Study	Trisomy 21		Trisomy 18	Trisomy 13	45X
	sensitivity	specificity	sensitivity	sensitivity	sensitivity
Chiu et al. 2011 <sup>4</sup>	100% (86/86)	97.9% (143/146)	–	–	–
Palomaki et al. 2011 <sup>5</sup>	98.6% (209/212)	99.8% (1468/1471)	–	–	–
Ashoor et al. 2012 <sup>6</sup>	100% (50/50)	100% (297/297)	98% (49/50)	–	–
Bianchi et al. 2012 <sup>7</sup>	100% (89/89)	100% (404/404)	97.2% (35/36)	78.6% (11/14)	93.8% (15/16)
Norton et al. 2012 <sup>8</sup>	100% (81/81)	99.9% (2887/2888)	97.4% (37/38)	–	–
Zimmermann et al. 2012 <sup>9</sup>	100% (11/11)	100% (126/126)	100% (3/3)	100% (2/2)	100% (1/1)
Dan et al. 2012 <sup>10</sup>	100% (143/143)	99.9% (10914/10915)	100% (47/47)	–	–
Nicolaidis et al. 2012 <sup>11</sup>	100% (8/8)	99.9% (1937/1939)	66.7% (2/3)	–	–
Palomaki et al. 2012 <sup>12</sup>	–	–	100% (59/59)	91.7% (11/12)	–
Ashoor et al. 2013 <sup>13</sup>	–	–	–	80% (8/10)	–
Jiang et al. 2012 <sup>14</sup>	100% (16/16)	–	100% (12/12)	100% (2/2)	75% (3/4)
<b>Overall</b>	<b>99.6% (693/696)</b>	<b>99.9% (18176/18186)</b>	<b>98.4% (244/248)</b>	<b>85% (34/40)</b>	<b>90.5% (19/21)</b>

† high-risk populations are variously described in these studies on the basis of maternal age (>35 years), findings of first and/or second trimester screening and a previous or family history of a chromosomal abnormality

screening does, however, provide other information. Ultrasound screening allows accurate dating of the pregnancy, recognition of structural (rather than chromosomal) anomalies and identification of multiple pregnancies. It may also identify pregnancies at risk of other adverse obstetric outcomes such as pre-eclampsia and fetal growth restriction.

At present, most national and international guidelines suggest that non-invasive prenatal testing should be restricted to women with a high risk of an affected pregnancy.<sup>21-23</sup> Although it is highly specific, the prevalence of a Down syndrome pregnancy is low in women who have not had previous screening or who are considered to have a low risk after prenatal screening. The positive predictive value (proportion of positive results that are true positives) in an unselected population is at best 50%. In other words, one in two positive test results in low-risk women are likely to be false positives – and test results need to be confirmed by amniocentesis before any intervention.

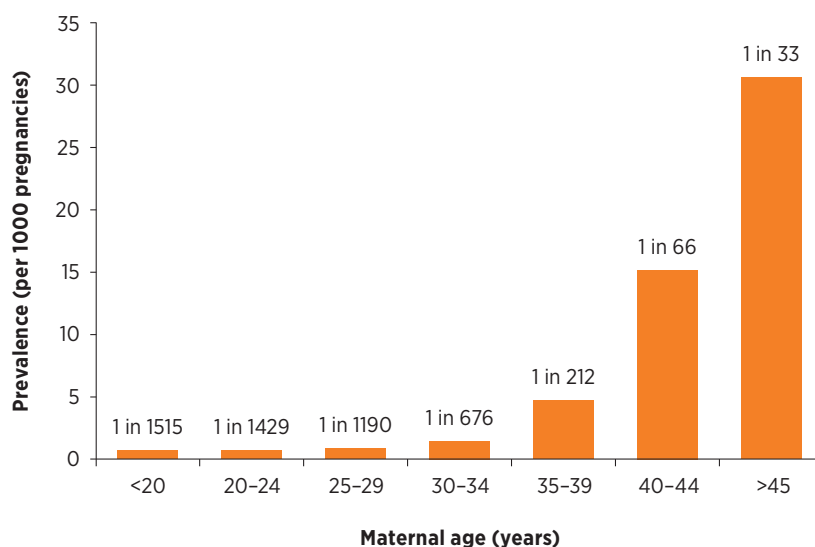
If non-invasive prenatal testing is restricted to patients who have previously been screened for Down syndrome and found to have a high risk, then a positive result will imply that the fetus is indeed affected, and a negative result will imply the fetus is unlikely to be affected. False positive results have been reported and all positive results should be confirmed by amniocentesis. Using quantitative fluorescent polymerase chain reaction, the result can be confirmed within 24 hours. If women have not had any previous screening or are considered to be low risk after prenatal screening, confirmation of a positive result will be more important.

One attraction of this test is that the sample is very stable so it can be transported long distances to a centralised facility. Combined first trimester screening relies on the ability to provide high quality obstetric ultrasound facilities locally. Non-invasive prenatal screening may help to reduce the inequality of access in rural areas.<sup>24</sup> However, at present the test is not reimbursed on the Medicare Benefits Schedule and may cost a patient over \$500.

### Options for screening strategies

As non-invasive prenatal testing is so sensitive, one option is to offer this test to women who have had a high-risk result from combined first trimester screening. It has been suggested that this may lead to 80% reduction in the current invasive testing rate. While this will improve the overall specificity of the screening strategy, it does not take advantage of the high sensitivity of non-invasive prenatal testing for the population as a whole.

Fig. 1 Maternal age-related risk for Down syndrome<sup>19</sup>



An alternative strategy is to offer all women non-invasive prenatal testing and an ultrasound scan. However, this will increase the cost of the screening program quite significantly.

A third strategy would be to change the reporting strategy of combined first trimester screening to identify three groups:

- a high-risk group (>1 in 50) offered invasive testing
- a low-risk group (<1 in 1000) reassured and advised no further screening is necessary
- an intermediate-risk group (1 in 50 to 1 in 1000) who would be advised about the availability of, and offered, non-invasive prenatal testing.

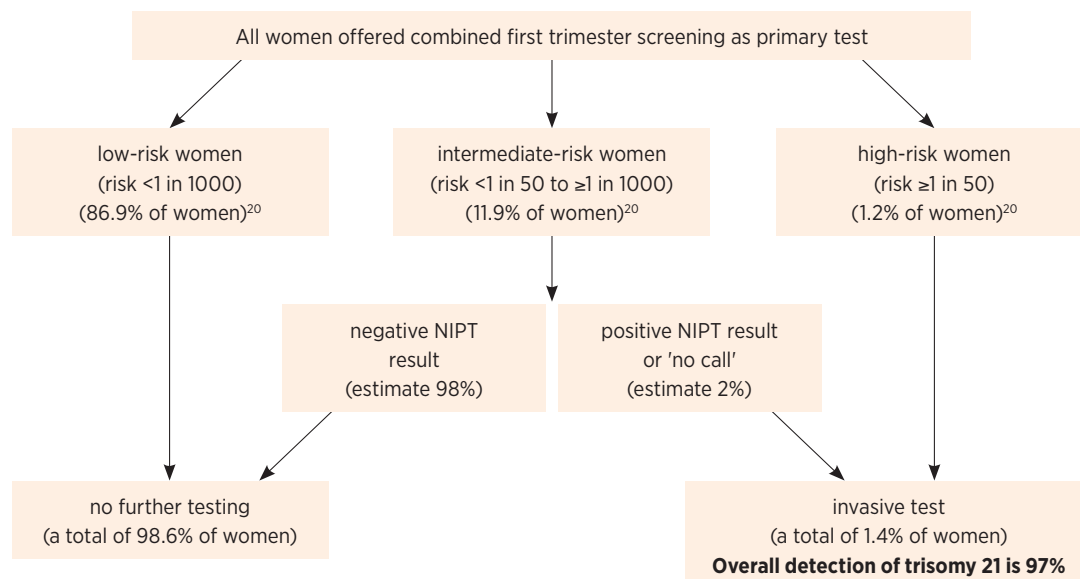
**false positive results have been reported and all positive results should be confirmed by amniocentesis**

This is described as a contingent screening model with the use of the test being contingent on the results of combined first trimester screening. The advantage of this strategy would be an overall increase in detection of trisomy 21 (97% sensitivity) with a reduction in the false positive rate (<1.5%). This model is outlined in more detail in Fig. 2.

