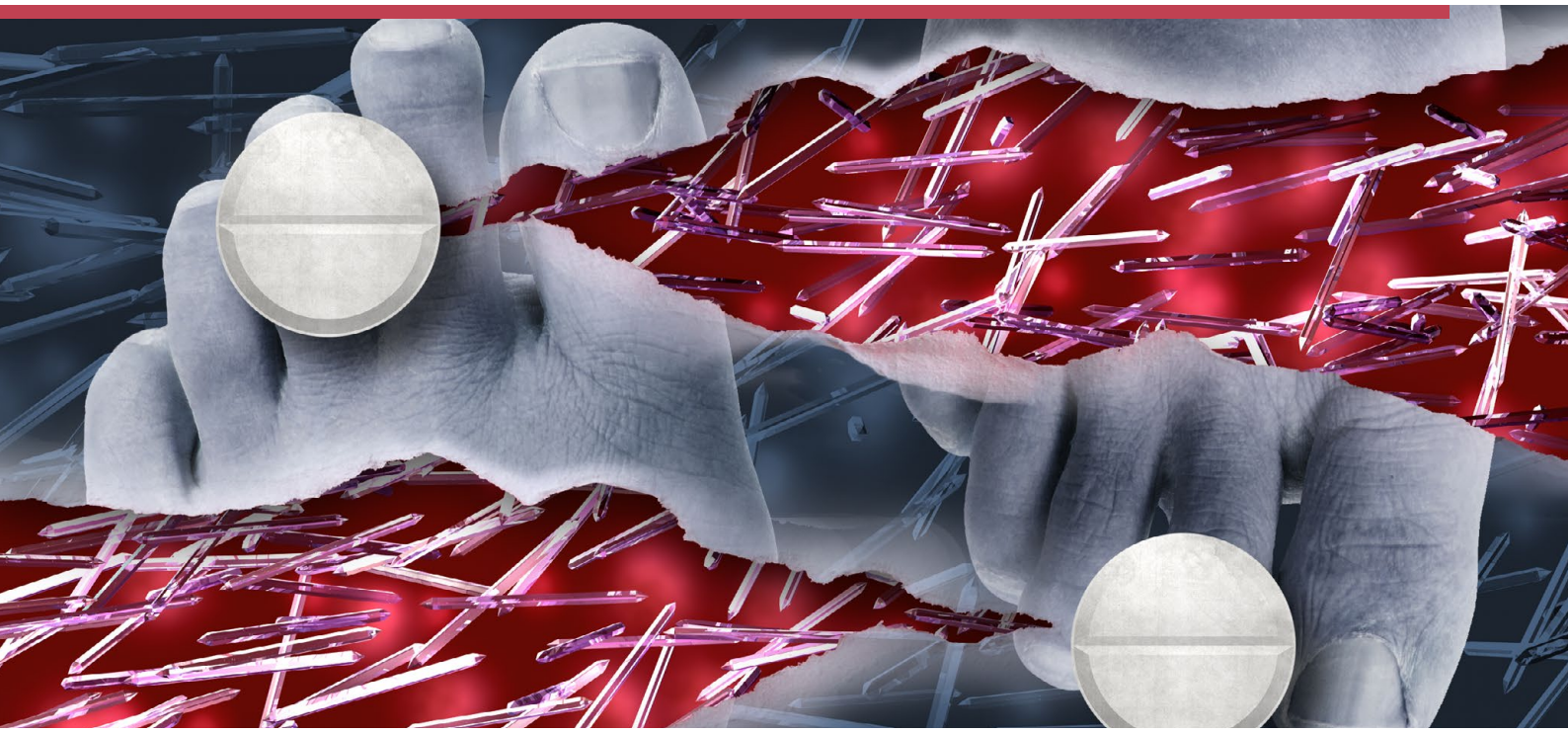

Managing gout in primary care

Part 2 – Controlling gout with long-term urate-lowering treatment

Urate-lowering medicines should be considered and discussed with patients with gout from the first presentation. Doses of urate-lowering medicines need to be titrated to effect so that patients consistently have serum urate levels that are below target. Three urate-lowering medicines are available in New Zealand and patients who are unable to achieve treatment targets with allopurinol alone should be offered an alternative regimen.

