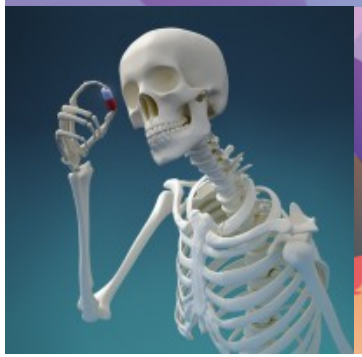
PHARMACOLOGY
433

King Saud University
College of Medicine
1st Year, 2nd Block

Drugs in Gout 5



MUSCULOSKELETAL BLOCK

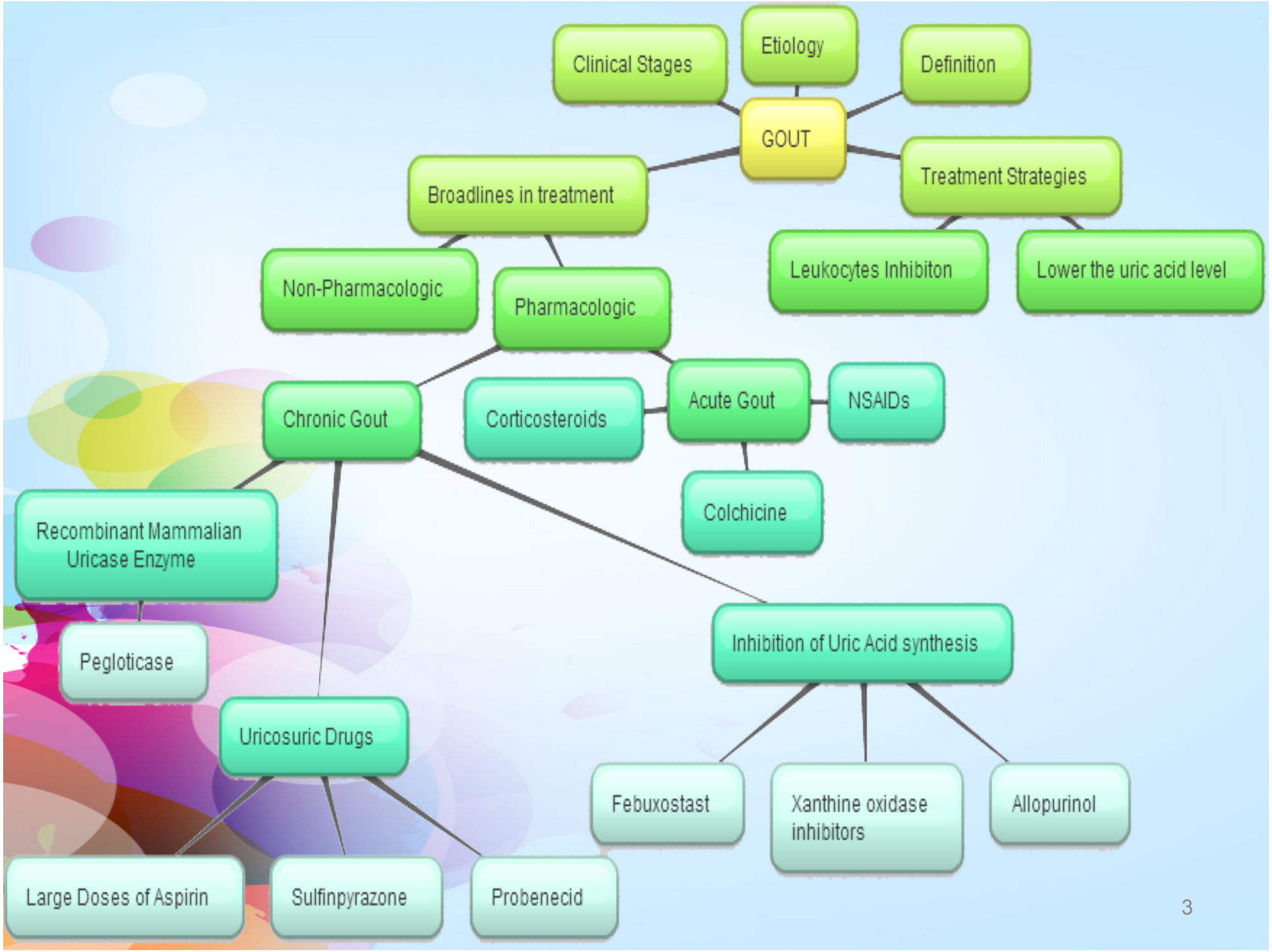
Objectives :

1	Define gout and describe its outlines of treatments.
2	Describe the treatment of gouty arthritis
3	Describe the mechanism of action, clinical uses and side effects of drugs used in acute attacks.
4	Classify and define each group of drugs used in chronic treatments.
5	Describe the mechanism of action, clinical uses and side effects of drugs used in chronic treatments.

