Drug Therapy for gout and management of hyperuricaemia

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Objectives

✓Contrast the treatment of acute and chronic gout

✓ Drugs used for management of an acute attack of gout (e.g. colchicine, certain NSAIDs & glucocorticoids).

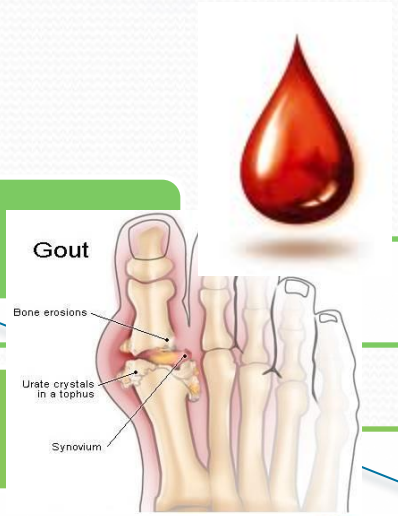
✓ Drugs used for the long-term management of gout (uricosuric agents & allopurinol)

✓ Mechanism of action, toxicities of the different groups of drugs used in the management of gout

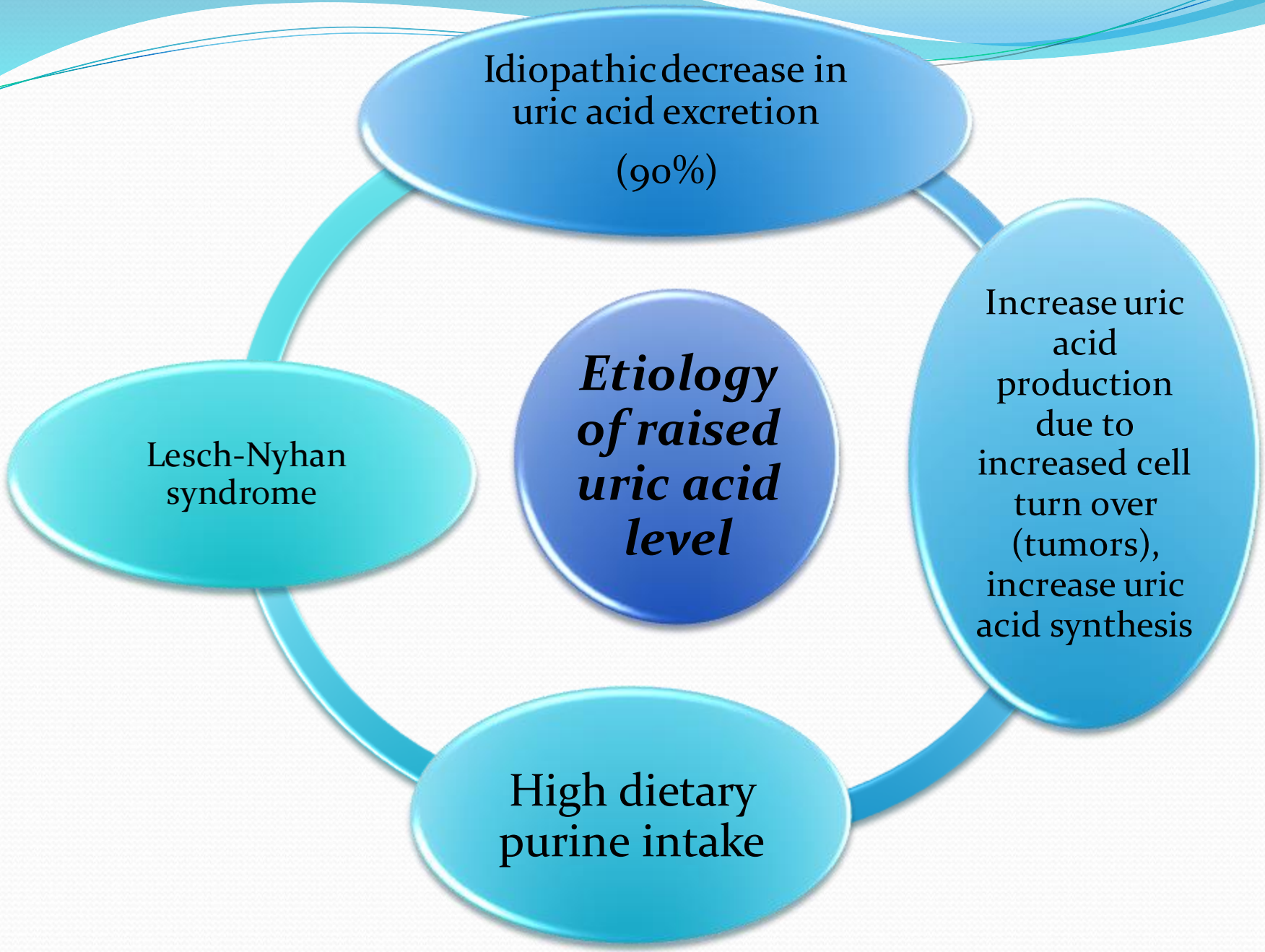
✓ List the drugs that can precipitate gout