KEY PRACTICE POINTS:

- Doses of urate-lowering medicines need to be titrated so that the patient achieves a serum urate level that is below 0.36 mmol/L; a target below 0.30 mmol/L is recommended for those with features of severe disease, e.g. tophi
- Allopurinol is the recommended first-line urate lowering medicine; renal function is used to determine the starting dose
- Probenecid and febuxostat are available for patients who find allopurinol ineffective or intolerable
- Patients with gout require ongoing management of cardiovascular risk and monitoring for associated co-morbidities, e.g. chronic kidney disease and diabetes; they should also be provided with adequate support to ensure regular medicine use

For further information about managing patients with gout, including treating flares, see: "Part 1: Talking about gout: time for a rethink" available from: **bpac.org.nz/2021gout-part1.aspx**

This is a revision of a previously published article. What's new for this update:

- Changes to urate-lowering medicines: general article revision
  - **Benzbromarone is to be discontinued.** Most people taking benzbromarone will have now switched to a different treatment and no new patients should be started on benzbromarone. Any patients remaining on benzbromarone should be changed to a different urate-lowering medicine as soon as possible.
  - Special Authority criteria has been amended for febuxostat; febuxostat is now funded for people with previous Special Authority approval for benzbromarone

Serum urate levels are treated to target

The goal of urate-lowering treatment is to reduce serum urate levels below saturation point in order to dissolve urate crystals, thereby preventing future gout flares.[1]

The recommended serum urate levels are:[2–4]

- < 0.36 mmol/L for most patients
- < 0.30 mmol/L for patients with severe gout, e.g. those with tophi, chronic gouty arthritis or frequent flares

After several years of symptom-free treatment and resolution of tophi, patients treated to < 0.30 mmol/L can be switched to the less stringent target of < 0.36 mmol/L.[1]

Testing of serum urate levels is recommended prior to dose adjustment, e.g. initially every four weeks, while urate-lowering treatment is being titrated and then every six to 12 months for monitoring.[4] During a flare, serum urate levels should not be tested for the purposes of monitoring the patient's response to treatment as their serum urate levels may be lower than normal.[5, 6]

Blister packs simplify treatment for patients and encourage adherence

Multiple medicines are often required for the initial treatment of gout, including acute flare management and prophylaxis, and increasing doses of allopurinol or another urate-lowering medicine. This requires careful instruction to ensure that the patient takes the right dose of the right medicine at the right time. A potential solution for some patients is to have medicines dispensed in a blister pack. In many cases, pharmacies will charge patients for this service, but some PHOs may fund this – check with your local PHO.

Table 1: Treatment options for flare prophylaxis.[1, 7, 8]

Medicine	Dose	Additional notes
Naproxen	250 mg, twice daily	Consider concurrent use of a proton pump inhibitor Avoid if eGFR < 30 mL/min/1.73m^2
Colchicine (unapproved indication)	Very low dose regimen: 500 micrograms, twice daily Reduce dose if required (see notes)	Reduce dose to 500 micrograms, once daily, or on alternate days, if not tolerated, e.g. diarrhoea develops, chronic kidney disease or concurrent use of CYP3A4/P-glycoprotein inhibitors (e.g. erythromycin, verapamil) Ideally avoid, or use with caution, in frail patients, those who weigh < 50 kg, or patients with hepatic or renal impairment (eGFR 10–50 mL/min/1.73m^2) Contraindicated if eGFR <10 mL/min/1.73m^2
Prednisone	5 mg, once daily	Second-line option if contraindications to NSAIDs or colchicine Taper slowly on withdrawal Monitor for corticosteroid-related adverse effects

Best practice tip: If the patient is receiving treatment for a gout flare with a NSAID or colchicine, continue the same medicine at a lower dose for prophylaxis once the flare has resolved. If a flare occurs during prophylactic treatment, stop the prophylactic dose and change to a regimen for acute treatment of a flare (for further information, see: "Medicines for gout flares are determined by the patient's characteristics" in Part 1 available from: **bpac.org.nz/2021gout-part1.aspx**).

