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GOUT: AN OLD DISEASE IN NEW PERSPECTIVE

***Dr. Dhrubo Jyoti Sen and Pritha Halder**

Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt-Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India.

***Corresponding Author: Dr. Dhrubo Jyoti Sen**
Department of Pharmaceutical Chemistry, School of Pharmacy, Techno India University, Salt-Lake City, Sector-V, EM-4, Kolkata-700091, West Bengal, India.

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ABSTRACT

Gout is a picturesque presentation of uric acid disturbance. It is the most well understood and described type of arthritis. Its epidemiology is studied. New insights into the pathophysiology of hyperuricemia and gouty arthritis; acute and chronic allow for an even better understanding of the disease. The role of genetic predisposition is becoming more evident. The clinical picture of gout is divided into asymptomatic hyperuricemia, acute gouty arthritis, intercritical period, and chronic tophaceous gout. Diagnosis is based on laboratory and radiological features. The gold standard of diagnosis is identification of characteristic MSU (Monosodium Ureate) crystals in the synovial fluid using polarized light microscopy. Imaging modalities include conventional radiography, ultrasonography, conventional CT, Dual-Energy CT, Magnetic Resonance Imaging, nuclear scintigraphy, and positron emission tomography. There is remarkable progress in the application of ultrasonography and Dual-Energy CT which is bound to influence the diagnosis, staging, follow-up, and clinical research in the field. Management of gout includes management of flares, chronic gout and prevention of flares, as well as management of comorbidities. Newer drugs in the pharmacological armamentarium are proving successful and supplement older ones. Other important points in its management include patient education, diet and life style changes, as well as cessation of hyperuricemic drugs.

KEYWORDS: Uric acid, Hypoxanthine, Xanthine oxidase, Gout, Big toe, Tophi

INTRODUCTION

Gout distinguished itself in the history of *Homo sapiens* since time immemorial. It appeared in medical records very early in the history of medical writing, and was also mentioned in the biographies of many famous names. It was depicted as the fate of a life of affluence as much as the challenge to a physician's skill, and truly it was. Modern ages witnessed remarkable progress in managing gout. More recently, thanks to quantum leaps in molecular biology, diagnostic modalities, and pharmacotherapy, we enjoy deeper understanding of the disease and a more sophisticated armamentarium.[1]

Gout is a common and complex form of arthritis that can affect anyone. It's characterized by sudden, severe attacks of pain, swelling, redness and tenderness in the joints, often the joint at the base of the big toe. An attack of gout can occur suddenly, often waking you up in the middle of the night with the sensation that your big toe is on fire. The affected joint is hot, swollen and so tender that even the weight of the sheet on it may seem intolerable.[2]

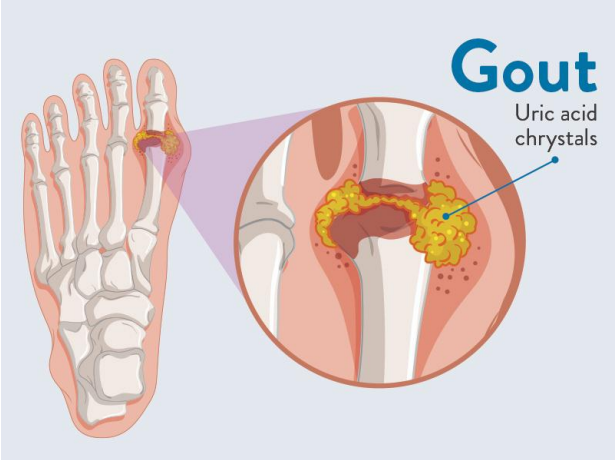


Figure-1: Gout.

