A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

ALLOPURINOL

KEY POINTS

Allopurinol is effective in reducing uric acid levels and gout recurrence. It reduces the development of tophi and risk of urate nephropathy.

Patients who remain hyperuricaemic have a higher risk of recurrent gout flares. The risk of recurrent gout is minimised if serum urate is maintained below 0.36mmol/L (<0.30mmol/L with tophi).

Gout may be associated with various precipitating factors (diuretic use, acute renal dysfunction, alcohol or dietary factors, acute dehydration). When these factors are improved, the need for treatment with allopurinol may be diminished.

Patients in clinical remission (no gout flare in ≥ 1 year) and without tophi, who have a low risk of relapse may be appropriate to consider for deprescribing of ULT.

Current guidelines recommend that when starting allopurinol the initial dose is based on renal function, while maintenance doses remain guided by serum urate levels.

CONTEXT

This guide considers the use of allopurinol as urate lowering therapy (ULT) to reduce relapses of acute gout, and it's complications.

RECOMMENDED DEPRESCRIBING STRATEGY

Determine key aspects of the patient gout history:

- Presence of factors that contributed to gout flare
- Whether the flare was less than or greater than 12 months previously
- Current serum urate level
- Dose of allopurinol

If the patient's gout flare was clearly due to precipitating factors such as acute renal failure, use of diuretics, dietary or alcohol indiscretion, which have since been eliminated/minimised, reduction/cessation of allopurinol may be reasonable.

If the patient's gout flare was more than 12 months previously and the serum urate is well in the normal range (<0.30mmol/L) then cessation of low dose (100mg or less) allopurinol may be reasonable (up to a 50% increase in uric acid may be expected).

This would need to take into account tophi, history of flares, and renal impairment (lower doses likely to provide greater impact). These recommendations are summarised in **Figure 1**.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduced risk of gout relapse	**Increased Benefit** • Recent gouty arthritis • Presence of tophi • Maintaining serum urate levels below 0.36mmol/L (<0.3mmol/L with tophi)	**Decreased Benefits** • Lower dose of allopurinol • Low risk of gout relapse
Main Harms Serious skin toxicity	**Reduced Harms** • Appropriate initial dose at commencement in the presence of renal dysfunction • Reducing or ceasing other medication that increase uric acid	**Increased Harms** • Presence of HLA-B*5801 allele

