Drugs Used to Treat Gout
The victim goes to bed and sleeps in good health. About two o'clock in the morning, he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follows chills and shiver and a little fever. The pain which at first moderate becomes more intense. After a time this comes to full height, accommodating itself to the bones and ligaments of the tarsus and metatarsus.

Now it is a violent stretching and tearing of the ligaments—now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room.

(Thomas Sydenham, 1683)
What is gout?

Gout describes a group of metabolic disorders where crystals of sodium urate (the sodium salt of uric acid) deposit in tissue.

This usually follows a prolonged period where uric acid levels in blood are raised.
Who gets gout?

Older men and women after the menopause, though it is always more common in men (10:1).

In men the number of cases rises with age from 2/1,000 in men aged 18-44, and 34/1,000 in men between 45 and 65.

In a population of 100,000 people there will be about 30 new cases a year with about 250 cases in total.
About 12% of gout is attributed to dietary causes.

This includes a strong association with the consumption of alcohol, sugar, and meat and seafood.

The intake of dairy products, vegetables, and the total protein intake do not affect the occurrence of gout.

A sedentary lifestyle also increases the risk of developing the disease.
Medical conditions

Metabolic syndrome (the combination of hypertension, diabetes, dyslipidemia, truncal obesity, increased cardiovascular disease risk)

Leukemia

A co-morbidity of other diseases, including polycythaemia, intake of cytotoxics, obesity, diabetes, Lesch-Nyhan syndrome, hypertension, renal disorders, and hemolytic anemia, solid organ transplants.

Kidney failure.

Lead poisoning
Pharmaceuticals

Diuretics have been associated with attacks of gout; low doses of hydrochlorothiazide (HCTZ), however, do not seem to increase the risk.
Diagnosing gout
(American College of Rheumatology criteria)

More than one attack of active arthritis
Maximum inflammation develops within one day
Oligoarthritis attack
Redness observed over joint
First metatarsophalangeal joint painful or swollen
Unilateral first metatarsophalangeal joint attack
Unilateral tarsal joint attack
Tophus (proven or suspect)
Hyperuricemia
Asymmetrical swelling within a joint on radiography
Complete termination of an attack
A definitive diagnosis of gout is based upon the identification of monosodium urate (MSU) crystals in the synovial fluid.

Hyperuricemia is a common feature of gout, so its presence supports a diagnosis of gout.

A critical differential diagnosis in gout is septic arthritis. The only way to definitively rule out this diagnosis is via a joint aspiration and culture.

Clinically, gout can be hard to distinguish from several other conditions, including chondrocalcinosis. Chondrocalcinosis is a very similar disease, caused by deposition of calcium pyrophosphate rather than uric acid.

Gouty tophi, particularly when not located in a joint, can be mistaken for basal cell carcinoma or another neoplasm.
Uric Acid Crystals
Uric acid is a product of purine metabolism, and in humans is normally excreted in the urine. Purines are generated by the body via breakdown of cells in normal cellular turnover, and also are ingested as part of a normal diet. The kidneys are responsible for approximately two thirds of uric acid excretion, with the liver responsible for the rest.
Urine 600 mg/d

Purines from diet 600 mg/d → Purine nucleotides → Purine bases → New purine synthesis 300-600 mg/d → Tissue nucleotides

Purine nucleotides → Purine bases → Uric acid pool (1200 mg)

Tissue nucleotides → Intestine 200 mg/d

Purines from diet 600 mg/d

Uric acid pool (1200 mg)
Determinates of Uric Acid Levels

Uric acid is the end product of purine metabolism.

Two thirds of the uric acid formed each day is eliminated in the gastrointestinal tract or kidneys.

The increase in blood uric acid results from increased purine intake (purines are precursors of uric acid), or increased turnover or production, or from decreased uric acid elimination by the kidneys, or a combination of all these.

Though higher purine intake may play a part in high blood uric acid levels, excretion by the kidney should increase to compensate.

