Treating gout in patients with comorbidities

Gout causes extremely painful episodes of acute inflammatory arthritis, joint damage and chronic tophaceous disease. Comorbidities are common, even though their exact relationship with hyperuricemia and gout is currently uncertain. These comorbidities need to be taken into account in people who have them when treating their gout with pharmacological and nonpharmacological management, including lifestyle modification. Gout can be successfully managed in these people with consideration of the influence of medications used for gout and their impact on the components of the metabolic syndrome and on chronic renal impairment. The impact of medicines used to treat the comorbidities upon the management of acute gout, and on the requirement for reduction of uric acid to the target range of less than 6 mg/dl (0.36 mmol/l), is also important, along with drug interactions. Although there is a shortage of randomized controlled trials to guide treatment, attention to these factors, including the incorporation of patient preferences, should lead to better adherence to therapy and improved health outcomes.

KEYWORDS: adherence ■ allopurinol ■ comorbidities ■ gout ■ hyperuricemia ■ lifestyle ■ metabolic syndrome ■ urate

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Gout, which is characterized by hyperuricemia and monosodium urate crystals within the joints and soft tissues, is the commonest inflammatory arthritis among men, particularly in those of Pacific or Maori ancestry, and is certainly one of the most painful. In addition, it has a major impact on work capacity and participation in society [1].

Gout is considered a useful red flag for the screening and detection of cardiovascular disease, diabetes, kidney disease and dyslipidemia, in that although the latter can be asymptomatic for many years, an acute attack of gout does not go unnoticed and the pain is sufficiently severe for sufferers to seek medical attention, in spite of the pain being considered a badge of courage among young men in some cultures [2]. In recent American studies, the metabolic syndrome has been detected in 63% of adult US men with gout, compared with 25% of those without gout [3]. Individual components ranged from 50% for hypertension, coronary artery disease in 18–25%, kidney stones in 15% and renal insufficiency in 5%. Choi reports that studies in UK and USA show only a weak association with diabetes with a prevalence of 5–6% [3], similar to the 5% prevalence in a Dutch study [4]. However, although there may not be an increase in diabetes among gout patients in the general population, the incidence in patients with gout in specialist rheumatology clinics is higher. For example, in a cohort of 100 patients with gout of 10 years median duration in our rheumatology clinic, including 71 Maori or Pacific patients [5], diabetes was present in 33%, with 60% having hypertension and 87% the metabolic syndrome.

Despite gout and hyperuricemia being associated with a number of comorbidities, including hypertension, diabetes and cardiovascular disease, with associated insulin resistance and metabolic abnormalities, their exact relationship to hyperuricemia is still to be determined. Although the direct influence of hyperuricemia as a cause of myocardial infarction awaits large-scale prospective randomized controlled clinical trials, there is strongly suggestive evidence from a recent study that showed the development of hyperuricemia, hypertension and the metabolic syndrome from increased ingestion of fructose, which was reversed by coadministration of allopurinol [6]. Similarly, although debate continues about the causative role of gout on renal function independent of hypertension, there is encouragement from the improvement in renal function over a 2-year period associated with allopurinol-induced reduction of uric acid, although the authors admit that alternative agents during the course of the study may have had an effect on both this and the improvement noted in cardiovascular events and hospitalizations [7]. This might include a reduction in the use of NSAIDs, since this has been shown to improve renal function [8].

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Regardless as to whether or not there is a causative relationship, an increasing number of patients will have comorbidities and the lack of an evidence base of best practice targeted specifically at this group means that the patient will need to be treated on an individual basis, using data from trials which almost certainly included among their cohort patients with these comorbidities. This will include managing the specific comorbidities, but also being aware that there may well be interactions of medicines used in their management, as well as the potential for individual medications to worsen the associated disease states.

Better treatment of gout will mean that fewer patients will be subject to long-term treatment with NSAIDs or prednisone, with associated benefits in blood pressure, diabetes and renal function. In this review I will summarize the European League Against Rheumatism (EULAR) recommendations for the management of gout [9], with an update on major advances since these were published, and the modifications that may well need to be considered when the patient with gout has comorbidities. The review will finish with a discussion on patient adherence and other behavioral factors that will need to be addressed if the result from controlled trials is to be reproduced with successful treatment in the context of the nontrial environment.

