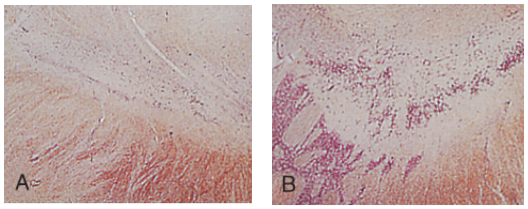
CNS Pharmacology Part III: Drugs for Neurodegenerative Disorders
Burchum: Ch. 21, 22, 23, 24 & 25

Legend:

Section Header | Concepts | Medication
Important information | Sub topics

DRUGS FOR PARKINSON'S DISEASE (CH. 21)

Pathophysiology review



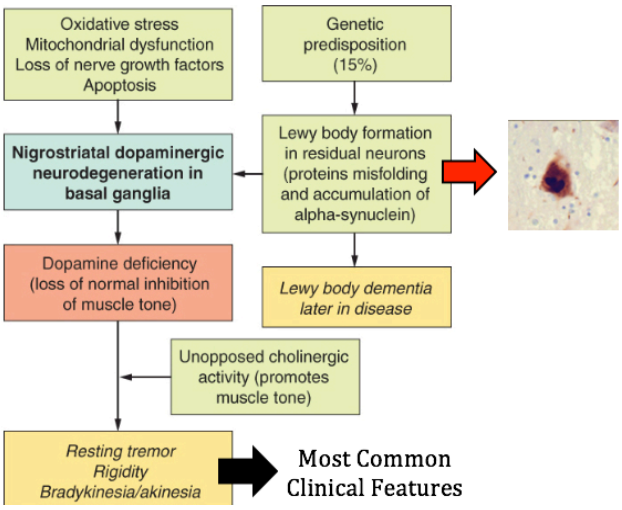
A = Atrophied Substantia Nigra
B = Normal Substantia Nigra

Parkinson's disease (PD)

- PD is a Slowly progressive neuromotor disease
- Motor + Behavioral dysregulations
  - 80% due to DA loss → Motor Sx onset
  - Noradrenaline neuron loss → Behavioral Sx
- Neurotransmission is disrupted primarily in the brain's striatum.
  - Degeneration of the Basal Ganglia DA Nigrostriatal pathways → ↓ DA neuron activity → Abnormal movement syndrome = Parkinsonism

PD: pathophysiology

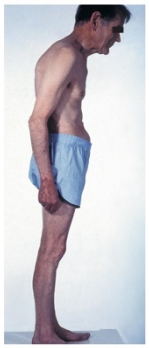
Lewy body dementia = Apoptosis of DA neurons in Substantia Nigra + Noradrenergic neurons in Locus Cerulus → leads to disease progression + behavioral symptoms



PD: Primary Symptoms

1. Resting tremors
- High Variability; Arms > Legs
- Cause: ↓ Inhibition of Basal Ganglia
  - Disappears temporarily during voluntary movement
  - Also disappears as PD progress towards Rigidity
2. Rigidity
- ↑ resistance to joint movement (ex.: cramps)
- Cause: Unknown → Possibly due to ↑ muscle activity of antagonistic muscles
3. Bradykinesia
- Cause: ↑Thalamus + Motor Cortex inhibition by subthalamic nucleus
- Affect all striated muscles
- Most debilitating aspect of PD
  - Motionless for hours; Extreme fatigue
  - Freezing = Inability to continue movement midway

PD: postural abnormalities



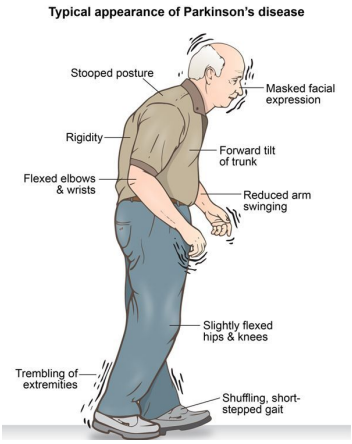
Caused by declining muscle function

1. Postural Fixation → ↓ reflexes + rigidity → Involuntary head+ neck flexion
2. Equilibrium Disorders → Loss of postural stability & adjustment mechanisms
3. Righting Disorders → Unable to switch from crouch or supine to standing or prone

