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# Therapeutic Brief

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## Diuretics: reducing harm

Diuretics are a valuable class of medicines commonly used in the treatment of hypertension and **heart failure**.<sup>1</sup> However, they are often overused.<sup>2</sup>

Older people are particularly vulnerable to their adverse effects, which commonly include fluid and electrolyte disturbances, renal impairment and metabolic abnormalities including hyperglycaemia and hyperlipidaemia.<sup>1,3-7</sup> Diuretics can also cause dermatitis<sup>3</sup>, urinary urgency<sup>2</sup> and secondary gout in older people.<sup>7</sup>

Most diuretic-related adverse effects can be avoided or minimised with appropriate use, by closely monitoring patients and by adjusting the dose of the diuretic as needed.<sup>8</sup>

### Analysis of Australian Government Department of Veterans' Affairs (DVA) data indicates monitoring of older DVA patients who are using diuretics can be improved<sup>9</sup>



1 in 2 DVA patients dispensed a thiazide diuretic were dispensed at least one other medicine that increases the risk of hyponatraemia<sup>9</sup>



3 in 4 DVA patients dispensed a potassium-sparing diuretic were dispensed at least one other medicine that increases the risk of hyperkalaemia<sup>9</sup>



1 in 3 DVA patients **DID NOT** have a claim for a serum biochemistry test within one month before, or within three months after being dispensed a thiazide diuretic<sup>9</sup>



1 in 5 DVA patients **DID NOT** have a claim for a serum biochemistry test within one month before, or within three months after being dispensed a loop diuretic<sup>9</sup>

## INSIDE

Monitor fluid status, electrolytes and renal function

A medicines review can be particularly beneficial

More frequent monitoring, dose adjustment or temporarily stopping the diuretic may be needed at times

### Key points

- Monitor fluid status, electrolytes and renal function before and after starting a diuretic, and at each re-prescription or every three to six months
- Devise a patient management plan which includes more frequent monitoring during episodes of acute illness and periods of hot weather
- Consider a medicines review for patients at high risk of diuretic-induced adverse effects, or if you have any concerns about their medicines use
- Consider that renal impairment or symptomatic hypotension from diuretic use may impact the optimal use of other medicines that reduce morbidity and mortality

## ✓ Monitor fluid status, electrolytes and renal function

Most diuretic-induced adverse effects are dose-related and can be minimised or avoided by selecting the lowest dose necessary for effective blood pressure or volume control, close monitoring (see Table 1) and adjusting the dose of the diuretic as needed.<sup>3, 8, 10, 11</sup> As a general guide, once the patient and treatment is stable, check fluid status, electrolytes and renal function at each re-prescription, or once every three to six months. Monitor more frequently if your patient becomes acutely unwell or treatments change.<sup>12</sup>

**Table 1.** Suggestions for monitoring patients using diuretics

Diuretic	Check before starting	Check after starting or increasing the dose	Frequency	Considerations
<b>Loop diuretics:</b> – furosemide (also called frusemide) – *bumetanide	– Fluid status – **Serum biochemistry <sup>12</sup> – Check that the patient is not using a thiazide diuretic (see Table 2)	– Fluid status – Serum biochemistry <sup>12, 13</sup>	– 1–2 weeks (or more frequently in high risk patients) after starting or increasing the dose – Then 3–6 monthly or more often if clinically needed <sup>2, 8, 12, 13</sup>	– For further information about how to optimise diuretic use in heart failure, go to the the Veterans' MATES topic <i>Heart failure: Getting the best quality of life</i> , at: <a href="http://www.veteransmates.net.au/topic-62-therapeutic-brief">www.veteransmates.net.au/topic-62-therapeutic-brief</a> or to the NPS MedicineWise topic <i>Heart failure: taking an active role</i> , at: <a href="http://www.nps.org.au/professionals/heart-failure-taking-an-active-role">www.nps.org.au/professionals/heart-failure-taking-an-active-role</a>
<b>Aldosterone antagonists (also called mineralocorticoid receptor antagonists)</b> – spironolactone – eplerenone <b>Other diuretics:</b> – amiloride (potassium sparing diuretic)	– Serum biochemistry – Blood pressure <sup>12</sup>	– Serum biochemistry – Blood pressure <sup>12, 13</sup>	– At 1–2, then at 4, 8 and 12 weeks after starting or increasing the dose, especially in heart failure patients <sup>8, 12, 13</sup> – Then 3–6 monthly or more often if clinically required <sup>2, 12, 13</sup>	– Hyperkalaemia: patients at high risk include those who are elderly with diabetes, renal impairment or are using an angiotensin converting enzyme (ACE) inhibitor, an angiotensin receptor blocker (ARB) or potassium supplements <sup>9</sup> – Risk of orthostatic hypotension, hyponatraemia and hypochloraemia is increased when combined with a thiazide diuretic <sup>10</sup>
<b>Thiazide and thiazide-like diuretics:</b> – indapamide – hydrochlorothiazide – chlortalidone	– Serum biochemistry – Blood pressure <sup>7</sup>	– Serum biochemistry – Blood pressure <sup>7, 10</sup>	– 3–6 weeks after starting or as clinically needed <sup>7</sup> – Then 3–6 monthly or more often if clinically required <sup>2</sup>	– Risk of hyponatraemia, hypokalaemia and renal impairment <sup>7, 8, 11</sup> – Hyponatraemia and hypokalaemia are uncommon at doses recommended for treating hypertension <sup>7</sup> – At doses used to treat hypertension, thiazide diuretics have a predominantly vasodilatory effect rather than a diuretic effect <sup>7</sup>

