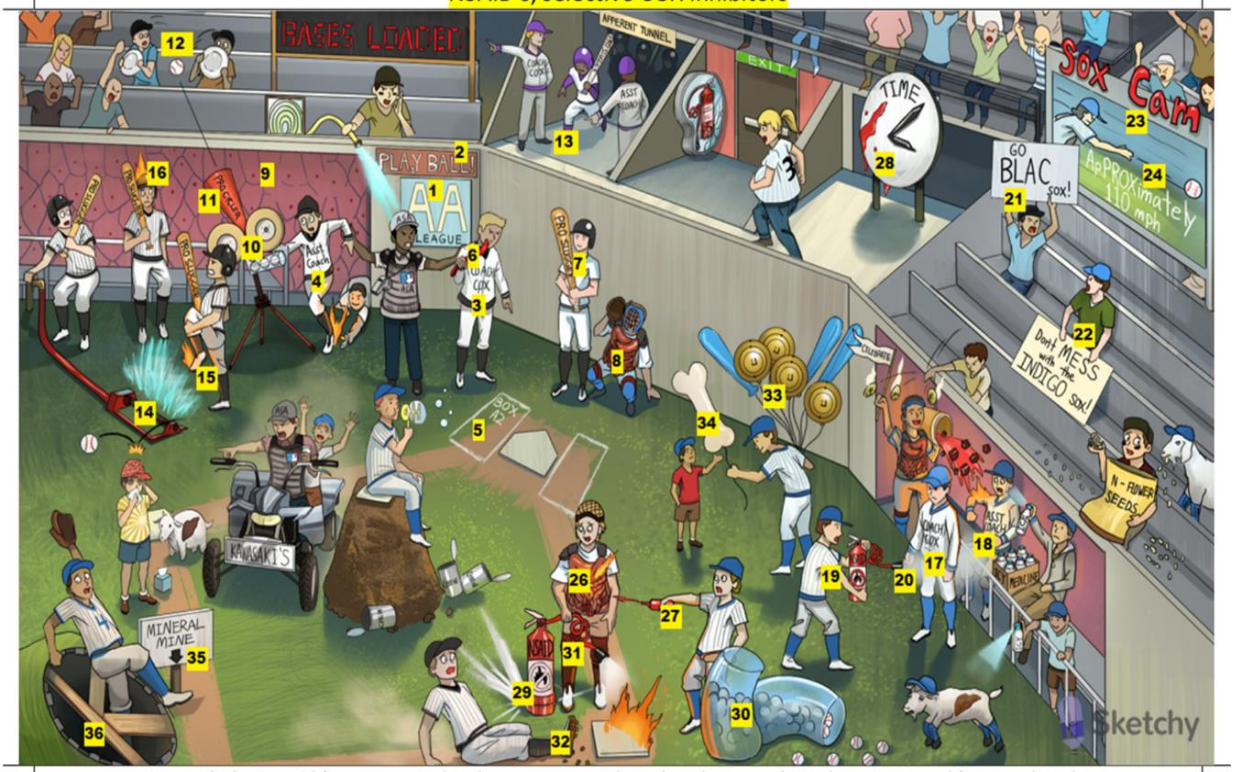
ديما اللحام

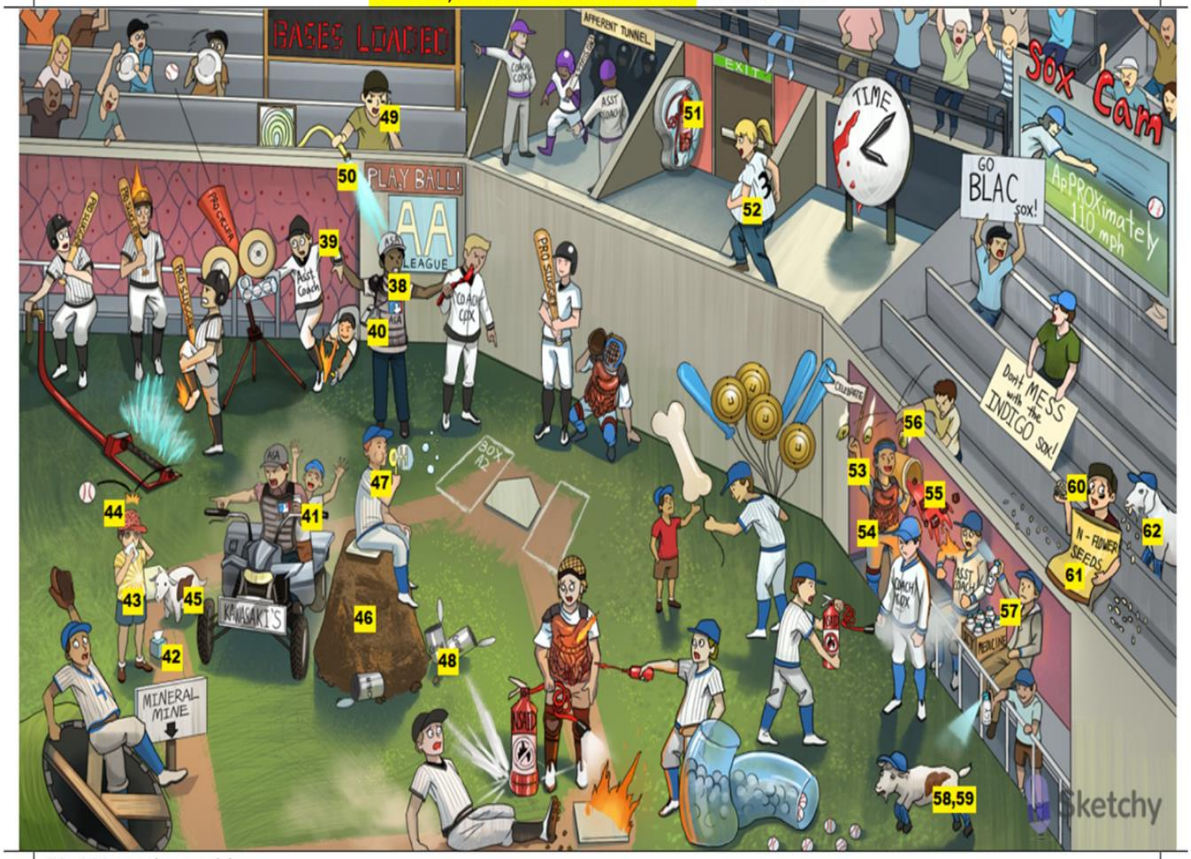
MSK Sketchy Pharma

NSAID's, selective COX inhibitors



1. **AA League: Arachidonic Acid** (precursor molecules to prostanoids and Leukotrienes) a poly unsaturated fatty acid in almost every cell membrane
2. Pla2y ball: phospholipase A2 (PLA2) hydrolyzes arachidonic acid from the cell membrane
3. Head coach cox: cyclooxygenase-1 (COX-1) is constitutively expressed and active in most cells
4. Assistant coach: COX-2 expression is induced by inflammation
5. Batter's box: thromboxane A2 (TXA2) is synthesized by COX-1, just like how the batter needs to step inside the box and now the plate is activated
6. Twisted red hat: TXA2(from COX-1) causes vasoconstriction
7. **Pro-slugger bat: prostaglandins, made by COX-1**
8. Pro-slugger protecting catcher with gastrointestinal pads: COX-1 synthesizes gastric cytoprotective prostaglandins
9. Assistant coach in endothelial dugout: COX-2 is expressed in vascular endothelial and smooth muscle cells and mediates vascular smooth muscle effects
10. Pro-cycle pitching machine: prostacyclin (PGI2) is synthesized by COX-2
11. Pro-cyclers dilated red barrel: PGI2 causes vasodilation
12. Pro cycler dispersing the plates in the audience: PGI2 inhibits platelet aggregation
13. Pro-sluggers at the afferent tunnel: COX-1 and COX-2 synthesize prostaglandins that dilate the afferent arteriole
14. Pro-slugger activating the sprinkler: COX-2 synthesizes prostaglandins that increase vascular permeability
15. Pro-Slugger in pain: COX-2 synthesizes prostaglandins that increase pain sensitivity
16. Pro-slugger with flaming head: COX-2 synthesizes prostaglandins that induce fever
17. Right dugout Head Coach Cox: Cyclooxygenase -1 is constitutively expressed