Pathogenesis of hyperuricemia: Urate is the ionized form of uric acid present in the body. Uric acid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/dL. Some factors may affect the solubility of uric acid in the joint. These include synovial fluid pH, water concentration, electrolytes level, and other synovial components such as

proteoglycans and collagen. Serum Uric Acid (SUA) level in the body is determined by the balance between its production either from purine intake in diet or endogenous production by cellular turnover and its excretion by the kidneys and GIT. Increased production of UA is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under-excretion. Factors affecting SUA levels include age and gender. SUA is low in children. After puberty, SUA levels start to increase to reach their normal levels. In men, levels are higher than in women. However, SUA levels in postmenopausal women increase to reach men's levels. This explains why gout is usually a disease of middle aged and older men, and postmenopausal women. Rarely, it may happen in children and young adults in some rare inborn errors of purine metabolism. These enzymatic defects result in increased SUA with consequent production of UA crystals in kidneys and joints.[3]

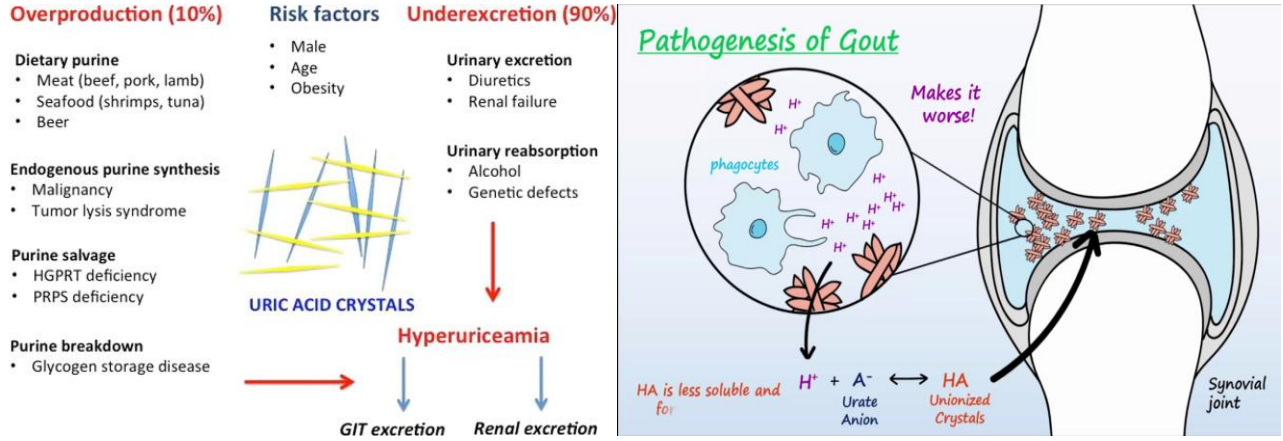


Figure-2: Physiology of gout.

What Is Gout? Gout is a form of arthritis that affects over three million Americans each year. Also known as gouty arthritis, the disease is caused by the formation of uric acid crystals in a joint (most often the big toe), triggering severe pain, redness, and tenderness. While certain factors, like genetics or kidney disorders, may predispose you to gout, diet, alcohol, and obesity can also contribute. Treatment can include over-the-counter (OTC) and prescription drugs to alleviate pain and reduce uric acid levels. You can further minimize the frequency of attacks by losing weight, exercising regularly, and avoiding trigger foods.[4]

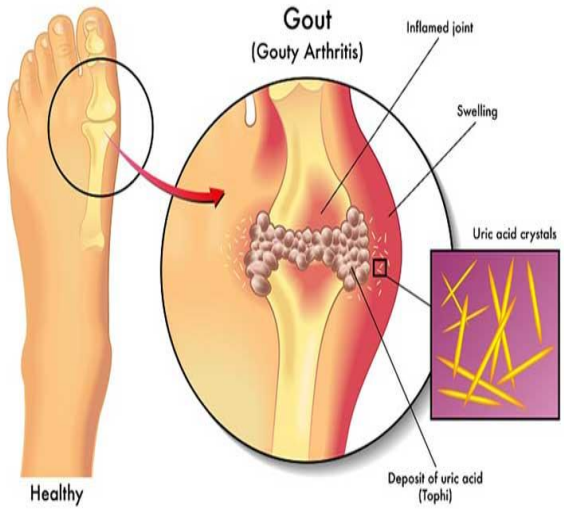


Figure-3: Uric acid deposition.

