Prescriber Update

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Reminder: Using Cough and Cold Medicines in Children is Inappropriate

Key Messages

- ⌘ All oral cough and cold medicines are contraindicated in children less than six years of age. Some cough and cold medicines, including codeine-containing products, are contraindicated in children less than 12 years of age.
- ⌘ Coughs and colds are self-limiting illnesses and do not require pharmacological interventions.

As the winter months approach, healthcare professionals are reminded that oral cough and cold medicines, including bromhexine, should only be used in adults and children six years of age and over. Products containing codeine used to relieve cough and cold symptoms should only be used in adults and children 12 years of age and over.

The Medicines Adverse Reactions Committee (MARC) reviewed the use of both bromhexine and codeine-containing cough and cold medicines in December 2014. These reviews were triggered by:

- reports of allergic reactions, including anaphylaxis, with the use of ambroxol (a metabolite of bromhexine)
- morphine-induced respiratory depression, with the use of codeine (codeine is metabolised to morphine).

The MARC concluded that for these medicines, the risks of harm outweighed the benefits of relieving the symptoms of coughs and colds in younger age groups[1]. Further information is available on the Medsafe website (**www.medsafe.govt.nz/safety/EWS/2015/BromhexineOrCodeine.asp**).

The package labelling for bromhexine-only containing products has been updated, but a limited amount of stock may still display the previous age restrictions.

Coughs and colds are self-limiting and do not require pharmacological interventions, which only relieve the symptoms[2]. Children with coughs and colds should be allowed to rest, be made comfortable and be given plenty of fluids. Simple analgesics such as paracetamol may be considered for symptomatic treatment of associated pain or fever, and saline drops or spray may be used for nasal congestion[2].

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Sulfonylureas – Associated with Cardiovascular Disease?

Key Message

- ⌘ Of the three sulfonylureas funded in New Zealand, glibenclamide appears to have the highest risk of causing adverse cardiovascular outcomes.

Sulfonylureas increase insulin release from pancreatic beta cells and are used to manage type 2 diabetes[1]. Glibenclamide, glipizide and gliclazide are approved and funded for use in New Zealand.

In general, sulfonylureas are used in addition to metformin in patients who have failed to reach target HbA1c levels. However, a sulfonylurea may also be used as monotherapy in patients intolerant of metformin[1,2].

The effect of different anti-diabetic medicines on cardiovascular outcomes is of significant interest. The Medicines Adverse Reactions Committee (MARC) recently reviewed the available scientific information on cardiovascular outcomes in patients managed with sulfonylureas (**www.medsafe.govt.nz/profs/adverse/Minutes165.htm**).

Information on cardiovascular outcomes in patients participating in randomised controlled trials of sulfonylureas is generally lacking. However, the SPREAD-DIMCAD study, which

compared glipizide and metformin management in Chinese patients, did measure this outcome[3]. Patients in the metformin group had fewer adverse cardiovascular events than those taking glipizide.

The interpretation of published observational studies in which cardiovascular outcomes are examined is limited by several factors. For example, in many studies there was a lack of information on confounding factors such as smoking status. In addition, patients managed with metformin were different to those taking sulfonylureas, as evidenced by the difference in baseline characteristics.

The MARC concluded that the available data were sufficient to determine that glibenclamide is associated with a higher risk of adverse cardiovascular outcomes than glipizide or gliclazide. It was also noted that glibenclamide is associated with a higher risk of hypoglycaemia than glipizide or gliclazide, which are the preferred sulfonylureas[2].

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The Ionic Truth about Hyponatraemia

Key Messages

- Hyponatraemia is the most common electrolyte disturbance seen in clinical practice.
- Sodium imbalances are more common in older female patients.
- Medicine-induced hyponatraemia usually involves a combination of medicines.
- Prompt intervention is important to prevent death.

Background

Hyponatraemia is the most common electrolyte disturbance seen in clinical practice[1]. It is defined as a serum sodium concentration of less than 135 mmol/L[1].

Hyponatraemia is primarily a disorder of water balance usually associated with a disturbance in the hormone that regulates water balance, vasopressin (also commonly called antidiuretic hormone [ADH])[1].

Symptoms of Hyponatraemia

Symptoms can range from mild and non-specific to severe and life-threatening (Table 1). The severity of symptoms depends on many factors including the duration of the condition, serum sodium levels and the acute or chronic nature of onset[2].

Severe symptoms are caused by cerebral oedema and increased intracranial pressure due to the movement of water into brain cells[1].

Table 1: Symptoms of hyponatraemia by severity[1]

Severity	Symptoms
Moderate	Nausea without vomiting Confusion Headache
Severe	Vomiting Cardiorespiratory distress Abnormal and deep somnolence Seizures Coma (Glasgow Coma Scale ≤8)

Determining the Cause of Hyponatraemia

Hyponatraemia occurs when the patient has excess free water relative to serum sodium levels[2]. It can be categorised according to the patient's extracellular fluid volume status[1,2].

