

Understanding Treatments for Gout

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Abstract

Gout is one of the most readily manageable of the rheumatic diseases. This article reviews basic pathways in purine metabolism, uric acid handling, and the pathogenic mechanism of clinical gout, as well as the areas in those pathways amenable to intervention. Attention is also given to associated comorbidities, such as hyperuricemia and obesity, hypertension, hyperinsulinemia, and coronary artery disease. The significance of lifestyle modifications, such as weight loss and alcohol reduction, is discussed as an important adjunct to pharmacotherapy in gout. Current and investigational agents used in gout management are also reviewed. Finally, treatment recommendations for acute and chronic gout are suggested.

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The clinical description of gout dates back to antiquity, and evidence of the disease has been found in early skeletal remains.¹ Physicians since the time of Hippocrates have sought to understand the origin of gout and alleviate its suffering. Modern medicine has led to a clearer understanding of the biochemical pathway of purine nucleotide metabolism, leading to the formation of monosodium urate (MSU) crystals and the pathogenesis of clinical gout.^{2,3} As a result, advances in therapy have made gout one of the most readily manageable rheumatic diseases.

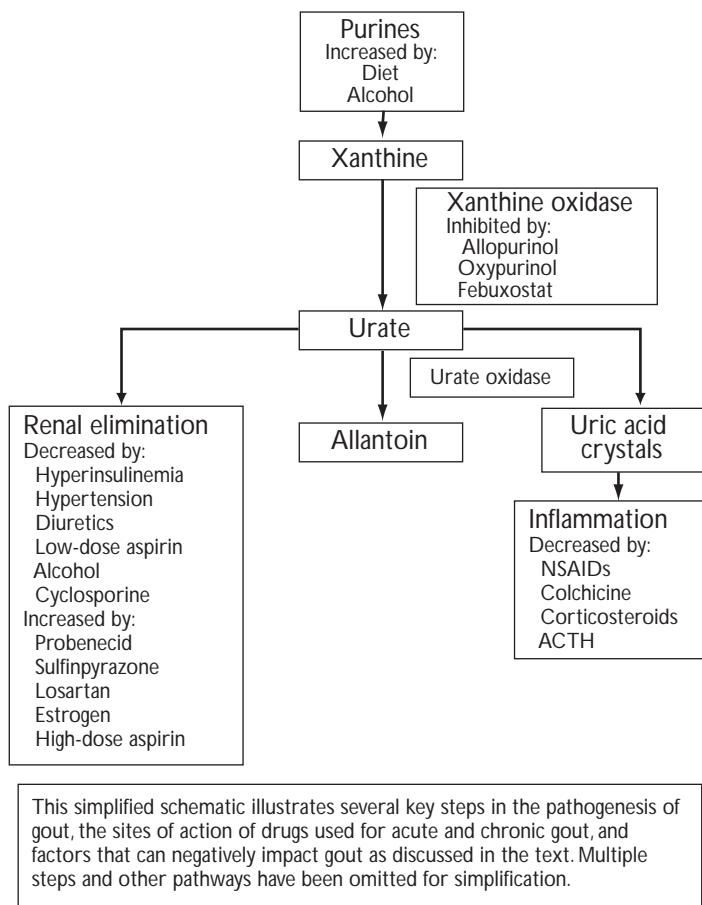
Although a complete review of purine metabolism, uric acid handling, and the pathogenic mechanism of clinical gout is beyond the scope of this article, a brief overview of each is warranted to better comprehend current therapeutic strategies for gout. **Figure 1** illustrates a simplified schematic of urate handling and the factors that can have both a negative and positive impact in the context of gout management.

Purine Metabolism and Hyperuricemia

Purines are crucial for a range of normal physiologic functions. They are the essential building blocks for nucleic acids (deoxyribonucleic and ribonucleic acid), extra- and intracellular messengers (adenosine triphosphate and G-protein coupled reactions), metabolic regulators (cyclic adenosine monophosphate), coenzymes, antioxidants, and neurotransmitters. In humans, uric acid is the end product of purine degradation. It exists as the urate ion at physiologic pH and has a very narrow window of solubility. The enzyme xanthine oxidase is required for the conversion of xanthine to urate. Humans lack the enzyme urate oxidase (uricase), which converts urate in other species to the highly soluble compound allantoin. This may have conferred a survival advantage because of the function of uric acid as an antioxidant. Urate oxidase is present in most fish, amphibians, and nonprimate mammals.⁴

