Final Pharmacology Summary

Drug	MOA	Uses	Side Effects	Notes
Steroid, glucocorticoid, corticosteroid	Phospholipase inhibitor	-Useful as anti-inflammatory agents		
Leukotriene modifiers: montelukast & zafirlukast	Inhibition of leukotriene(C_2/D_2/E_4) production	-Treatment of asthma		-They are receptor antagonists -They are very expensive
Colchicine	Binds to tubulin causing depolymerization of microtubules → disrupts migration of phagocyte into the affected area	-Treatment of gout -Treatment of cancer: (causes disruption of mitotic spindle)		
Zileuton	Inhibitor of lipoxygenase enzyme	-Treatment of asthma		-Expensive - It is not our first drug of choice in treating asthma, because it inhibits the whole LT synthesis pathway.
Aspirin (the synthetic form of salicylic acid)	-**irreversible** inhibitor of both isoforms (COX-1 and COX-2) of cyclooxygenase enzymes.	***Anti-inflammatory (dose higher than 325mg)** -Diminishes formation of prostaglandins that mediate inflammation. -first line of therapy for rheumatoid arthritis. -Decreases the pain process associated with inflammatory diseases like rheumatism -For treatment of gout, rheumatic fever and osteoarthritis. ***Anti-pyretic:** -inhibition of prostaglandins E2 in the CNS, in the thermoregulatory center in the hypothalamus. -It rapidly lowers the body temperature by increasing heat dissipation as a result of peripheral vasodilation and sweating (no effect on normal temperature)	***Respiratory system:** -in therapeutic doses, uncouples oxidative phosphorylation, → Elevation of Co_2 level → hyperventilation -At higher doses, it effects directly in on the respiratory center in the medulla → hyperventilation and respiratory alkalosis. -At toxic levels, paralysis in the respiratory muscles → acidosis. ***GI system:** - Prevents PGE2 synthesis in stomach **(**has a protective role by inducing a protective mucous layer in both the stomach and small intestine), →less mucous and increased gastric acid secretion.	-The prototype of NSAIDs. - it gets hydrolyzed by esterases into salicylic acid. -15% of patients show intolerance/allergic to aspirin. -It does not treat the cause; it treats the sign and symptoms of inflammation.. - Unlike all NSAIDs, Aspirin doesn't cause Interstitial nephritis. -After administration of aspirin, it gets absorbed in the un-ionized form from the stomach and the small intestine. - Binds to plasma **proteins** -Rectal absorption of the salicylate is **slow** and unreliable, but it's a useful route for administration to **vomiting children.**

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Drug	MOA	Uses	Side Effects	Notes
Aspirin (cont.)		***Analgesic effect:** -Decreases prostaglandin synthesis → prevention ov the sensitization of pain receptors at both mechanical and chemical stimuli. -it has some CNS effect on the inhibition of pain by decreasing pain stimuli at the sub-cortical spaces. -to relieve pain in **headache, arthralgia and myalgia.** ***Cardiovascular applications:** - inhibit platelet aggregation. -low doses (**81mg** prophylactically) to: Reduce the risk of recurring transient ischemic attacks (TIAs), stroke, reduce the risk of acute myocardial infection, angina and other thrombotic disorder. - **Patent ductus arteriosus** (the ductus arteriosus fails to close after birth) we give **indomethacin** or **ibuprofen**, which will stimulate closure of ductus arteriosus after birth. -Topically to treat corns and warts.	- GI irritation & increased susceptibility to a peptic ulcer. ***Platelet:** -<u>At low doses</u> it inhibits thromboxane (TXA2) production → decreasing platelet aggregation (will stay in the whole life cycle of the platelet because they do not have nuclei). *** Kidney:** -NSAIDs are nephrotoxic - inhibition of PGs their will cause vasoconstriction - Decreased synthesis of PG → retention of sodium and water → edema and hyperkalemia in some patients. - It causes REYE'S SYNDROME in children below 15 incase of a viral infection. **Toxicity (salicylism):** -Nausea, vomiting, hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).	**Drug interactions:** - Due to binding to plasma proteins, it could displace warfarin, phenytoin or valproic acid, resulting in higher free concentrations of the other agent. - We cannot use aspirin with **ketorolac** → increased risk of GI bleeding and platelet aggregation inhibition. **-Reye's syndrome:** affect children or teenagers below the age of 15 years old, if they take aspirin to treat pain or fever while they have a viral infection. -feature: rash, vomiting, liver damage and hypoglycemia. -The drug of choice to treat fever in this situation is **acetaminophen (paracetamol)** -Aspirin is categorized as pregnancy category C EXCEPT in the third trimester, where it is classified as category D → because it will close **ductus arteriosus.** - Ingestion of 10g of aspirin can cause death in children.
Propionic acid derivative	They are **reversible** inhibitors of cyclooxygenases	-Anti-inflammatory -Analgesic -Antipyretic activity	- GI effects are generally less intense than those of aspirin, although they have the GI irritation side effect. -ranging from dyspepsia to bleeding. **-CNS**: (headache, tinnitus, and dizziness).	- Include: **ibuprofen**, **naproxen**, **fenoprofe**, **ketoprofen**, **flurbiprofen.** -Bind to plasma proteins (almost totally bound to serum albumin). - Undergo hepatic metabolism, excreted by the kidney.