### When combined first trimester screening is not possible

Sometimes combined first trimester screening is not available, for example for those living in remote areas or presenting at more than 14 weeks gestation. In these circumstances non-invasive prenatal testing could be used, but only after an ultrasound scan to check that the pregnancy is viable and that the placenta has a normal appearance.

Fig. 2 Contingent screening model for Down syndrome



NIPT non-invasive prenatal test  
'no call' means the test could not be reported

Non-invasive prenatal testing may be best used in a contingent approach. Here, combined first trimester screening (maternal age, ultrasound, serum analytes) is offered to all women as an initial screening tool. From this, women are stratified by risk to determine further management. Women with a high risk are offered an invasive test (chorionic villus sampling or amniocentesis). Women with a low risk are reassured and advised that no further testing is needed. Women with an intermediate level of risk are offered a non-invasive prenatal test. Contingent screening allows highest detection (an estimated sensitivity of 97%) while reducing the false positive rate to 1.4%.

## Limitations of the test – informing the patient

Women who choose to have non-invasive prenatal testing rather than amniocentesis need to appreciate that some chromosomal abnormalities that would have been an incidental finding of a cytogenetic test will not be detected.

If there is a low fraction of fetal DNA in the sample (<4%), the non-invasive prenatal test cannot be reported (described as a 'no call'). Test failure (due to low fetal fraction – occurring in 2–5% of cases) is more likely at early gestations (for example at 10 weeks) and in obese patients.<sup>25</sup> However, it is not indicative of an abnormal result. As the test examines free DNA from both the mother and the fetus, there is a small risk that a maternal chromosomal abnormality could be identified and reported.

Women need to be aware that non-invasive prenatal testing is not a diagnostic test. While a positive result should be confirmed by amniocentesis, a negative result should be interpreted as meaning that it is very unlikely that the fetus is affected.

## Conclusion

Non-invasive prenatal testing has the potential to change the established paradigm of prenatal screening. This test performs an order of magnitude better in terms of sensitivity and specificity for common forms of aneuploidy. At current prices, it is difficult to see how this will be a cost-effective tool for population screening. However, it is a viable alternative to amniocentesis for detecting Down syndrome in high-risk pregnancies (identified from combined first trimester screening).

However, some 'atypical' chromosomal abnormalities that are identified through amniocentesis will be missed using this new technique. Parents need to be counselled as to the relative advantages and disadvantages of non-invasive prenatal testing when deciding which prenatal tests are of value. ◀

*Conflict of interest: none declared*



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# Revisiting old friends: update on opioid pharmacology

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**Key words**

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morphine, naloxone,  
pharmacogenetics

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## SUMMARY

Opioids are commonly prescribed for pain due to malignant and non-malignant diseases. They are effective, but have potentially fatal toxicities.

Opioid analgesics act as agonists at the mu opioid receptor. Some products combine a mu agonist and antagonist, but there are limitations to their use.

Genetic variations may explain why people respond differently to opioids. Some patients have an inadequate response to codeine because they poorly metabolise it to morphine.

Switching from one opioid to another is sometimes necessary, but must be done carefully. Use conversion tables as a reference, but be aware of their limitations.

## Introduction

Opioid drugs are prescribed for acute and chronic pain of moderate or severe intensity arising from both malignant and non-malignant diseases (see Table).<sup>1,2</sup> They benefit many patients, but there are increasing numbers of unintentional fatal overdoses.<sup>3</sup> A clinician weighing up the potential benefits and harms of opioids is also confronted with an array of newly available drugs and formulations. Understanding the pharmacology of opioids can assist decision making.

## Pharmacodynamics

Morphine and codeine, the main analgesic alkaloids produced from the opium poppy, were isolated in the 19th century, but it was not until the 1970s that their receptors were discovered. Since then, three opioid receptors – mu, kappa and delta – have been described and their genes cloned. A fourth receptor, the nociceptin-orphinan FQ receptor, is considered ‘opioid-like’ because of important structural and pharmacological differences.<sup>4</sup> The endogenous peptides which interact with these receptors are endorphin, dynorphin, enkephalin and nociceptin.

Opioid receptors are widespread. They are found not only within the nervous system but also in other tissues, including the gastrointestinal tract and the cardiovascular and immune systems.

### Mu opioid receptor

Activation of the mu opioid receptor (mu is named for morphine) results in:

- inhibition of adenylyl cyclase
- closure of voltage-gated calcium channels
- opening of potassium channels and membrane hyperpolarisation.

These cellular events can inhibit neuronal firing and neurotransmitter release.

All of the opioid analgesics act as agonists at the mu receptor. Mu activation inhibits the ascending pain pathway, which includes neurons passing through the dorsal horn of the spinal cord, brainstem, thalamus and cortex. Mu agonists also activate the inhibitory descending pain pathway, which involves sites in the brainstem. Peripheral mu receptors located at the site of tissue injury and inflammation may also mediate analgesia.<sup>5</sup>

Mu receptor agonism is responsible for the euphoria associated with opioids. This effect is distinct from the pain pathways and depends on the mesolimbic dopaminergic system. Other prominent mu effects include sedation, pupillary constriction, respiratory depression and constipation.

### Delta and kappa opioid receptors

Delta and kappa receptors are also present in the pain pathways and they may play a role in analgesia and adverse effects associated with some commonly used opioids. For example at least some of the analgesic properties of oxycodone appear to be related to kappa receptor agonism.<sup>6</sup>

### Non-opioid receptors

Some of the opioid analgesics also act at non-opioid receptors. These actions may be either therapeutic or unwanted.

Tramadol inhibits both serotonin and noradrenaline reuptake. Its active metabolite, desmethyltramadol, only inhibits noradrenaline reuptake. These monoaminergic effects contribute to analgesia, however serotonin toxicity is associated with the use of tramadol

Table Opioids commonly used for acute and chronic pain <sup>1,2</sup>

Drug	Formulations available	Oral bioavailability	Half-life (immediate-release formulation) *	Clearance mechanism	Comments
morphine	immediate release (oral, parenteral) sustained release 12 hourly or 24 hourly (oral)	30%	3 hours	liver metabolism (mainly glucuronidation) important active metabolites (M3G, M6G) renally cleared	active metabolites are problematic in renal failure
oxycodone	immediate release (oral, parenteral) sustained release 12 hourly (oral)	70%	2.5 hours	liver metabolism (mainly CYP) some active metabolites with small contribution to effect approximately 20% of dose renally cleared	also available combined with naloxone (sustained release only) for management of opioid bowel dysfunction
hydromorphone	immediate release (oral, parenteral) sustained release 24 hourly (oral)	30%	2.5 hours	liver metabolism (mainly glucuronidation) active metabolite H3G is both implicated in toxicity and renally cleared	significantly more potent than morphine and oxycodone
fentanyl	immediate release (buccal/oral, parenteral) sustained release (transdermal)	50% (lozenge)	3 hours (following an intravenous dose)	liver metabolism (mainly CYP3A4) no active metabolites	lowest dose patch (12 microgram/hour) is not suitable for opioid-naïve patients as it can cause serious toxicity suitable choice in renal failure
methadone	immediate release (oral, parenteral)	40–90%	15–60 hours	liver metabolism (mainly CYP) no active metabolites	due to complex pharmacokinetics should be commenced under specialist supervision
buprenorphine	immediate release (sublingual, used for opioid maintenance treatment) sustained release (transdermal)	30% (sublingual route)	35 hours (following sublingual administration)	liver metabolism (mainly CYP) active metabolites	a partial mu agonist that may induce withdrawal in an opioid-tolerant patient
codeine	immediate release (oral, parenteral)	60%	3 hours	liver metabolism (mainly glucuronidation) variable proportion of dose converted to morphine	not suitable for chronic pain significant variability in analgesic response between patients
tramadol	immediate release (oral, parenteral) sustained release (oral)	70%	6 hours	liver metabolism active metabolite is important for therapeutic effect	risk of serotonin toxicity in overdose or in combination with other serotonergic drugs

\* half-lives are approximate as published values vary depending on the study and the exact formulation used

M3G morphine-3-glucuronide

M6G morphine-6-glucuronide

CYP cytochrome P450

H3G hydromorphone-3-glucuronide

in combination with other serotonergic drugs, such as selective serotonin reuptake inhibitors, or in overdose. A newly available analgesic, tapentadol, is structurally and pharmacologically similar to desmethyldiamorphine. It is both a mu agonist and noradrenaline reuptake inhibitor.