- Euvolaemic (normal fluid status): Possible causes include medicines, syndrome of inappropriate ADH secretion (SIADH), central nervous system disorders, secondary adrenal insufficiency, pulmonary diseases, hypothyroidism and primary polydipsia.
- Hypervolaemic (fluid overload): Possible causes include heart failure, nephrotic syndrome, renal failure, Cushing syndrome and saline infusions.

- Hypovolaemic (fluid depletion): Possible causes include vomiting, diarrhoea, cerebral salt wasting, pancreatitis, burns, primary adrenal insufficiency and the use of diuretics.

Additional laboratory tests may be useful. These include urine osmolality, serum osmolality and urine sodium concentrations[2]. The cause of hyponatraemia in many patients may be unclear, but it recurs in the context of intercurrent illness.

Hyponatraemia in Older People

Patients presenting with hyponatraemia tend to be over 80 years of age, female and living in long-term care facilities[3].

Sodium imbalances are particularly common in older people partly because of the normal aging process that affects the body's ability to maintain water and sodium homeostasis[3].

Table 2: Medicines known to cause hyponatraemia and their underlying mechanisms[4]

Mechanism	Examples
Medicines affecting sodium and water homeostasis	
	Diuretics: • thiazides • indapamide • amiloride • loop diuretics
Medicines affecting water homeostasis	
Increased hypothalamic production of ADH	**Antidepressants:** • tricyclic antidepressants (eg, amitriptyline) • selective serotonin reuptake inhibitors (SSRIs) • monoamine oxidase inhibitors
	Antipsychotics: • phenothiazines (eg, trifluoperazine) • butyrophenones (eg, haloperidol)
	Antiepileptics: • carbamazepine • sodium valproate
	Anticancer agents: • vinca alkaloids (eg, vincristine, vinblastine) • platinum compounds (eg, cisplatin, carboplatin) • alkylating agents (eg, intravenous cyclophosphamide, melphalan, ifosfamide)
	Miscellaneous: • methotrexate • monoclonal antibodies
	Opiates
Potentiation of ADH effect	**Antiepileptics**: • carbamazepine • lamotrigine
	Anticancer agents: • alkylating agents (eg, intravenous cyclophosphamide)
	Non-steroidal anti-inflammatory drugs (NSAIDs)
Reset osmostat	**Antidepressants**: • venlafaxine
	Antiepileptics: • carbamazepine

Causes of hyponatraemia in older people include:[2]

- structural changes in the kidney leading to functional declines including decreases in glomerular filtration rate, creatinine clearance and renal plasma flow
- hormonal changes related to aging
- medicines (see Medicine-induced Hyponatraemia)
- low dietary sodium intake.

Medicine-induced Hyponatraemia

There are many medicines that can cause hyponatraemia through several pathological mechanisms (Table 2).

Diuretics are one of the most common causes of hyponatraemia[4]. Diuretic-induced hyponatraemia is mostly caused by thiazides; loop diuretics are rarely associated with hyponatraemia[4]. Selective serotonin reuptake inhibitors (SSRIs), antipsychotics and non-steroidal anti-inflammatory drugs (NSAIDs) are also known to cause hyponatraemia[4].

There have also been reports of hyponatraemia following treatment with ACE inhibitors, antibiotics (eg, co-trimoxazole and ciprofloxacin) and proton pump inhibitors[4].

Medicine-induced hyponatraemia usually develops within the first few weeks of starting treatment[4]. A combination of medicines may be responsible for hyponatraemia rather than just one medicine. The sodium lowering potential of medicines added to a patient's treatment regimen that already contains such a medicine should be considered.

New Zealand Cases

The Centre for Adverse Reactions Monitoring (CARM) received 146 reports of hyponatraemia from 2006 to 2015. Of these, 93 cases involved one suspect medicine and 53 involved multiple suspect medicines. The most frequently reported medicines are summarised in Figure 1.

In these cases, hyponatraemia was more common in females (74.7%) compared to males (25.3%) and the average age was 72 years.

Management

Prompt intervention is important to prevent fatalities[2]. Treatment may include oral fluid restriction, intravenous administration of hypertonic saline and treating underlying conditions while taking the patient's volume status into account[2].