In most (75%-90%) people with gout, clearance of uric acid by the kidney is significantly reduced.

Increased uric acid production or decreased renal clearance can be secondary to other disorders.
FORMATION OF URIC ACID IN THE BODY

ADENINE
PHOSPHATE + PHOSPHO-RIBOSYL-PYROPHOSPHATE SYNTHASE
ADENINE MONOPHOSPHATE
SUGAR + NUCLEOTIDASE
ADENOSINE
AMMONIA ↔ ADENOSINE DEAMINASE
INOSINE
GUANOSINE
SUGAR PHOSPHATE ↔ NUCLEOSIDE PHOSPHORYLASE
HYPOXANTHINE
GUANINE
SUGAR PHOSPHATE
XANTHINE OXIDASE
XANTHINE
URIC ACID
Renal Elimination of Uric Acid

Uric acid in the blood is saturated at 6.4-6.8 mg/dL at ambient conditions, with the upper limit of solubility placed at 7 mg/dL.

Urate is freely filtered at the glomerulus, reabsorbed, secreted, and then again reabsorbed in the proximal tubule.

A urate/anion exchanger (URAT1) has been identified in the brush border membrane of the kidneys and is inhibited by an angiotensin II receptor blocker, losartan.

A human organic anion transporter (hOAT1) has been found to be inhibited by both uricosuric drugs and antiuricosuric drugs, while another urate transporter (UAT) has been found to facilitate urate efflux out of the cells.

These transporters may account for the reabsorption, secretion, and reabsorption pattern of renal handling of urate.
Renal Elimination of Uric Acid

Underexcretion accounts for most causes of hyperuricemia. Urate handling by the kidneys involves filtration at the glomerulus, reabsorption, secretion, and, finally, postsecretory reabsorption.

Altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption. While decreased urate filtration may not cause primary hyperuricemia, it can contribute to the hyperuricemia of renal insufficiency.

Decreased tubular secretion of urate occurs in patients with acidosis (e.g., diabetic ketoacidosis, ethanol or salicylate intoxication, starvation ketosis). The organic acids that accumulate in these conditions compete with urate for tubular secretion.

Enhanced reabsorption of uric acid distal to the site of secretion is the mechanism thought to be responsible for the hyperuricemia observed with diuretic therapy and diabetes insipidus.
Gout occurs when crystals of uric acid, in the form of monosodium urate, precipitate on the articular cartilage of joints, on tendons, and in the surrounding tissues.

Uric acid is more likely to form into crystals when there is hyperuricemia, although hyperuricemia is 10 times more common without clinical gout than with it.

Gout can also occur when serum uric acid is normal, and when it is abnormally low (hypouricemia).

Paradoxically, acute attacks of gout can occur together with a sudden decrease in serum uric acid, such as due to use of drugs (uricosurics, xanthine oxidase inhibitors), or total parenteral nutrition.

Precipitation of uric acid is markedly enhanced when the blood pH is low. A similar pH-sensitive effect occurs in urine, contributing to uric acid nephrolithiasis.
Chemical Crystallization

An acute attack occurs as a result of an inflammatory reaction to crystals of sodium urate that are deposited in the joint tissue. The inflammatory response involves the local infiltration of granulocytes which phagocytize the urate crystals. Lactate is high in synovial tissues and in the leucocytes associated with the inflammatory process which also favors the deposition of uric acid.

Neutrophilic leucocytes avidly ingest microcrystals of sodium monourate, which causes the rapid degranulation and disintegration of the leucocytes, and fresh leucocytes ingest the debris and crystals liberated by the dead cells, and in their turn degranulate and die, thus possibly establishing a vicious circle in the system.

Whatever the cause of elevated uric acid levels, the key event in gout is the movement of uric acid crystals into the joint fluid. Inflammatory chemicals are released when the body’s defense mechanisms, engulf the uric acid crystals. All the signs of inflammation, including heat, redness, swelling and pain are caused by these chemicals. (cytokines) The inflammation attracts more white blood cells to the joint, which increases the inflammation.
High blood uric acid

High blood uric acid is defined as a serum urate level more than two standard deviations from the mean, or 0.42 mmol/L (7 mg/100 ml) for adult males and 0.36 mmol/L (6 mg/100 ml) for adult females.