Methadone is another opioid with clinically important actions at non-opioid receptors. The d-isomer of methadone is an N-methyl D-aspartate receptor

antagonist which contributes to analgesia and has a role in treating opioid-induced hyperalgesia. Methadone also inhibits the hERG potassium channel, prolonging the QT interval in some patients and increasing the risk of cardiac arrhythmia.<sup>7</sup>

### Tolerance and withdrawal

Opioids can cause tolerance and this can lead to an unpleasant withdrawal syndrome if ceased suddenly after chronic use. Tolerance and withdrawal may be

anticipated in all patients using a strong mu agonist, and withdrawal can be managed, for example by using a weaning regimen when stopping treatment.

The cellular events involved with tolerance are complex and begin even after a single dose of a mu agonist.<sup>8</sup> However, a period of days to weeks of consistent use is generally required for clinically significant problems to arise.

### Addiction

Opioid addiction, while related to the phenomena of tolerance and withdrawal, implies behaviours that result in adverse social and health outcomes for the patient. Addiction is a potentially catastrophic outcome of opioid treatment and may not be as rare as previously thought. One study of patients using opioids for chronic non-cancer pain suggested a 34.9% prevalence of DSM-5 diagnosable opioid-use disorder.<sup>9</sup> This figure is substantially higher than that found in earlier studies.<sup>10</sup> The potential for addiction should be considered before and during chronic opioid therapy. Tools such as the Opioid Risk Tool<sup>11</sup> may be used to facilitate assessment.

### Pharmacokinetics

Differences in the pharmacokinetics of opioid drugs influence the routes of administration and the problems that arise in disease states such as renal failure.

### Bioavailability

Knowing the oral bioavailability of opioids is useful when estimating the dose to prescribe when switching from the parenteral to oral routes and vice versa. The oral bioavailability of opioids ranges from low (for example buprenorphine 10%) to moderate (for example morphine 30%) and to relatively high (for example oxycodone 70%). The low oral bioavailability of buprenorphine is due to high first-pass metabolism and explains why it is given via the sublingual or transdermal routes.

As there are interindividual differences in the extent of absorption and first-pass metabolism for each drug, oral bioavailability tends to vary between patients. Generally, drugs with a higher oral bioavailability show less variability between patients.

### Distribution

All effective analgesic opioids are distributed to the central nervous system. There is evidence that efflux transport proteins such as P-glycoprotein influence the distribution of opioids to the central nervous system, but the clinical implications are unclear. The ability of P-glycoprotein to pump some opioid drugs out of the central nervous system is exploited in the case of loperamide. This is an effective peripheral mu agonist, but as it has low central nervous system concentrations at usual doses, it can be used to treat diarrhoea.

### Metabolism

The metabolism of opioids occurs mainly in the liver via the cytochrome P450 (CYP) system and conjugating enzymes. Metabolism can result in both inactive compounds (usually excreted by the kidneys) and active metabolites with their own pharmacological properties.

Fentanyl and methadone are metabolised to pharmacologically inactive metabolites, therefore metabolism is their clearance mechanism. Factors affecting metabolism such as hepatic dysfunction, metabolising enzyme polymorphisms and drug-drug interactions determine the steady-state concentrations of these drugs during chronic therapy.

Codeine is a prodrug which is converted by CYP2D6 to its active metabolite, morphine. Both morphine and tramadol also form active metabolites. Tramadol becomes desmethyltramadol which is a more potent mu agonist than the parent drug and is also a noradrenaline reuptake inhibitor.

Morphine is conjugated to form morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is a mu agonist and in chronic dosing is responsible for some of the analgesic effects and toxicity of morphine. As it is excreted unchanged by the kidneys, morphine-6-glucuronide exposure increases significantly in renal failure and can lead to toxicity. Although morphine itself is not cleared by the kidney, it is problematic in renal failure because of its renally excreted active metabolites.

By contrast, fentanyl is entirely metabolised to inactive compounds. It is therefore often preferred in moderate to severe renal failure.

### Half-life

The half-life is important when determining dosing intervals. Commonly prescribed oral opioids, such as morphine and oxycodone, have relatively short half-lives of around 2–4 hours. In chronic therapy, sustained-release formulations prolong their apparent half-life by extending the absorption phase. Depending on the product, these formulations allow once-daily or twice-daily dosing. They also reduce undesirable fluctuations in the plasma concentration.

Fentanyl, when formulated in a skin patch, is absorbed slowly, prolonging the apparent half-life and allowing patch changes every three days. It should be noted that fentanyl patches are not suitable for opioid-naïve patients – even the lowest strength patch available delivers a potentially toxic dose.

By contrast, methadone itself has a long half-life and can often be given twice daily as an analgesic for chronic pain. When used for opioid maintenance therapy it can be given once daily. However, the half-

life is variable (15–60 hours) so patients require careful titration of the dose under specialist supervision.

## Combination products

Opioids may be formulated with other drugs with the aim of increasing efficacy or reducing adverse effects.

### Codeine combinations

Products combining codeine with a non-opioid analgesic (for example, ibuprofen or paracetamol) and sometimes additional drugs (for example doxylamine) are available over the counter. While a combination is convenient, problems include the inability to alter the dose of the individual drugs and a scarcity of good quality evidence for their effectiveness.<sup>12</sup> The non-opioid component can also have serious toxicity, especially if taken in excessive amounts.

### Opioids combined with naloxone

Naloxone is an antagonist at opioid receptors. In Australia, naloxone is available in combination with buprenorphine or oxycodone.

The naloxone with buprenorphine combination is used for maintenance therapy in opioid addiction and is intended to deter patients from injecting the drug. Naloxone has minimal effects when administered sublingually, but can precipitate withdrawal symptoms if used parenterally.

The naloxone with oxycodone combination is marketed for chronic severe pain and treatment of the bowel dysfunction caused by opioids. Oral naloxone has a low systemic bioavailability and in its controlled-release formulation it antagonises opioid effects on the gastrointestinal tract with minimal effects on the central nervous system. There is evidence that the combination can reduce constipation without compromising analgesia or precipitating withdrawal.<sup>13</sup>

There are potential limitations with the oxycodone and naloxone combination. The product information advises against exceeding a total daily dose of 80 mg oxycodone/40 mg naloxone because of evidence that higher naloxone doses may reduce analgesia and precipitate withdrawal. Use of the combination is therefore limited to patients with low to moderate oxycodone requirements. Other situations that result in increased systemic exposure to naloxone, such as hepatic dysfunction, also present problems for this combination. Finally, opioids are usually only one of a number of factors causing bowel dysfunction and the naloxone/oxycodone combination should be prescribed in conjunction with other strategies, including laxatives.

