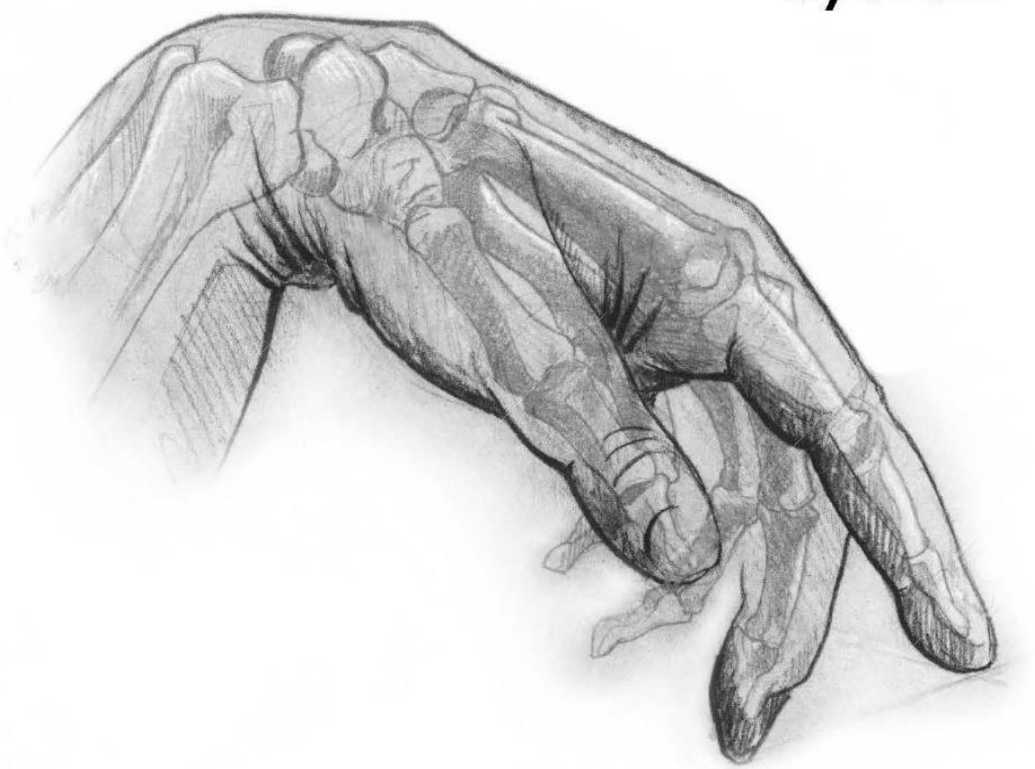
The

Musculoskeletal

System



Pharmacology

☑ Sheet ☐ Slide ☐ Handout

Number:	6
Subject:	NSAID,DMARDs & Gout
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Date: 0/00/0000

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In the first two lectures we talked about Aspirin, and now we'll continue talking about other NSAIDs.

Non-Selective COX Inhibitors

(They inhibit both, cyclooxygenase 1 and 2)

I. ***Naproxen*** and ***Ibuprofen***

- Their most common trade names are Nopain and Profen, respectively.
- These are similar to *aspirin*, in which they all are NSAID and are **Propionic acid** derivatives, and also they cause sensitivity of the gastrointestinal system, but to a lesser extent than aspirin, so we can substitute aspirin with these drugs because people can tolerate them.
- They also bind to serum proteins such as albumin, so we have to be careful regarding their drug-drug interactions.
- They are metabolized in the liver and then excreted from the kidneys.
- Their main side effect is **GI disturbances**, but rarely some **CNS** effects may appear, like headaches, tinnitus and dizziness. Some hearing loss cases were reported, too.
- In pregnancy these drugs are of **category C,** which means that they have been tested on animals and caused some teratogenic effects, but tests on humans haven't been done, so to use them we are going to weigh the (Benefit:Risk) ratio and decide whether to use them or not.