About one third of the daily urate load comes from dietary sources, with the remainder generated endogenously. Once urate has been formed, it can be eliminated by the gastrointestinal tract or kidneys, or deposited in tissue. Enteric excretion is responsible for handling one third of the daily urate load.⁵ The remainder is handled primarily by the kidneys. Approximately 95% of urate is filtered by the glomerulus and subsequently undergoes bidirectional proximal convoluted tubule (PCT) movement with presecretory reabsorption (99%), secretion (50%), and postsecretory reabsorption (40%-50%). The movement of urate is accomplished via several recently described anion transmembrane channels.^{4,6,7} The balance between the PCT's secretory and reabsorptive activities exerts a major

Figure 1. Simplified Schematic of Urate Handling



NSAIDs indicates nonsteroidal anti-inflammatory drugs; ACTH, corticotropin.

influence on renal excretion of uric acid. Although the secretory capacity of the kidneys can increase with hyperuricemia, the compensation is often not enough. Therefore, in the majority (90%) of patients with primary gout, hyperuricemia results from relative renal underexcretion, whereas in 10% of patients there is overproduction of endogenous uric acid.⁸

Gout Risk Factors and Disease Comorbidity

The transition from hyperuricemia to the formation of uric acid crystals and subsequent inflammation is dependent on several factors in the local microenvironment, including both pH and temperature. Once crystals form, an intense inflammatory response is triggered. There is an initial

interaction with mononuclear cells, which results in a release of inflammatory cytokines and chemokines, resulting in neutrophil recruitment and activation. Once neutrophils migrate to the site of inflammation, there is aggressive phagocytosis of the uric acid crystals, delayed phagocytic apoptosis, and, ultimately, neutrophil death with massive enzyme and mediator release, which leads to the clinical acute gouty attack.^{2,4}

Although it is clear that hyperuricemia is the harbinger of gout, both genetic and environmental factors are recognized contributors to the development of hyperuricemia.⁹ Hypertension, the use of thiazide or loop diuretics, obesity, a high alcohol intake, and certain dietary factors (ie, high meat intake) all contribute in an additive manner to the risk of developing hyperuricemia and gout.¹⁰⁻¹³ These are modifiable risk factors, and targeting lifestyle and health behaviors is important not only for secondary prevention and treatment of gout, but also for the overall health of the patient.

For example, a strong correlation exists between obesity, hyperuricemia,^{8,14,15} and gout.¹⁶ Furthermore, hyperinsulinemia and insulin resistance syndrome (metabolic syndrome) have been estimated to occur in 95% and 76% of gout sufferers, respectively.¹⁷ Hyperinsulinemia stimulates the renal tubular sodium-hydrogen exchanger to reabsorb sodium and uric acid, resulting in hypertension and hyperuricemia, respectively.¹⁸⁻²⁰ In addition to centripetal obesity, hypertension, and hyperuricemia, insulin resistance syndrome is often associated with hypertriglyceridemia, type 2 diabetes, and coronary artery disease. Indeed, numerous studies have shown an association of hyperuricemia with both cardiovascular morbidity and mortality.²¹ Thus, even in the absence of clinical gout, hyperuricemia may serve as an important surrogate marker of insulin resistance and warrant screening and treatment for its comorbidities.⁸

Gout Treatment: Lifestyle and Health Factors

Dietary Factors. Consumption of high-purine meats and shellfish has been associ-

ated with an increased risk of gout, but consumption of purine-rich vegetables, such as spinach, has not.²²

Traditional low-purine diets, once a mainstay of gout management, are difficult for patients to adhere to and less crucial now that potent and effective urate-lowering therapy is available.⁸ Dietary intervention has received recent attention, however, because of the association of hyperuricemia with insulin resistance. In a pilot study of men with gout, serum levels of urate and the rate of acute gouty attacks significantly decreased by 17.5% and 71%, respectively, with a diet moderately restricted in calories and carbohydrates and increased proportional intake of protein and unsaturated fats. Additionally, weight and triglycerides decreased significantly. The beneficial effects of this diet are likely mediated via improved insulin sensitivity, reduction of plasma insulin levels, and increased renal excretion of urate with concomitant lowering of serum urate levels.¹⁷