Symptoms

Gout: Open pop-up dialog box

The signs and symptoms of gout almost always occur suddenly, and often at night. They include:

- **Intense joint pain.** Gout usually affects the large joint of your big toe, but it can occur in any joint. Other commonly affected joints include the ankles, knees, elbows, wrists and fingers. The pain is likely to be most severe within the first four to 12 hours after it begins.
- **Lingering discomfort.** After the most severe pain subsides, some joint discomfort may last from a few days to a few weeks. Later attacks are likely to last longer and affect more joints.
- **Inflammation and redness.** The affected joint or joints become swollen, tender, warm and red.
- **Limited range of motion.** As gout progresses, you may not be able to move your joints normally.[5]

Causes: Gout occurs when urate crystals accumulate in your joint, causing the inflammation and intense pain of a gout attack. Urate crystals can form when you have high levels of uric acid in your blood. Your body produces uric acid when it breaks down purines — substances that are found naturally in your body. Purines are also found in certain foods, such as steak, organ meats and seafood. Other foods also promote higher levels of uric acid, such as alcoholic beverages, especially beer, and drinks sweetened with fruit sugar (fructose).

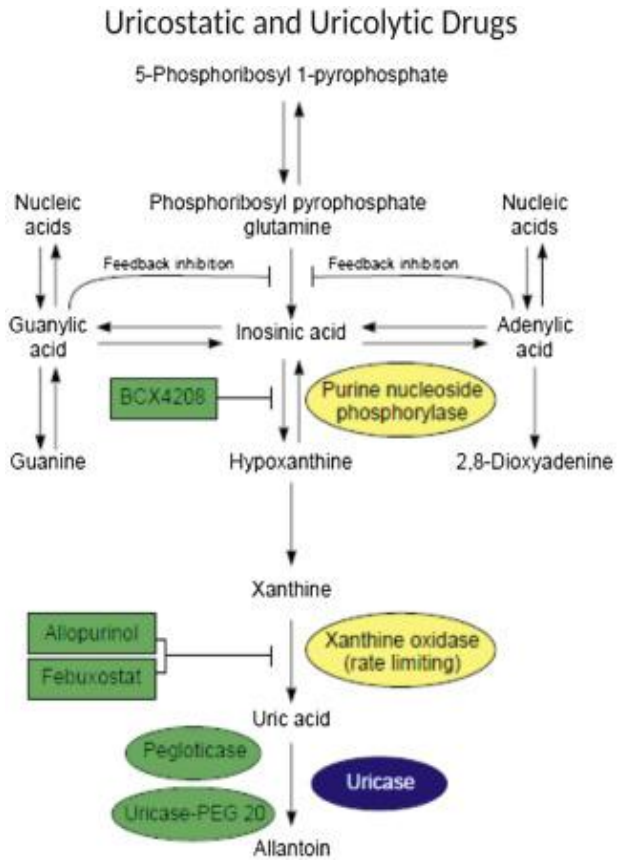


Figure-4: Biochemistry of Xanthine Oxidase and Xanthine Oxidase Inhibitors.

Normally, uric acid dissolves in your blood and passes through your kidneys into your urine. But sometimes either your body produces too much uric acid or your kidneys excrete too little uric acid. When this happens, uric acid can build up, forming sharp, needle like urate crystals in a joint or surrounding tissue that cause pain, inflammation and swelling.[6]

Risk factors: Develop gout if you have high levels of uric acid in your body. Factors that increase the uric acid level in your body include:

- **Diet.** Eating a diet rich in meat and seafood and drinking beverages sweetened with fruit sugar (fructose) increase levels of uric acid, which increase your risk of gout. Alcohol consumption, especially of beer, also increases the risk of gout.
- **Obesity.** If you're overweight, your body produces more uric acid and your kidneys have a more difficult time eliminating uric acid.
- **Medical conditions.** Certain diseases and conditions increase your risk of gout. These include untreated high blood pressure and chronic conditions such as diabetes, metabolic syndrome, and heart and kidney diseases.
- **Certain medications.** The use of thiazide diuretics — commonly used to treat hypertension — and low-dose aspirin also can increase uric acid levels. So can the use of anti-rejection drugs prescribed for people who have undergone an organ transplant.
- **Family history of gout.** If other members of your family have had gout, you're more likely to develop the disease.
- **Age and sex.** Gout occurs more often in men, primarily because women tend to have lower uric acid levels. After menopause, however, women's uric acid levels approach those of men. Men are also more likely to develop gout earlier — usually between the ages of 30 and 50 — whereas women generally develop signs and symptoms after menopause.
- **Recent surgery or trauma.** Experiencing recent surgery or trauma has been associated with an increased risk of developing a gout attack.

Complications: People with gout can develop more-severe conditions, such as:

- **Recurrent gout.** Some people may never experience gout signs and symptoms again. Others may experience gout several times each year. Medications may help prevent gout attacks in people with recurrent gout. If left untreated, gout can cause erosion and destruction of a joint.
- **Advanced gout.** Untreated gout may cause deposits of urate crystals to form under the skin in nodules called tophi (TOE-fie). Tophi can develop in several areas such as your fingers, hands, feet, elbows or Achilles tendons along the backs of your ankles. Tophi usually aren't painful, but they can become swollen and tender during gout attacks.
- **Kidney stones.** Urate crystals may collect in the urinary tract of people with gout, causing kidney stones. Medications can help reduce the risk of kidney stones.[7]

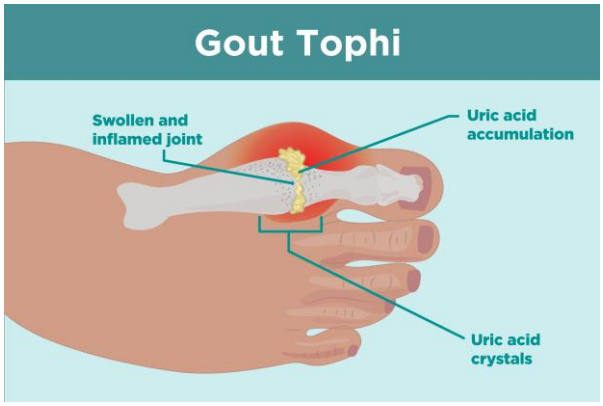


Figure-5: Gout Tophi.

Diagnosis

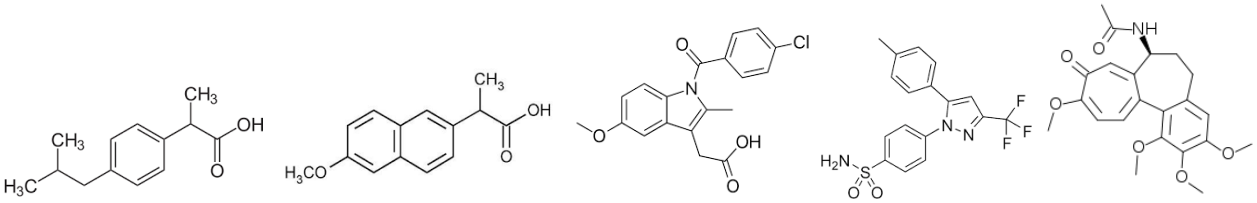
Tests to help diagnose gout may include:

- **Joint fluid test.** Your doctor may use a needle to draw fluid from your affected joint. Urate crystals may be visible when the fluid is examined under a microscope.
- **Blood test.** Your doctor may recommend a blood test to measure the levels of uric acid and creatinine in your blood. Blood test results can be misleading, though. Some people have high uric acid levels, but

never experience gout. And some people have signs and symptoms of gout, but don't have unusual levels of uric acid in their blood.