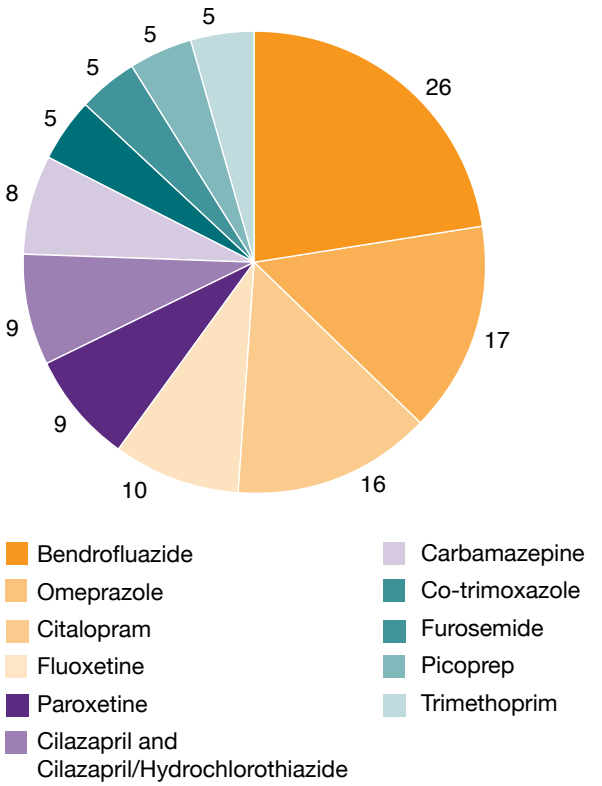

Figure 1: Medicines most frequently reported to CARM in association with hyponatraemia from 2006 to 2015

If medicine-induced hyponatraemia is suspected, the medicine(s) should be withdrawn. Hyponatraemia usually resolves within two weeks of stopping the offending medicine(s)[4].

Please continue to report any adverse reactions to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/**).

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Ghosts of Medicines Passed

Key Messages

- The remains of controlled-release formulations can appear in the stools.
- Commonly prescribed medicines can change the colour of urine.

Medicines Appearing in Stools?

A recent report to the Centre for Adverse Reactions Monitoring (CARM) described a patient whose venlafaxine tablets were being passed in the stools fully undigested.

The passing of a seemingly intact medicine may lead patients, carers and healthcare professionals alike to believe the medicine has not been absorbed[1,2].

With some controlled-release formulations it is expected that the empty intact shell that housed the medicine ('ghost-pill' or 'ghost-tablet'), or other insoluble formulation parts, will appear in the stools[1,2].

This is because controlled-release formulations (tablets, capsules and their parts) are designed to either disintegrate slowly to release the medicine over a predetermined period, or remain intact[1].

Medicines that can appear in the stools include (this is not an exhaustive list):

- Adefin XL (nifedipine)
- Arrow-Venlafaxine XR and Efexor-XR (venlafaxine)
- Concerta (methylphenidate)
- Duride (isosorbide mononitrate)
- OxyContin (oxycodone)
- Span-K (potassium chloride).

When prescribing such medicines, make sure patients are aware that remnants of the medicine can appear in their stools and provide reassurance that the active medicine will be released. However, if a patient reports a lack of medicine efficacy, further investigations may be required.

Medicines can Discolour Urine

The colour of urine can be changed by medicines, certain foods and medical conditions[3]. A detailed history can usually determine the cause[3].

There are a number of commonly prescribed medicines that can change the colour of urine (Table 1)[3].

Check the individual medicine data sheets and/or consumer medicine information (CMI) for more information (**www.medsafe.govt.nz/profs/datasheet/DSForm.asp** and **www.medsafe.govt.nz/consumers/cmi/CMIForm.asp**).

References

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3. Aycock RD, Kass DA. 2012. Abnormal Urine Color. *Southern Medical Journal* 105(1): 43–47.

Table 1: Examples of medicines that can change the colour of urine[3]

Colour of Urine	Examples
Red	Deferoxamine, hydroxocobalamin, ibuprofen, rifampicin, warfarin
Orange	Isoniazid, sulfasalazine, riboflavin
Brown	Metronidazole, paracetamol (overdose), nitrofurantoin
Black	Metronidazole, nitrofurantoin
White	Propofol
Blue or Green	Methylene blue, amitriptyline, metoclopramide, promethazine, propofol

Update: Oral Anticoagulants and Gastrointestinal Bleeding

Key Messages

- The oral anticoagulants currently funded for use in New Zealand are warfarin, dabigatran and rivaroxaban.
- Dabigatran can be taken with food and/or a proton pump inhibitor in patients with gastrointestinal (GI) symptoms.
- Patients taking rivaroxaban who are at risk of ulcerative GI disease can be prescribed an appropriate prophylactic treatment.

Warfarin, dabigatran and rivaroxaban are the three oral anticoagulants currently funded for use in New Zealand. Apixaban is also approved but is not currently funded.

The new oral anticoagulants (dabigatran, rivaroxaban and apixaban) all have a reduced risk of causing intracranial haemorrhage compared to warfarin[1].

The risk of gastrointestinal (GI) bleeding associated with the new oral anticoagulants remains unclear. Meta-analyses of randomised trials have identified higher rates of GI bleeding in patients taking dabigatran or rivaroxaban compared to those taking warfarin[1].

