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).

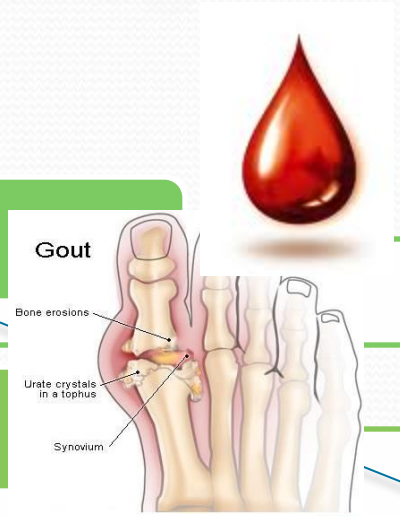
✓ Drugs used for the long-term management of gout (uricosuric agents & allopurinol)

✓ 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.

metabolism of DNA → (بطيء) purine

metabolism of purine → (بطيء) uric acid

إذًا هذا هو (end result of metabolism of purine) عند الإنسان و القرود

* لكن باقي (animals) يكون عندهم خطوة إضافية بتصير على uric acid وهي انه بجي انزيم اسمه (uricase) بحلل (uric acid) إلى (CO_2) و (H_2O) ويتخلّص منه لخارج الجسم

أكتر مكان بتأثر هو أصبع القدم الكبير

* هذا (uric acid) بترسب حوالين (joints) على شكل (mono sodium urate)

يكون مثل (الإبر)

* بتجي (macrophage) بتهاجم هذا الراسب ولكن لأنه مثل الإبر فبصير (rubture) مباشر للـ (macrophage) فبتطلع (cytokines) فبنتج عنها (arthritis)

يعتبر (uric acid) ← organic acid

لهيك اله آلية خاصة في (proximal convoluted tubule in Kidney)

عشان الجسم يتخلص منه

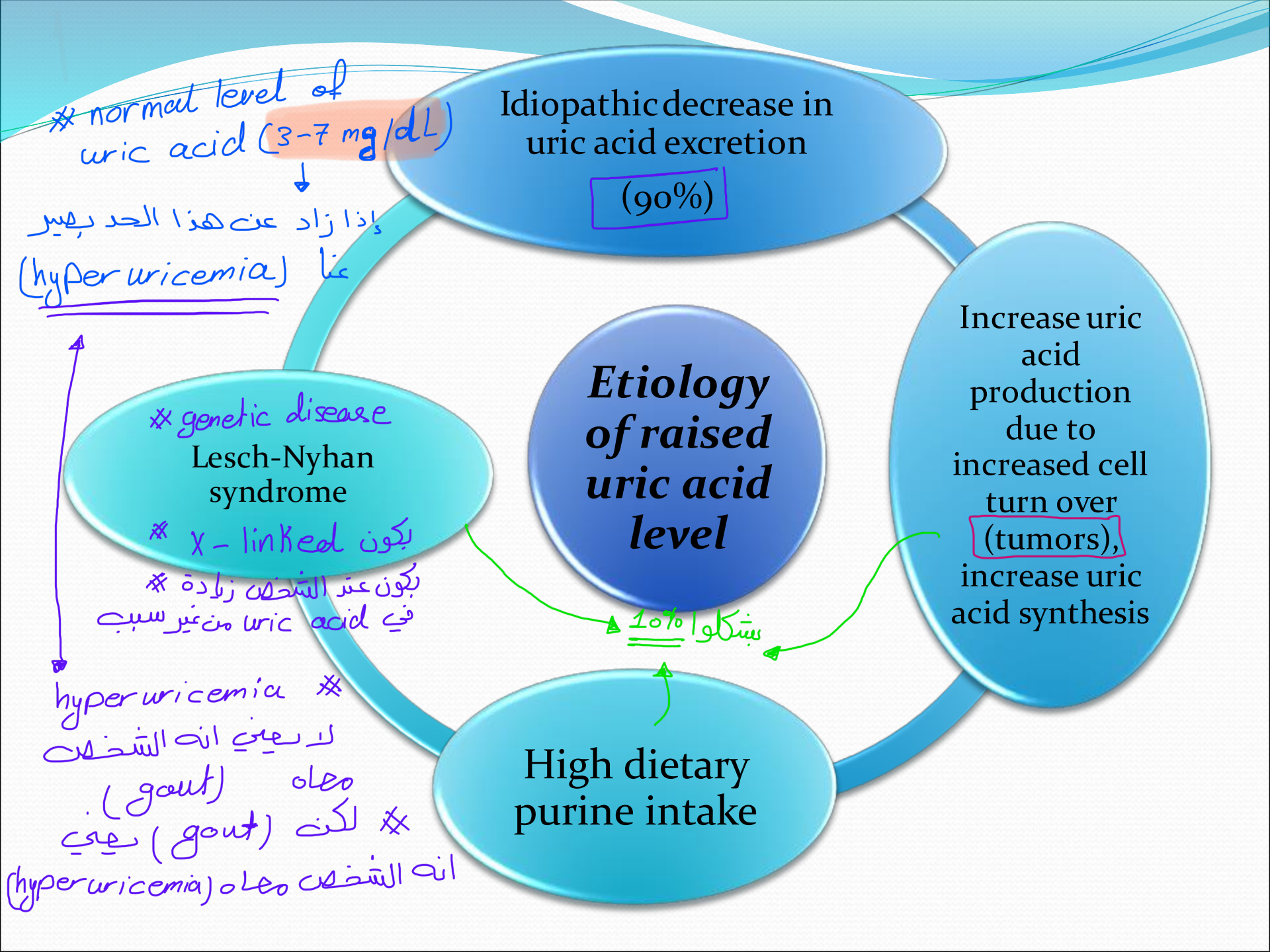
عنا (transporters of organic acid) بيتخلص من ((80%) of uric acid)