PD: Psychological Sx

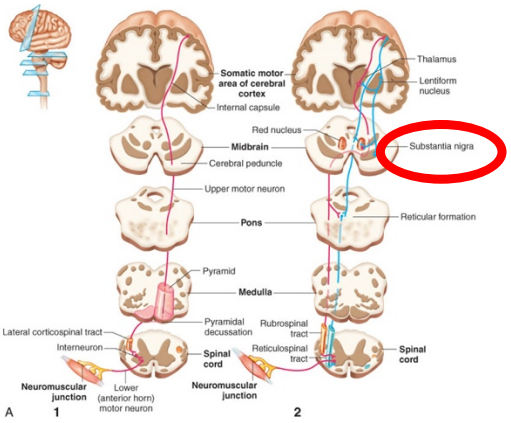
- Depression + Mild cognitive impairment
    - Endogenous Depression (caused BY the disease; not in response to it)
    - Slowness of thinking + poverty of thoughts
- Can evolve to (Lewy Body) Dementia
    - Patients with severe loss of cholinergic neurons
    - Accumulation of Lewy bodies → Plaques + Damages to brain capillaries
    - Leads to : Confusion + Memory Loss + Poor judgement & thinking processes
- Sensory dysfunctions + Sleep disorders
    - ↓ Taste; Smell and Pain
    - Sleep apnea

PD: Other Sx



- Autonomic & Neuroendocrine
    - Basal Ganglia communicates with Hypothalamus
    - Ex.: Orthostatic Hypotension; ↑ Sebum Secretion; Constipation
        - Distressing without being incapacitating
- Influence of:
    - Sleep → Beneficial
    - Stress → Detrimental
- Overall/Hallmark Sx:
    - Shuffling Gait + Postural Instability + Statue-like facial expression
    - Difficulty concentrating + Sleep Disorder

Somatic Motor Pathways



- Upper Motor Neuron = Within the CNS only. They modulate motor outputs, sensory inputs and reflex arcs (ALS = UMN disease)
- Lower Motor Neurons = CNS to PNS. Innervation of the actual muscle fibers

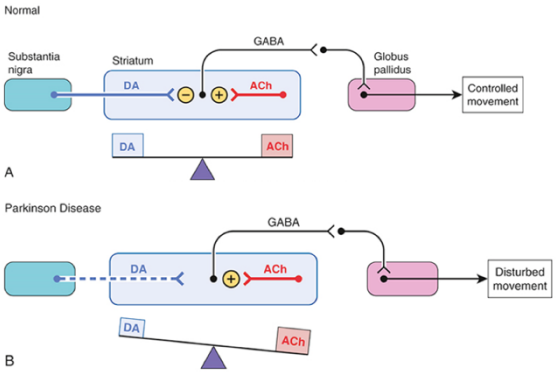
1) Pyramidal (Corticospinal) Tract
    - X-Over at Medulla
    - Movement Initiation

2) Extrapyramidal (Reticulospinal) Tract
    - X-Over at Midbrain
    - Balance & Posture Modulation

- The extrapyramidal tract is a motor pathway that transmits information coming from the brain, down to different muscles (for movement).
- The Substantia Nigra is part of the brain that contains a lot of dopamine neurons (they secrete dopamine)
    - This section of the brain is important for the relay of dopamine in the extrapyramidal pathway → necessary for balance & posture (which explains motor symptoms of PD)
- Parkinson patients have a dysfunction in the relay of dopamine in the substantia Nigra.

PD Neurotransmission

- The substantia nigra communicates with Striatum & Globus Pallidus to promote controlled movement
- A proper function of the striatum requires a balance between dopamine (DA) coming from the substantia nigra and acetylcholine (ACh) coming from the Striatum (Image A)
    - Dopamine is an Inhibitory transmitter
    - Acetylcholine is an excitatory transmitter
- The neurons that release DA inhibit neurons that release GABA (another inhibitory transmitter)
- In contrast, neurons that release ACh excite the neurons that release GABA (inhibitory transmitter).
- Movement is normal when the inhibitory influence of DA and the excitatory influence of ACh are in balance (image A)



- In PD, there is an imbalance between DA and ACh in the striatum (Image B). → The imbalance results from degeneration of the dopamine neurons in the substantia nigra that supply DA to the stratium.
    - In the absence of DA, the excitatory influence of ACh goes unopposed → causing excessive stimulation of the neurons that release GABA (inhibitory transmitter)→ Contributes to motor Sx

⇨ **Pharmacological intervention: Restore Dopamine**

Motor Symptom Management

- Therapeutic Goal: Sx Management only → No neurotoxicity reversal or prevention (Neurons that are loss cannot be recovered and neurotoxicity cannot be prevented either).
    - Some animal studies claim that some drugs (MAO-B & DA agonist) have neuroprotective properties (used to prevent neurodegeneration) → But Inconclusive data in human trials
    - Objective is to ↑ quality of life as much as possible
- Drugs Used: (1) Dopamine agonists (preferred) & (2) Anticholinergic Rx
- Drug Selection depends on severity of Sx:
    - Mild: MAO-B Inhibitor
    - Moderate/Severe with severe motor dysfunction: Levodopa/Carbidopa combination (Sinemet)
    - Moderate/Severe with drug-induced dyskinesia: DA Agonist preferred vs Levodopa/Carbidopa
        - Drug-induces dysksinesia mostly d/t Sinemet, so you don't want to make it worst