However, two recently published cohort studies found a similar risk of GI bleeding in patients taking dabigatran, rivaroxaban or warfarin[1,2]. The results from these studies are summarised in Table 1. In addition to these, other observational studies have reported inconsistent results on the rates of GI bleeding in patients taking dabigatran compared to warfarin treatment[2].

As such, caution is advised when prescribing any oral anticoagulant to older people, particularly those over 75 years of age, and those at increased risk of bleeding[1].

Dabigatran can also cause GI symptoms (eg, dyspepsia). If GI symptoms develop, patients should be advised to take dabigatran with a meal and/or a proton pump inhibitor should be prescribed[3]. Similarly, for patients at risk of ulcerative GI disease, an appropriate prophylactic treatment may be considered when prescribing rivaroxaban, taking into consideration that the absorption of rivaroxaban can be affected by food[4].

Patients should be informed about the signs and symptoms of GI bleeding and advised to seek immediate medical attention should they occur.

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Table 1: Summary of adjusted hazard ratios of GI bleeding with dabigatran or rivaroxaban compared to warfarin

	Adjusted Hazard Ratios (95% Confidence Interval)	
	Dabigatran vs Warfarin	**Rivaroxaban vs Warfarin**
Abraham et al[1]	Atrial fibrillation patients: 0.79 (0.61–1.03)	Atrial fibrillation patients: 0.93 (0.69–1.25)
	Non-atrial fibrillation patients: 1.14 (0.54–2.39)	Non-atrial fibrillation patients: 0.89 (0.60–1.32)
Chang et al[2]	All patients: 1.21 (0.96–1.53)	All patients: 0.98 (0.36–2.69)

Medicine-induced Lung Disease

Key Messages

- Drug-induced lung injury can be caused by myriad different medicines.
- Different patients can experience different types of lung injury from the same medicine.
- Diagnosis is difficult and is usually one of exclusion.
- Prompt discontinuation of the causal medicine is usually associated with better outcomes.

Background

The most common form of drug-induced lung injury (DLI) is interstitial lung disease (also called interstitial pneumonia or interstitial pneumonitis)[1]. Interstitial lung disease (ILD) is an umbrella term for a large group of lung diseases that cause scarring of lung tissue through inflammation and fibrosis[2]. Medicines, herbal medicines, supplements and recreational drugs can all cause DLI[3,4].

Incidence

The exact frequency of DLI is unknown, but it is probably underdiagnosed worldwide[3]. However, the incidence of lung adverse effects in patients taking amiodarone is around 5%[5].

Diagnosis

Recognition of DLI is difficult as the symptoms and clinical, radiological and histological findings are often non-specific[3]. No clinical disease types are specific to DLI. A medicine may induce lung injuries characteristic of different clinical diseases in different patients[3]. In addition, the same clinical disease can be induced by more than one medicine[2,6]. To complicate matters further, medicines that can cause DLI are often used to treat conditions associated with lung disease[1].

Patients typically present with dyspnoea, cough (often exacerbated by gastro-oesophageal reflux), general malaise and constitutional upset. The time course over which symptoms develop can sometimes help to differentiate the types of disease[6].

Diagnosis of DLI is mainly one of exclusion. Differential diagnoses include chronic obstructive pulmonary disease, bronchitis, emphysema, asthma, infection, heart disease and idiopathic ILD[1].

Diagnostic criteria for DLI include:[1,3,4]

- a history of ingestion of a medicine known to cause lung injury
- the clinical manifestations have been reported in association with the medicine
- other causes of lung disease have been ruled out (where possible)

Table 1: Examples of medicines and their pattern of induced lung injury[1,4]

Pattern of Lung Injury	Medicines Commonly Implicated
Acute interstitial pneumonia/diffuse alveolar damage	Amiodarone, amphotericin B, azathioprine, bleomycin, cetuximab, cyclophosphamide, erlotinib, etanercept, gefitinib, gold, infliximab, interferons, methadone, methotrexate, nitrofurantoin, panitumumab, phenytoin, rituximab, statins, sulfasalazine
Organising pneumonia/bronchiolitis obliterans with organising pneumonia	Amiodarone, bleomycin, cyclophosphamide, gold, methotrexate, penicillamine, phenytoin
Non-specific interstitial pneumonia	Amiodarone, gold, hydralazine, methotrexate
Hypersensitivity pneumonia/pneumonitis	Azathioprine, beta-blockers, fluoxetine, gefitinib, nitrofurantoin
Eosinophilic pneumonia	Amiodarone, aspirin, azathioprine, carbamazepine, clarithromycin, contrast media, diclofenac, G-CSF, gold, levofloxacin, methotrexate, minocycline, naproxen, paracetamol, penicillamine, penicillins, phenytoin, simvastatin

- improvement following discontinuation of the suspected medicine (dependent on injury and medicine)
- exacerbation of clinical manifestations following re-exposure to the suspected medicine (not generally recommended).