Flare prophylaxis is recommended when initiating urate-lowering treatment

During the first months of urate-lowering treatment the rapid decline in serum urate is thought to disrupt pre-formed monosodium urate crystals making them more likely to provoke a local inflammatory response which can result in an acute flare of gout.[7]

Prophylactic treatment (Table 1) should generally be provided for at least the first six months alongside urate-lowering treatment. However, new guidance suggests that three to six months might be sufficient for some people, e.g. those who are symptom free at their three-month review after initiating urate-lowering treatment and have had a substantial drop in serum urate levels.[2] Prophylactic treatment may be required for longer than six months in people with frequent ongoing flares or tophi, e.g. 12 months or more, but the risks of ongoing treatment (i.e. adverse effects of NSAIDs or colchicine) needs to be weighed up with the potential benefits.[2] Further emphasis on optimising urate-lowering treatment and modifiable factors may be required.

Gradual dose titration also reduces the risk of flares, compared to starting full doses of urate-lowering treatment. The increased risk of flares during initiation of urate-lowering treatment should be discussed with patients and advice given to persist with urate-lowering treatment if a flare does occur.

Allopurinol is the first-line urate-lowering medicine

Allopurinol is a xanthine oxidase inhibitor that decreases the production of urate by inhibiting the metabolism of purines; it is the first-line urate-lowering medicine for patients with gout.[2, 9]

The starting dose of allopurinol is determined by the patient's renal function

Allopurinol is started at a low dose and slowly titrated upwards, to minimise the occurrence of adverse effects, until the patient reaches the target serum urate level (Table 2).[2] Allopurinol can be safely used in patients who have reduced renal function, with a lower starting dose and slower titration. Dose reductions are not routinely required in patients with declining renal function who are already established on allopurinol.

Dose titration is essential to achieve serum urate targets

Once allopurinol has been initiated, regular follow-up with serum urate testing is required while the dose of allopurinol is titrated upwards, until the serum urate target is reached. In patients without renal dysfunction, 30 – 50% will require a dose of allopurinol in excess of 300 mg per day to achieve a serum urate target.[3] Treatment with up to 600 – 800 mg per day of allopurinol can be expected to achieve a serum urate target in 75 – 80% of patients with gout.[3]

Other urate-lowering medicines (see below) are available for patients who are unable to tolerate allopurinol or achieve the serum urate target with allopurinol alone. However, some patients who continue to have serum urate levels slightly above target despite their maximum tolerated dose of allopurinol may choose to persist with allopurinol alone, rather than taking an additional medicine, if flares are controlled.

Community pharmacists may have an increasing role in the titration of allopurinol dosing with the use of standing orders provided by general practitioners, e.g. in the Owning My Gout and Gout Stop initiatives, see: **https://www.arthritis.org.nz/wp-content/uploads/2020/07/Gout-Programmes-Evaluation-Report-April-2020.pdf** for further information.

Table 2: Suggested starting doses and dose titrations for allopurinol determined by renal function.[8]

Estimated glomerular filtration (eGFR) mL/min/1.73m^2	Initial dose of allopurinol	Dose increase
> 60	100 mg, daily	Increase by 100 mg, every four weeks*, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily
30 – 60	50 mg, daily	50 mg, every four weeks, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily†
< 30	50 mg, every second day	

* Some prescribers prefer a more rapid titration, e.g. every two weeks, although this needs to be balanced against the increased risk of adverse effects

† Many people with renal dysfunction will be unable to tolerate the maximum dose of allopurinol; consider referral to or discussion with a rheumatologist if serum urate targets are unable to be achieved and an increase in dose is not tolerated, e.g. over 300 mg allopurinol daily

Adverse effects of allopurinol are relatively uncommon

Allopurinol is generally well-tolerated, although some patients will experience gastrointestinal symptoms.[1, 8] Hypersensitivity reactions caused by allopurinol can occur, e.g. drug rash with eosinophilia and systemic symptoms (DRESS) and Steven-Johnson syndrome. DRESS is a rare, but potentially fatal, condition characterised by an erythematous, desquamating rash, fever, eosinophilia, leukocytosis, hepatitis and renal failure.[4, 8, 10] DRESS is estimated to occur in 0.1% of patients taking allopurinol, most often in the first few weeks to months of initiating treatment.[4, 10] The risk of DRESS can be substantially reduced by introducing allopurinol at a low dose and slowly titrating upwards after tolerance has been established.[10] Patients should stop taking allopurinol and seek medical advice if they develop a rash or itch; an alternative urate-lowering medicine can be trialled. Risk factors for DRESS in patients taking allopurinol include renal impairment, an elevated starting dose of allopurinol relative to renal function, the use of diuretics, and having the *HLA-B*5801* allele which is often present in people of Korean, Thai or Han Chinese descent.[2, 4, 8, 10] Genetic testing for this allele is available; it is recommended to discuss testing with a local laboratory or with Genetic Health Service NZ, **www.geneticehealthservice.org.nz**