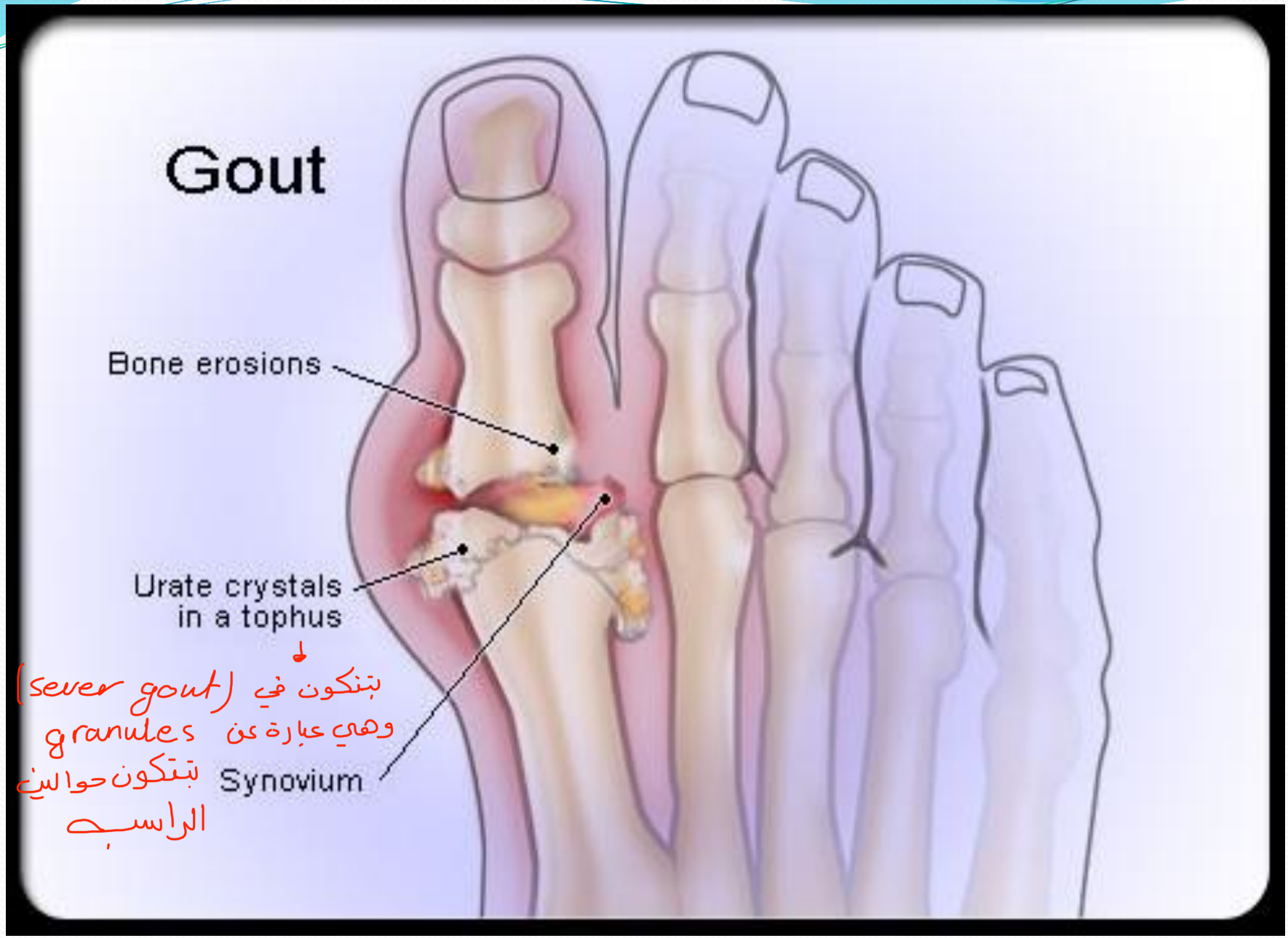
(20%) of uric acid ← بصير الهم (reabsorption) عن طريق transporters أخرى

