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ANALYSIS

# How clinical and research failures lead to suboptimal prescribing: the example of chronic gout

Despite the existence of several effective drugs for chronic tophaceous gout, management is often neither rational nor effective. **Wendy Lipworth and colleagues** examine the possible reasons

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An evidence based or "rational" approach to prescribing is thought to maximise the benefit and minimise the harm from prescription drugs. Unfortunately, prescribing often does not meet this ideal despite clinicians' best intentions. We use treatment of chronic tophaceous gout to show how apparently irrational prescribing arises from several interacting "failures" in both clinical practice and drug development.

## Treatment of chronic gout

Chronic tophaceous gout is the most common inflammatory arthritis in older men and affects about 1-2% of adults in the developed world.[1] For most patients, allopurinol—a xanthine oxidase inhibitor that blocks the synthesis of uric acid—is highly effective in preventing recurrent attacks of acute gout and the development of chronic tophaceous gout.[2] Allopurinol is easy to administer (generally requiring only a once daily dose), inexpensive, and generally well tolerated aside from the extremely rare, and sometimes predictable, allopurinol hypersensitivity reaction and other more common but generally minor or controllable adverse reactions.[3-5]

It seems, therefore, that allopurinol should be the mainstay for prevention and management of chronic gout and that this condition should be well controlled in the population. But in reality, many patients are prescribed subtherapeutic doses of allopurinol (usually ≤300 mg daily compared with a maximum of 800 mg approved by the US Food and Drug Administration for patients with normal renal function) and fewer than half of patients receive allopurinol for more than a year despite needing continuing prophylaxis.[6-8] Similarly, there is underuse of probenecid**,** a uricoscuric that is a safe, inexpensive, and effective alternative to allopurinol for patients who do not have a history of nephrolithiasis or serious renal impairment.[9-11]

There are several possible reasons for this underprescribing of allopurinol and probenecid, some of which relate to clinical practice and some to the drug development process.

## Failure of clinical practice?

The most obvious clinical reason for underuse of allopurinol would be that clinicians are concerned about allopurinol hypersensitivity syndrome, particularly in otherwise healthy patients. But given the low incidence of the syndrome, this is unlikely to be the sole explanation.

Another possible reason for undertreatment is that the doctors who manage chronic gout are often not specialist rheumatologists[12] and might not always recognise gout or realise the importance of treating both acute and chronic disease (acute gout is also often poorly managed).[13] Lack of knowledge about the appropriate treatment might arise because clinicians receive limited education about older (off-patent) therapies or because general physicians are unfamiliar with guidelines developed by specialist organisations and published in specialist journals.[14]

Thus, clinicians might be unfamiliar with the correct protocols for using uricosuric drugs[7] and might make oversimplistic correlations between plasma urate concentrations and treatment success.[15 16] Oversimplistic interpretation of early studies of allopurinol might also lead non-specialists to overestimate the frequency of allopurinol hypersensitivity syndrome,[17] and they might not know that it can be preventable or that allopurinol can be used in patients with chronic kidney disease without necessarily limiting the maximum dose.[18] Similarly, clinicians might be unaware that probenecid can be used safely in most patients provided the dose is increased slowly and patients are well hydrated.

Underprescribing could also be a consequence of the many well recognised barriers to rational prescribing, including habit, lack of motivation, and external barriers such as lack of time, resources, and organisational support.[19] Furthermore, in the case of chronic gout, the problem of poorly managed, treatment induced flares could lead to poor patient adherence and a

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reluctance to prescribe.[20] Compliance with prophylaxis might also be undermined by the stigma attached to the disease.[21]

## Failure of drug development?

But suboptimal treatment of chronic gout is not only the result of failure in clinical practice. Given that prescribing is only as rational as the evidence on which it based, we also need to consider the role of the drug development process.

The development of new drugs, although providing benefits for a small subset of patients, might not contribute much to the overall disease burden of chronic tophaceous gout and might carry considerable cost. One such example is febuxostat, a non-purine xanthine oxidase inhibitor approved by the European Medicines Agency in 2008 and by the FDA in 2009. On the face of it, there is nothing wrong with developing additional drugs for people who cannot use existing treatments. But new drugs like febuxostat (which is considerably more expensive than allopurinol) can easily become preferentially prescribed without a robust rationale or sufficient knowledge of long term safety—a concern with febuxostat, for which further data are needed on cardiovascular safety and hypersensitivity.