## Opioid rotation

Opioid rotation is defined as changing from one opioid to another, usually during chronic therapy, in an attempt to manage inadequate analgesia or

intolerable adverse effects. About 50% of patients may be expected to improve with opioid rotation.<sup>14</sup>

One strategy is to stop the current opioid and immediately replace it with a so-called equianalgesic dose of another opioid ('stop and go' approach). The dose of the new drug is chosen with the aid of published equianalgesic tables. This compares the various opioids back to a reference dose of morphine (such as 30 mg oral morphine). The dose is reduced (for example by 50%) to allow for incomplete cross-tolerance and intra-individual variability, and provision is made for breakthrough analgesia. Clinical monitoring during the changeover period is required.

This method of opioid rotation with the use of equianalgesic tables has been questioned. The tables could be contributing to the increase in opioid-related overdose and mortality by exposing patients to toxic drug concentrations.<sup>15</sup> Switching to methadone is particularly problematic because of the long time required to reach steady state and the variability in how patients respond to the drug.

Equianalgesic tables are also limited because they are usually derived from data that do not represent patients with chronic pain (for example patients with postoperative pain or even healthy people). A titration strategy for opioid rotation has been suggested in an attempt to overcome these problems. Using this strategy the dose of the current opioid is gradually reduced as the new opioid is introduced and its dose is up-titrated.<sup>16</sup>

## Pharmacogenetics

Genes affect the way in which the body processes and responds to drugs. Genetic differences explain some of the inter-individual variability in patients' responses to opioids. For example, the CYP2D6 genotype influences the response to codeine. Poor metabolisers (5–10% of Caucasians) do not convert codeine efficiently to morphine. They obtain little analgesia from codeine, whereas ultra-rapid metabolisers (1–2% of Caucasians) may experience toxicity. Reports of codeine-related deaths in children following tonsillectomy<sup>17</sup> have been linked to ultra-rapid metabolism. Consequently the US Food and Drug Administration has issued a black box warning for codeine use in children after tonsillectomy. As CYP2D6 genotyping is not routine before prescribing codeine, the potential for metabolic variation to result in poor response or toxicity should be considered.

Recent research has examined whether variations in the gene coding for the main target of opioid analgesic drugs (that is, OPRM1 which codes for the mu opioid receptor) affect clinical parameters such as opioid dose and adverse effects. Preclinical studies have linked an OPRM1 gene polymorphism



ARTICLE

Update on opioid pharmacology



SELF-TEST  
QUESTIONS

True or false?

3. Codeine is a prodrug of morphine.
4. Codeine may be ineffective in patients with ultrarapid CYP2D6 metabolism.

Answers on page 71

(118A>G which has an adenine nucleobase replaced by guanine) to the need for higher drug doses and a poorer analgesic response. However, a recent meta-analysis<sup>18</sup> found the genetic variation correlated poorly and inconsistently with parameters such as dose requirements. At present, genetic testing does not have a role in clinical decision making.

## Conclusion

Opioids are an important part of treatment for moderate to severe pain. In the past, these drugs were mainly used to treat the pain of cancer and trauma,

but are increasingly used for a wider spectrum of pain syndromes. Acute toxicity can have a fatal outcome. Repeated use can result in problems such as tolerance and addiction. It is therefore important that knowledge of opioid pharmacology is used by clinicians to balance the beneficial and harmful effects of the drugs. ◀

*Conflict of interest: none relevant to this article*

*Acknowledgements: Tom Polasek and Mark Voskoboynik for valuable advice*

See also Medicines Safety Update: Codeine use in children after tonsillectomy and/or adenoidectomy

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# Dental note

## Opioids in dental practice

### Neil Savage

Deputy Chair  
Dental Therapeutics  
Committee  
Australian Dental  
Association

Opioids are not generally regarded as a significant part of pain management protocols in general dental practice. Most dental pain can be managed with paracetamol, ibuprofen or a combination of these drugs.

An unsubstantiated emphasis is often placed on combination products containing codeine. The quantity of codeine in these combinations is insufficient for an effective analgesic effect and there is no greater benefit over paracetamol and ibuprofen alone.

Dental pain should always be addressed from a diagnostic approach. The pivotal step is identifying the cause of the pain. Once identified, managing the local cause such as an odontogenic infection will manage the pain. Analgesics then play a supportive but significantly less important role and paracetamol and ibuprofen are appropriate.

The main problems with opioids are patients who actively seek prescriptions. Contacting the patient's doctor is recommended.

Dental practitioners are responsible for the oral health care of patients on methadone programs. There are a number of very significant concerns with respect to the maintenance of oral health in an often adverse oral environment. When possible, patients should be under careful dental review with a stringent preventive program in place to intercept the irreversible damage that may be associated with methadone. The main concern is dry mouth. Salivary hypofunction is a major risk factor in the development of dental caries, but this can be overcome by careful education and support programs. Nausea and vomiting may also be problematic for some patients and should be discussed as a routine part of the dental consultation.

*Conflict of interest: none declared*



# Medicines Safety Update

Volume 5, Number 2, April 2014

## In this issue

- Olmesartan and sprue-like enteropathy
- Codeine use in children after tonsillectomy and/or adenoidectomy
- Methoxyflurane and occupational exposure

## Olmesartan and sprue-like enteropathy

Health professionals are advised that the Product Information documents for olmesartan-containing products have been updated with a precaution for sprue-like enteropathy.

Olmesartan is a selective AT<sub>1</sub> subtype angiotensin II receptor antagonist, which is used to treat hypertension. It has been on the Australian Register of Therapeutic Goods since 2005 and is listed on the Pharmaceutical Benefits Scheme.

### Case series

A TGA investigation was conducted after the publication of a case series involving 22 patients experiencing chronic diarrhoea and enteropathy while taking olmesartan.<sup>1</sup>

Each patient suffered chronic diarrhoea for more than four weeks and had no other identified cause for enteropathy, such as coeliac disease or tropical sprue. All patients experienced weight loss, with an average loss of 18 kg, and intestinal biopsy revealed villous atrophy in each case. In some instances the adverse events experienced were severe, with 14 of the 22 patients hospitalised to manage severe dehydration. Four of the patients suffered acute renal failure and four required total parenteral nutrition.

Where information was available, the mean duration of olmesartan use prior to onset of diarrhoea was 3.1 years.

All of the patients demonstrated clinical improvement after stopping olmesartan treatment.

### Product Information update

The Product Information (PI) for olmesartan-containing products had previously listed diarrhoea

and gastroenteritis as potential adverse events, but not more severe forms of enteropathy.

The updated PI includes a precaution for sprue-like enteropathy and lists it in the adverse effects section, under 'Post-marketing experience'.

### Adverse event reports

Between 2005 and 31 January 2014, the TGA received 10 reports of diarrhoea in patients being treated with olmesartan, including four which were serious. Two reports involved enterocolitis and acute renal failure, another described villous atrophy and dehydration, and the fourth included acute renal failure, villous atrophy and *Clostridium difficile* colitis. All four patients experiencing these serious adverse events recovered after discontinuing olmesartan treatment.

### Information for health professionals

Advise patients who are being treated with olmesartan to contact you if they develop severe, chronic diarrhoea with weight loss, even if these symptoms arise months or years after they started taking the drug.

If a patient experiences severe, chronic diarrhoea with weight loss while taking olmesartan, exclude other potential causes. If no other aetiology is identified, consider discontinuation of olmesartan.

In many reported cases in Australia and overseas, stopping olmesartan treatment has resulted in clinical improvement of sprue-like enteropathy symptoms in patients.

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**TGA** Health Safety  
Regulation

## Codeine use in children after tonsillectomy and/or adenoidectomy

Health professionals are advised of the risk of rare but very serious adverse events when using codeine to treat children after tonsillectomy and/or adenoidectomy.

Codeine is a widely used opioid analgesic and, in combination with paracetamol, can be prescribed for children after tonsillectomy and/or adenoidectomy.