Management of acute gout

The EULAR evidence-based recommendations for gout published in 2006 are based on a review of the evidence in the literature up until 2005, with randomized controlled trials being small in number [10], supplemented by key propositions by a task force using a Delphi consensus approach. For acute gout, oral colchicine and/or NSAIDs were recommended as first-line agents, although it was noted that high-dose colchicine had an unacceptable rate of side effects, and that NSAIDs were also effective, although caution was required because of gastrointestinal side effects and potential cardiovascular toxicity. Intra-articular aspiration and long-acting steroid injections were considered useful, as well as systemic steroids or adrenocorticotropic hormone for patients with multiple joints or joints not readily amenable to intra-articular injections, provided that septic arthritis was excluded. Prednisone in a dose of 35 mg daily for 5 days has subsequently been shown to be as effective as naproxen 500 mg twice daily [11].

Among the recommendations for future research developed through the Delphi rounds was the optimal dose and frequency of oral colchicine for the treatment of an acute attack. Although the usual regimen for colchicine was for 0.5 or 0.6 mg twice to three-times daily, with adjustments according to renal function, the appropriate dosage schedule of two colchicine (1.2 mg) at once and a further dose (0.6 mg) 1 h later being better in terms of efficacy and safety than hourly colchicine 0.6 mg for 6 h after a loading dose of 1.2 mg has added considerably to the utility of this medication [12]. However, it should be noted that the trial was performed in patients where the attack was less than 12 h in duration, and many patients do not present for treatment within this time frame, although others do keep a supply of colchicine at home for this eventuality (the aphorism among Pacific peoples for many years has been to take a dose or two of colchicine at the first sign of 'the tingle'). For those with acute gout of longer duration, colchicine and anti-inflammatory medications are often used together [9], although controlled trials are lacking for both combination therapy or for the treatment of acute gout with delayed treatment.

What impact does the presence of comorbidities have on the therapeutic aspects during the acute attack? For those patients with gastrointestinal disease, such as gastro-oesophageal reflux disease or a history of peptic ulceration, a COX-2 inhibitor, or coprescription of NSAID with a proton pump inhibitor, is recommended, particularly if prednisone is also being used as combination therapy.

As noted above, many patients have renal impairment, often as a result of concomitant hypertension and diabetes mellitus. Colchicine is therefore preferable to NSAIDs for acute gout treatment in such a context, particularly if treated early with a low-dose regimen. Dosage guidelines suggest no dose adjustment for creatinine clearance (CrCl) above 30 ml/min, although caution is required with a CrCl of less than 50 ml/min. For those who require ongoing colchicine to manage the acute attack, recent guidelines suggest colchicine 0.6 mg once daily for CrCl of 35–49, 0.6 mg every second to third day with CrCl of 10–34 and avoidance if CrCl less than 10 ml/min. It has also been suggested to halve the daily dosage regimens in patients over 70 because of impaired pharmacokinetics of colchicine in the elderly [13] and no further colchicine for 2 weeks after resolution of the acute attack. For those on dialysis a

single dose of 0.6 mg is recommended, repeated if necessary after 2 weeks. Similar recommendations are offered for those with severe hepatic involvement [14]. Caution is required for those on combination colchicine and NSAIDs, particularly if the latter are combined with thiazides and angiotensin-converting enzyme inhibitors, since diarrhea from colchicine, or reduced fluid intake to avoid the agony of walking to the toilet for urination, can lead to significant worsening of renal function.

For those with hypertension and cardiovascular disease though without congestive heart failure, renal impairment or gastrointestinal contraindications, the preferred NSAID may be naproxen, which has a reputation for lesser impact on cardiovascular complications [15,16], particularly if NSAIDs are going to be the prophylactic agent of choice, which can be the case if they have been required for osteoarthritic pain which is not responsive to simple analgesics.

The above regimen of NSAID and colchicine might also be considered the preferred option for patients with diabetes who do not have renal impairment. For those who do have congestive heart failure or renal impairment, and where colchicine does not provide sufficient relief because of its delayed administration, prednisone is often the preferred option [11], although requires close monitoring of glucose levels and adjustment of hypoglycaemic therapy. Although intra-articular and intramuscular long-acting steroids can lessen the impact of steroids in patients with diabetes, there is detectable steroid for 72 h after an intra-articular injection [17] and longer for intramuscular preparations.