- **X-ray imaging.** Joint X-rays can be helpful to rule out other causes of joint inflammation.
- **Ultrasound.** Musculoskeletal ultrasound can detect urate crystals in a joint or in a tophus. This technique is more widely used in Europe than in the United States.
- **Dual energy CT scan.** This type of imaging can detect the presence of urate crystals in a joint, even when it is not acutely inflamed. This test is not used routinely in clinical practice due to the expense and is not widely available.

Treatment: Treatment for gout usually involves medications. What medications you and your doctor choose will be based on your current health and your own preferences. Gout medications can be used to treat acute attacks and prevent future attacks. Medications can also reduce your risk of complications from gout, such as the development of tophi from urate crystal deposits.[8]



Ibuprofen **Naproxen** **Indomethacin** **Celecoxib** **Colchicine**

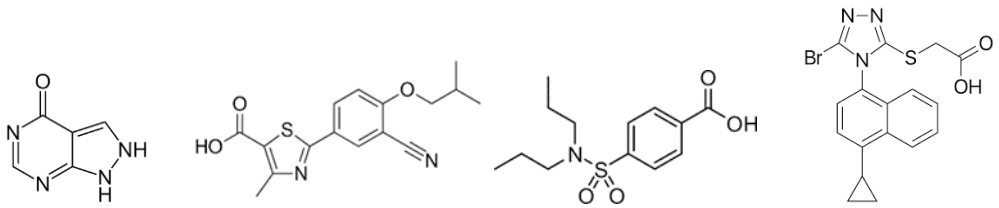
Figure-6: Medications for gout.

Medications to treat gout attacks

Drugs used to treat acute attacks and prevent future attacks include:

- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** NSAIDs include over-the-counter options such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve), as well as more-powerful prescription NSAIDs such as indomethacin (Indocin) or celecoxib (Celebrex). Your doctor may prescribe a higher dose to stop an acute attack, followed by a lower daily dose to prevent future attacks. NSAIDs carry risks of stomach pain, bleeding and ulcers.
- **Colchicine.** Your doctor may recommend colchicine (Colcrys, Mitigare), a type of pain reliever that effectively reduces gout pain. The drug's effectiveness may be offset, however, by side effects such as nausea, vomiting and diarrhoea, especially if taken in large doses.After an acute gout attack resolves, your doctor may prescribe a low daily dose of colchicine to prevent future attacks.
- **Corticosteroids.** Corticosteroid medications, such as the drug prednisone, may control gout inflammation and pain. Corticosteroids may be in pill form, or they can be injected into your joint. Corticosteroids are generally used only in people with gout who can't take either NSAIDs or colchicine. Side effects of corticosteroids may include mood changes, increased blood sugar levels and elevated blood pressure.

Medications to prevent gout complications: If you experience several gouts attacks each year, or if your gout attacks are less frequent but particularly painful, your doctor may recommend medication to reduce your risk of gout-related complications. If you already have evidence of damage from gout on joint X-rays, or you have tophi, chronic kidney disease or kidney stones, medications to lower your body's level of uric acid may be recommended.[9]



Allopurinol **Febuxostat** **Probenecid** **Lesinurad**

Figure-7: Xanthine Oxidase Inhibitors.

Options include

- **Medications that block uric acid production.** Drugs called xanthine oxidase inhibitors (XOIs), including allopurinol (Aloprim, Lopurin, Zyloprim) and febuxostat (Uloric), limit the amount of uric acid your body makes.

This may lower your blood's uric acid level and reduce your risk of gout.