18. Right dugout Assistant coach: cyclooxygenase-2 (COX-2) expression is induced by inflammation
19. Anti-inflammatory Fire extinguisher: NSAID's
20. Head coach and assistant couch doused by fire extinguisher: NSAID's reversible inhibit both COX-1 and COX-2
21. **BLAC sox: diclofenac and ketorolac (NSAID's)**
22. **INDIGO sox: Indomethacin (NSAID) closure of ductus arteriosus**
23. **SOX CAM: meloxicam and piroxicam (NSAID's)**
24. **Approximately 110 Mph: Naproxen (NSAID)** **25. Adverse effects**
26. Burned hole in the gastrointestinal pads: Inhibition of COX-1 by NSAID's can cause gastric inflammation, erosions, and ulceration
27. Ketchup on the gastrointestinal pads: inhibition of COX-1 by NSAID's can cause GI bleeding
28. Ketchup on clock: inhibition of COX-1 by NSAIDs can prolong bleeding time
29. Bursting from high pressure: NSAIDs can increase blood pressure due to COX inhibition in the kidney, decreasing sodium excretion
30. Baseball-filled kidney containers: NSAIDs can cause acute interstitial nephritis
31. Contracted proximal end of fire extinguisher hose: NSAID's cause afferent arteriole vasoconstriction, decreasing GFR. ACEinhibitors will effect GFR greatly when used with NSAIDS due to the great decrease of GFR, this can lead to …
32. Sloughing of cleat spikes: NSAIDs can cause renal papillary necrosis (sloughing of renal papillae)
33. Elevated "lift-ium" balloons: NSAIDs can increase serum lithium concentrations
34. Plastic bone-shaped balloon: NSAIDs (indomethacin generally) can cause aplastic anemia
35. Depleted mineral mine: NSAIDs will cause Impaired rennin secretion leading to hyperaldosteronism (decreased mineralcorticoids) that will lead to hyperkalemia, type IV RTA
36. Big K: NSAID induced hyperaldosteronism can cause hyperkalemia

NSAID's, selective COX inhibitors ... continued