JUST READ IT

FDA Pharmaceutical Pregnancy Categories	
Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.

-These drugs inhibit prostaglandins, and as you know prostaglandins induce labor, so using these inhibitors for a long period can delay labor. *Naproxen* also causes premature closure of ductus arteriosus in the heart of the fetus (this happens in late pregnancy), so *Naproxen* (and also Ibuprofen) is considered as category **D** after the 30^{th} week of gestation, and before that it is of category **C**.

- Doses:
  Ibuprofen can be taken up to 3200mg a day, and it shouldn't exceed that. Usually, it's present as pills of 200mg, so you can take four pills daily, two for each dose.
  It is advised to take them with food, to avoid GI disturbances.
- These drugs are used to reduce pain in many cases, such as:
  Gout, rheumatoid arthritis, and many regular kinds of pain, like headaches and menstrual cycle pain (by affecting cytokines and reducing the contraction of the uterus, which will decrease the intensity of the period).

II. **Acetic acid derivatives**

Indomethacin

- What's special about this drug is that it enhances lithium toxicity by reducing its excretion by the kidneys, that is, its discharge in the urine.
  Note: Lithium is used to treat some psychiatric conditions, like bipolar disorder and depression. So Indomethacin is contraindicated in those cases because it will increase lithium's concentration in the blood other than the expected concentration that the doctor prescribed.
- It also increases plasma renin activity and aldosterone levels (by enhancing the RAS) and it also enhances the effects of vasopressin, so it's going to affect the cardiovascular system, increase the retention of sodium and potassium causing **hyperkalemia** and **hypernatremia**, then lead to **edema** and swelling because of fluid retention, and that will elevate the blood pressure (**hypertension**).
  Note: The RAS (renin-angiotensin system) is a hormone system that regulates blood pressure and fluid balance.

III. **Oxicam derivatives**

Piroxicam *and* ***Meloxicam***

- It was mentioned in one of the previous lectures that *Meloxicam* is considered as a selective inhibitor for COX2, it actually inhibits both 1 and 2, but has a preference for 2.
- It is used for osteoarthritis, rheumatoid arthritis (RA) and ankylosing spondylitis (a form of spinal arthritis).
  As you can notice, we reserve those drugs for severe inflammatory conditions because they have more **potency** in relation to the anti-inflammatory effect than other non-steroidal drugs.
- They have a very long half-life, so we only take the pill one time a day.

IV. **Fenamates**

- Like fenamic acid.
- One special thing about them is that they cause diarrhea as a side effect and it'd be especially evident and serious when there's an inflammation in the bowel. It also might, rarely, cause hemolytic anemia.

V. **Heteroaryl acetic acids**

- The famous drug of this family is ***Diclofenac*** (*Diclofenac sodium* is commercially known as Voltaren).
- It can be given orally, topically, intramuscularly, or as a suppository.
- It reduces fever and pain, so it's a very potent drug, more **potent** than *indomethacin* or *naproxen.*
- It's used in rheumatoid arthritis because it accumulate in the synovial fluid in the joint where we have the inflammation.
- Another form of *Diclofenac* is ***Diclofenac potassium*** (Voltfast), which has a faster onset of action, it's considered as category **C** in pregnancy.

Acetaminophen

- *Acetaminophen* is NOT a non-steroidal anti-inflammatory drug, but we put it with this family because it is a pain killer (**analgesic**).
  It's also an **antipyretic**, but does not have an anti-inflammatory effect.
- It reduces prostaglandins synthesis, but it does so centrally in the brain (CNS), and that is why it doesn't affect the inflammation in the musculoskeletal system.
- It also doesn't affect the platelets function because it acts centrally, not peripherally.
- It isn't considered as an opioid because it doesn't work on the receptors of the brain, but on the prostaglandins themselves and their synthesis in the CNS, so it won't cause addiction.
- Acetaminophen has many trade names, like Panadol, Panda, Paracetamol, Revanin... etc.
- It's widely used because, generally, it's a really safe drug, and that is why it's one of the most preferred drugs to use during pregnancy, it's of category **B**. Also it is used for little children (especially those with viral infections, since we wouldn't use Aspirin or NSAID as they cause Reye's syndrome).