### Ultra-rapid metabolism of codeine

Patients may respond differently to codeine treatment due to genetic differences. Codeine is partially metabolised to morphine in the liver via the cytochrome P450 enzyme 2D6 (CYP2D6). Patients who are deficient in or lacking this enzyme cannot convert codeine to morphine and therefore may not experience adequate pain relief. Conversely, patients who metabolise codeine to morphine very rapidly ('ultra-rapid metabolisers') are at increased risk of morphine toxicity, even at low codeine doses.

Cases of respiratory depression and death following the use of codeine in children after tonsillectomy and/or adenoidectomy have been reported in the United States.<sup>1,2</sup> The US Food and Drug Administration (FDA) found that many of the cases of serious adverse events relating to such codeine use occurred in children with obstructive sleep apnoea. The affected children were also identified as being ultra-rapid metabolisers of codeine.

It is estimated that up to 10% of Caucasians may be ultra-rapid metabolisers. Estimated rates for other ethnic groups are generally lower, with the exception of North African and Middle Eastern people (10–29%).<sup>3</sup>

### Reported cases in Australia

The TGA has received no reports of death in children after tonsillectomy and/or adenoidectomy in which codeine has been a suspected drug in Australia.

To January 2014, there have been seven adverse event reports in children and adolescents involving codeine that are suggestive of respiratory depression. All except one of them included co-administration of morphine, pethidine or midazolam.

The TGA further investigated this issue by checking the National Coronial Information System database for

child deaths involving codeine and child deaths after tonsillectomy and/or adenoidectomy. No cases similar to the situation described by the FDA were found.

The TGA continues to monitor this issue.

### Information for health professionals

Health professionals may wish to consider using an alternative analgesic for children after tonsillectomy and/or adenoidectomy. If codeine is used, it should be at the lowest effective dose for the shortest time possible.<sup>4</sup>

You are also encouraged to educate parents and caregivers about possible adverse events associated with the general use of codeine in children, including codeine-containing products purchased over the counter. You should advise parents and caregivers to stop using codeine and seek medical attention if symptoms of toxicity are observed in a child.

Symptoms of morphine toxicity or overdose may include:

- somnolence
- difficulty waking
- confusion
- shallow breathing
- nausea/vomiting
- constipation
- lack of appetite
- coma.

The effects of morphine toxicity or overdose can be reversed with the narcotic antagonist, naloxone.

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## Methoxyflurane and occupational exposure

Health professionals are reminded of the risks associated with extended or repeated occupational exposure to methoxyflurane.

Methoxyflurane is an anaesthetic that is only approved for short-term use as an analgesic in stable, conscious patients. It is a volatile liquid intended for vaporisation and administration by inhalation.

While still used as an analgesic in the emergency setting, methoxyflurane has been withdrawn from use as an anaesthetic due to its well-documented nephrotoxicity and hepatotoxicity risks.<sup>1</sup>

The potential risk of extended or repeated occupational exposure for health professionals administering methoxyflurane, particularly in closed or poorly ventilated environments, is well known. There is a precaution for occupational exposure in the Product Information that states that multiple use creates additional risk and recommends health professionals consider using an optional activated carbon scavenging unit, which is available with the inhaler.

Health facilities and ambulance services have workplace occupational health and safety guidelines that mitigate risks for employees. Health professionals who administer methoxyflurane are advised to familiarise themselves with and follow these guidelines.

NPS MedicineWise has also published advice for health professionals on its website regarding this issue.<sup>2</sup>

Despite widespread use of methoxyflurane in Australia, there has been a comparatively low number of adverse event reports. From 1985 to 31 January 2014, there have been 11 adverse event reports for methoxyflurane, none of which involved occupational exposure for health workers.

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### What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, and herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the October issue of *Australian Prescriber*
- **online** at [www.tga.gov.au](http://www.tga.gov.au)
- **by fax** to (02) 6232 8392
- **by email** to [ADR.Reports@tga.gov.au](mailto:ADR.Reports@tga.gov.au)

For more information about reporting, visit [www.tga.gov.au](http://www.tga.gov.au) or contact the TGA's Office of Product Review on 1800 044 114.

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## New drugs

### Clevidipine

**Approved indication: hypertension**

**Cleviprex (The Medicines Company)**

**glass vials containing 25 mg/50 mL and 50 mg/100 mL**

**Australian Medicines Handbook section 6.3.5**

Occasionally, patients present with a hypertensive crisis which requires their blood pressure to be rapidly reduced. Controlling hypertension is also vital in patients having cardiac surgery.

Clevidipine is a short-acting intravenous dihydropyridine calcium channel blocker. In perioperative patients, the blood pressure is reduced by up to 5% within 2–4 minutes of starting an infusion. Clevidipine is rapidly metabolised and has a terminal half-life of 15 minutes. Its effect on blood pressure is gone within 5–15 minutes of stopping the infusion.

Six different doses of clevidipine were tried in a placebo-controlled study of 91 patients who had undergone cardiac surgery. The proportion of patients whose blood pressure reduced in response to clevidipine increased with the dose. Despite blood pressure falling by at least 10% there was no significant change in heart rate although beta blocker use was not controlled for.<sup>1</sup>

The ESCAPE trials enrolled patients having cardiac surgery. In ESCAPE-1, 152 hypertensive patients were randomised to receive clevidipine or a placebo infusion before surgery. The target blood pressure was reached in a median of six minutes with clevidipine. Treatment only failed in 7.5% of the patients given clevidipine compared with 82.7% of the placebo group.<sup>2</sup> ESCAPE-2 assessed the effect of clevidipine on postoperative hypertension. After surgery 110 patients were given clevidipine or a placebo. Only 8.2% failed to respond to the drug compared with 79.6% of the placebo group. The median time to reach the target blood pressure with clevidipine was 5.3 minutes.<sup>3</sup>

The ECLIPSE trials were safety studies, but also reported on blood pressure control. They compared clevidipine with nicardipine, sodium nitroprusside and glyceryl trinitrate in 1512 hypertensive patients having cardiac surgery. Clevidipine was significantly more effective than sodium nitroprusside and glyceryl trinitrate at keeping the blood pressure within a target range. There was not a significant difference between clevidipine and nicardipine for the specified range.<sup>4</sup>

Clevidipine has also been used to control acute severe hypertension. In an open-label trial, 131 people who presented with a systolic blood pressure above 180 mmHg or a diastolic blood pressure above 115 mmHg were given an infusion of clevidipine for at least 18 hours. The dose was titrated to keep the blood pressure within a target range. That range was reached within 30 minutes by 88.9% of the patients. Most patients were able to switch to oral therapy within six hours of stopping clevidipine.<sup>5</sup>

Patients who are not given oral antihypertensives need monitoring, after prolonged infusions, for at least eight hours after the infusion stops. This is because of the risk of rebound hypertension. More common adverse effects of clevidipine in severe hypertension are headache, nausea and vomiting.

Some of the adverse effects of clevidipine can be anticipated from its action. These include hypotension, tachycardia and a negative inotropic effect which can exacerbate heart failure. In perioperative use there are reports of atrial fibrillation.<sup>2,3</sup> In ESCAPE-1, 9.4% of the patients developed acute renal failure compared with 2% of the placebo group.<sup>2</sup> In the ECLIPSE trials, the overall incidence of death, myocardial infarction, stroke or renal dysfunction at 30 days was similar for clevidipine and its comparators.<sup>4</sup>

Clevidipine is presented as an emulsion containing phospholipids. It is contraindicated in patients who are allergic to egg and soy products. Severe aortic stenosis is also a contraindication.

Clevidipine is likely to be more expensive than the drugs currently used to reduce blood pressure urgently, and it may be no safer overall. Although there were fewer deaths than with sodium nitroprusside, clevidipine did not reduce the overall rate of death, myocardial infarction, stroke or renal dysfunction significantly more than its comparators.<sup>4</sup>

**T T** manufacturer provided additional useful information

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Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.