38. ASA umpire: aspirin

39. ASA umpire ejecting the coaches: aspirin **irreversible** inhibits COX-1 and COX-2
40. Acetylation whistle: aspirin acetylates COX-1 and COX-2 resulting in irreversible inhibition
41. Child in Kawasaki's ATV: aspirin is useful in Kawasaki's disease (the most common vasculitis in children) manifests as fever, conjunctivitis, erythema of lips and oral mucosa, rash, and cervical lymphadenopathy
42. Tissue box: Reye's syndrome occurs when a child is given aspirin in the setting of a viral illness. Consists of rapidly progressive encephalopathy with hepatic dysfunction after apparent recovery of a viral illness
43. Rays shirt pattern: aspirin use in children can lead to development of Reye's syndrome
44. Cerebral baseball cap: Reye's syndrome encephalopathy (confusion, seizure, coma)
45. Fat liver spot on cow: Reye's syndrome hepatic dysfunction (hepatic steatosis, hepatomegaly)
46. Mudpile: aspirin toxicity can cause an anion gap metabolic acidosis
47. Blowing "OH-" bubbles: aspirin causes respiratory alkalosis prior to metabolic acidosis
48. Tin Cans: aspirin can cause tinnitus
49. Charcoal lines: activated charcoal can be used to control aspirin in the setting of acute toxicity, alkanlinization of the serum allows you to pull aspirin out of the CNS
50. Bases loaded hose: alkalinization of the serum and urine with a basic solution (sodium bicarb) increases the renal excretion of aspirin
51. Fire extinguisher behind cracked kidney-shaped glass: minimize NSAID use in patients of risk for acute kidney injury, because it can exacerbate renal insufficiency, same with MI, or any other issue that may decrease renal perfusion
52. Exiting pregnant lady: avoid NSAIDs in 3rd trimester due to risk of premature closure of ductus arteriosus (highest risk with indomethacin and ibuprofen)