Medications used for pain are categorized as the following:

1- Opioids (like Morphine, we'll take them in the CNS)
2- NSAID
3- Acetaminophen (paracetamol)
   So, Acetaminophen is a category by itself.

- Adverse effects:
  The maximum dose in a day is 4mg and any more than that would be dangerous because it's **hepatotoxic**. That is because during its metabolism a highly reactive metabolite will be produced, which is *A*cetyl*b*enzo*i*mino*q*uinone, and this will interact with the proteins in the body, mainly in the liver, and it will kill those cells it interacts with.
  So, there's an enzyme in our body called glutathione that removes the radicals from this metabolite, but if we take more than 4mg per day, glutathione won't be able to get rid of all the excessive metabolite and so it'll accumulate and lead to liver dysfunction or necrosis and damage its tissue.

  The symptoms of hepatic toxicity does not appear right away. Although the liver directly stops functioning, but it doesn't show until 24 hours later. It is good to give the patient an antidote (for that metabolite) called ***acetylcysteine*** in the first 8 hours, but if you wait more than 8 hours you may not be able to rescue the patient and may need to perform a liver transplant surgery.

  Acetaminophen toxicity is widely spread because it's a very commonly used drug and is available everywhere, so hospitals should always have *acetylcysteine*.
  Before, in the US they used to treat infants with ***Tylenol***, which is a very concentrated eye drop of *Acetaminophen*, and it was made this way so as not to give the baby a very big dose of *Tylenol* (just like 0.5mL), but later on it was withdrawn from the market because mothers were so ignorant and didn't read the instructions and would give the infant a high dose, which caused toxicity.

Cyclooxygenase 2 Inhibitors

Meloxicam, ***Rofecoxib***, and ***Celocoxib***

These drugs are selective for COX2, and targeting COX2, which isn't present in the stomach, reduces the GI irritation effects.

However, these drugs are associated with another side effect, and that is **cardiovascular thrombosis**. COX2 doesn't produce thromboxane (a mediator linked to COX1 that causes platelet aggregation), so we aren't affecting coagulation here and are increasing COX1 action, and so increasing thromboxane. This is why some people have reported incidents of strokes or emboli with the use of these drugs, and one them was actually withdrawn from the US market.

So, those drugs are used as pain killers, and we can also use them in anti-inflammatory conditions like rheumatoid arthritis (especially for patients whose GI tract becomes severely irritant when they use nonspecific COX inhibitors).

Disease-modifying anti-rheumatic drugs (DMARDs)

They are also used to treat rheumatoid arthritis (like NSAIDs).

They are used to:

- Reduce swelling and inflammation
- Decrease pain
- Improve function

The drugs in this group are further categorized into synthetic and biological.

In the biological group, monoclonal antibodies target certain cytokines or factors that mediate the inflammation.

<u>Synthetic DMARDS</u>:

Methotrexate (MTX)

- It's an anti-cancer drug, it inhibits dihydrofolate reductase (an enzyme that is required for the synthesis of thymidine and purine), so it inhibits cell propagation (replication and growth) and also inhibits one of the inflammatory pathways (by inhibiting the recruitment or activation of B-cells and T-cells)
- Side effects:
  - Bone marrow suppression (because it inhibits cell proliferation)
  - Dyspepsia (عسر هضم)