It is therefore among such patients with concomitant diabetes, renal impairment or congestive heart failure that the use of IL-1 antagonists [18] may well become the therapeutic agents of first choice in the future, with favorable cost benefit for those hospitalized patients who are unresponsive to traditional medicines, or those in whom there are contraindications to these due to the risk of unacceptable toxicity. The results have been variable in uncontrolled studies [19], although in a controlled trial of the humanized monoclonal antibody canakinumab [20] this was shown in patients with contraindications to NSAIDs or colchicine to reduce the pain of acute gout after 72 h significantly better than 40 mg intramuscular triamcinolone acetonide, which also showed a favorable response. In this study the number of infections were ten (7%) among the canakinumab patients and four (7%) in the triamcinolone group, with no deaths. Because of the significant immunosupression with this agent it is important to rule out infection, particularly septic arthritis, with joint aspiration, or cellulitis, before using this therapy, which is not yet approved for clinical use.

Management of chronic gout

Lifestyle modification to lower uric acid is recommended. Although most patients will require urate-lowering therapy (ULT) to lower the uric acid concentration to the target level of 6 mg/dl (0.36 mmol/l) to minimize the risk of further attacks of acute gout, lifestyle modification to control uric acid is recommended for all patients [9]. Details of lifestyle changes have been well described in a review article by Choi [3] based on his landmark studies which include the Health Professionals follow-up study and the Third National Health and Nutrition Examination Survey (NHANES III). His recommendations included the following:

- Exercise daily and reduce weight;
- Limit red meat intake;
- Tailor seafood intake to the individual;
- Drink skimmed milk or consume other low-fat dairy products;
- Consume vegetable protein, nuts, legumes and purine rich vegetables;
- Reduce alcoholic beverages, particularly beer;
- Limit sugar sweetened soft drinks and beverages;
- Allow coffee drinking if already drinking coffee;
- Consider taking vitamin C supplements.

Choi notes that many of these lifestyle changes will not only reduce uric acid levels and the risk of recurrent gout but will also improve the health status of those with comorbidities, particularly diabetes and cardiovascular disease. In patients with a high cardiovascular risk profile, weight loss of 10 kg or more increases the odds of achieving serum urate level of less than 0.36 mmol/l by nearly fourfold [21]. It should be noted that although chronic aerobic exercise reduces uric acid levels, acute exercise lasting between 0.5 h and 3 h increases uric acid in proportion to the exercise intensity [22] with acute gout often being reported to me by patients commencing vigorous exercise which can thereby diminish the motivation for them to undertake this activity.

The time interval before starting hypouricemic therapy was one of the propositions for future research identified by the EULAR task force, and although the presence of a low urate load may allow the introduction of hypouricemic therapy as soon as the acute attack subsides or even during the acute attack, this research has not yet been performed so that an interval of 2–4 weeks is usually recommended.

The question regarding concomitant prophylactic use has been answered with trials of colchicine and the human monoclonal antibody canakinumab. Trials with allopurinol induction with 1.2 mg of colchicine daily showed that there was a significantly lower rate and decreased severity of attacks over a 6-month period compared with placebo [23]. ULT with allopurinol or febuxostat and either twice-daily naproxen 250 mg, or colchicine 0.6 mg showed that flare prophylaxis for up to 6 months during the initiation of ULT showed greater benefit with 6 months than with 8-weeks therapy [24]. The usual practice after an acute attack has resolved is to continue the agent that brought the acute attack under control, or to change to an alternative agent such as low-dose colchicine if there are contraindications to long-term NSAIDs and prednisone.

The starting dose and the rate at which ULT is introduced has not been studied although traditional wisdom is to start with a low initial dose and to increase this at intervals ranging from weeks to months [25] to reach a target level of below 6 mg/dl (0.36 mmol/l) [9] or 5 mg/dl (0.30 mmol/l) [26], with tophi more likely to resolve if the latter target is reached [27].