Alcohol Intake. Alcohol consumption is also closely associated with gout, and it is estimated that more than one half of gout sufferers drink excessively.²³⁻²⁵ Several factors contribute to this relationship: transient lactic acidemia from acute alcohol excess reduces renal urate excretion²⁶; long-term alcohol ingestion stimulates purine production²⁷; alcohol (especially beer²⁸) contains purines^{26,27}; and lead-contaminated beverages (ie, moonshine) reduce renal urate excretion.²⁹ In patients with hyperuricemia, an alcohol history should be sought, with strong recommendations to reduce or discontinue drinking.⁸

Hypertension and Medications. Hypertension reduces renal excretion of urate^{4,30} leading to hyperuricemia. Thiazide and loop diuretics, often used in the treatment of hypertension, further increase serum urate levels by interfering with renal tubular ion transport and lead to effective volume depletion, which causes PCT urate reabsorption.³¹ Cyclosporine, an immunosuppressant commonly used to prevent graft rejection in patients undergoing solid organ transplantation, substantially reduces the

renal clearance of serum urate, leading to both hyperuricemia and an increased risk of gout.³² Other commonly used medications that influence renal handling of uric acid are aspirin and estrogen. Low-dose aspirin (up to 1-2 g/day) decreases renal urate excretion, especially in the setting of low albumin. Paradoxically, high-dose aspirin actually has a uricosuric effect, leading to an increase in urate excretion. Estrogen also exerts a uricosuric effect. It is possible that declining use of postmenopausal estrogen replacement may lead to an increase in postmenopausal gout and an earlier age of onset.^{2,33} As discussed below, 2 cardiovascular drugs, losartan and fenofibrate, also have uricosuric effects.

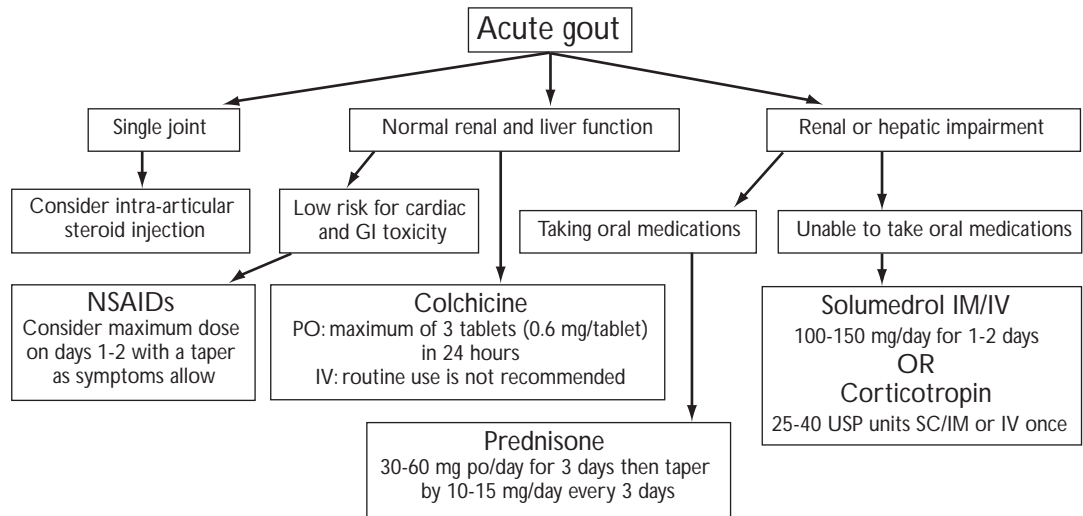
Gout Treatment: Pharmacotherapy

Although nondrug therapy certainly plays an important role in gout management, pharmacologic therapy remains the mainstay. Most people with asymptomatic hyperuricemia do not develop clinical gout; therefore, in most cases, treatment is not necessary.^{34,35} However, hyperuricemia should be thought of as a marker for associated comorbidities, as outlined above, and these comorbidities should be screened for and treated.