- Oral ulcers.
- Hepatotoxicity
- Pneumonitis
- Teratogenicity

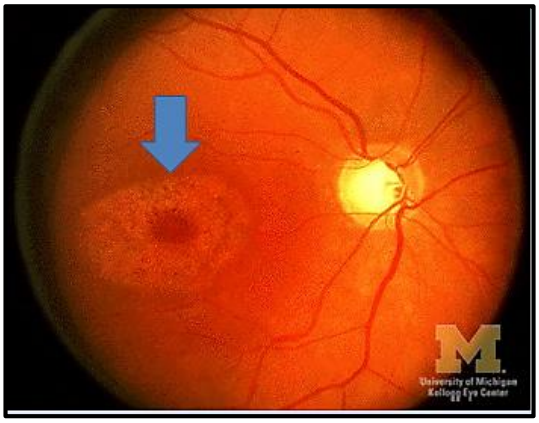
When using this drug we have to monitor the patient by making a full/complete blood count (FBC or CBC), and also monitor their creatinine levels because it can affect the function of the kidney.

Sulphasalazine

- It's usually a combination of two drugs Sulphapyridine + 5-aminosalicylic acid.
- It acts as a scavenger of free radicals (that stimulate the inflammatory pathway, like hydrogen peroxide and superoxide).
- This drug is eliminated from liver, so you have to be careful when you use it with patients who have liver dysfunction.
- Side effects:
  - Dyspepsia
  - Rashes
  - Bone marrow suppression

Chloroquine/Hydroxychloroquine

- Their exact mechanism of action is not really known, but they do interfere with antigen processing. When a foreign material enters the body, first the cell will recognize the antigen material then engulfment will happen, then the antigen will be processed so it will be expressed on the surface of these cells. So this drug is thought to affect this step, but it isn't known how it does so.
- It's used for mild conditions of rheumatoid arthritis.
  -Side effects: It can cause **retinal toxicity** (irreversible) and **corneal deposits.**



- Notice the opaque material.

You have to monitor the eyes during the use of this drug (every six months you should perform an ophthalmologic evaluation), if there is any effect then we have to stop the treatment because if we stop it early the effects can be reversed, but if there is an accumulations it can lead to blindness, or opacities that affect vision.

Leflunomide

- Competitive inhibitor of dihydrooratate dehydrogenase (an enzyme involved in the synthesis of pyrimidines).
- Because we have this enzyme, we worry about affecting the function or progression of RBCs (red blood cells).
- It reduces lymphocytes proliferation.
- It is given orally.
- Its half-life is long.
- It goes through the enterohepatic circulation, so it is subjected to the first pass effect.
- It interferes with the proliferation of the blood cells, so it is teratogenic, and that is why it should not be used in pregnancy. Also it can affect the ovum, so women should avoid getting pregnant until after two years of taking this drug.

Usually, we don't use one of these drugs solely, they are given as combinations of two or three of these disease modifying drugs.

- Triple Therapy:
  Methotrexate, ***Sulfasalazine***, and ***Hydroxychloroquine***
- Double Therapy: (Methotrexate in addition to any of these agents)
  Methotrexate & ***Leflunomide***
  Methotrexate & ***Sulfasalazine***
  Methotrexate & ***Hydroxychloroquine***

<u>Biological DMARDS:</u>

- Complex protein molecules that are made using recombinant DNA technology.
  They are either produced in prokaryotic or eukaryotic cells. We use bacteria (like E.coli) to produce our proteins. So, we'll bring a human gene and put it in the bacteria, transfecting this bacteria and then we'll multiply these bacteria, and so it'll start encoding (replicating) the gene we put in it.

  So if we want to make insulin for example, unlike in the past where we used to get insulin from animals, nowadays we make human insulin by this technology, and this is how we make those proteins as well.

Note: Transfection is the process of inserting a genetic material (like DNA or RNA) into cells.

There are different families in this group. They mainly target a protein called TNFα (alpha).

We have soluble TNFα receptors and other types of receptors that are present on the cell membrane, so the soluble type is going to stay in the blood stream and initiate certain inflammatory reactions, while the membrane bound TNFα is going to bind to its receptor in any kind of cells and cause activation of the inflammatory pathway.