لأنه (uric acid) اله فائدة في أجسامنا بأنه عبارة عن (most powerful anti-oxidant) اللي بتحمي الخلايا

فهو أحسن من vitamen(c)

لأنه vitamen(c) ما بتم تصنيعه في الجسم فبنحصل عليه من الغذاء


* normal level of uric acid (3-7 mg/dL)
إذا زاد عن هذا الحد يصير عنا (hyperuricemia)
Idiopathic decrease in uric acid excretion (90%)
Increase uric acid production due to increased cell turn over (tumors), increase uric acid synthesis
Etiology of raised uric acid level
* genetic disease
Lesch-Nyhan syndrome
* X - linked يكون
* يكون عند الشخص زيادة في uric acid من غير سبب
10% يشكلوا
hyperuricemia *
لا يعني انه الشخص عنده (gout).
* لكن (gout) يجي
انه الشخص عنده (hyperuricemia)
High dietary purine intake



(severe gout) بتتكون في granules وهي عبارة عن بتتكون حوالين الراسب

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. الطحال والفشت
  - 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.

(6) تعتبر saturation point هي هي النقطة اللي بيلش uric acid عندها تترسب في joint

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 الإنزيم
- 3- Increasing uric acid metabolism uricase enzyme

Anti-inflammatory drugs

In acute attack

- NSAIDs
- Cortecosteroids
- Colchicine

Drugs used for acute gout

مش مطلوب (dose) ※

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

هذه dose حفظ

Uricosurics (1000mg - 1500mg) → خلال اليوم

Probenecid - 0.5g/day: proben tab. 500mg (one tablet = 500 mg)

2-3 tab./day

Synthesis inhibitors:

Allopurinol: single daily dose: 100mg in the morning

Colchicine

لـ أول ما نكتشف المرض بنعطي المريض (one tablet) بعد ساعة بنعطيه (tablet) ثانية بعد (١٢ ساعة) بنعطيه (tablet) ثالثة بعدين بنصير كل (١٢ ساعة) نعطيه (tablet)

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.

أقوى واحد لهيك
بعطي نتيجة مؤكدة في العلاج

Low dose ← (Aspirin) لما يكون ←

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

(المقصود الأحبة)

transporter على (uric acid) لأنه رح يتقاتل مع
↳ (excreation) تبع

* لكن إذا كان (Aspirin) ← (High dose)
رح يروح يتقاتل مع (uric acid) على transporter
reabsorption تبع ← منشان High dose لهيك

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 (بعد ١٢ ساعة بظهر تأثيره) 2- Sever side effects
- FAD recommended to stop using colchicine, it is a second choice after cortecosteroids and NSAIDs. (يعني بستخدمه مع الحالات اللي ما بقدر أستعمل معها باقي الأدوية)

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. يطلع عن طريق (urin) عن طريق (kidney) وع عن طريق (feces) عن طريق (gall bladder)

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 → لازم يتم معالجتها حتى ماتتحول إلى (gout)

- 1- Primary hyperuricemia of gout
- 2- Secondry hyperuricemia: cancer chemotherapy, Lesch-Nyhan syndrome
- Chronic gout: > 2 attacks of acute gout/ year

أكتم من حياتي هذه المعلومة *

Allopurinol ← half life تبعه ساعتين

بس لما يصير الـ (metabolism) بتحول إلى (oxipurinol) ← وهذا الـ halflife (٢٤ ساعة) لهيك بنوخذ الدواء مرة وحدة باليوم

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. → عشان يبلش معالجة من أول اليوم بهي من أول ما يتم تصنيع (uric acid)
- 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:

urico suric

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).

transporter قليل (dose) عند رح يكون لـ of excreation

عالي (dose) عند

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

- Sulfinpyrazone, a derivative of phenylbutazone,

non-steroidal

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????**

بس شرط يكون low dose

* ممكن نستخدم (probenecid) مش للعلاج ← فبنعطيه مع (penicillin) عشان نقلل جرعة (penicillin) اللي بوخذها المريض وعشان نزيد الـ (half life) عن طريق انه بتفاعل مع transporter of excreation على penicillin

① ما بستخدمه مع (Acute arthritis)

② بخلي المريض يشرب ماء كتير عشان يطلع uric acid مع البول

③ ما بستخدم small dose of Aspirin

④ / Alkalization بعمل البول عشان يطلع uric acid

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