Add probenecid if serum urate targets are not achieved with allopurinol alone

Probenecid can be added to allopurinol if despite taking a relatively high dose of allopurinol, e.g. 600 mg daily, the patient is unable to achieve the serum urate target; assess for regular use of allopurinol first.[3] Probenecid can also be prescribed as monotherapy to patients who are intolerant or resistant to allopurinol.[9]

Probenecid dosing is titrated according to the patient's serum urate concentration:[8]

- Initially, 250 mg, twice daily, for one week, then 500 mg, twice daily, with the dose increased by 500 mg every four weeks, to a total of 1 g, twice daily, if required

Probenecid should be avoided in patients with an eGFR < 30 mL/min/1.73m^2.[8] Probenecid is contraindicated in patients with urolithiasis.[2, 9] Patients should be advised to drink plenty of fluids, at least two litres per day, to prevent the formation of uric acid stones and to take the medicine with, or just after, a meal.[8, 9] The most common adverse effects associated with probenecid are nausea and vomiting.[8]

Febuxostat is a further option for urate-lowering

If treatment with allopurinol and/or probenecid is ineffective or cannot be tolerated, febuxostat is a second-line xanthine oxidase inhibitor.[2, 4]

The recommended dose of febuxostat for patients with gout is:[8]

- 80 mg, once daily, increased to 120 mg*, once daily, after two to four weeks if the serum urate is > 0.36 mmol/L

* The maximum daily dose of febuxostat for patients with mild hepatic impairment is 80 mg

Special Authority for febuxostat has changed

The Special Authority criteria for febuxostat has been amended amid plans to discontinue benzbromarone (see: "Benzbromarone to be discontinued"). Febuxostat is now funded with Special Authority approval in New Zealand for patients with gout who:[8]

- Have a serum urate level > 0.36 mmol/L after having been treated with allopurinol at doses of at least 600 mg per day in addition to probenecid at doses up to 2 g per day or to a maximum tolerated dose; or
- Have intolerable adverse effects associated with allopurinol treatment requiring treatment discontinuation and have trialled probenecid at doses up to 2 g per day or to a maximum tolerated dose; or
- Have had treatment with allopurinol optimised, however, renal impairment means that probenecid cannot be added or is that it is likely to be ineffective; or
- Have had previous Special Authority approval for benzbromarone for the treatment of gout

Key prescribing points for febuxostat

Renal impairment. Febuxostat can be used in patients with renal dysfunction as this is not a significant route of elimination, however, caution is advised in patients with an eGFR < 30 mL/min/1.73m^2 due to a lack of safety data; although, as probenecid should be avoided in patients with an eGFR < 30 mL/min/1.73m^2, febuxostat is the recommended choice in this patient group (if allopurinol is not tolerated or adequate).[1, 8]

Hepatic impairment. Febuxostat should be avoided in patients with moderate or severe hepatic impairment as limited dosing information is available. Patients with mild hepatic impairment should not exceed a daily dose of 80 mg.[8] A liver function test is recommended prior to initiating febuxostat to provide a baseline as abnormal liver function tests have been observed in approximately 5% of patients taking febuxostat; liver function tests are recommended periodically thereafter based on clinical judgement.[8]

Cardiovascular disease risk. Caution is advised when considering prescribing febuxostat to patients with a history of CVD, however, this is not a contraindication.[2, 8] Some studies have suggested that febuxostat use is associated with an increased risk of CVD and all-cause mortality compared with

allopurinol.[2] The United States Food and Drug Administration (FDA) therefore updated prescribing information with a boxed warning in 2019, advising that clinicians should discuss the elevated cardiovascular risk with their patients and inform them about important symptoms to look out for, e.g. shortness of breath, chest pain.[11] More recent studies, however, have not found an increase in the risk of all-cause mortality associated with febuxostat compared with allopurinol, and one study even demonstrated a lower risk.[2, 12] Clinicians should ensure patients are aware of the evidence around CVD risk and febuxostat use as part of a shared decision making discussion.[2]

Combination treatment. Probenecid can be added to the treatment regimen if the patient is unable to achieve the target serum urate level with febuxostat alone, however, this combination is associated with a much more rapid decline in serum urate and can trigger flares in some people; prophylactic management with either a NSAID or colchicine is essential when using it for at least the first six months.[1, 7]

