A GUIDE TO

deprescribing

CPS CONSULTANT PHARMACY SERVICES

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ALLOPURINOL

KEY POINTS

- **Allopurinol is effective in reducing uric acid levels and gout recurrence.**
- **Both uric acid levels and frequency of gout recurrence are reduced for up to 12 months after an initial attack of gout and treatment with allopurinol.**
- **Patients who have a history of gout and remain hyperuricaemic have a higher risk of an acute gout attack.**
- **The risk of recurrent gout is minimised if serum uric acid is maintained below 0.36mmol/L.**
- **In the presence of renal dysfunction, the dose of allopurinol should be reduced to lower the risk of serious adverse effects .**
- **When precipitating factors associated with gout are improved, treatment with allopurinol may become unnecessary.**

CONTEXT

This guide considers the use of allopurinol in the management of gout.

RECOMMENDED DEPRESCRIBING STRATEGY

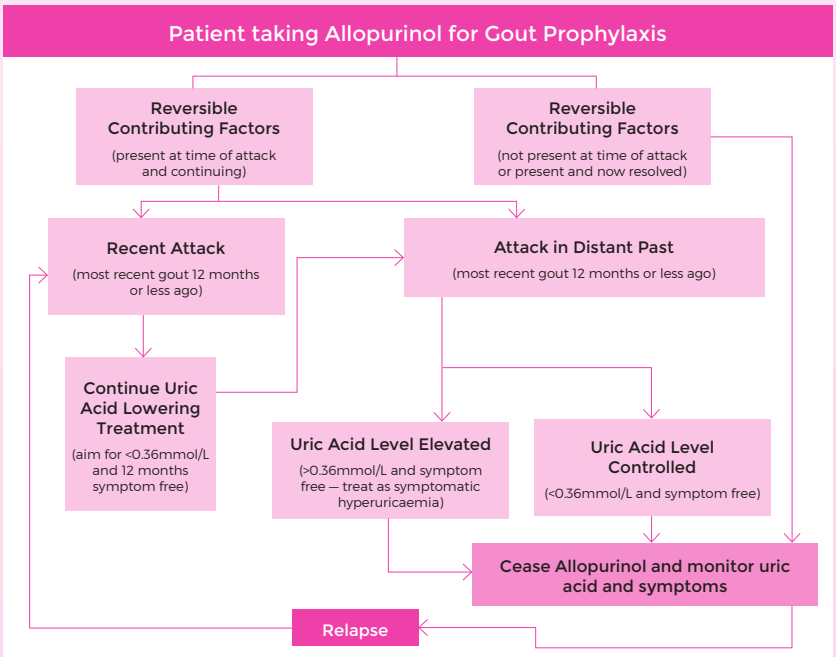
Determine key aspects of the patient's gout history:

- Presence of factors that contributed to gout attack
- If the attack was less than or greater than 12 months previously
- Current uric acid level
- Dose of allopurinol

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

If the patient's gout attack was more than 12 months previously and the serum uric acid is well in the normal range (<0.36mmol/L) then cessation of low dose (100mg or less) allopurinol may be reasonable (no more than a 50% increase in uric acid may be expected). They can then be considered as a patient with asymptomatic hyperuricaemia.

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



BACKGROUND

Gout is a major issue worldwide and is the most common form of inflammatory arthritis. The risk of both an initial gout attack and recurrent gouty arthritis increases with uric acid levels.

Hyperuricaemia, a precondition for gout, is associated with the metabolic syndrome and 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 involved as 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]

The management of gout is complicated by the episodic nature of the disease.

In a population study of 2389 patients in South Australia, the overall prevalence of (self reported) gout was 5.2% (males 8.5%; females 2.1%).[4] Hyperuricaemia (uric acid >0.42mmol/L for men and > 0.34mmol/L for women) was present in 17.8% of males and 15.4% of females.

In the Framingham Heart Study, there was a level dependent increase in both incidence and relative risk of developing gout with serum urate (see **Figure 1**).[5]

The likelihood of recurrent gouty arthritis also increases with elevation of the serum uric acid level, with ~35% of patients with an average uric acid level of 0.42mmol/L having an attack 12 months or more after an initial attack (see **Figure 2**).[6]

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

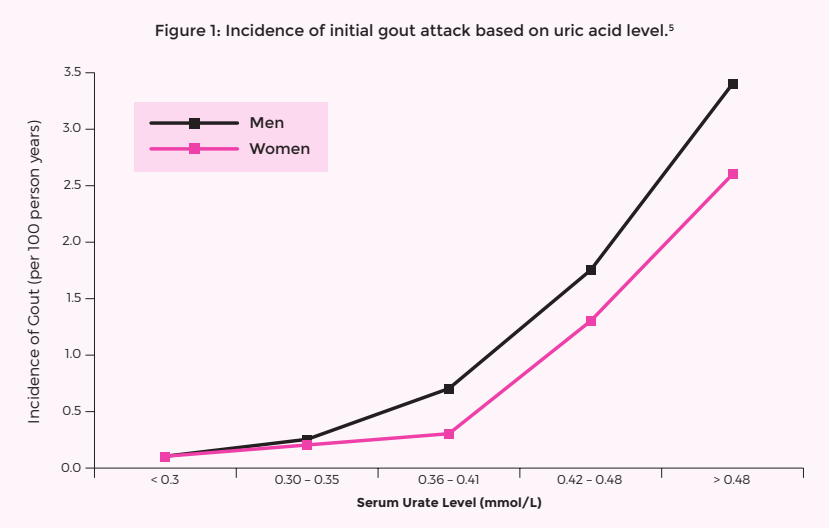


Figure 1: Incidence of initial gout attack based on uric acid level.[5]