In gout, febuxostat might be prescribed more often than necessary partly because the judgment that a patient has "failed to respond" to allopurinol is highly subjective and could be made in patients with suboptimal dosing or because of an "irrational" fear or misdiagnosis of hypersensitivity syndrome.[4] Furthermore, trials supporting the registration of febuxostat compared therapeutic doses of febuxostat to subtherapeutic (albeit commonly prescribed) doses of allopurinol, and therefore the relative efficacy of febuxostat could have been overestimated.[22] The drug industry's interest in promoting a patented and costly new product, and the enthusiastic and relatively uncritical endorsement of febuxostat by many clinical leaders,[23] is likely to have further eroded the (appropriate) use of allopurinol and probenecid.

Another reason for concern about the adequacy of drug development processes surrounds the withdrawal from the market of benzbromarone, a potent, long acting uricosuric drug that was at least as effective as allopurinol and probenecid and was suitable for patients with mild to moderate renal impairment.[9] Sanofi-Synthélabo withdrew the drug from the European market in 2003, on the eve of its loss of patent protection, citing reports of serious liver reactions. However, benzbromarone had been associated with very few cases of hepatotoxicity and some of the reported cases might have had other contributing factors.[4] Benzbromarone is now available (from generic manufacturers) in only some markets and under special access arrangements in other countries—this situation may not be in the best interests of patients with gout given the limited alternatives for patients with renal impairment who do not tolerate allopurinol.[4]

The US approach to licensing colchicine is also a concern. Colchicine is used primarily to treat acute gout but is also used in chronic gout to prevent the flares that can occur when urate lowering therapy is started. In October 2009, the FDA gave URL Pharma three years of market exclusivity on the basis it had shown that a lower dose regimen of colchicine (Colcrys) was as effective as, and safer than, the higher dose regimen recommended for the existing drug.[24] This was an important clinical finding but came at a price—the new patented formulation is more than 50 times more expensive than the older one (which is no longer available in the US). As Kesselheim and Solomon have noted, the "curious case of colchicine" shows "important limitations of our current system for rewarding innovation in the pharmaceutical market."[25]

## Complex care in a complex environment

Taken together this leaves us in a situation that is indeed "curious." Firstly, we have two drugs (allopurinol and probenecid) that, when used appropriately, are effective, inexpensive, and safe but are repeatedly underprescribed. Secondly, we have a far more expensive "alternative" (febuxostat), which has a place for the few people who cannot tolerate allopurinol or the uricosurics but is probably being used unnecessarily. Thirdly, we have lost benzbromarone, which was a safe alternative to allopurinol, probenecid, and febuxostat. And finally, we have granted a patent to a company for a drug (colchicine) that had been available off-patent for over half a century.

Although gout provides an excellent illustration of the potential for both clinical and regulatory forces to militate against rational prescribing, this is in no way a unique situation. The underuse of warfarin to prevent stroke in patients with atrial fibrillation is another case in point: the evidence of benefit is strong, but undertreatment persists for a number of reasons including lack of conviction about benefit, concerns about side effects, and inconvenience.[26] At the same time, several new oral anticoagulants are being licensed (and heavily promoted to both doctors and patients) that have advantages over warfarin (such as not requiring monitoring) but also have disadvantages (such as being irreversible and more expensive).[27] Another example is the treatment of alcohol dependence, for which supervised disulfiram is effective but has been largely displaced by more expensive drugs.[28] Many other underprescribed (or otherwise misused) medicines are subject to similar complex forces.

Clearly neither clinicians nor drug developers are exclusively responsible for this unsatisfactory state of affairs. Ultimately, however, the case of chronic tophaceous gout provides a warning that both clinical leaders and regulators must act to ensure that the drug development process actually facilitates rational prescribing and that new drugs are used appropriately. Possible strategies that might facilitate better development and use of medicines include developing better mechanisms for comparative effectiveness and cost effectiveness research; enhancing clinical leadership and finding better ways of disseminating unbiased information to clinicians (particularly to non-specialists) and patients; and providing clinicians with feedback about their prescribing practices.

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