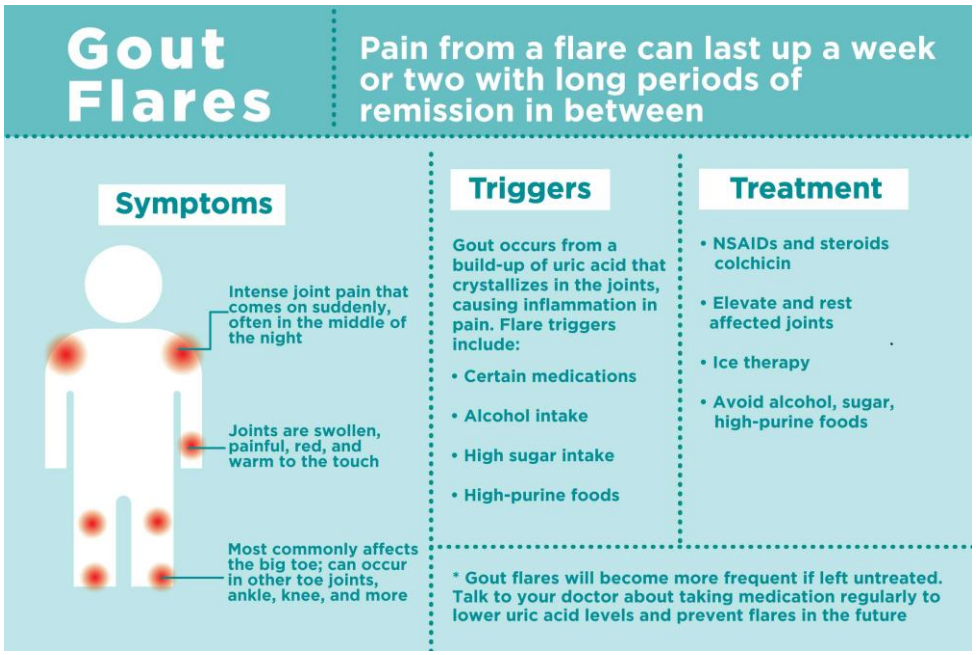


Figure-8: Gout flares.

Side effects of allopurinol include a rash and low blood counts. Febuxostat side effects include rash, nausea, reduced liver function and an increased risk of heart-related death.

Medication that improves uric acid removal. These drugs, called uricosurics, include probenecid (Probalan) and lesinurad (Zurampic). Uricosuric drugs improve your kidneys' ability to remove uric acid from your body. This may lower your uric acid levels and reduce your risk of gout, but the level of uric acid in your urine is increased. Side effects include a rash, stomach pain and kidney stones. Lesinurad can be taken only along with an (Xanthine Oxidase Inhibitor) XOI.[10]

Prevention: During symptom-free periods, these dietary guidelines may help protect against future gout attacks:

- **Drink plenty of fluids.** Stay well-hydrated, including plenty of water. Limit how many sweetened beverages you drink, especially those sweetened with high-fructose corn syrup.
- **Limit or avoid alcohol.** Talk with your doctor about whether any amount or type of alcohol is safe for you. Recent evidence suggests that beer may be particularly likely to increase the risk of gout symptoms, especially in men.
- **Get your protein from low-fat dairy products.** Low-fat dairy products may actually have a protective effect against gout, so these are your best-bet protein sources.
- **Limit your intake of meat, fish and poultry.** A small amount may be tolerable, but pay close attention to what types — and how much — seem to cause problems for you.
- **Maintain a desirable body weight.** Choose portions that allow you to maintain a healthy weight. Losing weight may decrease uric acid levels in your body. But avoid fasting or rapid weight loss, since doing so may temporarily raise uric acid levels.

CONCLUSION

Several drugs show moderate-to-high evidence of benefit in terms of reducing pain in patients with acute gout. It is clear that urate lowering therapy achieves its goal of lowering urate levels. Decreased serum urate should lead, over time, to a reduction in gout attacks, but the benefits and harms of long-term urate lowering therapy have yet to be demonstrated directly. Patient preferences are likely to be important in decision-making (as specified above), and having better estimates of the size of the benefit of urate lowering therapy will make clinicians and patients more knowledgeable about the risk: benefit trade-off for the different decisions.

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