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Drug	MOA	Uses	Side Effects	Notes
Naproxen and ibuprofen			-Increase the risk of cardiovascular thrombotic event (higher affinity towards COX-2 inhibition) -MI -Stroke -Increase risk of GI bleeding	-They are propionic acid derivative. - **Pregnancy:** category C (1st and 2nd trimester), category D (3rd trimester) - take with food or with water to avoid GI effect. -
Acetic acid derivative		-They have high anti-inflammatory properties, so they are used to treat **rheumatism**, **gouty arthritis**, **spondylitis**.	-They have higher toxicity than other NSAIDs.	-they include: **indomethacin**, **sulindac**, and **etodolac** - **Etodolac** has effects like those of the other NSAIDs. - The adverse reactions caused by **sulindac** are less severe than, those in indomethacin
Indomethacin	-Non-selective COX inhibitor -Inhibits phospholipases A & C -Reduce neutrophil migration -Decrease T and B cell proliferation	-Juvenile rheumatoid arthritis -gout -ankylosing spondylitis - patent ductus arteriosus -Inhibit inflammation after certain ophthalmic surgeries (conjunctival inflammation) -Oral rinse form → reduce gingival inflammation	-Highly toxic -GI bleeding -CNS toxicities -Mental confusion -Diarrhea -Frontal headache.	
Oxicam derivatives (Piroxicam & mMeloxicam)	-Inhibit both isoform of COX enzyme, meloxicam has preferential binding for COX-2	-Rheumatoid arthritis -ankylosing spondylitis -osteoarthritis	-GI side effects: -Meloxicam has less GI side effects than piroxicam.	-Long half-lives -Excreted in the urine
Fenamates		- They are used for menstrual pain.	-Diarrhea -Hemolytic anemia	-**MEFENAMIC ACID** is a fenamate derivative - they are not preferential to be used as the first choice for the treatment of inflammatory conditions.

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Drug	MOA	Uses	Side Effects	Notes
Heteroayyl acetic acid (diclofenac, tolmetin, and ketorolac)	They are COX-1 inhibitors	-rheumatoid arthritis -osteoarthritis	-- **Diclofenac** accumulates in synovial fluid	**- Diclofenac** is more potent than **indomethacin** or **naproxen** **- Ophthalmic** preparation is also available -Primary route of excretion is the kidney
Diclofenac sodium & Diclofenac potassium			**- Pregnancy:** Category C	-**Diclofenac potassium** has quicker absorption which results in a quicker response than Diclofenac sodium.
Acetaminophen (Paracetamol)	-Weak PGs inhibitor - Mainly works in the **CNS** (Modules the endogenous cannabinoid system)	-It is an analgesic -antipyretic **-but** has v. **WEAK** anti-inflammatory activity -The analgesic/antipyretic of choice for children with viral infections or chickenpox	-Normal dose: free of any sig. side effects. -Large doses: -**Hepatotoxicity:** causes death of hepatocytes (hepatic necrosis) -Rarely: renal necrosis & hypoglycemia coma -Overdose if not treated quickly within 12 hours → may cause death -Antidote for toxicity → N-acetylcysteine	- It is the safest drug to be used in pregnancy (A) - Not: anti-inflammatory, Platelets inhibitor, Ulcerogenic (GI irritation), Teratogenic. - A substrate for cytochrome p450 - N-acetylbenzoimin-oquinone is one of acetaminophen metabolites, highly reactive and potentially dangerous and toxic, it reacts with glutathione forming a nontoxic substance. - Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen.
Celocoxib	COX2- inhibitor	-Anti-inflammatory	-May increase the incidence of edema and hypertension. -Higher incidence of cardiovascular thrombotic events (cardiotoxicity). -Causes infertility	-Rofecoxib is also COX2 selective but was WITHRDRAWN. -Do not affect platelet function. -Less gastro irritant (half of COX2-non selective drugs).
GOUT				
NSAIDs (Indomethacin Naproxen Ibuprofen, Sulindac, Ketoprofen)	-Anti-inflammatory (MOA was mentioned before)	-Used in the first (1-10) days.		-NSAIDs are used initially along with steroids for 10 days, followed by prolonged treatment with low doses of colchicine then allopurinol (refer to slide 49 please)