One regimen to consider for those commencing allopurinol at an early stage of gout presentation in a patient with normal renal function is to wait 3 weeks after an acute attack resolves, to then commence allopurinol in a dose of half a 300 mg tablet for 3 weeks, then to increase to 300 mg daily for 6 weeks and then to review the serum urate level and adjust the dose to achieve the target level of 0.36 mmol/l, with colchicine being continued after a period of no acute attacks and urate within the target zone for a further 3 months. This has promise to be successful and easy for the patient to remember, particularly when supplemented with written educational material, which clarifies the target urate level and documents progress towards this. For patients with tophi, colchicine will probably need to be continued for longer than the usual 6 months, with a close check on side effects such as neuromyopathy [28] or drug interactions, as noted above.

Allopurinol has traditionally been the ULT agent of choice, in that it is not contraindicated by the presence of renal impairment or a history of urinary calculi. Because of the presence of under excretion in the majority of patients with gout, and the association with genetic factors such as *GLUT9* and *URAT1*, probeneicid is an alternative for those who do not tolerate allopurinol and who have chronic gout with a CrCl above 50 ml/min. The usual regimen is to start with a dose of 250 or 500 mg daily and increase by 500 mg increments at weekly to fortnightly intervals up to 1 g twice daily, with a high fluid intake being encouraged and the urine pH being maintained above six to reduce the likelihood of urinary calculi [25,29]. Benzbromarone, whose mechanism of action is linked to *URAT1*, is another useful uricosuric medicine, in those countries where it is registered. Benzbromarone 100–200 mg daily is effective in patients with a lower CrCl (greater than 20 ml/min) [30] and although linked with hepatotoxicity this does not appear to be greater than other ULTs [31,32].

Since 2006 there have been studies to answer one of the other EULAR task force's research questions relating to combination therapy. Although there were initial concerns that the increased excretion of allopurinol would outweigh the benefits of probenecid, it has been shown that although the plasma oxypurinol level falls with this combination, the hypouricemic effect is greater than either of these agents on their own [33]. Several papers by Reinders *et al.* have shown that the addition of probenecid to allopurinol is effective when allopurinol is not sufficient to achieve the target urate level [34], and that 600 mg allopurinol daily is as effective as benzbromarone 200 mg daily, achieving 78% success rate in reaching a target of 0.30 mmol/l [31].

The other ULT agents that have been studied extensively over the last 5 years [35] include uricase (pegloticase), which is effective at reducing uric acid to levels as low as 2 mg/l, although with gout flares occurring in up to 88% as a result of the marked decreases of uric acid, there remains issues to be addressed such as infusion reactions, phenolic glycolipid antibody development and febuxostat an alternative xanthine oxidase inhibitor. Febuxostat is increasingly being used for those patients who do not respond to allopurinol or uricosuric agents, alone or in combination. It is used in a dose of 40 mg daily, increasing after 2–4 weeks to 80 mg to achieve target urate levels. Febuxostat

has been shown to be more effective than allopurinol, particularly with mild-to-moderate renal impairment [35].

What are the impacts of these ULTs, as well as colchicine, in the induction phase of therapy, when comorbidities are present in the patient? One of the important considerations is the potential interaction from medications used to treat comorbidities. For colchicine these include medications that inhibit P-glycoprotein and CYP3A4. This is because colchicine is metabolized by cytochrome P4503A4 (CYP3A4) and excreted by the P-glycoprotein transport system. These inhibitors include cyclosporine, erythromycin and clarithromycin, and the statins lovostatin, simvastatin and artorvastin, with the side effects of the latter including myopathy and even rhabdomyolysis [36]. These risks are of relevance in view of the increased predisposition to infection of people with diabetes, in that there is a close relationship between diabetes and gout in those patients who are admitted to hospital, where clarithromycin is often used for the treatment of cellulitis. The association of gout with hyperlipidemia means that prophylactic colchicine needs monitoring for neuromyopathy with regular creatinine kinase estimations when statins are used to lower cholesterol levels. Caution is required particularly when there is renal or hepatic impairment [13]. For patients with a CrCl of less than 50 ml/min, clarithromycin and cyclosporine should not be coprescribed with colchicine.

The risk of allopurinol drug interactions includes a number of medicines. In addition, the rash associated with allopurinol, occurring in 2% of patients, is said to more frequent with the administration of ampicillin, amoxicillin, thiazide diuretics and angiotensin-converting enzyme inhibitors, with potentially fatal allopurinol hypersensitivity occurring in 0.1%. Azathioprine deserves particular mention because of the variability of the interaction with allopurinol so that many would recommend that the two agents should never be coprescribed. Warfarin levels can be increased by allopurinol, so that dose adjustment may be necessary [37].