Remember That :

*We've known before in Drugs Metabolism lecture that Xanthine oxidase enzyme (in the oxidase classification of the non-microsomal oxidation reactions of phase I) metabolizes the Xanthine, and if it wasn't working properly it will cause accumulation of uric acid which will cause Gout.

*Colchicine is a drug that targets for Tubulin protein in the microtubules, and it is used to treat Gout.


Clinical Stages
Etiology
Definition
GOUT
Broadlines in treatment
Treatment Strategies
Leukocytes Inhibiton
Lower the uric acid level
Non-Pharmacologic
Pharmacologic
Chronic Gout
Corticosteroids
Acute Gout
NSAIDs
Colchicine
Recombinant Mammalian Uricase Enzyme
Pegloticase
Inhibition of Uric Acid synthesis
Uricosuric Drugs
Febuxostast
Xanthine oxidase inhibitors
Allopurinol
Large Doses of Aspirin
Sulfinpyrazone
Probenecid

Characteristics of Gout

High blood uric acid level

- Due to excessive breakdown of Purine (nucleic acid) metabolism.

Urate stone in kidney

- Get treated by Xanthine Oxidase Inhibitors.

♂>♀

- Men are 3-4 times more at risk for gout than women. And it's rare before puberty

Manifestations : redness, swallowing and pain.

- It most commonly affects the big toe.

Etiology of Gout

"Renal Functions"

75%

Idiopathic renal secretion

- Idiopathic decrease in uric acid secretion due to increase net uric acid reabsorption.

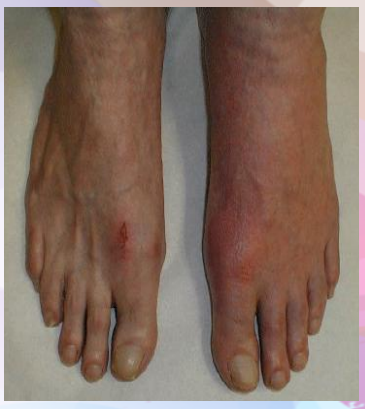
25%

Renal Dysfunction

- High dietary purine → intake purine nucleic acid.
- Increase uric acid production due to increased cell turn over (tumors).
- increase uric acid synthesis.
- Impaired uric acid excretion secondary to Thiazide diuretics, chronic Renal failure

Clinical stages of Gout

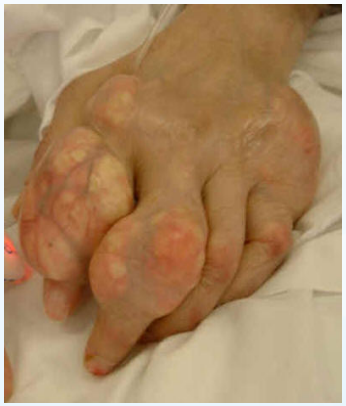
1. Asymptomatic stage :
   Urate levels rise in blood, but without producing any symptoms.



2. Acute stage : presented by fever and pain.

3. Inter-critical stage : symptom-free intervals between gout episodes.
   Most people\ have a second attack from 6 months-2 years.
   Others\ symptom-free for 5-10 years.

4. Chronic Stage : presented by numbness and pain, recurrent attacks after the inter-critical stage.



Strategies For Treatment

First therapeutic strategy :

Lowering the uric acid level

below the saturation point

(<6 mg/dL), thus preventing the deposition of urate crystals.

This can be done by:

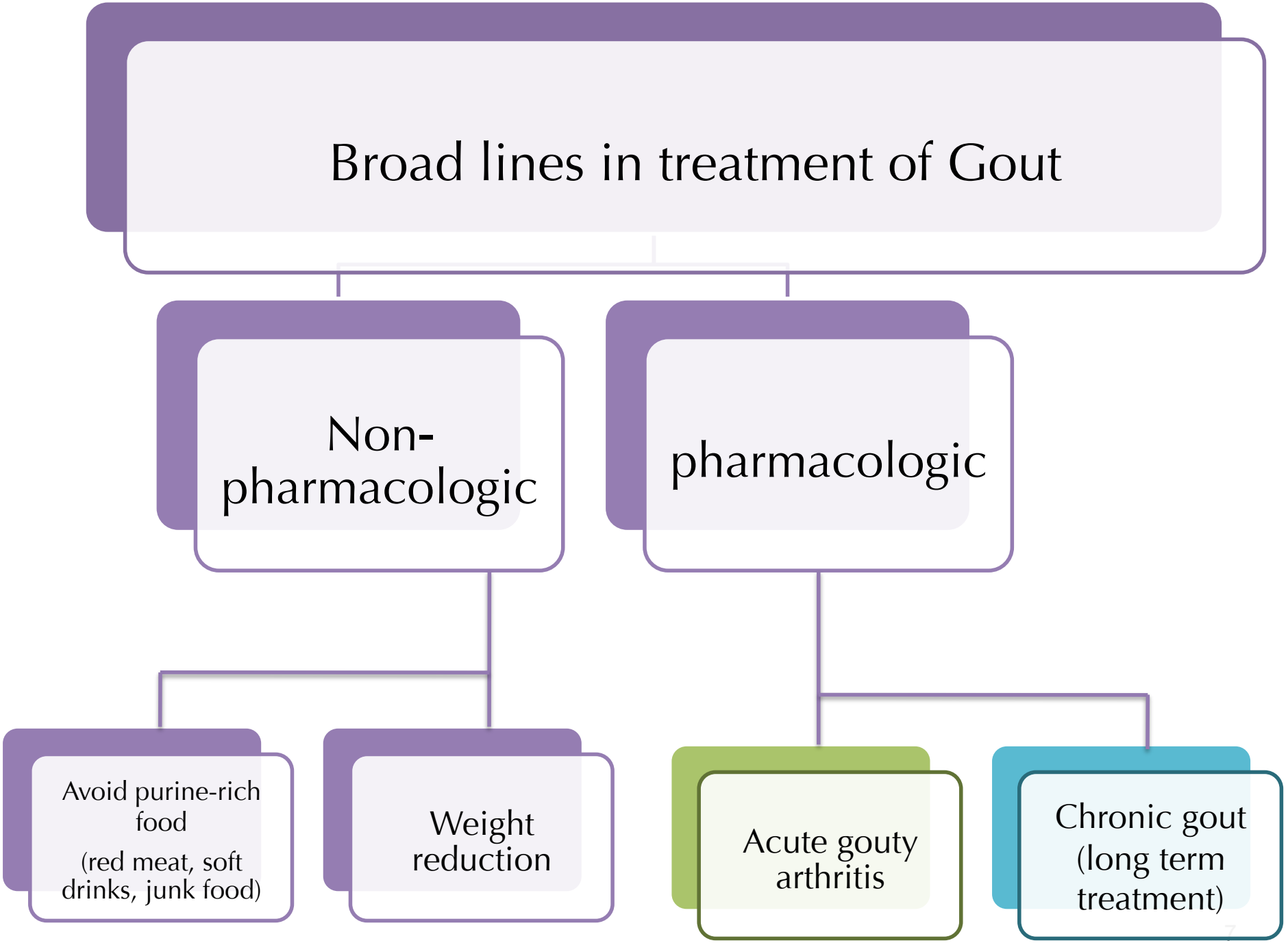
***Decreasing uric acid synthesis "by Allopurinal"**

Increasing uric acid excretion "by Probenecid or Sulfinpyrazone"

Second therapeutic strategy :

1-**Inhibiting leukocyte** entry into the affected joint.

2- Administration of analgesic & anti-inflammatory drugs. (NSAIDs)


Broad lines in treatment of Gout
Non-pharmacologic
pharmacologic
Avoid purine-rich food
(red meat, soft drinks, junk food)
Weight reduction
Acute gouty arthritis
Chronic gout (long term treatment)

Pharmacologic Treatment :

Acute gouty arthritis

NSAIDs

Both selective and non-selective
except Paracetamol and Aspirin.
"small doses of Aspirin cause acute gout whereas large doses treat chronic gout"

Colchicine

*Inhibit pain and inflammation.

*Inhibit urate crystal and phagocytosis, by:
decreasing the migration of granulocytes into the inflammatory area.