The adverse effects of febuxostat

Adverse effects most often associated with febuxostat are diarrhoea, nausea, elevated liver enzymes, oedema, headache and rash.[8] Rarely, hepatotoxicity or severe hypersensitivity reactions can occur in patients taking febuxostat.[8] Hypersensitivity reactions most often occur in the first weeks of treatment, including Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria and anaphylaxis.[8]

There is an increased risk of flares in patients taking febuxostat, compared to allopurinol, therefore flare prophylaxis is particularly important in the first months of treatment.[1]

Benzbromarone to be discontinued

Benzbromarone has not been included as a treatment option for long-term gout prophylaxis in this article as it is set to be delisted from the Pharmaceutical Schedule.*[13] Most people taking benzbromarone will have now switched to a different treatment and no new patients should be started on benzbromarone. Any patients remaining on benzbromarone should be changed to a different urate-lowering medicine as soon as possible.[13] The amendment of the Special Authority for febuxostat now allows patients who were taking benzbromarone to access funded febuxostat treatment.[13]

* As of July, 2021, there is no date set for delisting – for up to date information, visit the **PHARMAC website**

Supporting patients taking urate-lowering medicines[1]

- Acknowledge that taking a medicine every day for gout can be challenging. Regularly ask the patient how they are coping with this process and continue to encourage on-going use of urate-lowering medicines to prevent gout flares.
- Once the patient achieves their serum urate target, continue to measure serum urate levels at least every six to 12 months and make any necessary adjustments to the treatment regimen if the target level is not maintained. Titrating and identifying the optimal dose of a urate lowering medicine can be challenging, and patients need to be supported and reassured throughout this process.
- Re-iterate that although biological factors (e.g. chronic kidney disease, genetic variation) and some medicines (e.g. diuretics) are important causes of gout, other modifiable factors such as diet can trigger flares. By being aware of these triggers, and taking urate-lowering medicines consistently, future flares can be prevented. In some cases, patients will eventually be able to consume small portions of trigger foods, such as kaimoana (seafood), without experiencing a gout flare.
- Use motivational interviewing to encourage lifestyle changes including weight loss and regular exercise which in turn may help to reduce co-morbid cardiovascular and diabetes risk (see: "Part 1: Talking about gout: time for a rethink" available from: **bpac.org.nz/2021gout-part1.aspx**). Other medicines such as statins and antihypertensives may need to be added, if appropriate.
- Track any changes in clinically relevant biomarkers, e.g. at least an annual assessment of blood pressure, HbA_{1c} and renal function

The appropriate selection and use of cardiovascular medicines

For patients with gout and hypertension, losartan or calcium channel blockers are the antihypertensive medicines of choice as they reportedly have mild uricosuric (urate-excreting) properties.[2] Diuretics are known to reduce urate excretion and therefore contribute to the onset or exacerbation of gout. Patients who are taking diuretics for hypertension, for reasons other than heart failure, should be switched to an alternative antihypertensive, if possible.[2] Aspirin is also known to decrease excretion of uric acid, however, patients who are taking low-dose aspirin for the secondary prevention of cardiovascular disease should continue to do so.[2]

Reducing the risk of kidney stones

Kidney stones occur in one in seven patients with gout and patients taking uricosuric medicines, e.g. probenecid, are at increased risk.[1, 4] Increasing water consumption will decrease the risk of uric acid stone formation for all patients with gout (e.g. aim for ≥ 2L water daily). Treatment with a xanthine oxidase inhibitor, e.g. allopurinol, and a reduction in dietary purines (see: "Part 1: Talking about gout: time for a rethink" available from: **bpac.org.nz/2021gout-part1.aspx**) will also decrease the likelihood of uric acid stones forming.[2]

Further information on managing kidney stones and renal colic is available from: **https://bpac.org.nz/bpj/2014/april/colic.aspx**

When to consider referral to a rheumatologist

Patients should be discussed with or referred to a rheumatologist if they have:

- A serum urate level consistently ≥ 0.36 mmol/L, despite adherence to optimal urate-lowering treatment
- Persistent arthritis, despite a serum urate level that is persistently < 0.36 mmol/L
- Significant renal dysfunction and there are concerns about increasing the dose of urate-lowering treatment

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