Diagnosis may take over one year from the onset of breathing problems[2].

Causal Medicines

Over 450 drugs have been implicated with ILD[1,6]. A list of these and the types of lung toxicity they are known to cause can be found at **www.pneumotox.com**

The more common medicines and lung injuries are outlined in Table 1.

Other non-medicine causes of DLI include talc and cocaine[6].

Risk Factors

The likelihood of developing adverse pulmonary effects secondary to medicines remains largely unpredictable and idiosyncratic[1]. However, possible risk factors include:[1]

- smoking
- age (risk is increased in childhood and old age)
- ethnicity (higher rates are reported in Japan)
- dose (eg, amiodarone[7] and bleomycin)
- pre-existing lung disease
- interactions (eg, the use of radiation therapy with bleomycin or contrast media with amiodarone)[5].

Mechanisms

The mechanisms of DLI are unknown, but may include:

- a direct toxic effect due to high local concentrations of the medicine or the large surface area of the lungs[1]
- lung-specific metabolism of a medicine to a toxic metabolite[1]
- immune activation, if the medicine mimics an antigen or acts as a hapten[1,4]
- deposition of phospholipids within cells (eg, amiodarone causes phospholipidosis)[1,4].

Management

The primary goal of treatment is to suppress the inflammatory response and prevent the deposition of fibrotic tissue. Failure to appreciate the relationship between the medicine and lung injury may lead to significant morbidity or death[1].

Therefore, any medicine that is suspected of causing a DLI should be discontinued immediately, unless the benefits clearly outweigh the risks of DLI. Discontinuation in mild cases can be followed by spontaneous improvement and no further management is required[1].

Patients with moderate to severe DLI should also receive steroids and supportive treatment[4].

If the patient requires continued treatment, it is recommended to switch to a medicine less likely to cause lung injury, if possible[4].

Prognosis

If DLI is diagnosed early, the patient may make a full recovery. Delayed diagnosis can lead to significant morbidity or death. This is related to the degree of fibrosis and comorbidity rather than severity of the initial clinical presentation. As an example, the overall mortality in patients with amiodarone DLI is less than 10%, but rises to 20% to 33% if the diagnosis is delayed[1].

New Zealand Cases

The Centre for Adverse Reactions Monitoring (CARM) has received 296 reports of DLI. These reports involved 341 suspected medicines as more than one suspected medicine was described in some reports. The most frequently reported medicines are shown in Figure 1.

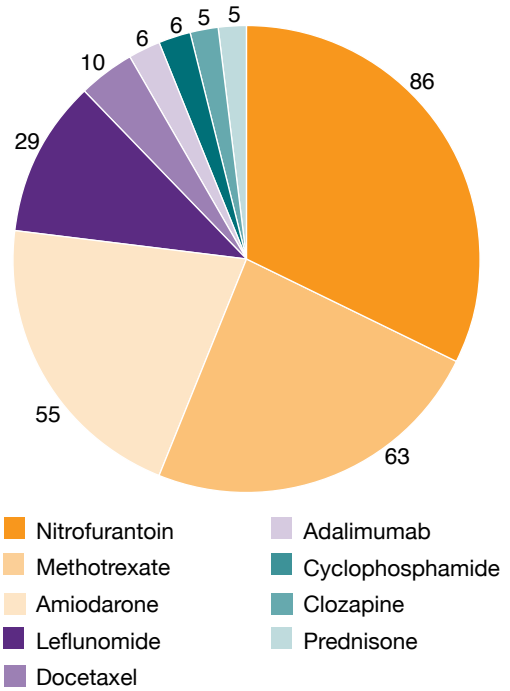

Figure 1: Medicines most frequently associated with DLI in the CARM database

The average age of the patients experiencing a DLI was 67 years. The youngest patient was 16 years and the oldest was 97 years.

Time to onset was reported for 280 of the 341 suspected medicines. For eight of the suspected medicines, the onset was reported to have occurred within one day of treatment initiation. For 100 of the suspected medicines, the onset was longer than one year.

In 95 of the 296 cases, the patient was reported to have fully recovered, while 38 cases reported a fatal outcome.

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WE NEED YOUR HELP!

Please send your reports for these potential safety issues* listed in the table below.

M² MEDICINES MONITORING

Medicine	Potential Safety Issue	Active Monitoring Ends
Ticagrelor	Depression, Suicidality	30 September 2016
Dabigatran, Rivaroxaban, Apixaban	Hair loss (Alopecia)	31 December 2016

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* The appearance of a possible safety issue in this scheme does not mean Medsafe and CARM have concluded that this medicine causes the reaction.