Although somewhat controversial, possible treatment exceptions include uric acid levels >13 mg/dL (733 μ mol/L) in men and >10 mg/dL (595 μ mol/L) in women because of a possible nephrotoxic risk; urinary uric acid excretion of >1100 mg/day (6.5 mmol/day), which increases the risk of nephrolithiasis. Additionally, urate-lowering therapy is indicated in patients at risk for tumor lysis syndrome because of high cell turnover, such as those undergoing treatment for leukemia.³⁶

Treatment of Acute Gout. The goal of therapy is rapid resolution of pain and inflammation (**Figure 2**). Nonsteroidal anti-inflammatory drugs (NSAIDs) are the treatment of choice in most patients with acute gout who are otherwise healthy. A number of head-to-head studies have shown most NSAIDs to be equivalent; thus, the choice of NSAID is not as important as initiating therapy early in an attack. More than 90% of patients will experience complete resolution

Figure 2. Acute Gout Treatment Algorithm



GI indicates gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; PO, by mouth; IV, intravenous; IM, intramuscular; USP, United States Pharmacopeia; SC, subcutaneous.

of the attack within 5 to 8 days.^{37,38} Higher doses may be needed in the first 24 to 48 hours and should be tapered as symptoms allow. Unfortunately, the use of NSAIDs is limited by adverse effects, and they should be used cautiously or not at all in patients with any of the following: significant renal impairment, poorly controlled congestive heart failure, history of or active peptic ulcer disease, anticoagulation therapy, or hepatic dysfunction.^{38,39}

Colchicine is derived from the autumn crocus and has been in widespread use since the early 1800s,⁴⁰ first as a plant extract and later in pill form. The mechanism of action is due to interference of tubulin dimers⁴⁰ and subsequent leukocyte functions, including diapedesis, lysosomal degranulation, and chemotaxis. Colchicine is most effective during the first 12 to 24 hours of an attack. It can be given orally or intravenously; however, it has the smallest benefit-to-toxicity ratio of all the drugs used in the management of gout and should therefore be used with caution.⁴¹

Oral colchicine is limited by nausea, vomiting, diarrhea, and abdominal pain. The major nongastrointestinal toxicity of colchicine is neuromyopathy, which is more common in patients with renal insufficiency and those taking concomitant cyclo-

sporine or statins.^{9,42} Colchicine should not be used in patients with leukopenia or significant renal or hepatic impairment. Intravenous (IV) colchicine should be used only in a hospital setting by physicians experienced with its use, and patients should not have received oral colchicine for at least 7 days before the IV administration. The total IV colchicine dose should not exceed 3 to 4 mg. Not available for use in many countries, IV colchicine can cause tissue necrosis with venous extravasation and anaphylaxis. Death has been reported with the inappropriate use of IV colchicine,⁴³ and its routine use is not recommended.

Corticosteroids can be used for patients with a suboptimal response or contraindications to either colchicine or NSAIDs, and can be administered orally, intravenously, intramuscularly, or indirectly via corticotropin (ACTH). Corticosteroids are effective therapy because of their anti-inflammatory effects.^{44,45} Intra-articular corticosteroids are particularly beneficial if only 1 or 2 joints are involved. Oral prednisone can be given at a dose of 30 to 60 mg daily for 1 to 3 days then tapered over 1 to 2 weeks. Parenteral steroids are useful if the patient cannot take oral medications, but have no therapeutic advantage over oral dosing. Most patients will note improvement within the first 12 to 24

hours, with resolution of symptoms in the next 7 to 10 days.⁴⁵

ACTH is secreted from the pituitary gland and stimulates the adrenal cortex to produce cortisol, corticosterone, and other androgens. The exact mechanism of action for its efficacy in gout is unknown, but may be due to release of anti-inflammatory hormones or leukocyte modulation via ACTH receptors.⁴⁶ ACTH has been shown to work faster than indomethacin^{47,48} but time to resolution is similar to that with systemic steroids.⁴⁴ ACTH can be used in patients with multiple medical problems, including congestive heart failure, chronic renal insufficiency, and peptic ulcer disease; however, its use is limited by patient comfort (administered by intramuscular injections), cost, and availability.