*treat acute attacks and prevent recurrent attacks with other drugs.
(drugs of choice for young, healthy adults without any other serious medical condition

usually taken orally at their highest safe dosage as long as gout symptoms persist and for three or four days after

low doses of NSAIDs may be used to prevent gout attacks, including in patients who are starting anti-hyperuricemic therapies)

Corticosteroids

Colchicine

Overview	Mechanism	pharmacokinetics
A plant alkaloid	Binds to tubulin (microtubular protein, as mentioned before that tubulin is a target for this drug) ➔ disrupt cellular function, such as migration of granulocytes to affected area	Given orally, followed by rapid absorption from the GI tract Reaches peak plasma levels within 2 hours
A Selective drug used only for the treatment of **acute gouty arthritis** and prophylaxis Prophylactic effect which reduces the frequency of acute attacks	Inhibits the synthesis and release of leukotrienes & interleukin-8 Decrease production of TNF-α by macrophages	Excreted unchanged in the faeces & urine. Also available combined with *Probenecid*
No analgesic effects	Blocks cell division by binding to mitotic spindles	Should be used with caution in patients with renal impairment. "should be avoided in patients with a creatinine clearance of less than 50 mL/min."

Colchicine

Theraputic uses	Adverse effects	Contraindications
The anti-inflammatory activity of colchicine is specific for acute gout, alleviating the pain within 12 hours.	1)**Diarrhea** is a common adverse effect. 2)Nausea. 3)Vomiting. 4)Abdominal cramps.	pregnancy
Colchicine is used as prophylaxis to prevent recurrent attacks in more than 80 percent of patients	If used chronically : 1)alopecia "hair loss" 2)bone marrow depression 3)peripheral neuritis 4)myopathy.	Precaution : Should be used with caution in hepatic, renal or cardiovascular diseases.
Treatment for Mediterranean Fever	*Affects fertility *Acute intoxication (large and over doses) : 1)Burning pain in throat 2)Bloody diarrhea 3)Shock 4)Hematuria "blood in urine" 5)CNS depression	

Pharmacologic Treatment :

Chronic gout

Inhibition of uric acid synthesis

- Xanthine oxidase inhibitors
  - Allopurinol
  - Febuxostat

Uricosuric drugs
(Increase the excretion of uric acid)

- Probenecid
- Sulfinpyrazone
- Large doses of Aspirin

Recombination mammalian uricase enzyme
(by genetic engineering)

Pegloticase:
*Uric acid specific enzyme, converts it into allantoin, given by I.V (peak decline uric acid level within 24-72).
Adverse effects: Infusion reactions (anaphylaxis), gout flare, nephrolithiasis, arthralgia, muscle spasm, headache.

Allopurinol

Mechanism of action

Inhibits the Xanthine oxidase enzyme, this enzyme's function :
Converts hypoxanthine → Xanthine → Uric acid.
So this drug inhibits the enzyme that makes the uric acid.

Pharmacokinetics

*Well absorbed orally (80%).
*Metabolized in the liver into Oxypurinol (which is responsible for its urate-lowering effect)
*Given once daily.
*Excreted through the kidneys.
*Dose adjustment is needed in renal impairment.

Therapeutic uses

*Treatment of primary hyperuricemia.
*Impaired renal functions.
*Uric acid stones or nephropathy.
*both gout & coronary artery disease
*In cancer patients receiving chemotherapy. "which causes tissue damage and release of purines, we prescribe allopurinol to reduce production of purines (Gout has nothing to do with this)"

Side effects

***Exacerbation of an acute attack of gout** "Due to the inhibition of the enzyme xanthine oxidase, mobilization of uric acid from its storage places (joints and tophi) to the blood causing augmentation of the inflammatory process and secondary attack of gout.
We can inhibit this by giving (colchicine or NSAIDs).
Tophi: nodules filled with uric acid crystals, it takes place in the joint or kidney or even on the skin"
***Skin rash.**
***Nausea and diarrhea.**
***fever and headache.**
***vasculitis, Thrombocytopenia and Epistaxis (nose bleeding).**

Drugs interactions

*With Warfarin and Dicumarol (anticoagulants): inhibits Allopurinol action, which will cause bleeding.
*With 6-mercaptopurine (anticancer drug): Allopurinol inhibits their metabolism so doses of anticancer must be reduced up to 75%
*With Ampicillin: Increases frequency of skin rash

Febuxostat

Overview

*Is a new oral non-purine Xanthine Oxidase XO inhibitor.

*Is structurally different from Allopurinol as it lacks purine ring.

*Selective and potent inhibitor of XO than allopurinol has no effect on other enzymes involved in purine or pyrimidine metabolism.

Pharmacokinetics

*Well absorbed orally (84%).
*Given once daily.
*Can be given with or without food.
*Metabolized in liver.
*Excreted in urine and feces.
*No dose adjustment is needed in renal impairment.
*Suitable than Allopurinol in patients with impaired renal function as no dose adjustment is required.