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Drug	MOA	Uses	Side Effects	Notes
Colchicine	-Inhibits microtubule polymerization by binding to tubulin → inhibits mitosis (replication).	-Reduces inflammatory response to deposited crystals (anti-inflammatory) -Diminishes PMN phagocytosis of crystals -Blocks cellular response to deposited crystals -Used after the initial treatment with NSAIDs & steroids	-Toxic drug → stops replication of cells -Gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain) -Hematologic (agranulocytosis, aplastic anemia, thrombocytopenia) -Muscular weakness	-Not an analgesic -Does not affect renal excretion of uric acid nor plasma solubility of uric acid -Neither raises nor lowers serum uric acid -High dose → treatment of gouty arthritis -Low dose → prevention of recurrent gouty arthritis -Adverse effects are dose-related & are more common when patient has renal or hepatic disease
Allopurinol	Inhibitor of xanthine oxidase → effectively blocks formation of uric acid	-Management of hyperuricemia of gout -Management of hyperuricemia associated with chemotherapy -Prevention of recurrent calcium oxalate kidney stones -Can't be used in pts with renal disease	*Common reactions: -Diarrhea, nausea, abnormal liver tests -Acute attacks of gout -Rash *Serious reactions: -Hypersensitivity: Starts with f ever, rash → toxic epidermal necrolysis (SJS) → death -hepatotoxicity, marrow suppression -Vasculitis -Drug interactions (ampicillin, thiazides, mercaptopurine, azathioprine)	-Pregnancy Category C -Hypersensitivity is more common with impaired renal function -Not given as an initial treatment because it might cause acute attacks of gout, usually given after colchicine (after 10 days of initial treatment).
Febuxostat	Oral xanthine oxidase inhibitor	-Given incase of allergy to allopurinol or a renal disease	-Minimal adverse events -High dose could lead to cardiovascular toxicity & GI irritation	-Not used right on because it is expensive -Chemically distinct from allopurinol
PEG-uricase	Transforms uric acid into a more soluble form	-Treatment of resistant gout -Speeds resolution of tophi		-PEG-conjugate of recombinant porcine uricase (from pigs) -We don't have uricase in our body (used to in the past) -PEG → a chemical modification that prolongs the half life of the enzyme

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Drug	MOA	Uses	Side Effects	Notes
Probenecid (Uricosuric therapy)	Blocks tubular reabsorption of uric acid & enhances urine uric acid excretion → increases urine uric acid level → decreases serum uric acid level		-Increases risk of nephrolithiasis -Not used in patients with renal disease -Elevated urine uric acid level -Frequent, but mild, side effects	-Moderately effective -Less effective in elderly patients (impaired renal function)
Skeletal Muscle Relaxants				
Neuromuscular blockers	Depolarizing and non-depolarizing drugs	-Skeletal muscle paralysis -Used in surgical procedures and intensive care units (ICU) → ease the intubation process during anesthesia or in the ICU. -Reduced muscle tone will make it easier to dissect through the muscles and perform the surgery -Increased the safety of anesthesia because less anesthetic is required to produce muscle relaxation. -Respiratory paralysis → artificial ventilation necessary before anesthesia.	***Cardivascular Effects:** – Mediated by autonomic or histamine receptors. – Both sympathetic and parasympathetic ganglia and muscarinic receptors in the heart can be stimulated → cause hypotension, can be attenuated by antihistamines. ***Hyperkalemia:** -Patients with burns, nerve damage, or neuromuscular disease, head injury, and other trauma → Can result in cardiac arrest. ***Increased Intraocular Pressure:** – Due to tonic contraction of myofibrils or transient dilation of ocular choroidal blood vessels. *** Increased Intragastric Pressure:** – In obese, heavily muscled, diabetics, traumatic patients, fasiculations of succinylcholine can cause regurgitation and aspiration of gastric contents. ***Muscle Pain**: – Due to unsynchronized contractions of adjacent muscle fibers just before the onset of paralysis.	-Structure of all neuromuscular blockers: One or two quaternary nitrogen's, double acetylcholine molecules linked end to end → concealed, bulky semi- rigid ring systems (highly polar). -Must be given parenterally (IV). **-Drug interactions:** 1. Anesthetics (Mostly with isoflurane, and least with nitrous oxide): May be due to a central action, increased muscle blood flow → Can cause Malignant Hyperthermia 2. Antibiotics: Depress release of acetylcholine due to blockade of specific P-type of calcium channels. 3. Local anesthetics and antiarrhythmic Drugs 4. Other Neuromuscular Blockers. -Incase of intoxication: the antidote is reversible acetylcholinesterase inhibitors such as neostigmine, pyridostigmine, or edrophonium