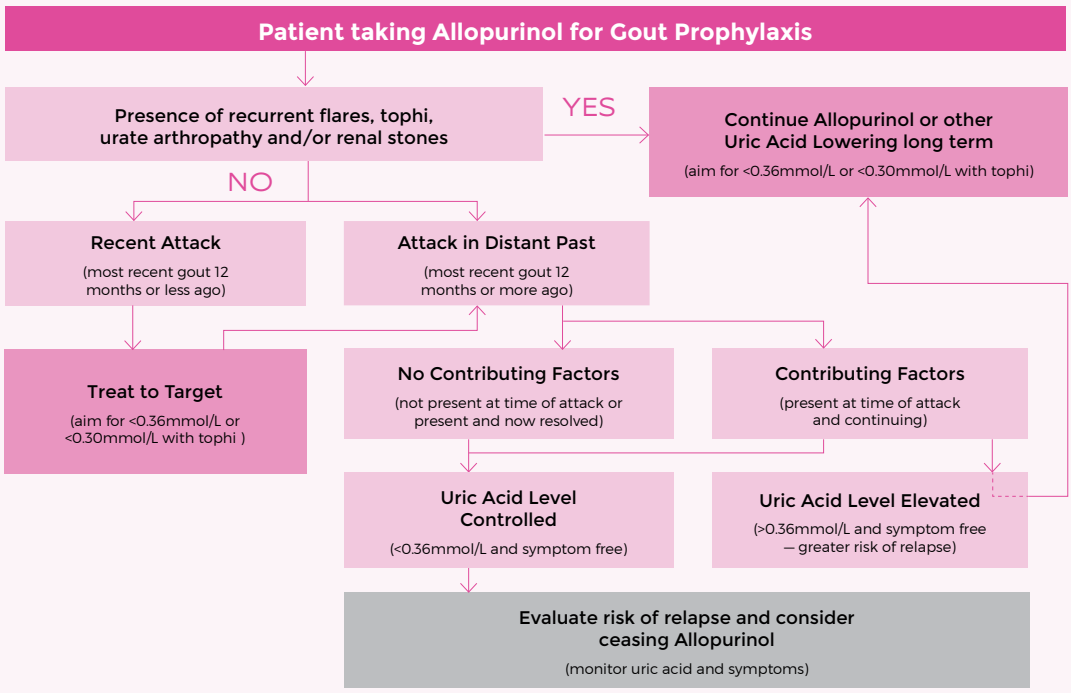

Figure 1: Deprescribing algorithm for allopurinol

BACKGROUND

Gout is a major issue worldwide and is the most common form of inflammatory arthritis. Hyperuricaemia, a precondition for gout, is an independent risk factor for chronic kidney disease, stroke and possibly ischaemic heart disease.[1] It is associated with multiple adverse health effects including hypertension, cardiovascular disease and is an important aspect of the metabolic syndrome.[2] In addition, hyperuricaemia is now being considered as a modifiable risk factor for deterioration of renal function.[3]

Australian population data from 2017-18 estimated the prevalence of (self-reported) gout was 6.0% (males 9.8%; females 2.4%)[4] and a 2016 study from South Australia found the prevalence of hyperuricaemia (uric acid >0.42mmol/L for men and > 0.34mmol/L for women) to be 16.6% (males 17.8%; females 15.4%).[5] Rates of both gout and hyperuricaemia have been increasing, with recognised risk factors including male gender, advancing age, and increased weight.

The majority of people with hyperuricaemia do not go on to develop gouty arthritis, and current evidence does not support the treatment of asymptomatic hyperuricaemia. However, there is an increase in both incidence and relative risk of developing gout with increased serum urate levels, as seen in the Framingham Heart Study (see **Figure 2**).[6]

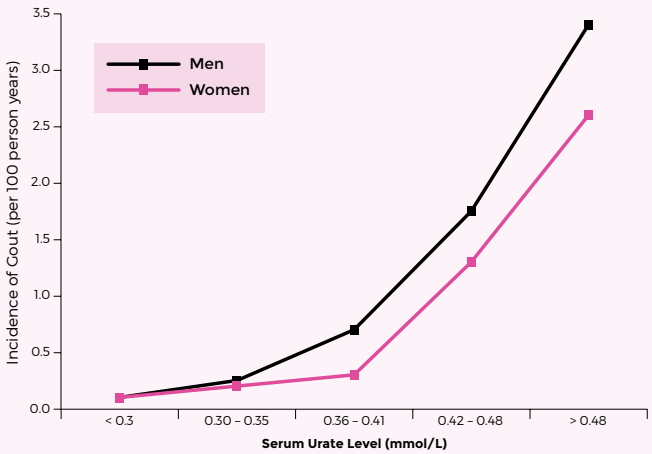

Figure 2: Incidence of initial gout attack based on serum urate level.[6]

The likelihood of recurrent gouty arthritis increases with elevation of the serum urate level, with 50% of patients with an average urate level of 0.46mmol/L having a flare 12 months or more after an initial attack. An average uric acid level of 0.36mmol/L or less was associated with a risk of relapse of less than 20% (see **Figure 3**).[7]

Reducing the urate level below 0.36mmol/L also results in the mobilisation of urate crystals out of joints and soft tissue. The lower the serum urate, the faster the resolution of the crystal deposition.