53. Celebrating catcher in the dugout drenching the assistant coach: celecoxib is a selective COX-2 inhibitor

54. Clean gastrointestinal pads: celecoxib has reduced ulcer and bleeding risk by avoiding COX-1 inhibition
55. Thrombus ice cubes: celecoxib may increase the risk of ischemic cardiovascular disease, avoid in acute MI and stable angina
56. Rotten sulfa eggs: celecoxib is a sulfa drug
57. **Icy-medicine spray on assistant coach: acetaminophen** inhibits COX-2, acting as an antipyretic and analgesic (NOT antiinflammatory) used for mild to moderate pain, osteoarthritis and some Rheumatoid arthritis
58. Goat scared by the icy medicine: toxic levels of acetaminophen deplete glutathione in the liver (glutathione will inactivate the toxic metabolite NAPQI) goat:glutathione
59. Liver spot on goat: acetaminophen causes hepatotoxicity (via the toxic metabolite: NAPQI)
60. Charcoal lines on the fan above acetaminophen spray: activated charcoal can be used to absorb acetaminophen in setting of acute toxicity
61. N Flower seeds: n-acetylcysteine (antidote for acetaminophen overdose)
62. Goat attracted to N-Flower seeds: N-acetylcysteine restores hepatic glutathione stores to treat acetaminophen hepatoxicity

Traditional Disease-Modifying Antirheumatic Drugs (DMARDs)

	Methotrexate	Hydroxychloroquine	Leflunomide	Sulfasalazine
MOA	folic acid antagonist, inhibits dihydrofolate reductase	unknown (for autoimmune diseases)	Inhibits dihydroorotate dehydrogenase (DHODH)	unclear
ACTION	immunosuppression and anti-inflammatory • Mainstay in the treatment of RA	•Used for early-mild RA	Lymphocyte cell arrest • Used as an alternative or in combination with methotrexate	
RESPONSE	3-6 weeks • Monotherapy → inadequate response? →combination	6 weeks to 6 months		1-3 months
DOSE	dose used for RA is less than anticancer dose (given once weekly)			
AE	❑Mucosal ulceration, nausea ❑Cytopenias ❑Liver cirrhosis ❑Acute pneumonia-like syndrome	ocular toxicity, GI upset and skin discoloration	Hepatotoxic	GI disturbances, leukopneia
Advantages:	• Slow the course of the disease • Induce remission • Prevent further tissue destruction - Usually started as soon as possible - Monotherapy is preferred; combinational therapy for advanced			

Biologic Disease-Modifying Antirheumatic Drugs B-DMARDs

	CHEMISTRY	MOA	USES	ROUTE	AE
Adalimumab	Recombinant monoclonal antibody against TNF-α	• Blocks the interaction between TNF-α and its cell surface receptor	• For moderate to severe RA • Monotherapy or in combination with methotrexate • Other uses: psoriatic arthritis, ankylosing spondylitis, and Crohn disease.	• Given SubQ	headache, nausea, agranulocytosis, rash, reaction at the injection site, or increased risk of infections (UTIs, URTIs)
Certolizumab		• potent neutralizer of TNF-α biological actions	Similar TO Adalimumab	Similar	Similar
Etanercept	• Recombinant, fully human receptor fusion protein	• binds to TNF-αand blocks its interaction with cell surface TNF-α receptors	• For moderate to severe RA • Monotherapy or in combination with methotrexate [Etanercept+methotrexate > each drug alone] • Other uses: ankylosing spondylitis and psoriasis		• Same adverse effects
Golimumab		• neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors	• Monotherapy or with methotrexate		• Can be associated with hepatitis B reactivation