Serum is saturated with sodium urate at 0.42 mmol/L, but higher concentrations of urate can remain stable in solution in a super-saturated state.

When something triggers it, the supersaturated solution in blood or tissue (including joints) produces crystals.
Stages of Untreated Gout

1. **Asymptomatic hyperuricemia**

   Crystals probably take a long time (months or years) to accumulate, most commonly in peripheral connective tissues in and around synovial joints, especially in the lower limbs. During this period there may well be no symptoms whatsoever. About 95% of people with hyperuricemia will remain asymptomatic throughout their lives.

2. **Acute attacks**

   A single peripheral joint is almost always involved in all initial episodes, and most often this is the metatarsophalangeal joint between wrist and finger. Typically local irritation and aching proceeds to tissues becoming swollen, red, hot, shiny and extremely painful. The pain is often described as the worst ever experienced. By 24 hours inflammation is maximal, and it then resolves slowly over a week or so, often with itching and flaking of overlying skin.
Stages of Untreated Gout

3. **Intercritical gout**

There are asymptomatic periods between attacks. Some never have a second attack, or perhaps after many years, but in most the second attack occurs with a year. The frequency of attacks and number of sites then increase with time, leading eventually to joint damage and chronic pain, after an average of about 10 years.

4. **Chronic tophaceous gout**

Large crystal deposits, or tophi, produce irregular firm nodules, predominantly around the upper surfaces of the fingers and hands, but other places as well, including forearms or Achilles tendons or ears. When untreated, these can lead to severe deformity.
Treating Gout

Treating acute attacks

Here treatment aims to reduce pain and inflammation, usually with nonsteroidal antiinflammatory drugs (NSAIDs) given in full dosage. Oral colchicine is also used, but it produces severe diarrhea, cramps and nausea accompany when administered in effective doses. Joint aspiration and lavage are also used to treat acute attacks.
Treating Gout

Long-term management

The aims here are to try and eliminate any modifiable factors that cause high blood uric acid, and then use treatments to reduce high uric acid levels in serum.

Lifestyle changes in early primary gout involve weight loss reduction in alcohol consumption and avoidance of toxins like low-dose aspirin and lead. With diuretic-induced gout stopping the diuretic may be possible and be all that is required.

The usual choice for reducing uric acid levels is allopurinol, because it inhibits xanthine oxidase and can depress new purine synthesis. Probenecid prevents proximal tubular reabsorption of urate.
Drug Treatment of Gout

Colchicine
NSAIDs
Uricosuric Agents
Allopurinol
Febuxostat
Glucocorticoids
Colchicine

An alkaloid isolated from the autumn crocus

Used since ancient times to treat painful joints

Absorbed orally, t1/2 for elimination 9 hours

More effective than NSAIDS, but also more serious side effects.
Colchicine
(mechanisms of action)

Binds to intracellular protein tubulin.
Prevents tubulin polymerization in microtubules.
Inhibition of leukocyte migration and phagocytosis.
Inhibits leukotriene B₄ formational
Colchicine
(indications)

More specific in gout than NSAIDs.
Prophylaxis of recurrent gouty attacks.
Prevention of acute Mediterranean fever.
Sarcoid arthritis.
Hepatic cirrhosis.
Treatment and prophylaxis in chronic calcium pyrophosphate deposition disease.
Colchicine
(adverse effects)

Diarrhea most common
Abdominal pain
Nausea
Vomiting
Hepatic necrosis
Acute renal failure
Disseminated intravascular coagulation
Seizures
Colchicine
(adverse effects)

Alopecia
Bone marrow depression
Peripheral neuritis
Myopathy
Death
Colchicine
(acute intoxication)

Burning throat pain
Bloody diarrhea
Shock
Hematuria
Oliguria
Fatal CNS depression
Organic acids that act at the anion transport sites in the proximal tubule.