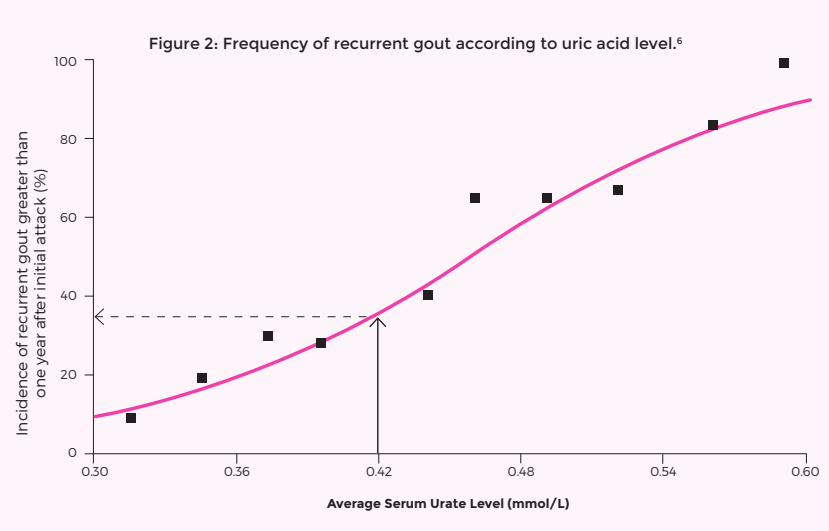


Figure 2: Frequency of recurrent gout according to uric acid level.[6]

EFFICACY

Urate lowering therapy is indicated in patients who have had an acute gout attack and whose uric acid level remains high, increasing the risk of a subsequent attack.

The effect of allopurinol on uric acid 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.[7,8] As can be seen in **Figure 3**, doses of 300mg or more are required to achieve a 50% or more reduction in uric acid level.

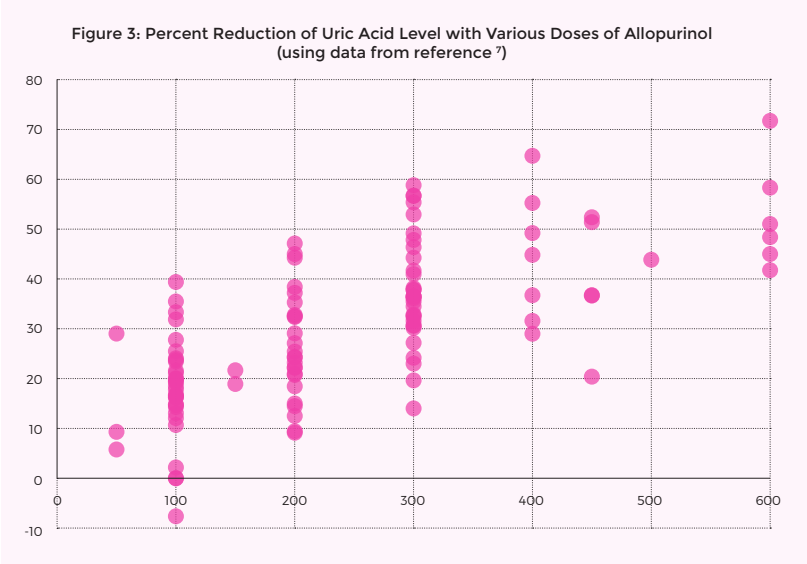


Figure 3: Percent Reduction of Uric Acid Level with Various Doses of Allopurinol[7]

It is recommended that the dose of allopurinol be reduced in the presence of renal dysfunction in order to reduce the risk of serious adverse effects from accumulation of oxipurinol, the suspected toxic metabolite. There is little information available about the potential for reduced efficacy in this setting, but it would be expected that a lower dose would have lower efficacy. In addition, patients with a degree of renal dysfunction have reduced elimination of uric acid, further limiting the efficacy of xanthine oxidase inhibitors, which reduce production of uric acid.

Studies of allopurinol used at an appropriately adjusted dose (based on creatinine clearance) have shown reduction of uric acid to target post-gout range (< 0.36mmol/L) in ~20% of patients at three months and ~40% of patients at 6-12 months.

A review of allopurinol for chronic gout summarised all available literature to January 2014. Acute gout attacks 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).[9]

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).[10]

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- Many of the precipitating factors for gout are avoidable or modifiable.
- It is unclear to what extent pharmacological management of hyperuricaemia in combination with modification of avoidable factors has on the recurrence of gout.
- 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 have improved.
- It is unclear whether patients with metabolic syndrome (i.e. glucose intolerance, hypertension, dyslipidaemia and obesity) or chronic kidney disease will gain a benefit from reducing elevated uric acid levels.

AGAINST DEPRESCRIBING

- Ongoing use of allopurinol is indicated if the person has:
  - recurrent attacks of gout
  - evidence of uric acid nephropathy or urolithiasis
  - presence of tophi.
- 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.

RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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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, hypersensitivity syndrome. [11, 12]

It is the increased likelihood of this potentially life-threatening adverse effect that has brought about the renal function-based dose recommendations for allopurinol.[13] Commencement of allopurinol should therefore be with a low dose, generally no more than 100mg daily. Slow increases may be made at monthly intervals according to response, aiming for a plasma urate concentration <0.36 mmol/L.

Recommended commencement doses based on eGFR are:

- >60mL/minute/1.73m², initially 100mg once daily
- 45–60mL/minute/1.73m², initially 50mg once daily alternating with 100mg once daily
- 30–45mL/minute/1.73m², initially 50mg once daily
- 15–30mL/minute/1.73m², initially 50mg on alternate days
- <15mL/minute/1.73m², initially 50mg twice a week

DISCONTINUATION SYNDROMES

None described

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