\* Bumetanide is not listed on the Pharmaceutical Benefits Scheme or the Repatriation Pharmaceutical Benefits Scheme

\*\*Serum biochemistry: electrolytes, creatinine clearance and urea

## ✓ A medicines review can be particularly beneficial

### Analysis of DVA data indicates diuretic use is very common among older DVA patients



1 in 4 DVA patients aged 65 years or older were dispensed a diuretic<sup>9</sup>



1 in 3 DVA patients living in a residential aged care facility were dispensed a diuretic<sup>9</sup>

Older patients taking a diuretic who are frail or cognitively impaired, or have renal impairment, comorbid complexity or polypharmacy, are more likely to experience adverse effects.<sup>4, 8, 11, 12, 14</sup> **In this population, diuretic-induced adverse effects can contribute to dehydration, falls and fractures, declining attention and cognitive function, worsening renal**

**impairment, reduced quality of life, and institutionalisation.**<sup>2, 5, 10, 14-16</sup>

A collaborative medicines review can be particularly beneficial in detecting, preventing or resolving diuretic-related problems.<sup>17, 18</sup>

The pharmacist conducting the medicines review can assess and consider:

- if the diuretic is still needed (see Box 1)
- pathology results, including electrolyte and renal, and further monitoring required
- potential drug-drug or drug-disease interactions of concern
- compliance and knowledge issues, and the patient's ability to manage their medicines, including their diuretic medicines on sick days and during hot weather.<sup>18</sup>

Detailed information about a Residential Medication Management Review (RMMR) under item number 903 and a Home Medicines Review (HMR) under item number 900 is available at: [www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=900&qt=ItemID](http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=900&qt=ItemID)

### Box 1. Is the diuretic necessary?

Reviewing the need for ongoing use of a diuretic is particularly important in frail or cognitively impaired patients, and in those who have falls or have been using a diuretic long-term. In particular, consider stopping the diuretic where there is no clear benefit, the diuretic is being used for an indication that is no longer an issue, the risks outweigh the benefits, or the treatment no longer aligns with your patient's preferences.<sup>16, 19</sup>

**Review and consider stopping the diuretic if prescribed for idiopathic ankle oedema or peripheral lymphoedema, or if drug-induced oedema is present:**

- Diuretics are not indicated for the treatment of idiopathic oedema or peripheral lymphoedema.<sup>16, 20</sup> Offer to treat the oedema with fitted pressure stockings and limb elevation, and explain to your patient that being physically active may help resolve the oedema.<sup>16, 20</sup>
- Some medicines, including dihydropyridine calcium channel blockers, pregabalin and gabapentin, pioglitazone, prednisolone and non-steroidal anti-inflammatory drugs (NSAIDs), can induce or exacerbate peripheral oedema:<sup>10, 21, 22</sup>
  - Dihydropyridines, such as amlodipine, commonly cause peripheral oedema by

redistributing extracellular fluid rather than retaining fluid, which does not respond to treatment with diuretics.<sup>10</sup>

- Offer non-pharmacological strategies to address the oedema and stop or change the medicine where possible.<sup>10, 21</sup>

#### Pro re nata (PRN) use of diuretics

There is potential for harm associated with the use of PRN “when necessary” orders for medicines, particularly in frail older people.<sup>23, 24</sup> Avoid PRN orders for diuretics and prescribe as a stat dose or regular dose or cease.