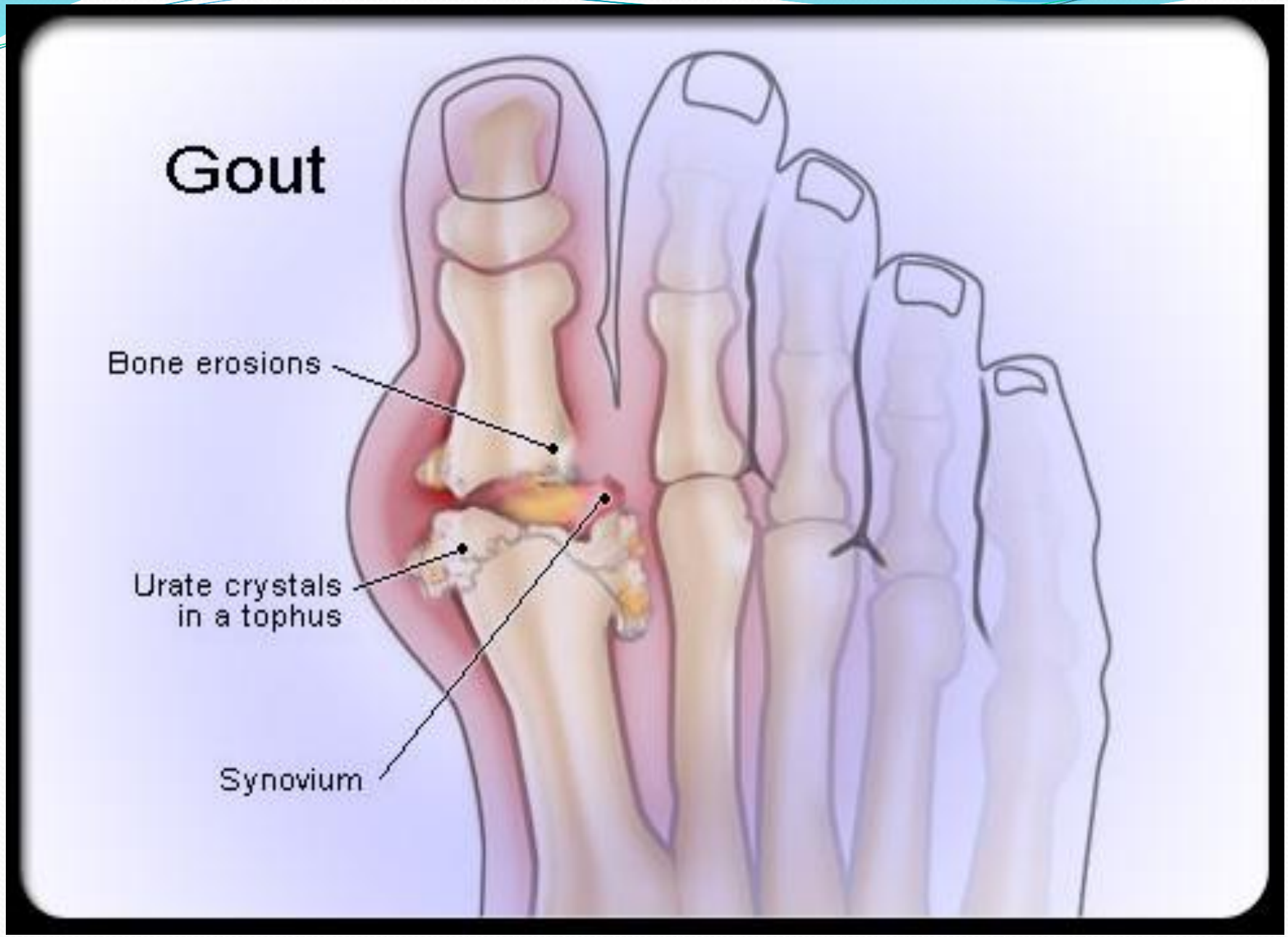
What is gout?