Quarterly Summary of Recent Safety Communications

The early warning system provides current and historical information on safety concerns for medicines and medical devices. These warnings are intended to help consumers and healthcare professionals make informed decisions about their use of medicines and medical devices.

More information about the early warning system can be found on the Medsafe website (**www.medsafe.govt.nz/Projects/B2/EWS.asp**).

Consumer information leaflets provide information about medicines and medical devices or medical conditions to consumers.

Date	Communication	Topic
2 March 2016	Alert	Vit.D3 – important information for patients with a peanut or soya allergy
3 March 2016	Monitoring	M² Ticagrelor (Brilinta) and a possible association with depression/suicidality added to the Medicine Monitoring scheme
9 March 2016	Consumer Information	Quitting Smoking and the Effect on Medicines
29 March 2016	Consumer Information	Medicines for depression or other mental disorders and difficulties with sex

If you would like to receive Medsafe's early warning communications you can subscribe at **www.medsafe.govt.nz/profs/subscribe.asp**

Jadelle and the Impact of Weight

Key Messages

- Jadelle (levonorgestrel implants) is one of the most effective methods of contraception.
- The available evidence suggests a small reduction in the efficacy of levonorgestrel with increasing body weight.
- Patients over 60 kg have the option to change their Jadelle implants after four years.
- Healthcare professionals should discuss with women when to change or remove their Jadelle implants prior to insertion.

Jadelle (levonorgestrel implants) is a contraceptive implant for long-term (up to five years) use and is one of the most effective methods of contraception.

The New Zealand data sheet for Jadelle states that the implants are effective for five years in women who weigh up to 60 kg and that the implants may be removed after four years in women who weigh over 60 kg[1].

In March 2016, the Medicines Adverse Reactions Committee (MARC) reviewed the current data on the weight-based efficacy of Jadelle[2]. The MARC considered that the available evidence suggests a reduction in the efficacy of levonorgestrel with increasing body weight over time. However, the current information is insufficient to determine at what time point efficacy may be reduced.

Healthcare professionals are asked to discuss the replacement time for Jadelle with patients before insertion. Women over 60 kg may wish to replace their Jadelle implants earlier than five years.

Please report any adverse events, including unintended pregnancy with Jadelle, to the Centre for Adverse Reactions Monitoring (CARM). It is particularly helpful if the patient's weight and body mass index (BMI) at insertion and later time points are included in your report (**https://nzphvc.otago.ac.nz/carm/**).

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MARC's Remarks: March 2016 Meeting

The Medicines Adverse Reactions Committee (MARC) met on 10 March 2016 to discuss a number of medicine-related safety issues.

The MARC discussed the association between the risk of pulmonary arterial hypertension and **interferons alfa** and **beta**. The MARC concluded that it would be helpful to prescribers to include pulmonary hypertension as an adverse event in the data sheets for both interferon alfa and beta.

The MARC reviewed the available evidence regarding the weight-based efficacy of a **levonorgestrel** contraceptive implant (Jadelle). The MARC considered that the evidence suggests a reduction in efficacy with increasing weight. Further information can be found in this edition of *Prescriber Update*.

The MARC discussed the risk of cardiovascular events in patients taking **sulfonylureas**. The MARC considered that the available evidence indicated an increased risk of cardiovascular effects with glibenclamide compared to gliclazide. Further information can be found in this edition of *Prescriber Update*.

Following the 164th meeting held on 3 December 2015, the European class warning regarding the use of **hormone replacement therapy** and the risk of ovarian cancer was published. The MARC considered that the European wording is suitable in the New Zealand environment. Consequently, the MARC recommended that Medsafe request sponsors update data sheets for hormone replacement therapy products with the European wording.

Further information on the 165th meeting held on 10 March 2016 can be found on the Medsafe website (**www.medsafe.govt.nz/profs/adverse/Minutes165.htm**).

My Patient Missed a Dose; What Should I Advise?

Healthcare professionals are often asked by patients for advice on missed doses.

When managing a missed dose, consider:

- the patient's condition and indication for which the medicine is being used
- the pharmacokinetics of the medicine, in particular the half-life
- the pharmacodynamics of the medicine.

The Patient's Condition and Medicine Indication

The severity of a patient's condition may determine whether clinically significant effects will occur due to a missed dose[1].

Vulnerable patients include those taking medicines with a low therapeutic index, or requiring a minimum effective concentration (eg, anticonvulsants and anticoagulants)[1]. In contrast, for most patients with conditions such as hypertension or hypercholesterolaemia, a single missed dose will be of little consequence[1].

Pharmacokinetics

The half-life of a medicine is useful when deciding how to manage a missed dose. It takes four to five half-lives for a medicine to be completely eliminated[1]. The half-life can usually be found in the medicine data sheet that can be accessed from the Medsafe website (**www.medsafe.govt.nz/profs/datasheet/DSForm.asp**).