Treatment of Chronic Gout. Although there is little argument that acute gout should be treated to try to minimize patient discomfort, there is debate about when to initiate urate-lowering therapy. Urate-lowering therapy is cost effective for patients who have 2 or more attacks of gout per year.¹⁶ Some physicians advocate treating gout in patients who experience more than 4 attacks per year because of the varying nature of the intercritical periods.⁴⁹ The general goal of antihyperuricemic therapy is to lower serum urate concentration to at least 5 to 6 mg/dL (297-357 μ mol/L), a level substantially below that at which MSU is saturated in extracellular fluids.⁵⁰

Regardless of the urate-lowering therapy chosen, it is important to consider the need for anti-inflammatory prophylaxis (see "Treatment Recommendations" below), because rebound gout flares are perhaps the most common adverse effect complicating the management of chronic gout. Furthermore, some patients will have an acute flare of gouty arthritis while receiving maintenance urate-lowering therapy (ie, during an acute illness), and, in those cases, the urate-lowering therapy should be continued and the acute gouty flare treated appropriately.

The most commonly used class of urate-lowering drug is the uricostatic agents, which inhibit xanthine oxidase and lead to decreased production of uric acid. Allo-

purinol and its active metabolite oxypurinol (not yet commercially available in the United States) reduce serum and urine uric acid levels. Allopurinol is given in a once-daily dose but must be adjusted for renal function. Side effects include rash, pruritis, cytopenias, diarrhea, and fever. Desensitization can be attempted if minor hypersensitivity reactions, such as rash, occur but symptoms may recur.⁵¹ A dose-dependent allopurinol hypersensitivity syndrome exists that includes fever, eosinophilia, rash, hepatic and renal dysfunction, and vasculitis, with a mortality rate of approximately 20%.⁵² Patients with renal insufficiency on diuretic therapy are at the greatest risk. Allopurinol has 2 drug interactions that merit attention: one is potentiation of the immunosuppressive and cytolytic effects of azathioprine. Combined use should be avoided if possible, or the dose of azathioprine should be markedly reduced. Second, concomitant use with ampicillin causes a maculopapular rash.

A second class of urate-lowering drugs is the uricosuric agents, probenecid and sulfinpyrazone, which act on the renal uric acid anion transport pathway to increase uric acid excretion in urine. These agents should be used only in patients whose hyperuricemia results from underexcretion of uric acid (800 mg/24 hours). When therapy is initiated, intense uricosuria may result in deposition of uric acid crystals in the renal tubules and urinary stones. To minimize this risk, these agents should be started at low doses and gradually increased. A high urine volume should also be maintained and alkalization of urine considered. Uricosuric agents should be avoided in patients with a history of nephrolithiasis and are ineffective when given to patients with renal insufficiency.⁵³ The major side effects include rash, gastrointestinal intolerance, and uric acid stone formation. One limitation of uricosuric medications is that low doses of aspirin can block their uricosuric effects.⁹

Losartan is an angiotensin II receptor antagonist with a uricosuric effect. Losartan also raises urinary pH, which prevents stone formation. Micronized fenofibrate is a fibric acid derivative used to lower serum lipids. Fenofibrate also reduces renal tubular reab-

sorption of uric acid and enhances its excretion. With both agents, the uricosuric effect is independent of the angiotensin antagonism and lipid-lowering effect, respectively. These agents may be particularly useful in patients with gout with concomitant hypertension or hyperlipidemia.^{2,37}

Several investigational agents are being studied for treatment of chronic gout. Febuxostat is a novel oral nonpurine selective inhibitor of xanthine oxidase. Daily oral dosing significantly reduces serum uric acid, and it is well tolerated.⁵⁴ Febuxostat is metabolized by the liver and appears to be relatively well tolerated in patients with renal insufficiency. To the extent that some of the untoward effects of allopurinol are related to its purine analog compound and not xanthine oxidase inhibition, febuxostat may be a good option in patients intolerant to allopurinol. Additionally, febuxostat appears to have a significantly more potent urate-lowering effect than allopurinol in standard doses, suggesting that this agent may be particularly helpful in difficult-to-treat patients.⁵⁵

A second investigational agent is urate oxidase (uricase), which mediates the conversion of uric acid into a more soluble molecule allantoin. Preparations include recombinant and nonrecombinant urate oxidase from fungi, including rasburicase from