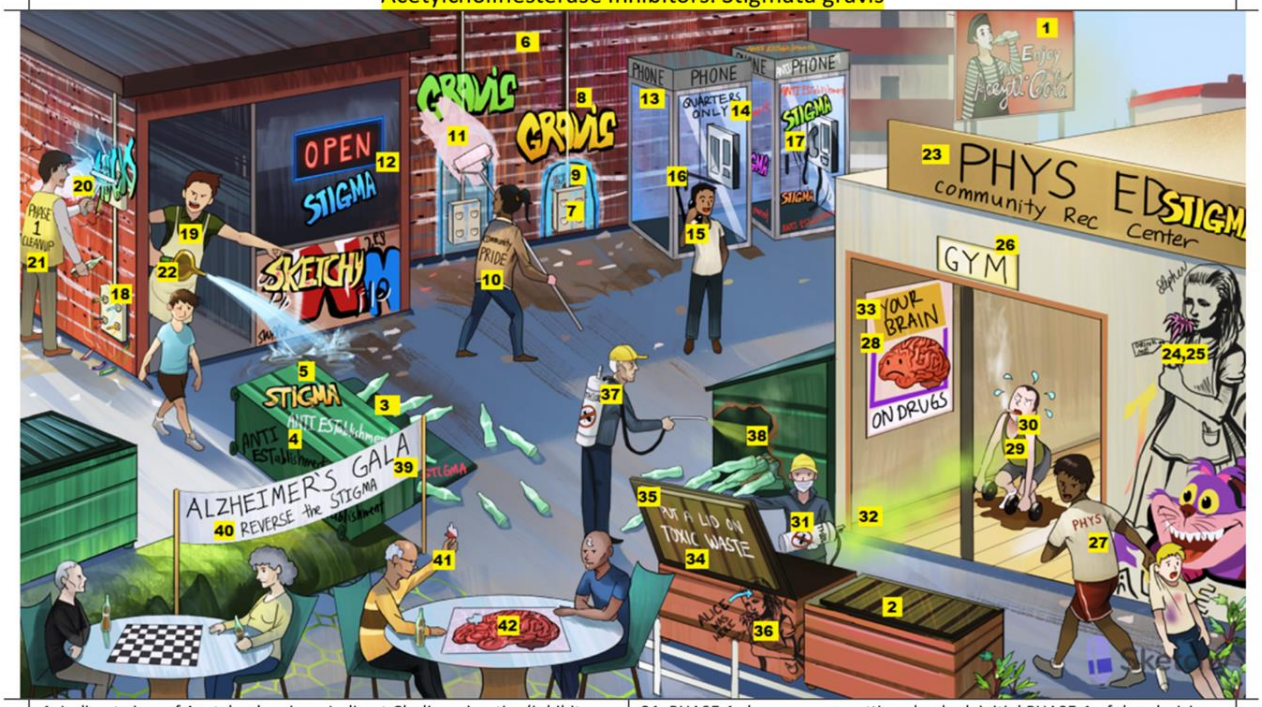
	CHEMISTRY	MOA	USES	ROUTE	AE
Infliximab	• chimeric monoclonal antibody	• binds specifically to human TNF-α and inhibits binding with its receptors	• Approved for patients with inadequate response to methotrexate monotherapy • Not used as a single agent • Other uses: plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn's disease	• Given IV	Similar adverse effect profile to the other TNF-α inhibitors
Abatacept	• a soluble recombinant fusion protein	• Competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation (STEP II)	• For moderate to severe RA, no response to DMARDs or TNF-α inhibitors	• Given IV	• Adverse effects: headache, upper respiratory infections, nasopharyngitis, and nausea
Rituximab	chimeric monoclonal against CD20	• B cells can perpetuate the inflammatory process in the synovium by' 1) activating T lymphocytes 2) producing autoantibodies and rheumatoid factor 3) producing proinflammatory cytokines, such as TNF-α and IL-1. • Causes B-cell depletion	• Used in combination with methotrexate for moderate to severe RA		

	CHEMISTRY	MOA	USES	ROUTE	AE
Tocilizumab	• Monoclonal antibody	• IL-6 receptor blocker	• Monotherapy or with methotrexate or other DMARDs • For moderate to severe RA	• Given IV	
Tofacitinib		• Oral inhibitor of Janus Kinases	For moderate to severe RA		• Hb must be > 9 g/dL to start tofacitinib (risk for anemia)
Anakinra		• Anakinra is an IL-1 receptor antagonist\ • IL-1 mediates degradation of cartilage and stimulation of bone resorption	• Infrequently used for RA		