The European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of gout suggest lowering of uric acid for people with recurrent flares, tophi, urate arthropathy and/or renal stones.[8] They recommend treatment be lifelong in such patients (based on a 40% relapse of gout over 5 years after cessation of uric acid lowering therapy).

The 2020 American College of Rheumatology recommendations confirm support for treating to target, aiming for a serum urate level <0.36mmol/L in patients with gout, and <0.30mmol/L for patients with tophaceous gout.[9]

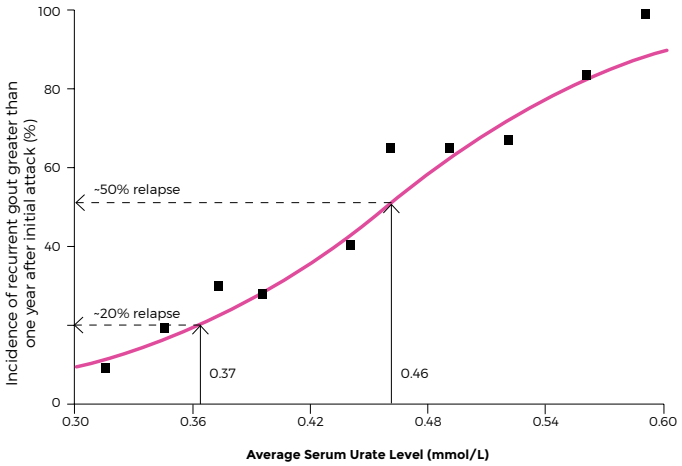

Figure 3: Frequency of recurrent gout according to serum urate level.[7]

Febuxostat

This guide considers the use of allopurinol as it remains the recommended first-line urate-lowering therapy and is the most common agent seen in practice. Febuxostat is an alternate xanthine oxidase inhibitor available, for those who cannot tolerate allopurinol or fail to achieve target urate levels. Much of the information in this guide could also be applied to febuxostat so some key information has been summarised.

A non-purine analogue (compared to allopurinol) febuxostat is predominantly metabolised by the liver. Minimal renal excretion may make it an option for some patients with significant renal dysfunction (maximum dose is reduced however with creatinine clearance <30mL/min).

A recent study of 940 patients found febuxostat and allopurinol were equally effective for achieving serum urate targets and reducing hyperuricaemia and flare rates.[10] No difference was noted in those with chronic kidney disease (patients with creatinine clearance 30-60mL/min).

Febuxostat 40mg is thought to be clinically equivalent to approximately allopurinol 300mg. Some studies have shown greater urate reduction with higher doses of febuxostat (≥120mg).[11]

The CARES trial found an increased risk of cardiovascular death with febuxostat compared to allopurinol. Whilst further research provides some reassuring evidence regarding cardiovascular safety, caution is still recommended with febuxostat in patients with significant cardiovascular disease.[12]

Skin rashes are possible, though this agent likely remains the choice for those with a history of allopurinol hypersensitivity syndrome or the HLA-B*5801 allele.

As with allopurinol, febuxostat requires initial flare prophylaxis, gradual dose up-titration, and has serious interactions with azathioprine and mercaptopurine.

EFFICACY

Urate lowering therapy is indicated in patients who have had an acute gout attack and whose serum urate level remains above target, increasing the risk of a subsequent flare.

The effect of allopurinol on urate level is dose dependent and variable. Graham et al examined blood levels of uric acid in 112 samples from patients taking various doses of allopurinol for at least one month (see **Figure 4**)'.[13]

Caution (and use of lower doses) has previously been recommended with allopurinol in the presence of renal impairment in order to reduce the risk of serious adverse effects from accumulation of oxipurinol, the suspected toxic metabolite. However, it is important to recognise that renal impairment is a risk factor for hyperuricaemia, so there may be a greater likelihood that patients with renal impairment may warrant urate lowering therapy. Current guidelines recommend that when starting allopurinol in people with renal impairment the initial dose is reduced, but that there is no need to limit the maintenance dose, which should still be determined based on serum urate (SUA) levels and an individualised urate target appropriate for the patient.