Aspergillus flavus. Rasburicase has been effective in the prevention of acute tumor lysis syndrome, but when given parenterally can be highly immunogenic, triggering anaphylaxis.^{56,57} Modification by covalent attachment of polyethylene glycol (PEG) appears to reduce immunogenicity and prolong the circulating half-life of the enzyme, making the use of PEG-uricase a potentially feasible treatment for gout. Studies examining the efficacy and tolerability of parenteral PEG-uricase in gout treatment are currently under way.^{58,59}

Treatment Recommendations

Although gout is readily treated, medication errors are common.⁶⁰ The goal of treatment of acute gouty flares is to rapidly control inflammation and reduce pain and suffering. When initiating treatment, comorbid conditions dictate medication selection. In patients who are healthy, initial therapy with an NSAID or oral colchicine is acceptable. In patients with renal insufficiency (serum creatinine 2 mg/dL or creatinine clearance 50 mL/minute), prednisone 30 to 60 mg/day may be appropriate. Intra-articular corticosteroid therapy should be considered when a single joint is affected. Treatment with oral agents is usually tapered with symptomatic improvement and can be discontinued within 2 weeks in most cases. Urate-lowering drugs should not be started until after the acute attack has completely resolved.

Most rheumatologists would agree that urate-lowering therapy should be started in patients with at least 2 flares of acute gouty arthritis per year and in those with tophaceous deposits or gouty erosions on radiography. The **Table** outlines clinical pearls for treatment of chronic gout. The choice of long-term therapy should again be guided by comorbid conditions. In most cases without contraindications, prophylactic therapy with colchicine (0.6 mg daily to twice daily), NSAIDs, or oral corticosteroids are started concomitantly to avoid rebound flares during uric acid level fluctuation. At least 1 recent study suggested that prophylactic therapy should be extended for at least 3 to 6 months during the initiation of urate-lowering therapy.⁶¹ Although low-dose

Table. Treatment of Chronic Gout: Clinical Pearls

<ul style="list-style-type: none"> • Consider the initiation of urate-lowering therapy in patients with more than 2 attacks per year. • Do not start urate-lowering drugs during an acute attack. If a patient on a urate-lowering drug has an acute flare, do not discontinue the urate-lowering medication. • Twenty-four-hour urinary uric acid excretion is not routinely measured, although should be considered before initiating a uricosuric. • Allopurinol is usually the drug of choice for initial therapy, but uricosurics may be used in allopurinol-allergic patients with normal renal function, uric acid underexcretion, and no history of nephrolithiasis. • Use concomitant prophylaxis with oral colchicine or NSAIDs (if no contraindications) when initiating urate-lowering therapy. • Routinely measure serum uric acid levels (every 3-6 months) and adjust medications until a target uric acid of <6 mg/dL is achieved. • Consider and treat associated comorbidities such as obesity, hypertension, hyperlipidemia, and coronary artery disease.
<p>NSAIDs indicates nonsteroidal anti-inflammatory drugs.</p>

colchicine and/or NSAIDs can be used long-term to prevent gout attacks in the absence of urate-lowering therapy, it is important to understand that use of these drugs alone does not prevent tissue deposition of urate or tissue damage occurring as a result.

In choosing a urate-lowering therapy, allopurinol is usually the drug of choice and should be started at a low dose (50 mg/day) in patients with a history of renal insufficiency (ie, those at greatest risk for allopurinol hypersensitivity syndrome). Uricosuric agents (ie, probenecid and sulfapyrazone) should not be used in patients with significant renal insufficiency or a history of nephrolithiasis. After urate-lowering therapy has been initiated, serum uric acid measurements should be checked regularly (every 3-6 months) and medication doses adjusted to achieve a uric acid level <6 mg/dL.

Behavioral modifications, such as weight reduction and cessation of alcohol consumption, should also be recommended. Furthermore, patients without contraindications need to be encouraged to remain on urate-lowering therapy, because adherence is difficult to maintain.⁶² The importance of lifelong intervention has been shown in several studies examining the effect of allopurinol withdrawal in otherwise stable patients with gout.^{63,64}

Conclusion

Gout is a readily treatable and rewarding disease to manage because of the current and expanding therapies available. In adopting a comprehensive approach to gout care, it is imperative that healthcare providers consider and search for associated comorbidities. Furthermore, therapeutic strategies should be guided by the global health of the patient, keeping in mind the significant drug interactions and side-effect profiles that complicate disease management.

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