- High blood uric acid level
- Acute arthritis
- monosodium urate stone in kidney
- ♂ > ♀



Breakdown of product of the body's **purine** (nucleic acid) metabolism.


Idiopathic decrease in uric acid excretion (90%)
Increase uric acid production due to increased cell turn over (tumors), increase uric acid synthesis
High dietary purine intake
Lesch-Nyhan syndrome
Etiology of raised uric acid level


Gout
Bone erosions
Urate crystals
in a tophus
Synovium

Non- pharmacological treatment of gout

•Patients should be educated about: the importance of lifestyle changes.

• In overweight patients - dietary modification to achieve ideal body weight should be recommended ('crash dieting‘ and high protein/low carbohydrate (Atkins-type) diets should be avoided).

•Reduction of high purine foods and red meat:

- liver, kidney and sweetbreads.
- Red meat. Limit serving sizes of beef, lamb and pork.
- Seafood.
- Cola beverages- alcohol

Drugs Employed in the Treatment of Gout:

- Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney.

- Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia.

- Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (<6 mg/dL), thus preventing the deposition of urate crystals.

What is the treatment for gout ?

Gout drugs

Hypouricemic drugs

In chronic gout

Uric acid levels> 7 mg/dl

- 1- Increasing uric acid excretion: uricosuric drugs
- Probencid
- 2- Decreasing uric acid synthesis allopurinol: selective inhibitor of the terminal steps in the biosynthesis of uric acid: inhibitor of xanthine oxidase
- 3- Increasing uric acid metabolism uricase enzyme

Anti-inflammatory drugs

In acute attack

- NSAIDs
- Cortecosteroids
- Colchicine

Drugs used for acute gout

NSAIDs Corticosteroids and Colchicine

- **Colchicine tablet: 0.6 mg**

One tablet, then after one hour: one tablet, then after 12hs: one tablet /12 hs

Drugs used for chronic gout /hyperuricaemia

Uricosurics

Probenecid - 0.5 g/day: proben tab. 500mg

2-3 tab./day

Synthesis inhibitors:

Allopurinol: single daily dose: 100mg in the morning

Treating acute gout:

- Acute gout manifests as sudden onset of severe inflammation in a small joint due to precipitation of urate crystals in the joint space.

- Acute gouty attacks can result from several conditions, including excessive alcohol consumption, a diet rich in purines, or kidney disease.

- Acute attacks are treated with **indomethacin** to decrease movement of macrophages into the affected area; NSAIDs other than indomethacin are also effective at decreasing pain and inflammation.

Note: Aspirin is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.

Colchicine

- Colchicine a plant alkaloid, used for the treatment of acute gouty attacks.
- It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout.