Probenecid is completely reabsorbed by the renal tubules and is eliminated by hepatic metabolism (t1/2 5-8 hours)

Sulfinpyrazone or its active metabolite is rapidly excreted by the kidneys.

A predisposition to formation of renal stones is augmented, thus urine volume should be kept high and urine pH should be kept above 6.0 by the administration of an alkali.
Uricosuric Agents
(Indications)

Should be initiated in gouty impaired excretion of uric acid and when allopurinol is contraindicated or when tophi are present.

Treatment should not be started until 2-3 weeks after an acute attack of gout.
Uricosuric Agents
(Adverse Effects)

GI irritation
Rash
Probenecid has been associated with nephrotic syndrome
Rare aplastic anemia
Allopurinol

Preferred and standard treatment of gout between acute episodes.

Reduces total uric acid body burden by inhibiting xanthine oxidase.
Inhibition of Uric Acid Synthesis by Alopurinol

\[
\begin{align*}
\text{Allopurinol} & \xrightarrow{\text{Xanthine oxidase}} \text{Alloxanthine} \\
\text{Hypoxanthine} & \xrightarrow{\text{Xanthine oxidase}} \text{Xanthine} \\
& \quad \xrightarrow{\text{Xanthine oxidase}} \text{Uric acid}
\end{align*}
\]
**Allopurinol**

80% absorbed after oral administration

Serum t1/2 1 to 2 hours

Its metabolite alloxanthine also inhibits xanthine oxidase and has a long enough t1/2 that allopurinol need be given only once daily.

Inhibits the last step in uric acid synthesis resulting in a fall in the plasma urate levels and in the size of the urate pool.

The more soluble xanthine and hypoxanthine are increased.
Allopurinol
(Indications)

When starting treatment, NSAIDs and colchicine should be continued until serum urate levels are reduced to less than 6 mg/dL.

Used as an antiprotozoal agent

Used to prevent massive uricosuria after therapy of blood dyscrasias.
Allopurinol
(Adverse Effects)

Nausea, vomiting, diarrhea
Peripheral neuritis
Necrotizing vasculitis
Bone marrow depression
Aplastic anemia (rare)
Uricosuria after therapy of blood dyscrasias
Hepatotoxicity
Interstitial nephritis
Pruritic maculopapular rashes in 3% of patients.
Allopurinol
(Adverse Effects)

Hepatotoxicity
Interstitial nephritis
Pruritic maculopapular rashes in 3% of patients
Exfoliative dermatitis
Cataracts
Allopurinol

(Cautions)

When given with chemotherapeutic mercaptopurines, dosage must be reduced by about 75%

Might increase the effect of cyclophosphamide

Inhibits metabolism of probenecid and oral anticoagulants

Might increase hepatic iron content
Febuxostat (Uloric®)

Nonpurine inhibitor of xanthine oxidase

First new drug for treatment of gout in over 40 years

No better than allopurinol.

Adverse effects are liver function abnormalities, diarrhea, headache, and nausea.

Can be used in patients intolerant to allopurinol.
Lifestyle

Dietary and lifestyle choices may decrease the risk of gout. Lowering intake of meat and seafood, consuming adequate vitamin C, limiting alcohol and fructose ingestion, and avoiding obesity have all been shown to be effective in preventing gout.

Any lifestyle change that reduces blood pressure will have a favorable effect, but there are concerns that medications for hypertension may aggravate gout.

A low-calorie diet in obese men decreased uric acid levels by 100 μmol/L.

Vitamin C intake of 1,500 mg per day decreases the risk of gout by 45% compared to 250 mg per day.

Coffee but not tea consumption is associated with a lower risk of gout.
The problems that can result are:

- Acute inflammatory arthritis
- Chronic erosive and deforming arthritis
- Kidney and/or bladder stones
- Chronic renal disease or hypertension.