What TNFα does is affecting certain cells in the body, and here we're concerned about how it'll affect the osteoclasts, synoviocytes and the inflammatory cells, which are all associated and affected by rheumatoid arthritis and osteoarthritis.

So, once TNFα activates the **osteoclast** it causes bone resorption, once it activates **synoviocytes** it will cause joint inflammation, and with **chondrocytes** it's going to cause cartilage degradation.

By that we can conclude that if we inhibit TNFα by different drugs, we will inhibit all of these effects.

Those drugs are:

- **Monoclonal Antibodies that target TNFα (*Infliximab*, *Adalimumab*):**
  They can also be used to treat other autoimmune conditions.
- **Soluble Receptor Decoy for TNFα (*Etanercept*):**
  These are peptides that are very similar to the structure of TNFα, which is a protein, so we take part of it that is not going to activate the receptor but would act as a decoy (like a camouflage), so it'll deceive/trick the receptor by binding to it without causing activation of the inflammatory pathway.
- **Receptor Antagonist to IL-1 (*Anakinra*):**
  Another way to modulate TNFα action, we know that TNFα can stimulate the production of IL-1, so we have receptor antagonist to IL-1.
- **Monoclonal Antibody to CD-20 (*Rituximab*):**
  Another factor that is expressed on the inflammatory cells is CD-20, so we have monoclonal antibody against CD-20.

- Side effects:
  By inhibiting the inflammatory pathway, we're basically reducing the response of the body against pathogens. So, if an infection occurs, the adequate inflammatory pathway that normally responds won't be ready to do that, and that is why patients using these drugs will be more prone to infections, such as common **bacterial infections** (like tonsillitis, streptococcal or staphylococcal infections), or an **opportunistic infection** (like tuberculosis). Sometimes it can lead to **malignancy** because we are affecting the immune system. (Next year we will know how cancer can be considered as an immune disease as the body will stop seeing the cancer cells and it will recognize them as one of its own cells, and so it won't terminate its growth).

Gout

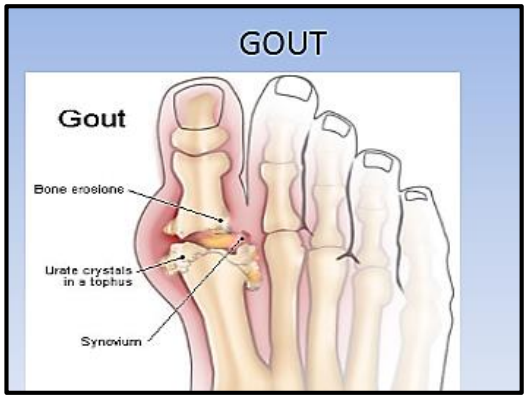
The main problems of gout are the inflammation and accumulation of uric acid crystals.

To treat this problem we have two alternatives:

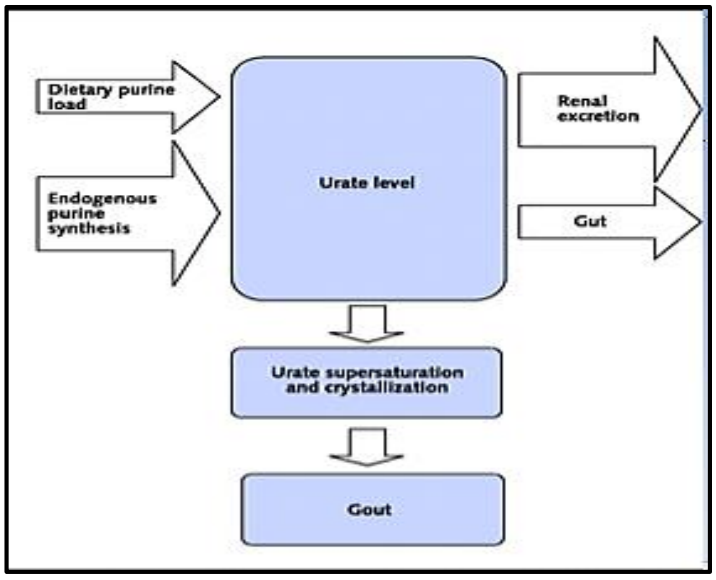
1- To reduce the inflammation:
   By the use of anti-inflammatory drugs and non-steroidal anti-inflammatory drugs.
2- To remove the accumulation of uric acid:
   Uric acid can be synthesized in the body, so we can stop the enzyme that makes up uric acid, or we can increase the excretion of uric acid.