In general, medicines or their active metabolites with a long half-life create fewer problems when a dose is missed than medicines with a short half-life[1]. Medicines with a short half-life may lose their therapeutic effect rapidly[1]. For example, patients taking paroxetine (half-life of about one day[2]) may experience withdrawal symptoms if they miss or are late taking a dose. Whereas, patients taking fluoxetine may not experience withdrawal symptoms if they miss a dose as the active metabolite has a long half-life (four to 16 days)[3].

However, missing several consecutive doses of a medicine with a long half-life can make it difficult to re-establish therapeutic concentrations[1]. Loading doses may be needed in these situations for some medicines such as digoxin[1].

Pharmacodynamics

The clinical effect of some medicines is related more to their pharmacodynamic, rather than pharmacokinetic, properties. This usually occurs when the medicine is:[1]

- acting via an irreversible mechanism (eg, aspirin's effect on platelets)
- acting via an indirect mechanism (eg, warfarin's effect on blood coagulation).

Medicines with first-dose effects (eg, ACE inhibitors) may need to be restarted at a lower dose than the patient's maintenance dose to

Table 1: What to do in the event of a missed dose (adapted from the CMI for each medicine; this is not an exhaustive list)[4-7]

Medicine	Consumer Medicine Information
Dabigatran	A forgotten dose can be taken up to six hours prior to the next dose. The dose should be omitted if the remaining time is less than six hours to the next dose. A double dose should not be taken.
Alendronate (weekly)	The forgotten dose can be taken the next morning. Two tablets should not be taken on the same day. The patient should then return to taking one tablet once a week.
Phenytoin	A forgotten dose can be taken up to four hours prior to the next dose. If the patient remembers within four hours of the next dose they should skip the dose and take the next one as scheduled. A double dose should not be taken.
Carbamazepine	A forgotten dose can be taken up to two hours prior to the next dose. If the next dose is due within less than two hours the patient should skip the missed dose then take the next dose as normal. A double dose should not be taken.

avoid adverse effects[1]. Similarly, a dose reduction may be needed for medicines where tolerance occurs (eg, opioids) if more than one dose has been missed.

Overall, few studies have examined the clinical significance of a missed dose[1].

Provide Education

Talk to patients about using consumer medicine information (CMI). CMI are available for most commonly prescribed medicines and are produced by the medicine sponsor. CMI include a section *'If you forget to take it'* (Table 1). CMI can be accessed from the Medsafe website (**www.medsafe.govt.nz/consumers/cmi/CMIForm.asp**).

Make sure patients know which medicines they should not forget to take and who to consult if they miss a dose.

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Inhaled and Systemic Corticosteroids and Mood Disorders

Key Messages

- Inhaled and systemically available (oral and injectable) corticosteroids have been associated with adverse psychiatric and behavioural reactions.
- Reactions may include euphoria, insomnia and irritability or personality changes, depression and very rarely psychosis.
- The risk of these reactions is lower with short-term, occasional treatment or local application.

Corticosteroids are used in the treatment or symptom control of a number of different medical conditions. Indications for use range from endocrine disorders such as adrenal insufficiency, to allergic skin reactions, blood disorders (eg, leukaemia), pulmonary disorders (eg, asthma and emphysema) and connective tissue disorders (eg, systemic lupus erythematosus). However, not all corticosteroids are approved for all indications.

Corticosteroids are available in a variety of different formulations including tablets, injections, aerosols for inhalation, eye drops and topical applications.

Healthcare professionals are reminded that inhaled and systemically available (oral and injectable) corticosteroids have been associated with adverse psychiatric and behavioural reactions. Adverse effects may include euphoria, insomnia and mood swings such as irritability and hyperactivity, or personality changes, severe depression and even psychosis[1,2,3].

Particular care is needed when considering the use of corticosteroids in patients with existing or a previous history of severe affective disorders as these tendencies may be aggravated by corticosteroid use[1].

The Centre for Adverse Reactions Monitoring (CARM) received 48 reports containing 70 adverse psychiatric or behavioural reactions associated with corticosteroid treatment from 1 January 2000 to 31 December 2015 (Table 1).

The reaction terms most frequently reported include agitation (six reports), insomnia, confusion, anxiety and depression (five reports each). Somnolence, hallucination and psychosis have also been reported.

Table 1: Number of adverse psychiatric or behavioural reactions reported in association with different corticosteroids in New Zealand (1 January 2000 to 31 December 2015)

Corticosteroid	Number of Reports
Prednisone	14
Fluticasone, Dexamethasone	6
Hydrocortisone, Triamcinolone	5
Prednisolone, Budesonide (with Eformoterol), Betamethasone	3
Budesonide	2
Beclomethasone	1

There have been no reports of psychiatric reactions with methylprednisolone or fludrocortisone. Tetracosactide was not included as used only for diagnostic purposes.