Mechanism of action: colchicine

- Colchicine blocks cell division by binding to mitotic spindles (microtubules).
- Mitotic blocker: inhibition of mitotic division in macrophages: inhibition of release of cytokines.
- **Disadvantages:**
- 1- Slow onset 2- Sever side effects
- FAD recommended to stop using colchicine, it is a second choice after cortecosteroids and NSAIDs.

Therapeutic uses:

- The anti-inflammatory activity of colchicine is specific for gout, usually alleviate the pain of acute gout within 12 hours.

(Note: Colchicine must be administered within 24 to 48 hours of onset of attack to be effective).

Pharmacokinetics:

- Orally, followed by rapid absorption from the GI tract.
- Colchicine is recycled in the bile and is excreted unchanged in the feces or urine.

Avoided in patients with a creatinine clearance of less than 50 ml/min.

Adverse effects:

- **Most common**: Colchicine treatment may cause nausea, vomiting, abdominal pain, and **diarrhea**.
- **Most rare:** Chronic administration may lead to myopathy, neuropathy and alopecia.
- **Most dangerous**: aplastic anemia: bone marrow depression 50% mortality
- Overdose colchicine produces kidney damage,CNS depression, intestinal bleeding death is due to muscular paralysis and respiratory failure.
- PRECAUTIONS:The drug should not be used in pregnancy, and it should be used with caution in patients with hepatic, renal, or cardiovascular disease. The fatal dose has been reported as low as 7 to 10 mg.

Allopurinol:

➢ Allopurinol is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase.

Therapeutic uses: chronic hperuricemia

➢ 1- Primary hyperuricemia of gout

➢2- Secondry hyperuricemia: cancer chemotherapy, Lesch-Nyhan syndrome

➢ Chronic gout: > 2 attacks of acute gout/ year

Pharmacokinetics:

➢ Completely absorbed after oral administration.

➢ The primary metabolite is oxipurinol t ½ is up to 24 hours; the half-life of allopurinol is 2 hours.

➢ Inhibition of xanthine oxidase can be maintained with once-daily dosage (100mg/day) in the morning.

➢The drug and its active metabolite are excreted in the feces and urine.

Adverse effects:

hypersensitivity (skin rash with fever): may be fatal:

Stevens-Johnson syndrome (SJS)

- Headache, drowsiness, nausea, vomiting, diarehoea
- **Precautions:**
- 1- Acute gouty arthritis: never use
- 2- Allopurinol interferes with the metabolism of the anticancer agent 6-mercaptopurine and the immunosuppressant azathioprine, theophylline requiring a reduction in dosage of these drugs.

Uricosuric agents:

Probenecid and sulfinpyrazone:

- These drugs are weak organic acids that promote renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption (transpoter of reabsorption).

- Probenecid, a general inhibitor of the tubular secretion of organic acids,

- Sulfinpyrazone, a derivative of phenylbutazone,

Adverse effects:

Probenecid and sulfinpyrazone

- Gastric distress may force discontinuance of sulfinpyrazone.
- Probenecid blocks the tubular secretion of penicillin and is sometimes used to increase levels of the antibiotic. It also inhibits excretion of naproxen, ketoprofen, and indomethacin.
- **Precutions during probencid therapy????**

Pegloticase

- Pegloticase is a pegylated enzyme containing a recombinant form of mammalian uricase enzyme derived from a genetically modified strain of E. coli.
- Pegloticase lowers uric acid by promoting the oxidation of uric acid to allantoin, which is then renally excreted.
- Pegloticase was initially approved in the U.S. in 2010.
- T1/2: 12 days
- 8mg IVI/2 weeks
- In chronic gout: sever and complicated cases

Drugs contraindicated in gout

- These drugs may precipitate an acute attack of gout by blocking the renal tubular elimination of urates, thus, raising serum uric acid concentrations.

They include:

- Thiazide and loop diuretics.
- Salicylates in small dose.
- Acetazolamide.
- Pyrazinamide (antituberculous drug)

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Thank you