Therapeutic uses

*Used for treatment of chronic hyperuricemia in gout patients.

*Given to patients who do not tolerate Allopurinol.

Adverse effects

*Recurrent attacks of acute gout during the first few months of treatment.
*Increase level of liver enzymes (damages the liver).
*Nausea, Diarrhea.
*Headache.
*Numbness of arm or leg.

Uricosuric Drugs

(Probenecid, Sulfinpyrazone, Large doses of Aspirin)

Mechanism of action

Block the active transport sites of the proximal tubules causing:

Reduction of Uric acid re-absorption → **increase uric acid excretion.**

Clinical uses

Chronic gout

(Urine volume should be maintained at a high level, and urinary pH kept alkaline)

because the delivery of uric acid to the kidney will increase so, the crystallization or kidney stone may occur.

to prevent this is alkalization by of the drug.

Adverse effects

*Acute attack of gout
*Risk of uric acid stone
*GIT upset
*Allergic rash
*Probenecid causes nephrotic syndrome.
*Aplastic anemia "low WBC" (not a common ad. effect).

Drug interactions

Probenecid: prolong the action of some antibiotics like Penicillin and Cephalosporins. "so the antibiotic dose should be decreased"

Aspirin can prevent probenecid from being fully effective

Sulfinpyrazone: can aggravate peptic ulcer disease

Aspirin products can interfere with sulfinpyrazone's effects

Sulfinpyrazone can enhance the action of certain diabetes medicines

Contraindications

*History of urinary tract stones.
*Impaired renal function.
*Recent acute gout attack.
*Administration of low doses of Aspirin.

MCQS

1- Symptom-free interval between gout episodes is:
A-Chronic stage
B-Asymptomatic stage
C-Intercritical stage
D-Acute stage

2- Drugs that are used for acute gouty arthritis:

A-NSAIDs
B-Colchicine
C-Corticosteroid
D-All of the above

3- Colchicine is used for the treatment of:

A-Mediterranean Fever
B-Diarrhea
C-Vomiting
D-None of the above

4- Adverse effect of chronic use of colchicine:

A-Shock
B-Myopathy
C-Burning pain in the throat
D-Hematuria

5- Colchicine is contraindicated in:

A-Pregnancy
B-Cardiovascular disease
C-Renal disease
D-Hepatic disease.

1-C 2-D 3-A 4-B 5-A 6-B 7-D 8-C 9-B 10-A

6- Allopurinol is excreted through the:
A-Liver
B-Kidney
C-Sweat
D-Lungs

7- Allopurinol is used for treatment of hyperucemia secondary to other conditions such as:

A-Impaired renal function
B-Uric acid stones or nephropathy
C-In patients receiving cancer chemotherapy
D-All of the above

8-Less common side effects of allopurinol include

A-Fever
B-Vacuitis
C-Both A & B
D-Maculopopular skin rash

9- Numbers of arm or leg is one of the adverse effects of:

A-Probenecid
B-Febuxostat
C-Allopurinol
D-None of the above

10- Example of vricosuric drugs:

A-Probenecid
B-Ampicillin
C-Febuxostat
D-Colchicine

SUMMARY

Drug	Treatment	Mechanism of action	Pharmacokinetics	Adverse effects	Contraindications
NSAIDS except Paracetamol & Aspirin	Acute Gouty Arthritis	----------	Mostly orally, weak acids.	----------	----------
Colchicine	Acute Gouty Arthritis	Binds to tubulin as a first step	Given orally, rapidly absorbed.	-Diarrhea -Nausea -vomiting	Pregnancy
Corticosteroids	Acute gouty arthiritis	----------	----------	----------	----------
Allopurinol	*Chronic gout *Primary hyperuricemia	Inhibits Xanthine Oxidase enzyme	-Well absorbed orally -Given once daily	-Exacerbation of an acute attack of gout -Nausea -diarrhea	----------
Febuxostat	Chronic hyperuricemia in gout patients	----------	-Well absorbed orally -Given once daily	Increase liver enzymes.	----------
Probenecid	Chronic gout	Increase uric acid excretion	----------	Acute attack of gout -risk of uric acid stones. -Nephrotic syndrome	urinary tract stones
Pegloticase	chronic gout in adults	Converts uric acid to Allantoin	Given I.V.	Anaphylaxis	----------

PHARMACOLOGY 433

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We hope that we made this lecture easier for you

Good Luck !