Cautions

- **Increased risk for infections (tuberculosis and sepsis)**
- **Increased risk of fungal opportunistic infections**
- **Pancytopenia**
- **Live vaccinations should not be administered while on TNF-α inhibitor therapy.**
- **Should be used very cautiously in those with heart failure (can worsen heart failure).**
- **Increased risk of lymphoma**

Acetylcholinesterase Inhibitors: Stigmata gravis



1. Indirect view of Acetyl-cola mime: Indirect Cholinomimetics (inhibit acetylcholinesterase) bind either reversibly or irreversibly to acetylcholine to either raise acetylcholine, or increase the length of time acetylcholine is at the synapse
2. Dumpster of acetyl-cola bottles: acetylcholinesterase degrades acetylcholine (aCh)
3. Knocked over dumpster with acetyl-cola spilling out: acetylcholinesterase inhibitors increase synaptic concentrations of Ach
4. Anti-ESTablishment: anti-cholinesterase, AKA acetylcholinesterase inhibitor
5. STGMA: -"-Stigmine" drug suffix of acetylcholinesterase inhibitors
6. Skeletal muscle brick wall: acetylcholinesterase inhibits effects of Ach at the NMJ (increase activity of NICOTINIC Ach receptors) leading to increased strength of contractions
7. Electrical end plate: Motor end plate (at the NMJ)
8. GRAVIS graffiti: myasthenia gravis (MG) → antibodies against nicotinic Ach receptors at motor end plate (skeletal muscle NMJ)
9. Graffiti covering motor end plates: MG causes progressive muscle weakness, Ptosis, diplopia (inactivated nicotinic receptors at motor end plate)
10. **Community PRIDE: PYRIDOstigmine (acetylcholinesterase inhibitor used as long term treatment for MG)**
11. Removing graffiti on end plates: Acetylcholinesterase inhibitors increase Ach at NMJ endplate to outcompete MG antibodies
12. **Neon sign STIGMA: neostigmine (acetylcholinesterase inhibitor used to treat MG)**
13. **Phone Booth: edrophonium (acetylcholinesterase inhibitor that transiently reverses symptoms of MG)**
14. Quarters only: pyridostigmine, neostigmine and edrophonium are quaternary amines and do not penetrate into the CNS (only relives symptoms for 5-15 minutes)
15. Phone in working order: edrophonium REVERSES muscle weakness in undertreated MG patients (POSITIVE tensilon test)
16. Phone Wire tension: tensilon test → edrophonium reverses (positive) or fails to reverse (negative) muscle weakness
17. Phone out of order with anti-esterase graffiti: edrophonium FAILS to reverse muscle weakness during cholinergic crisis (NEGATIVE tensilon test)
18. **CURARE crayons stuck in end plate: non-depolarizing neuromuscular blocking agents (tubucurarine, pancuronium, cisatracurium) inhibit nicotinic Ach receptors are NMJ endplate**
19. Neon sign store owner kicking out CURARE crayon kid: acetylcholinesterase inhibitors (neostigmine) reverse non-depolarizing neuromuscular blockade
20. SUCKS: Succinylcholine is a depolarizing neuromuscular blocking agent (Nicotinic Ach receptor AGONIST), that overstimulates the NMJ, causing muscles to remain depolarizes and unable to respond to stimulus
21. PHASE-1 cleanup crew getting shocked: initial PHASE-1 of depolarizing blockade is IRREVERSIBLE (acetylcholinesterase inhibitors potentiate blockade)
22. Bladder hose: acetylcholinesterase inhibitors can be used to treat urinary retention (muscarinic activation)
23. **PHYS ED center: PHYSostigmine (acetylcholinesterase inhibitor with CENTRAL effects)**
24. Atropine in Wonderland: Atropine overdose → "mad as a hatter, Hot as a hare, Blind as a bat (reversed by physostigmine)
25. Deadly nightshade: belladonna flower is a naturally occurring form of atropine (overdose treated by physostigmine)
26. GYM Weeds: Jimson weed is a naturally occurring form of atropine (overdose reversed by physositgmine) "Gardeners mydriasis"
27. **PHYS ED teacher reprimanding atropine "artist": physostigmine reverses atropine overdose (peripheral and central effects)**
28. "your brain on drugs": physostigmine (and organophosphates) enters CNS to cause central cholinergic effects
29. DUMBBELS: acetylcholinesterase inhibitor toxicity (diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Lacrimation, salivation, sweating)
30. Weak nicotine kid: Acetylcholinesterase inhibitor toxicity includes flaccid paralysis (NMJ nicotinic Ach receptor over-activation)
31. **THIOL spray: insecticides (parathion, maltion, echotiophate) are organophosphates, a type of acetylcholinesterase inhibitor (also includes nerve agents and herbicides)**
32. Green fumes: organophosphates are a major cause of acute cholinergic toxicity (DUMBBELSS)
33. "your brain on drugs": physostigmine (and organophosphates) enters CNS to cause cholinergic effects
34. Closing LID on TOXIC spray: praLIDoxime reverses organophosphates toxicity (DUMBBELSS) by hydrolyzing the covalent bond
35. New toxic waste dumpsters: pralidoxime regenerates Acetylcholinesterase at muscarinic and nicotinic receptors (reverses cholinergic toxicity INCLUDING FLACCID PARALYSIS)
36. Atropine Alice on the side of the dumpster: Atropine reverses both peripheral and Central muscarinic toxicity from organophosphate poisoning (pralidoxime is peripheral only)
37. Old Pest control man: Aging of the organophosphate-cholinesterase complex leads to irreversible binding
38. Corroded dumpster: pralidoxime is ineffective once aging of organophosphate-cholinesterase complex has occurred
39. **Alzheimers GALA: galantime (acetylcholinesterase inhibitor used to treat Alzheimer's disease**
40. **Reverse the Stigma: Rivastigmine (acetylcholinesterase inhibitor used to treat Alzheimer disease)**
41. **Done with the Puzzle: Donepezil (acetylcholinesterase inhibitor used to treat Alzheimer's disease)**
42. Brain puzzle: galantine, rivastigmine, and donepezil penetrate the CNS