There is increasing interest in the impact of renal function on adverse effects of allopurinol, and particularly allopurinol hypersensitivity syndrome. Although a relationship has been established there is now evidence that genetic factors may be important in some ethnic groups [38] and that the dosage guidelines produced in 1984 [39] after a number of patients were reported with allopurinol hypersensitivity syndrome were not evidence based, but were extrapolated from oxypurinol concentrations and were probably overcautious, particularly at the milder levels of renal impairment with a CrCl above 55 ml/min. A review of this topic [40] and the recent paper by Stamp *et al.* [41] supports higher levels of allopurinol to reach target levels of urate, even in the presence of renal impairment. However, although the numbers of patients with moderate-to-severe renal failure was not mentioned in the paper, it is understood to be small and caution needs to be exhibited until larger studies are performed in this group of patients before the title of the paper can be considered proven, although treating to target of 6 mg/dl (0.36 mmol/l) with increasing dosage of allopurinol is recommended when the CrCl is above 55 ml/min. Of interest in view of the comorbidities of hypertension and congestive heart failure was the requirement in this study to use higher doses of allopurinol to reach the target level of urate in patients who were being treated with furosemide. TABLE 1 summarizes the treatment of acute and chronic gout, including notes on the impact of comorbidities when present.

Impact of gout control on comorbidity management

The comorbidities associated with gout, such as obesity, hyperlipidemia, hypertension, diabetes and insulin resistance need to be managed appropriately. For those at high cardiovascular risk, low-dose aspirin can be continued despite its mild hyperuricemic effect, but alternatives to thiazide diuretics should be considered for those with gout and hypertension. Lifestyle factors such as exercise and nutrition have an important role in the management of these conditions, as well as gout and randomized controlled trials of these interventions, such as the change in diet identified in observational studies, are awaited with interest.

The timing of the introduction of hypouricemic therapy was considered by the EULAR task force who recommended further evaluation of the indications, which they listed as tophi, gouty arthropathy, radiographic changes of gout, multiple joint involvement or associated nephrolithiasis [9]. It could be argued that the presence of comorbidities such as renal impairment, cardiovascular disease and diabetes should lower the threshold for the introduction of this therapy, even for those with milder disease who have had only one or two attacks of acute gout. The task force recognized that

Table 1. Management of gout with comorbidities.

Gout ± comorbidities	Acute gout	Urate-lowering therapies (daily dose) (+ colchicine prophylaxis 6/12)
Gout alone	NSAIDs (± proton pump inhibitors) COX-2 inhibitors Corticosteroids (oral, i.m, i.a) Colchicine (low dose)	Allopurinol (50–800 mg) Probenecid (1–3 g) Allopurinol (600 mg) plus probenecid (1g b.d.) Febuxostat (40–120 mg) Benzbromarone (50–100 mg) Uricases
Renal impairment	Determine CrCl especially in elderly Caution with NSAIDs (prednisone safer) Colchicine (reduced dose)	Allopurinol adjustment where CrCl <55 ml/min Probenecid (where CrCl >50 ml/min) Benzbromarone (where CrCl >30 ml/min) Avoid NSAID prophylaxis
Diabetes	NSAIDs Caution with prednisone Colchicine	As in gout alone Caution with colchicine prophylaxis if infection treated with clarithromycin
Gastrointestinal disease	Caution with NSAIDs (use proton pump inhibitors as cotherapy, or COX-2 inhibitors) Consider low-dose prednisone/colchicine	Caution with colchicine and clarithromycin when latter used for helicobacter eradication (use lower dose) Avoid allopurinol if azathioprine used for autoimmune hepatitis
Cardiovascular disease	Caution with NSAIDs (avoid NSAID use with warfarin)	Caution with NSAIDs as prophylaxis (naproxen may be preferred option) Note interaction with allopurinol and warfarin Monitor colchicine for myopathy (CK) if on statins Caution with colchicine and CYP3A4 inhibitors diltiazem and verapamil Stop diuretics if acceptable alternative (e.g., in hypertension) Continue aspirin despite slight increase in urate

b.d.: Twice daily; CK: Creatinine kinase; CrCl: Creatinine clearance; i.a: Intra-articular; i.m: Intramuscular.

there was a balance between risks and benefits of medications, but more importantly the wishes of the patient need to be considered. This raises issues around the limitations of education as the sole contributor to behavior change and the important, though understudied, topic of adherence to long-term medication in the treatment of gout. This was noted in a study in 1984 by Murphy and Schumacher [42], which showed that education by a doctor and the provision of a booklet improved knowledge about gout but had no impact on urate levels or gout outcome compared with input from a nurse where a behavioral approach led to a fall in urate and a halving of the incidence of acute attacks, regardless of whether follow-up phone calls were made or not.