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## Glycopyrronium bromide

**Approved indication: chronic obstructive pulmonary disease**

**Seebri breezhaler (Novartis)**

**capsules containing 50 microgram powder for inhalation**

**Australian Medicines Handbook section 19.1.2**

Long-acting bronchodilators have a role in the maintenance treatment of patients with symptomatic chronic obstructive pulmonary disease (COPD). One option is a long-acting anticholinergic drug and prescribers can now choose between tiotropium and glycopyrronium bromide.

Glycopyrronium is not a new drug. Also known as glycopyrrolate, an injectable form has been used by anaesthetists to dry up secretions. It blocks acetylcholine at muscarinic receptors. In the lung, acetylcholine acts on smooth muscle to cause bronchoconstriction, so antagonising this with inhaled glycopyrronium will result in bronchodilation. This begins within five minutes and is sustained for 24 hours.

After the dry powder is inhaled, using a specific device, about 40% is absorbed, mainly through the lungs. Most of the absorbed dose is excreted in the urine. After inhalation the elimination half-life is 33–57 hours. Clearance will be reduced by renal disease, but no dose reduction is recommended for patients with a glomerular filtration rate above 30 mL/min/1.73 m<sup>2</sup>.

The approval of glycopyrronium is based on two main trials, GLOW 1<sup>1</sup> and GLOW 2<sup>2</sup>. Both trials assessed lung function in patients over 40 years old with a smoking history of at least 10 pack-years. These patients had moderate-to-severe COPD with a forced expiratory volume in one second (FEV<sub>1</sub>) that was under 80%, but more than 30%, of the predicted value after bronchodilation. Approximately 50% of the patients were using inhaled corticosteroids.

In GLOW 1, 552 patients were randomised to inhale 50 microgram glycopyrronium once daily while 270

were randomised to take a placebo. Although the trial was for 26 weeks, the primary outcome was a measurement of mean trough FEV<sub>1</sub> at 12 weeks. At the start of the trial the mean post-bronchodilator FEV<sub>1</sub> was 1.49 L in the glycopyrronium group and 1.45 L in the placebo group. The FEV<sub>1</sub> improved from the first day of active treatment. After 12 weeks the trough FEV<sub>1</sub> (measured just before the next dose) was 1.408 L with glycopyrronium and 1.301 L with placebo. The 108 mL difference in FEV<sub>1</sub> is statistically significant and the advantage over placebo was still present at 26 weeks.<sup>1</sup>

GLOW 2 was also placebo controlled, but also included an open-label tiotropium arm. There were 529 patients randomised to take glycopyrronium, 269 to take placebo and 268 to take tiotropium (18 microgram once daily). All the patients had a mean post-bronchodilator FEV<sub>1</sub> of 1.5 L at the start of the 52-week study. The primary outcome measure was the mean trough FEV<sub>1</sub> at 12 weeks. These values were 1.469 L for glycopyrronium, 1.455 L for tiotropium and 1.372 L for placebo. The advantage over placebo, 97 mL for glycopyrronium and 83 mL for tiotropium, was statistically significant.<sup>2</sup>

The GLOW trials studied several secondary outcomes. Compared to placebo, glycopyrronium reduced dyspnoea and the risk of exacerbations.<sup>1,2</sup> The smaller GLOW 3 trial showed improved exercise tolerance after three weeks in 55 patients who took glycopyrronium compared with the 53 who took placebo.<sup>3</sup>

As glycopyrronium is a muscarinic receptor antagonist it has predictable anticholinergic adverse effects. Dry mouth is the most common and there is a possibility of precipitating urinary retention and narrow-angle glaucoma in susceptible patients. Although it is uncommon, some patients develop atrial fibrillation. Inhaling a dry powder can cause coughing and throat irritation. There are no studies of pregnant or lactating women.

Inhaled glycopyrronium has a greater effect than placebo, but more experience is needed to see if improvements in lung function lead to improved clinical outcomes. Many patients will not respond. In a pooled analysis of GLOW 1 and GLOW 2 the proportion of patients with a clinically meaningful improvement ( $\geq 100$  mL) in trough FEV<sub>1</sub> was 52% at week 12 and 49.7% at week 26. After a year only 42.5% of patients had a clinically meaningful improvement. Similarly, many patients' symptoms did not improve significantly. After 26 weeks, 57.8% of patients had a clinically relevant improvement in their quality of life compared with 61% of the tiotropium group and 47.6% of the placebo group.<sup>4</sup> GLOW 3 showed a significant benefit, but the absolute improvement in exercise endurance compared to placebo was under 90 seconds.<sup>3</sup>

## NEW DRUGS

Although glycopyrronium has an early onset of effect, it is not approved for acute bronchospasm. On current evidence, glycopyrronium does not seem to have any advantages over tiotropium.

**X** manufacturer did not respond to request for data

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First published online 21 February 2014

## Ivacaftor

### Approved indication: cystic fibrosis

#### Kalydeco (Vertex)

#### 150 mg film-coated tablets

#### Australian Medicines Handbook Appendix A

The prognosis of patients with cystic fibrosis has improved, but most treatments are dealing with the consequences of the disease. In contrast, ivacaftor is aimed at the cause of the disease.

Patients with cystic fibrosis have a mutation in a gene which codes for a specific protein called the cystic fibrosis transmembrane conductance regulator (CFTR). The mutation results in defective transport of water and chloride leading to thickened mucus and salty sweat. Ivacaftor enhances chloride transport by potentiating the action of the CFTR protein. Early research showed ivacaftor had its greatest effect on cells with a particular mutation identified as G551D. This is found in 4–5% of patients with cystic fibrosis.

A range of doses of ivacaftor were studied in 39 adults with the G551D mutation. Compared to placebo, there was a significant reduction in the sweat chloride concentration after 14 and 28 days of treatment. Ivacaftor also resulted in small improvements in lung function. The median increase from baseline in the forced expiratory volume in one second (FEV<sub>1</sub>) after 28 days was 0.2 L with placebo and 0.25 L with ivacaftor 150 mg twice daily.<sup>1</sup> This dose was used in the later phase III trials of patients with the G551D mutation.

One trial enrolled patients aged 12 years or older (mean age 25.5 years) and randomised 161 to take ivacaftor or a placebo for 48 weeks. The primary end point of the study was the change in FEV<sub>1</sub> as a

percentage of the predicted value at week 24. At that time the increase from baseline was 10.4% with ivacaftor versus a decrease of 0.2% in the placebo group. The mean increase in FEV<sub>1</sub> was 0.367 L with ivacaftor and 0.006 L with placebo. This statistically significant difference was maintained at the end of the study. At week 48, 67% of the ivacaftor group had not had a pulmonary exacerbation compared with 41% of the placebo group. The patients taking ivacaftor put on an average of 3.1 kg during the trial while the placebo group gained 0.4 kg.<sup>2</sup>

A similar trial randomised 52 children aged 6–11 years. After 24 weeks the change from baseline in the percentage of predicted FEV<sub>1</sub> was 12.6% with ivacaftor and 0.1% with placebo. FEV<sub>1</sub> had increased by 0.303 L with ivacaftor and by 0.067 L with placebo. This difference was still statistically significant after 48 weeks. There was only a small number of exacerbations with no difference between the groups. The children taking ivacaftor gained 5.9 kg in weight over 48 weeks compared with a weight gain of 3.1 kg in the placebo group.<sup>3</sup>

During the trials the common adverse events with ivacaftor included headache (24%), upper respiratory tract infections (23%), abdominal pain (16%), diarrhoea (13%), rash (13%) and dizziness (9%). Although some patients interrupted their treatment because of adverse events, more patients in the placebo group discontinued completely.<sup>2,3</sup> Some patients discontinued ivacaftor because of altered liver function, so liver function tests are recommended before treatment and then every three months during the first year of treatment.