Note (based on a student's question):

Colchicine is a drug that inhibits microtubules formation (that are necessary for the function of macrophages), and one of the things that aid up in causing gout is the recruitment of macrophages to the site of inflammation, so we can stop this recruitment if we inhibit microtubules formation by using colchicine.



In gout we have a problem with the small joints, and there will be swelling and inflammation in the affected area (usually the toes, sometimes in the elbow, or fingers). It can be very painful and also it will cosmetically affect the patient and may alter the function of these organs, especially the foot.



-This is the way that we're going to approach gout: we have high levels of urate, then we'll have urate crystals deposition.

So, to solve this we can:

- Increase renal excretion.
- Increase gut excretion.
- Stop the synthesis of urate.

We want to rapidly end up the acute gouty episodes (flares) and prevent them from happening again later on. And that is why when we have an <u>acute gouty flare</u> we use:

1- Non-steroidal anti-inflammatory drugs, to reduce the pain (***NSAIDs***)
2- ***Colchicine***, to decrease inflammation.
3- ***Corticosteroids***, which are a big part of the therapy of all inflammatory conditions (they work by inhibiting the central pathway, inhibiting phospholipase and the production of arachidonic acid)

Colchicine

- It prevents the migration of neutrophils (macrophages) to joints (inflammation site).
- It also reduces pain, swelling, and inflammation because we are inhibiting the recruitment of the inflammatory cells and are inhibiting the production of cytokines (the interleukin) that are producing the pain in these patients.
- Usually, the pain will stop after using colchicine –in the treatment of acute conditions- for 12 hours or sometimes up to 48 hours.
- Side effects:
  Nausea, vomiting, diarrhea and rash.
  These are very common side effects that most drugs have.

Note: Here the doctor clarified that she will not be asking us in the exam about the common side effects, but about the important landmarks of each drug.

- Colchicine is under research to be used in the treatment of cancer, why? Because it acts by preventing the microtubule formation (parts of the mitotic spindle that are going to separate two chromatids from each other), so by that we will be stopping the division of cells and thus inhibiting cell mitosis. Of course, by that it can affect the replication of other tissues in the body.

Now, to prevent the recurrence of gouty flares we can:

1- Eliminate the uric acid (urate crystals) which are present in the joint.
To do that we can interfere with the renal excretion by **uricosuric** drugs that help us eliminate uric acid through the urine, example; ***probenecid***.

2- Inhibit the enzymes that synthesize urate, and so reduce its amount in the body.
Urate is a product of pyrimidine and purine synthesis. Xanthine oxidase is an enzyme that is involved in this pathway as it converts hypoxanthine to xanthine which is further converted to uric acid.
So, we use drugs that inhibit xanthine oxidase, like Allopurinol.

3- Decrease the amount of consumption of foods that will aid up in uric acid formation (mainly proteins), so people are advised to decrease their meat consumption (for example) to diminish their dietary intake of uric acid, and so decrease its crystallization and deposition in the body.

Summary

To treat rheumatoid arthritis, or osteoid arthritis we have different options:

- ***NSAIDs***
- ***DMARDs***, again these are also used to treat other autoimmune conditions, but they are good for the treatment of osteoarthritis because we are inhibiting inflammation by decreasing mainly TNFα production or its cytokines (interleukins).
- ***Glucocorticoids***.

Note: Leishmaniasis is not required for the exam.

-END OF TEXT

This sheet has been corrected and edited