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Drug	MOA	Uses	Side Effects	Notes
-Non-depolarizing drugs (Tubocurarine, Mivacurium, Atracurium…)	-Compete with acetylcholine at the nicotinic receptor sites at the NMJ. -In high doses, can enter the pore of the ion channel to cause a more intense blockade. -Can also block prejunctional sodium channels to interfere with the mobilization of acetylcholine at the nerve ending	Causes motor weakness followed by flaccidity. -Starts with small muscles, large muscles are more resistant to blockade and recover more rapidly. Diaphragm is last to be paralysed. -Effects lasts for 45-60 minutes.		-Tubocurarine is the prototype. -Onset of effect is very rapid. -Excreted in the kidney or metabolized by the liver. -Tubocurarine, mivacurium, pancuronium, metocurine, and doxacurium are excreted in the urine unchanged. While, atracurium is spontaneously degraded in the plasma by ester hydrolysis (HOFMAN ELIMINATION). -Mivacurium is metabolized by cholinesterases - Rocuronium and Vecuronium get metabolized by the liver.
Depolarizing drugs (succinyl-choline)	1. Phase I(depolarizing): succinycholine reacts with nicotinic receptors → cause depolarization of the motor end plate → spread to adjacent membranes → contractions of muscle motor units. –Can enter the channel to produce a prolonged "flickering" of the ion conductance. -The depolarized membranes remain depolarized and unresponsive to subsequent impulses causing flaccid paralysis (augmented by cholinesterse inhibitors)	-Action stars by transient muscle fasiculations over the chest and abdomen within 30 seconds. -Paralysis develops rapidly (within 90 seconds), the arm, neck, and leg muscles followed by the respiratory muscles. -Blockade lasts less than 10 minutes.	- Malignant Hyperthermia if combined with an anesthetic. -Apnea → delayed or prolonged apnea due to paralysis of the diaphragm.	-Extremely short duration (5-10 minutes). - Metabolized by cholinesterases in the plasma and liver. -Only a small percentage reaches the neuromuscular junction. - Some patients have a genetically abnormal variant of plasma cholinesterase, this is measured by dibucaine number. -Dibucaine Number: is a measure of the ability of a patient to metabolize succinylcholine.

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Drug	MOA	Uses	Side Effects	Notes
Depolarizing drugs (Cont.)	2. Phase II Block (desensitizing): with continued exposure, depolarization decreases → the membrane becomes repolarized and can not be depolarized again because it is desensitized. This may be due to blockade of ion channel, which might be more important than the action of the agonist at the receptor, i. e. the channels behave as if they are in a prolonged closed state. -This phase is reversed by acetylcholinesterse inhibitors.			
Diazepam	Acts at $GABA_A$ receptors in the CNS.	-Used in patients with muscle spasm of almost any origin (including local muscle trauma).	-Sedative (produces sedation at the doses required to reduce muscle tone) -Tolerance & dependence	-A spasmolytic drug -Benzodiazepines facilitate the action of GABA in the central nervous system.
Baclofen	Acts at $GABA_B$ receptors, resulting in hyperpolarization and presynaptic inhibition through reducing calcium influx – Can also reduce spasticity by inhibiting release of substance P in the spinal cord	-Treatment of muscle spams – Can reduce craving in alcoholics and in migraine.	--Less sedative, but can cause drowsiness.	-A spasmolytic drug -Can be given intrathecally

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Drug	MOA	Uses	Side Effects	Notes
Tizanidine	Alpha 2 agonist	-Used to treat muscle spasticity due to spinal cord injury or multiple sclerosis -Antihypertensive (lowers blood pressure)	-Side effects: dizziness, weakness, depression, hallucinations – dry mouth	-A spasmolytic drug -Related to clonidine
Gabapentin		-An antiepileptic Glycine		-A spasmolytic drug
Dantrolene	-Interferes with excitation-contraction coupling in the muscle fibers by interfering with the release of activator calcium by binding with the ryanodine receptor (RyR) channel of the sarcoplasmic reticulum (inhibits release of calcium)	-Used for treatment of Malignant Hyperthermia induced by succinylcholine and general anesthetics (refer to slides for more details)	-Can cause weakness, sedation, and hepatitis.	-A direct-acting drug -Related to phenytoin, an antiepileptic
Botulinum Toxin	Inhibits acetylcholine release	-Used for opthalmic purposes -Local muscle spasms -In the cosmetic treatment of facial wrinkles around the eyes and mouth -For generalized spastic disorders like cerebral palsy	-Food poisoning caused by this toxin can result, within 12-36 hours, in diplopia, dysphagia, dysarthria, and dyspnea.	-Produced by Botulinum bacteria

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