Ivacaftor is metabolised mainly by cytochrome P450 3A. Concentrations of ivacaftor will therefore be increased by enzyme inhibitors such as ketoconazole and grapefruit juice and decreased by enzyme inducers such as carbamazepine, phenytoin and St John's wort. Ivacaftor may also interact with digoxin and benzodiazepines. The terminal half-life of ivacaftor is 12 hours with most of the metabolites being excreted in the faeces. As fat increases the absorption of ivacaftor the tablets should be taken with fatty food.

Some of the patients in the clinical trials continued to take ivacaftor. The improvements in FEV<sub>1</sub> were maintained, but as cystic fibrosis is a lifelong disease ongoing evaluation is required. There is also a need to investigate whether starting treatment at the time of diagnosis will prevent organ damage. Although ivacaftor is an advance, most patients with cystic fibrosis will not benefit as they do not have the G551D mutation. A phase II trial involving patients with the most common mutation found that ivacaftor was no better than placebo.<sup>4</sup>

**T T T** manufacturer provided clinical evaluation

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## Meningococcal B vaccine

### Approved indication: immunisation

#### Bexsero (Novartis)

#### 0.5 mL pre-filled syringe containing suspension for injection

#### Australian Medicines Handbook section 20.1

Meningococcal disease is caused by the Gram-negative bacterium *Neisseria meningitidis*. Asymptomatic carriage of meningococci in the nasopharynx is relatively common (5–10% of people), but occasionally the bacteria invade and cause septicaemia or meningitis. Infection can be rapid and fatal and mainly affects children under two years. However, there is also a peak of incidence in adolescents associated with increased carriage rates. More than 80% of cases of meningococcal disease in Australia are caused by serogroup B isolates. Up until now, the only vaccines available protect against serogroups A, C, W and Y (Aust Prescr 2011;34:29-30). Vaccines based on the serogroup B capsule have been poorly immunogenic, probably because of similarities with carbohydrate residues found on human tissue.

This is the first vaccine to be approved for serogroup B disease. It contains the following components from serogroup B *N. meningitidis* strains:

- heparin binding protein
- adhesin A
- factor H binding protein
- outer membrane vesicles containing the porA P1.4 protein.

These antigens are adsorbed to the adjuvant aluminium hydroxide.

The immunogenicity of the vaccine has been investigated in babies and adolescents. As protection from meningococcal disease correlates

with antibodies that kill meningococci, efficacy was inferred by measuring bactericidal antibody titres to several serogroup B reference strains. These were measured in sera one month after vaccination. A four-fold increase in titres from baseline is considered to be protective against invasive disease.<sup>1</sup>

In a phase III study of 2627 babies, the vaccine was immunogenic after three intramuscular injections at 2, 4 and 6 months of age (given with routine childhood vaccinations). Most babies developed antibody titres that correlated with protection. In an extension study, waning antibody titres were boosted by a fourth injection at 12 months.<sup>2</sup>

In a dose-finding trial of 1631 adolescents (aged 11–17), two doses of the vaccine given 1–6 months apart resulted in protective antibody titres.<sup>3</sup> In a cohort of 257 teenagers from the study, 77–94% maintained protective antibody titres 18–24 months after the initial immunisation of two doses.<sup>4</sup>

There are numerous different circulating serogroup B strains in the population. It is not clear if antibodies to this vaccine will be cross-protective against other serogroup B strains. However, preliminary results of a survey of 373 invasive isolates from Australia predicted that 76% of the strains would be killed by sera from vaccinated individuals. Similar results were observed in a study of European isolates.<sup>5</sup>

The safety of the vaccine has been assessed in a cohort of 6555 individuals. In babies and toddlers, the most common adverse events were irritability (93%), injection-site reactions and fever. Fever within six hours of the injection was more common when the vaccine was given concomitantly with routine immunisations compared to when routine vaccinations were given alone (65.3% vs 32.2% babies).<sup>2</sup>

Paracetamol is recommended if fever develops. Sleepiness (87%), unusual crying (85%), diarrhoea (44%), vomiting (27%) and rash (13%) were also very common.<sup>2</sup> In adolescents and adults, injection-site reactions, malaise, headache, nausea, myalgia and arthralgia were the most common events.

The vaccine is indicated from two months of age and is given by intramuscular injection. Three primary doses are recommended for babies aged 2–5 months and two doses for those aged 6–11 months. These children should also have a booster dose at 12–23 months. Children over one year and adults should have two doses. It is unclear whether they need a booster injection.

The vaccine produces bactericidal antibody titres that correlate with protection against serogroup B reference strains. However, the actual efficacy of the vaccine including the coverage and duration of protection will not be known until after marketing.

NEW DRUGS

Parents should be warned that fever is very common with this vaccine and advised to use paracetamol if this occurs.

☒ manufacturer did not respond to request for data

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## Micafungin

### Approved indication: invasive candidiasis

#### Mycamine (Astellas)

#### vials containing 50 mg or 100 mg powder for reconstitution

#### Australian Medicines Handbook section 5.2

Like anidulafungin and caspofungin, micafungin is an echinocandin antifungal drug. It selectively inhibits an enzyme, glucan synthase, required for fungal cell wall synthesis. Micafungin has in vitro activity against *Candida albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei*, *C. guilliermondii* and *C. parapsilosis*. It also has activity against *Aspergillus* species.

Following slow intravenous infusion of micafungin once a day, steady-state concentrations are reached within 4-5 days. Micafungin undergoes minimal hepatic metabolism and has a terminal half-life of around 10-17 hours. It is mainly eliminated in the faeces. The clearance of micafungin in premature infants is 2-6 times faster than in adults.

The efficacy of micafungin has been assessed for the treatment of invasive and oesophageal candidiasis<sup>1-5</sup> (Table). In the trials, *C. albicans* was the most common species isolated from patients, with *C. tropicalis*, *C. parapsilosis* and *C. glabrata* being less common.

Micafungin was compared to liposomal amphotericin B for invasive candidiasis in adults<sup>1</sup> and children<sup>2</sup> (including newborn and premature babies). The median dose of micafungin was 100 mg/day in adults and 2 mg/kg in children, for 15 days. A successful response was defined as mycological eradication and complete or partial clinical improvement. Micafungin was found to be comparable to amphotericin B in both studies.<sup>1,2</sup> Similar results were found in another comparison with caspofungin<sup>3</sup> (Table).

Micafungin (100-150 mg/day) has also been compared to fluconazole in two trials of adults with oesophageal candidiasis. As this is an opportunistic infection, most of the patients had HIV. In both studies, endoscopic cure rates for micafungin were found to be comparable to fluconazole after two weeks of treatment (see Table).<sup>4,5</sup>

Micafungin has also been investigated for the prevention of invasive fungal infections in adults and children undergoing stem cell transplant.<sup>6</sup> Patients received intravenous micafungin (50 mg/day or 1 mg/kg in patients less than 50 kg) or fluconazole (400 mg/day or 8 mg/kg in patients less than 50 kg) within 48 hours of starting the transplant conditioning regimen. (Most patients were neutropenic at baseline.) Treatment continued until the patient's neutrophil count had recovered or they developed a fungal infection (mean duration of 19 days for adults and 23 days for children). The proportion of patients who remained infection free was higher in the micafungin group than in the fluconazole group (see Table).

Microbial resistance and reduced susceptibility to micafungin has been reported and is thought to be associated with mutations in a gene encoding the major subunit of the glucan synthase. Persistence of *Candida* species at the end of micafungin treatment occurred in 9% of adults<sup>1</sup> and 15.5% of children<sup>2</sup> with invasive candidiasis.

In a safety cohort of 3028 patients, adverse reactions possibly caused by micafungin included allergic reactions such as rash (1.9%) and rigors (1.1%), injection-site reactions (2.5%), headache (1.8%), nausea (2.8%), vomiting (2.5%), diarrhoea (2%), fever (2.1%), abdominal pain (0.9%) and pruritus (0.8%). Anaphylactic reactions occurred in two patients. Serious adverse events that led to treatment discontinuation included hepatic, renal and allergic or infusion-related events.