The risk of experiencing these adverse reactions is lower with short-term, occasional corticosteroid treatment or local application (eg, into the eyes, onto the skin or an injection into the joint). The incidence of these reactions increases with increasing corticosteroid dose.

These reactions often occur within days or weeks of starting treatment and dose reduction or withdrawal usually helps symptom resolution[1]. Dose tapering needs to be carefully managed to avoid hypothalamic-pituitary-adrenal (HPA) axis suppression, which may result in secondary adrenal insufficiency, recurrence of the underlying condition or corticosteroid withdrawal syndrome[1]. As with many other medicines, corticosteroids should be titrated to the lowest effective dose.

Healthcare professionals are encouraged to continue reporting adverse reactions to corticosteroids to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/reporting/**).

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Medicine-induced Hearing Loss

Key Messages

- ⌘ Consider the possibility of a medicine-related cause in patients who develop sensorineural hearing loss.
- ⌘ Hearing loss may develop or persist after the ototoxic medicine has been discontinued.
- ⌘ Risk factors for medicine-induced hearing loss include renal impairment, dehydration, age, co-administration of two or more ototoxic medicines and perforated ear drum (for topically administered medicines).

The Centre for Adverse Reactions Monitoring (CARM) received 76 reports of hearing loss from 1 January 2006 to 31 December 2015. The five most frequently reported medicines were:

- gentamicin (six reports)
- erythromycin (six reports)
- thyroxine (five reports, all associated with a formulation change)
- cisplatin (four reports)
- influenza vaccine (four reports).

Medicine-induced ototoxicity is the functional impairment of the inner ear (cochlea and/or vestibular system) or eighth cranial nerve secondary to a pharmaceutical agent[1]. Ototoxic medicines that may cause hearing loss include aminoglycosides, macrolide antibiotics, antimalarials, platinum-based antineoplastic agents, anti-inflammatory medicines and loop diuretics (Table 1)[2].

The mechanisms by which ototoxic medicines cause hearing loss are poorly understood[3]. Cisplatin and the aminoglycosides are believed to cause sensory hair cell apoptosis via a process involving the production of reactive oxygen species[4,5]. Loop diuretics may alter the potassium gradient between the chambers of the cochlear, affecting its function[6]. Topical preparations instilled into the auditory canal can lead to damage to middle ear structures if the ear drum

has been perforated or tympanostomy tubes have been inserted[7]. Medicines that cause peripheral neuropathy may also affect hearing through damage to the auditory nerve.

Hearing loss can occur at any time during or after treatment with an ototoxic medicine and may be gradual or sudden in onset. Hearing loss may be unilateral or bilateral and may fluctuate in severity. Medicine-induced damage to the cochlea usually affects the ability to hear high frequencies initially, but may progress to lower frequencies. Cochlear damage may also manifest as tinnitus.

Risk factors for medicine-induced hearing loss include:[2,3,6]

- the patient's age (greater risk in children and older people)
- dehydration
- reduced medicine elimination (particularly due to renal failure)
- co-administration of two or more ototoxic medicines
- perforated ear drum (for medicines administered topically into the external auditory canal)
- genetic predisposition (eg, aminoglycoside and cisplatin ototoxicity).

When prescribing potentially ototoxic medicines, patients should be advised of the possibility of hearing loss and to report any hearing difficulties to their healthcare provider. Audiological monitoring is recommended for potent ototoxic medicines such as cisplatin[1].

Please continue to report any cases of medicine-induced hearing loss to CARM. Reports can be submitted on paper or electronically (**https://nzphvc.otago.ac.nz/reporting/**).

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Table 1: Ototoxic medicines associated with hearing loss (adapted from Drug-induced hearing loss, *Prescrire International*[2]; this is not an exhaustive list)

Medicine Class	Examples
Medicines recognised as causing hearing loss	
Antibiotics	Aminoglycosides, macrolides, tetracyclines, vancomycin
Antifungals	Itraconazole, terbinafine
Anti-inflammatory medicines	Aspirin, COX-2 inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs)
Antimalarials	Chloroquine, mefloquine, quinine
Antineoplastics	Bortezomib, carboplatin, cisplatin, docetaxel, nilotinib, vinblastine, vincristine
Iron chelating medicines	Deferasirox, deferoxamine
Loop diuretics	Bumetanide, furosemide
Phosphodiesterase type-5 inhibitors	Sildenafil, tadalafil, vardenafil
Other medicines	Bromocriptine, febuxostat, hydroxychloroquine, interferon alfa, isotretinoin, sodium valproate, tacrolimus
Medicines that have been reported to cause hearing loss	
Amphotericin B, artemether, bisphosphonates (eg, alendronic acid, zoledronic acid), boceprevir, chlormethine, deferiprone, enalapril, flumazenil, nitrous oxide gas, thalidomide, verteporfin	

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