## ✓ More frequent monitoring, dose adjustment or temporarily stopping the diuretic may be needed:

### ⊕ When starting medicines that can interact with a diuretic

Drug-drug interactions are more common among older patients, often because they have underlying factors contributing to greater vulnerability which include pathophysiological changes associated with aging and a high number of medicines used to treat multimorbidity.<sup>25</sup>

**Table 2.** Examples of medicines commonly used by DVA patients that can interact with diuretics

Medicine combination	Potential adverse effects	Considerations
A loop diuretic or a thiazide diuretic with an ACE inhibitor or ARB <sup>10</sup>	<ul style="list-style-type: none"> <li>– Renal impairment</li> <li>– Hypotension</li> <li>– Hypokalaemia<sup>10</sup></li> </ul>	<ul style="list-style-type: none"> <li>– Start, titrate and stop loop diuretics only to manage congestion in heart failure patients.<sup>13, 26</sup> To avoid symptomatic hypotension, consider withholding the loop diuretic or reducing the dose for 24 hours before starting an ACE inhibitor or ARB.<sup>10, 27</sup></li> <li>– When treating patients with heart failure, prioritise use of medicines that decrease mortality, including ACE inhibitors and ARBs over the use of loop or thiazide diuretics.<sup>13, 26</sup></li> <li>– Consider reducing the dose or stopping the diuretic before making any adjustments to the ACE inhibitor or ARB to avoid renal impairment or symptomatic hypotension.<sup>27</sup></li> <li>– Avoid NSAIDs (and advise patients to avoid over the counter NSAIDs) when using a loop diuretic together with an ACE inhibitor or ARB as use of these medicines together substantially increases the risk of acute kidney injury.<sup>12</sup></li> <li>– Monitor renal function, electrolytes and fluid status closely.<sup>10</sup></li> </ul>
A loop diuretic, potassium sparing diuretic or a thiazide diuretic with NSAIDs, particularly indometacin <sup>27</sup>	<ul style="list-style-type: none"> <li>– Renal impairment<sup>27</sup></li> <li>– Hyperkalaemia<sup>10</sup></li> <li>– Reduced diuretic effect<sup>8, 27, 28</sup></li> </ul>	<ul style="list-style-type: none"> <li>– NSAIDs can cause renal impairment, especially in dehydrated or elderly patients.<sup>27</sup> People most at risk of adverse effects include older patients with liver cirrhosis, heart failure and renal impairment.<sup>27</sup></li> <li>– Monitor renal function, electrolytes and fluid status closely.<sup>10</sup></li> </ul>
Loop diuretic with a thiazide diuretic <sup>10</sup>	<ul style="list-style-type: none"> <li>– Renal impairment</li> <li>– Increased diuresis</li> <li>– Electrolyte disturbances<sup>10</sup></li> </ul>	<ul style="list-style-type: none"> <li>– Avoid combination, unless advised by other medical specialists.</li> <li>– Check renal function within 5 days of starting, then every 5–14 days, depending on the patient's stability.<sup>12</sup> Monitor fluid status closely. Once stable, check at re-prescription or 3–6 monthly unless there is a change in dose, an intercurrent illness or worsening renal function.<sup>12</sup></li> </ul>
A loop diuretic with a peripheral alpha-1 blocker <sup>28</sup>	<ul style="list-style-type: none"> <li>– Urinary incontinence in older women<sup>28</sup></li> </ul>	<ul style="list-style-type: none"> <li>– Avoid combination where possible.<sup>28</sup></li> </ul>
A selective serotonin re-uptake inhibitor or carbamazepine with a thiazide diuretic <sup>29</sup>	<ul style="list-style-type: none"> <li>– Hyponatraemia, especially in elderly women<sup>29</sup></li> </ul>	<ul style="list-style-type: none"> <li>– Check electrolytes within two weeks of starting.<sup>29</sup></li> </ul>

⊕ During episodes of acute illness, such as diarrhoea, vomiting or fever

During episodes of acute illness, such as diarrhoea, vomiting or fever, volume depletion, renal impairment and electrolyte disturbances can be made worse with diuretic use.<sup>30</sup>

- Monitor patients closely, especially those with heart failure, during episodes of acute illness where there is risk of volume depletion and acute kidney injury. **Consider reducing the dose or temporarily withholding the diuretic until the patient is eating and drinking normally again.**<sup>12,30</sup> Check renal function if symptoms persist beyond two days.<sup>12</sup>

**The risk of hyperkalaemia may be increased in heart failure patients during acute illnesses**

A retrospective study of 64 heart failure patients aged 75 years or over prescribed spironolactone together with an ACE inhibitor and experiencing sepsis, vomiting or diarrhoea found:

- 36% developed hyperkalaemia (5.5 mmol/L or greater)
- 11% developed severe hyperkalaemia (6.0 mmol/L or greater)
- 38% sustained a 50% rise in creatinine concentration.<sup>31</sup>

- Gastroenteritis is a common illness in residents in aged care facilities and is associated with high morbidity and mortality.<sup>32,33</sup> Be aware of diuretic use (especially loop diuretics) in residents during episodes of gastroenteritis or other acute illnesses where there is risk of volume depletion and acute kidney injury.<sup>30</sup> **Ensure staff have clear instructions about diuretic use during this time, particularly if diuretics are included in a dose administration aid, or a fixed-dose combination product, where the diuretic can be overlooked or the dose cannot be adjusted.**<sup>2,34</sup>
- An individualised sick day card may be helpful for patients managing their own

medicines at home during episodes of fever, diarrhoea or vomiting. Consider including sick day instructions for diuretic use in a General Practitioner Management Plan. To see an example of a Medicine Sick Day Rules card (NHS Scotland and Scottish Patient Safety Program), go to: <https://ihub.scot/media/1398/20180424-medicine-sick-day-rules-patient-leaflet-print-v20.pdf>

⊕ During hot weather

In the presence of comorbidities and polypharmacy, the risk of dehydration and heat-related illness during hot weather is significantly increased for many older people.<sup>5,35</sup>

A retrospective analysis of 6,700 Australian veterans with an average age of 85 years found that in the year after starting:

- a diuretic, they were almost two times more likely to be hospitalised for dehydration or a heat-related illness during hot weather, compared to the year before starting the medicine (see Figure 1)<sup>5</sup>
- a diuretic together with an ACE inhibitor, they were almost three times more likely to be admitted to hospital for dehydration or a heat-related illness than the year before starting this combination of medicines (see Figure 1).<sup>5</sup>

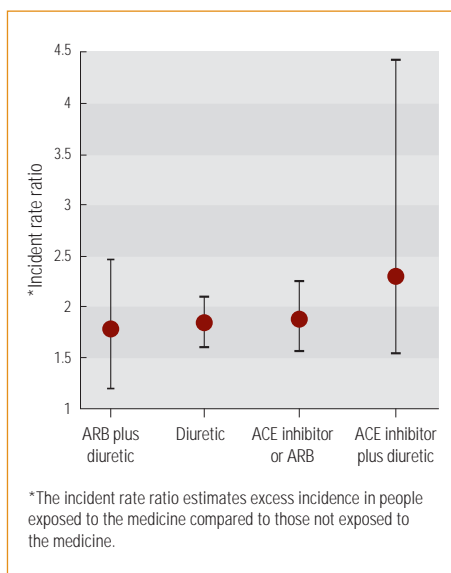


Figure 1. Risk of hospitalisation for dehydration or heat-related illness after initiating a diuretic alone or in combination with an ACE inhibitor or ARB.<sup>5</sup>

**Where appropriate, consider reducing the dose of the diuretic or temporarily withholding the diuretic on hot days, or devise an individualised plan for patients who are able to adjust their own diuretic dose.**

Ensure patients have a good understanding of how to stay hydrated and well during hot weather, and encourage them to make an appointment to see their doctor within a few days if they adjust their diuretic dose.<sup>36</sup>

For information on managing other medicines during hot weather, refer to the Veterans' MATES topic, *Medicines and hot weather: Reducing the risk of dehydration and heat-related illness*, at: [www.veteransmates.net.au/topic-40-therapeutic-brief](http://www.veteransmates.net.au/topic-40-therapeutic-brief)

**Diuretics, hyponatraemia and falls**

- Hyponatraemia is a common electrolyte disturbance in older people, especially in those who are frail, female or live in aged care facilities.<sup>14</sup>
- Mild hyponatraemia can go unrecognised in older people. Symptoms of mental confusion may be misattributed to age-related cognitive decline rather than hyponatraemia. Even mild hyponatraemia can affect cognition, attention, balance, gait and bone strength, increasing the risk of falling, and ultimately reducing quality of life.<sup>8,14,37,38</sup>
- Thiazide and thiazide-like diuretics, such as indapamide and hydrochlorothiazide, are common causes of hyponatraemia, particularly if high doses are used.<sup>14</sup>
  - Consider the risk of hyponatraemia in older people who use thiazide diuretics, including fixed-dose combination products that include a thiazide diuretic, for example, indapamide with perindopril, or hydrochlorothiazide with amlodipine.<sup>10</sup>
  - Mild hyponatraemia that is seemingly asymptomatic requires serum biochemistry for diagnosis.<sup>14</sup>