Haematological adverse reactions were observed in up to 10% of patients - leucopenia, neutropenia and anaemia were the most common. Thrombocytopenia was reported less frequently (0.9%). Electrolyte disturbances such as low potassium, magnesium and



calcium were also common. Renal effects, including increased serum creatinine and urea, were observed in 1.7% of patients receiving micafungin.

Micafungin was associated with significant liver impairment in healthy volunteers and patients (8.6% in the safety cohort), and hepatic failure has been reported. Monitor liver function and if problems develop, consider stopping treatment. In pre-clinical studies, rats treated with micafungin developed liver tumours after three months. Alternative treatment options may need to be considered for patients with preneoplastic conditions such as liver cirrhosis, viral hepatitis, advanced liver fibrosis and neonatal liver disease, and for those receiving concomitant hepatotoxic or genotoxic drugs.

Some adverse events were more common in children than in adults. Increases in liver enzymes were twice as likely in those under one year. Renal effects were also more common (acute renal failure occurred in 1% of children) as were thrombocytopenia, tachycardia, hypertension and hypotension (1–2% of children).

Micafungin is contraindicated in people who have hypersensitivity to other echinocandin drugs. In animal studies, micafungin was associated with fetal abnormalities and increased abortion rates. It is a category C pregnancy drug and should only be used if the benefit outweighs the risk. Caution is also urged during breastfeeding.

The efficacy of micafungin seems to be comparable to several other antifungal drugs and provides another option for patients with, or at risk of, serious fungal infections. However, allergic and infusion-site

reactions are a problem in some patients and hepatic effects may limit treatment.

In clinical practice guidelines, micafungin is one of the options recommended as first-line therapy for candidiasis in adults. However, in neonates the guidelines recommend its use be limited to incidences of fluconazole resistance or toxicity.<sup>7</sup>

**T T** manufacturer provided additional useful information

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Table Success rates of micafungin in comparative trials <sup>1-6</sup>

Indication	Overall treatment success	
<b>Invasive candidiasis ‡</b>	<b>micafungin</b>	<b>amphotericin B</b>
adults <sup>1</sup>	74.1% (183/247)	69.6% (172/247)
children <sup>2</sup>	72.9% (35/48)	76% (38/50)
	<b>micafungin</b>	<b>caspofungin</b>
adults <sup>3</sup>	100 mg: 76.4% (146/191) 150 mg: 71.4% (142/199)	72.3% (136/188)
<b>Oesophageal candidiasis §</b>	<b>micafungin</b>	<b>fluconazole</b>
adults <sup>4</sup>	87.7% (228/260)	88% (227/258)
adults <sup>5</sup>	100 mg: 77.4% (48/62) 150 mg: 89.9% (53/59)	86.7% (52/60)
<b>Prophylaxis in patients undergoing stem cell transplant §</b>	<b>micafungin</b>	<b>fluconazole</b>
adults and children <sup>6</sup>	80% (340/425)	73.5% (336/457)

‡ eradication of *Candida* species and clinical improvement for treatment trials

§ endoscopic cure rates

§ absence of proven or probable fungal infection in the prevention trial



## Mirabegron

**Approved indication: overactive bladder**

**Betmiga (Astellas)**

**25 mg and 50 mg film-coated tablets**

**Australian Medicines Handbook section 13.1**

People with overactive bladder have urgency with or without frequency and nocturia. Antimuscarinics such as oxybutynin, tolterodine, solifenacin (Aust Prescr 2006;29:138-43) and darifenacin are the mainstay of drug treatment (Aust Prescr 2014;37:10-3). They are often used in conjunction with bladder training.

Mirabegron is an agonist of beta<sub>3</sub> adrenergic receptors. It works by activating these receptors in the detrusor muscle of the bladder. This relaxes the muscle and increases bladder capacity.

The safety and efficacy of mirabegron has been evaluated in three placebo-controlled, 12-week studies.<sup>1-3</sup> A pooled analysis of the trials found that once-daily 50 mg and 100 mg doses statistically improved incontinence and micturition frequency (see Table).<sup>4</sup> However, there was no dose-response effect. The mean number of incontinence episodes per day fell by 1.48 with mirabegron 50 mg and by 1.54 with the 100 mg dose. Incontinence episodes fell by 1.09 a day with placebo. Although an active control was included in one of the trials (extended-release tolterodine), a statistical comparison with mirabegron was not reported.<sup>2</sup>

The most common adverse effects with mirabegron and placebo included hypertension (7.3% vs 7.6% of participants), nasopharyngitis (3.4% vs 2.5%), urinary tract infection (3% vs 1.8%), headache (2.9% vs 3.1%), dry mouth (2% vs 2.1%) and constipation (1.6% vs 1.4%).<sup>4</sup> Tachycardia was common, occurring in 1.2% of people taking mirabegron 50 mg. Palpitations and atrial fibrillation have also been reported. Blood pressure monitoring is recommended, especially in patients with hypertension, and mirabegron is not recommended in uncontrolled hypertension.

Caution is urged in those who may have a prolonged QT interval.

In a long-term extension study of safety (52 weeks), 11 of 820 people who received mirabegron 100 mg had a neoplasm (benign or malignant). Only 1 of 812 people reported a neoplasm with mirabegron 50 mg and 4 of 812 people who received tolterodine.

Following an oral dose, mirabegron reaches peak plasma concentrations after 3–4 hours. Steady-state concentrations are achieved after seven days. The terminal half-life is approximately 50 hours and the drug is eliminated in the urine (55%) and faeces (34%). This drug is not recommended in patients with end-stage renal disease or severe hepatic impairment.

In animal studies, mirabegron has shown reproductive toxicity and is excreted in milk. It is therefore not recommended in pregnancy or lactation.

Mirabegron is transported and metabolised by multiple pathways so there is potential for drug interactions. Monitoring and dose adjustment may be needed with concomitant drugs that are extensively metabolised by CYP2D6 and have a narrow therapeutic index, such as flecainide and imipramine. Mirabegron also increases exposure to concomitant digoxin so digoxin should be started at a low dose and titrated based on serum concentrations.

Mirabegron is indicated for urgency, increased micturition frequency and urgency incontinence in adults with overactive bladder. It showed only modest efficacy in the trials with the average number of incontinence episodes being reduced by around 1.5 a day. This was compared to people given placebo who had approximately 1.1 fewer incontinence episodes a day. Currently, there are limited comparative and long-term efficacy data with this drug. In the UK<sup>5</sup>, mirabegron is only recommended when antimuscarinic drugs are contraindicated, ineffective or not tolerated.

**T T** manufacturer provided additional useful information

**Table Efficacy of once-daily mirabegron 50 mg and 100 mg from a pooled analysis<sup>4</sup> of three phase III trials<sup>1-3</sup>**

Intervention	Total number of patients	Mean number of incontinence episodes/24 hours <sup>†</sup>		Mean number of micturitions/24 hours	
		baseline	12 weeks	baseline	12 weeks
placebo	1328	2.73	1.64	11.58	10.39
mirabegron 50 mg	1324	2.71	1.23	11.70	9.93
mirabegron 100 mg	890	2.79	1.25	11.58	9.83

<sup>†</sup> included only patients who reported ≥1 incontinence episode at baseline (858 patients for placebo, 834 for mirabegron 50 mg, 567 for mirabegron 100 mg)

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', *Aust Prescr* 2014;37:27.

\* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA ([www.fda.gov](http://www.fda.gov)).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency ([www.ema.europa.eu](http://www.ema.europa.eu)).

<sup>A</sup> At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration ([www.tga.gov.au/industry/pm-auspar.htm](http://www.tga.gov.au/industry/pm-auspar.htm)).

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