However, patients with renal dysfunction are likely to have reduced elimination of uric acid, which may limit the efficacy of xanthine oxidase inhibitors, which exert their effect by reducing production of uric acid rather than increasing elimination.

A study of allopurinol used at an appropriately adjusted dose (based on creatinine clearance) has shown reduction of uric acid to target range (< 0.36mmol/L) in ~20% of patients at three months and ~40% of patients at 6-12 months.[14]

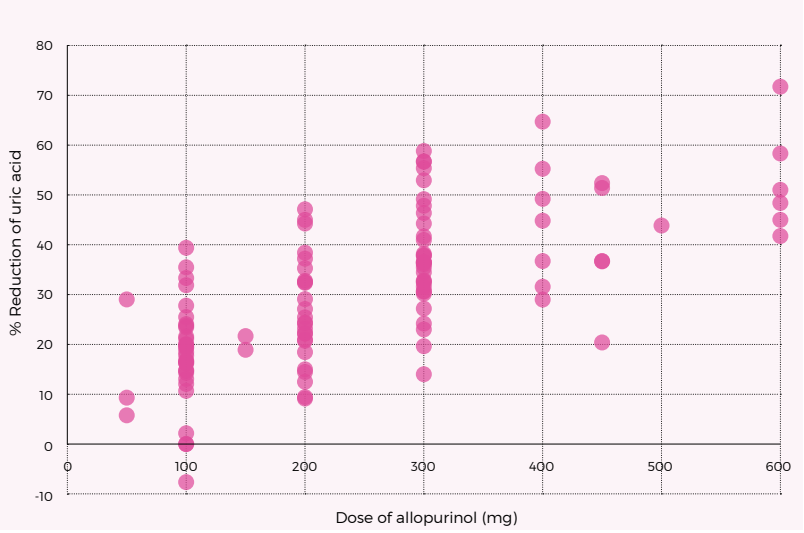

Figure 4: Percent reduction of uric acid level with various doses of allopurinol (using data from reference 13)

A Cochrane review of allopurinol for chronic gout found that acute gout flares occurred at a rate of 12 per 100 patients over 30 days with placebo, compared to 7.7 per 100 patients with allopurinol [36% relative risk reduction, Absolute Risk Reduction 4% (95%CI -21-12); NNT 25).[15]

Over a longer period of time, the percentage of patients who required treatment for gout flares in the first month of treatment with allopurinol (following an attack) was ~11%, compared to ~4% in the sixth month of treatment (over half of the acute gout treatment were required in the first 3 months after the attack).[11] Guidelines now recommend prophylaxis for gout flares (with low dose colchicine, NSAID, or prednisolone) for 3 to 6 months following allopurinol initiation.

ADVERSE EFFECTS

Allopurinol is usually well tolerated, with the main adverse effects of concern being dermatological in nature. These include mild to moderate skin rashes which are usually maculopapular and pruritic. More rarely, a purpuric and exfoliative rash can occur as part of a severe (and sometimes fatal) systemic hypersensitivity syndrome. The highest incidence of allopurinol hypersensitivity syndrome appears to be within the first 3 months of starting the drug.

It was concern for this potentially life-threatening adverse effect that originally led to recommendations for caution in the use of allopurinol for those with renal impairment.[16]

A 2019 cohort study of 130,325 Canadians reviewed hospital admissions for severe cutaneous adverse reactions within 3 months of initiating allopurinol. The overall incidence of these admissions was rare (1 per 1196 patients), however 78% of these patients had allopurinol starting doses greater than 100mg. The highest risk factors found for severe cutaneous reactions were the presence of chronic kidney disease (RR 1.88, 95% CI: 1.17-3.02) and allopurinol-initiating dose >100mg (RR 2.78, 95% CI 1.75-4.43), The presence of heart disease in addition resulted in an 11-fold increase in relative risk compared to patients without these factors.[17]