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Reversible)

	Edrophonium	Physostigmine	Neostigmine	Pyridostigmine
notes	•Short-acting Rapid •onset:1-2minutes	•Found naturally •Stimulates nicotinic receptors both N and M	•Synthetic	
Duration Of action	Short 10-20minutes	30mins to2hours	Similar physostigmine	intermediate 3 to 6 hours
uses	•Used in the diagnosis of myasthenia gravis(Tensilon test) •Used to reverse the effects of NMJ blockers	•Used to increase intestinal/bladder motility •Used to treat atropine overdose	•Used to stimulate gut/bladder Used as antidote e for NMJ blockers •Used for myasthenia gravis	•AChE inhibitor chronic management of myasthenia gravis
AE OR ANTIDOTE		Miosis , hypotention Bradycardia Contation of SMC	diarrhea, abdominal pain , salivation, decreased BP , BC ,flushing	

Indirect-acting Cholinergic Agonists: Anticholinesterase Agents (Irreversible)

1)Echothiophate	•Organophosphate •Covalently binds a phosphate group at the active site of AChE •Phosphorylated AChEreleases one of its ethyl groups (aging) •Impossible for chemical activators such as pralidoxime to break bond between drug and enzyme •Uses: cholinergic activation, muscle paralysis, ophthalmic uses

2)

•Irreversible AchE inhibitors (organophosphates) are used as insecticides

•Possibility for accidental poisoning

•Suicide/homicide

•Warfare/chemical terrorism(nerve gas)

Reactivation Of Acetyl choline esterase

Pralidoxime	•reactivate inhibited AChE •displaces the phosphate group of the organophosphate (e.g., echothiophate)and regenerates the enzyme •Does not cross BBB. What does this mean? •Would it overcome the toxicity of reversible AChEinhibitors?