A systematic review on medication adherence reported three studies on adherence with gout therapy [43]. These include a study of 17 patients initiating urate-lowering drugs with 74% of hypouricemic drug doses being taken as prescribed. In two large studies based on administrative data, the percentage who were adherent to therapy more than 80% of the time was 26% of 2405 allopurinol users and 18% of 5597 allopurinol users with the median length of continuous treatment being 3 months in the former study and overall adherence in the second study being 56%.

The impact of the above data cannot be underestimated. Patients who do not understand their medication and are nonadherent are prone to restart their medication at the time of an acute attack, with subsequent prolongation of the painful episode, since this is one indication where restarted allopurinol should be discontinued, in contrast to continuing the same dose that has been previously stable. Among local communities this scenario has led to an undeserved reputation for allopurinol as the 'gout maker'. Among a study of recurrent hospital attendees [44], significantly higher urate levels were recorded compared with a control group of outpatient hospital clinic attendees. The success of the latter has in large part been due to the comprehensive multidisciplinary outpatient gout programme, using a population perspective and implementing systems to identify those patients at high risk. This model of specialist physician-led community-based prevention and self management has been outlined in a thought provoking paper from Australia [45] influenced by qualitative studies among indigenous patients with gout [46]. The programme includes coordinated care by doctors, nurses and cultural health workers, and has been transferred to the primary care context. Preliminary results from a pilot study of this

shared care programme in general practice in Counties Manukau, Aotearoa (New Zealand), where the estimated number of patients with gout is 10,000 among a population of half a million, has shown a 10% improvement in urate levels, together with decreased absence from work, and the implementation of a comprehensive programme of cardiovascular assessment and appropriate intervention.

A coordinated programme that meets the needs of patients for all their comorbidities to be managed well to improve their quality of life, linked to electronic shared personal health records, and a commitment to not only keep these accurate, but to act upon them with the patients and their families, will lead to better outcomes with currently available medicines, while improved therapeutic agents are developed for further research. This will not only be of benefit to patients and their families but will also lead to more satisfaction among members of the clinical professions who are involved in their management.

Future perspective

The EULAR evidence-based recommendations for gout reported a future research agenda, which included research on the efficacy of educational programmes for lifestyle modifications (e.g., weight loss, reduced alcohol intake and restrictions of dietary purines) in patients with gout. Additional factors have subsequently been identified in long-term observational studies, which could be explored in randomized controlled trials, with stratification into patients with and without associated comorbidities.

It is also important that further studies on the factors which impact on adherence to chronic hypouricemic therapy are performed, including qualitative research, to explore which of these influence the decision by patients to take continuous therapy to reduce urate concentration to the target range of less than 0.36 mmol/l.

Similarly, factors influencing doctors to improve the treatment of gout, including requests for urate levels in the intercritical period, and action to prescribe appropriate urate-lowering therapy, deserve further attention.

Studies are required of specialist physician led-systems of healthcare improvement for people with chronic diseases or long-term conditions.

More work is required in the area of health literacy and self management programmes, assisted by electronic health records.

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Executive summary

- There is a paucity of controlled trial data relating to the management of gout in patients with comorbidities where the presence of these have influence on the response to therapy, or require modification to achieve a successful outcome for the patient.
- Until evidence-based information is available, therapy will require management of all the comorbidities present, using a combination of pharmacological and nonpharmacological measures, with improved recognition of potential adverse interactions.
- Better use of currently available gout medication will lead to improvement in outcome for the population of gout sufferers at minimal marginal cost.
- Access to newer more effective medications will lead to better outcomes for those where current therapies are ineffective or contraindicated because of actual or potential adverse effects, including the presence of comorbidities.
- The perspective of the patient will need to be given higher priority, to encourage strategies to improve adherence of both the patients and their attendant clinicians.

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