The presence of the Human Leucocyte Antigen (HLA)-B*5801 allele is also associated with a 100-fold increased risk of developing Stevens-Johnson syndrome (SJS), syndrome of drug rash with eosinophilia and systemic symptoms (DRESS), or toxic epidermal necrolysis (TEN) during treatment with allopurinol.[18] It has been estimated that -in patients with the allele the number needed to harm (NNH) with allopurinol is 14. The frequency of the HLA-B*5801 allele varies across ethnic groups. It is recommended that screening for the HLA-B*5801 allele be considered in patient groups with a known high frequency of this allele (patients of Han Chinese, Korean, or Thai descent, and African Americans) prior to initiation of allopurinol.[19,20] In patients with the allele, febuxostat may be an alternative option (see call out box).

MODIFIABLE FACTORS

Modifiable factors for hyperuricaemia.

It is not uncommon for an acute gout attack to occur when there are sudden changes in uric acid levels. This can occur in acute renal failure, with the use of diuretics, or as a result of significant dietary/alcohol intake factors.

In patients with uric acid levels that are tightly controlled on allopurinol, optimising lifestyle factors (managing obesity and diabetes, moderating alcohol intake) and medication (see below) may in some cases allow for reduction of urate-lowering therapy.

Medication:

Drugs used for other conditions can also impact serum urate levels (predominantly by affecting urinary reabsorption/excretion). This is worth considering when treating co-morbidities (e.g. heart failure management with diuretics) as well as when reviewing patients with mild hyperuricaemia. Adjusting contributing medications may help reduce hyperuricaemia or may allow for allopurinol reduction.

Drugs that can increase uric acid: thiazide diuretics, frusemide (reduces action of allopurinol) and low-dose aspirin (up to 300mg daily), with weaker evidence for beta-blockers, levodopa, omeprazole, and ticagrelor among others.[21]

Drugs that can reduce uric acid: losartan, fenofibrate, calcium-channel blockers, SGLT2 inhibitors, atorvastatin (weak effect).[22,23]

The ACR 2020 Guidelines recommend that patients with gout reduce alcohol and purine intake, lose weight if overweight or obese, preference alternate antihypertensives over the use of thiazide diuretics (where possible), and consider the use of losartan over other ACE inhibitors/angiotensin receptor blockers.[9]

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

Many of the risk factors for gout are avoidable or modifiable (diuretics, diet) and modification of these may be sufficient to prevent gout attacks in some patients.

Reducing or ceasing of allopurinol may be possible in patients who have ceased or reduced diuretics, or whose renal function has improved, or whose dietary and alcohol intake has improved.

It is unclear whether patients with metabolic syndrome in the absence of gout (i.e. glucose intolerance, hypertension, dyslipidaemia and obesity) or chronic kidney disease will gain a benefit from reducing elevated urate levels.

AGAINST DEPRESCRIBING

Ongoing use of allopurinol is indicated if the person has

- recurrent flares of gout (≥2 per year)
- evidence of uric acid nephropathy or urolithiasis,
- presence of tophi, or chronic gouty arthritis
- risk factors for hyperuricaemia that cannot be modified
- a preference for continuing ULT
- contraindications/previous intolerance to use of therapies for acute gout attacks

If the patient's gout attack was less than 12 months previously and the serum urate is high (>0.36mmol/L) then a dose increase or change of urate-lowering therapy may be required in an attempt to achieve this target.

Ongoing treatment may also be indicated if the patient has an underlying condition (e.g. severe renal disease or a myeloproliferative disease) that may be improved by controlling the hyperuricaemia.

DISCONTINUATION SYNDROMES

Relapse of gout can occur in patients following cessation of urate-lowering therapy. The predominant risk factor appears to be a higher serum urate level prior to drug discontinuation, highlighting the importance of initial treatment to target.[24]

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