	Non depolarizing (Competitive) Blockers	Depolarizing Blockers
MOA	At low doses •Competitively block Ach at nicotinic receptors(no stimulation) •Prevent the depolarization of muscle cell membrane •Cause muscle paralysis At high doses •block the ion channels Of the motor end plate •further weakening of neuromuscular transmission	•Work like Ach→ depolarize the membrane of the muscle fiber Succinylcholine attaches to the nicotinic receptor and acts like Ach to depolarize the junction •Succinyl choline is more resistant to degradation by AChE •Succinyl choline persists at high concentrations in the synaptic cleft •Produces constant stimulation of the receptor •Phase I:opening of nicotinic receptor-associated Na+channel fasciculations •Phase II : continuous binding leads to receptor desensitization flaccidparalysis
Action	•Inequal muscle sensitivity •Small rapidly contracting more sensitive face and eye >fingers, limbs, neck, and trunk muscles >intercostal muscles >diaphragm	•Brief muscle fasciculations(causes muscle soreness)flaccidparalysis •The respiratory muscles are paralyzed last •Redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes).

https://youtu.be/eTYxzLw6jeo

	Competitive Blockers	Depolarizing Blockers
Pharmacokinetics:	•Given IV (sometimes IM) •Very poor membrane penetration (including BBB) •Mostly, action is elimination is by redistribution •Variable onset/duration of action of different members of this class Rocuronium Cisatracurium Pancuronium Atracurium	•IV •Short duration of action(onset~30seconds) •Eliminated by redistribution and hydrolysis by plasma pseudocholine sterases. •Drug effect disappears upon discontinuation
AE		A.Malignanthyperthermia -rare,life-threateningcondition -caused by excessive skeletal muscle aerobic metabolism -circulatory collapse and death -antidote :dantrolene b.Apnea -due to paralysis of diaphragm -due to rapid to rapid release of K+ C.Hyperkalemia Succinylcholine increases potassium release from intracellular stores
Drug interactions	1.Cholinesterase inhibitors: e.g., neostigmine ⍰overcome the action of non depolarizing NM blockers. Remember low vs high dose. 2.Halogenated hydrocarbon anesthetics: e.g., desflurane ⍰enhance the neuromuscular blockade 3.Aminoglycoside antibiotics: e.g., gentamycin ⍰inhibit Ach release from cholinergic neurons	

	4.Calcium channel blockers: may increase the neuromuscular blockad	

Therapeutic Uses	**Main Therapeutic Use** :Adjunct to General Anesthesia -Muscle relaxation :orthopedic , abdominal surgeries -Facilitation of intubation , mechanical ventilation -Succinylcholine during electro convulsive therapy
	Sugammadex •Selective relaxant-binding agent •Terminates the action of both:rocuronium and vecuronium •Wraps the NM blocker in1:1ratio •Rapid reversal of neuromuscular blockade

Skeletal Muscle Relaxants

Baclofen	Dantrolene	Tizanidine	Orphenadrine	Carisoprodol	Cyclobenzaprine	Metaxalone
• Chemistry: structurally similar to γ aminobutyric acid (GABA)	structurally related to phenytoin	related to clonidine	analog of diphenhydramine	analog of diphenhydramine	similar to tricyclic antidepressants (TCA)	
• MOA: GABA B agonist→ Inhibits transmission at spinal level → CNS depression	Inhibits Ca+2 release from sarcoplasmic reticulum in skeletal myocytes	: α2 -adrenergic agonist→ presynaptic inhibition of motor neurons/excitatory interneurons	antimuscarinic (central atropine-like effects)	unknown. CNS depression?	reduces tonic somatic motor activity (alpha and gamma motor neurons), others similar to TCA	General CNS depression, sedation, no direct effect on muscles
•Indications:MS, spinal chord lesions	MS, CP, malignant hyperthermia	: MS, Spinal chord disease	muscle spasm, Parkinson's disease	acute treatment of musculoskeletal pain	acute treatment of musculoskeletal pain, muscle spasm	acute treatment of musculoskeletal pain, muscle spasm
• Kinetics:oral or intrathecal						
• Adverse Effects: drowsiness, fatigue, nausea, dose adjustment in renal disease	risk of hepatotoxicity, not used for low back pain	dry mouth, somnolence, hypotension, avoid in hepatic impairment	Dry mouth, urinary retention, blurred vision, mydriasis	possible abuse potential (due to GABAA modulation)	drowsiness, dry mouth	GI disturbance, nausea, vomiting, dizziness