<u>Motor Fluctuation Management:</u>

- 'Off Times' → Temporary period in which patient becomes unresponsive to treatment (responsiveness to treatment returns eventually, but you don't know when).
    - Do not stop taking the drug during this time to prevent Off time from being prolonged
    - As the disease continues to progress, Off Times become longer and more frequent
    - During Off Times, **Entacapone (**COMT inhibitor) & **Rasagiline** (MAO-B inhibitor) can take over or help reduce off time period.
- Levodopa-induced dyskinesia → Involountary movements
    - Usually, parkinson's patients have bradykinesia (slow movement, tromors) → Give Levidopa to correct → going overboard → Excessive movement (opposite Sx)
    - The only drug recommended for dyskinesias is **Amantadine** (DA-releasing agent)
    - If drug induced dyskinesia occurs → Switch from Levodopa to a DA agonist since they don't produce as much dyskinesias (safer).

Nonmotor Symptom Management (Drug choice depends on specific nonmotor symptoms)

- ANS Symptoms:
    - Erectile Dysfunction → Viagra
    - Urinary Incontinence → Peripheral anticholinergic Rx
    - Orthostatic Hypotension → ↑ Salt & Fluid intake
    - Constipation → Exercises & Fibers → Laxatives as last resort
- Sleep Disturbances: Insomnia + Abnormal limb movements during sleep
    - Levodopa/Carbidopa + Melatonin

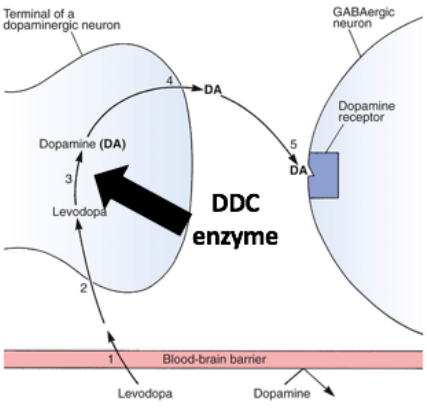
- Depression (in response to gradual debilitation)
    - **Amitryptiline** (TCA) = Only scientifically supported efficient Rx for depression of PD patients
        - Unfortunately exacerbates dementia & orthostatic hypotension
- Dementia: Anticholinesterase agents used for Alzheimer's disease (Ex.: **Rivastigmine & Donepezil**)
- Psychosis induced by anti-Parkinson Rx
    - SGAs **(clozapine & quetiapine)** → Quetiapine preferred because no risk of agranulocytosis
    - Avoid FGAs because they are DA antagonism → which would exacerbates motor impairments

Dopaminergic Agents Overview → All drugs that increase the transmission of dopamine neurons

Drug	MOA	Therapeutic Role
DOPAMINE REPLACEMENT		
Levodopa/Carbidopa	Levodopa undergoes conversion to DA in the brain and then activates DA receptors (carbidopa blocks destruction of levodopa in the periphery)	First-line drug, or supplement to a dopamine agonist.
DOPAMMIINE AGONISTS		
Nonergot Derivates - Apomorphine - Pramipexole - Ropinirole - Rotigotine	Directly activate DA receptors	- Pramipexole and ropinirole are first line drugs or supplements to Levodopa - Apomorphine is reserved for rescue therapy during "off time" - Ergot derivates are generally avoided. **Also useful to manage EPS effects of antipsychotics**
Ergot Derivates - Bromocriptine - Cabergoline		
COMT IINHIBITORS		
- Entacapone - Tolcapone	Inhibit breakdown of Levodopa by COMT	- Adjunt to Levodopa to decrease wearing off - Entacapone= more effective + safer vs Tolcapone
MAO-B INHIBITORS		
- Rasagiline - Selegiline	Inhibit breakdown of DA by MAO-B	Used in newly diagnosed patients and for managing off times during levodopa therapy
DOPAMINE RELEASER		
- Amantadine	- Promotes release of DA from remaining DA neurons - May also block DA reuptake	May help reduce levodopa-induced dyskinesias

Levodopa

MOA: Reduces symptoms by increasing dopamine synthesis in the striatum.



1) Levodopa enters the brain via active transport systems into the BBB
2) In the dopamine neurons found inside the brain, Levodopa is converted to dopamine by DDC enzyme.
    - DDC enzymes are found in both in the brain and in the periphery.
    - Only a small fraction reaches the brain (The majority is metabolized in the periphery by DDC into dopamine).
        - Dopamine is the precursor of NE. By adding dopamine to the periphery, more NE synthesis = ↑ sympathetic activation= cardiac effects & ↑ Hypertensive crisis
3) Dopamine neurons release more dopamine → Restores balance between Dopamine & Acetylcholine.

PD is treated with Levodopa and not with dopamine for 2 reasons:

1. Dopamine cannot cross the BBB
2. Dopamine has such a short half-life in the blood that it would be impractical to use even if it would cross the BBB

Usage

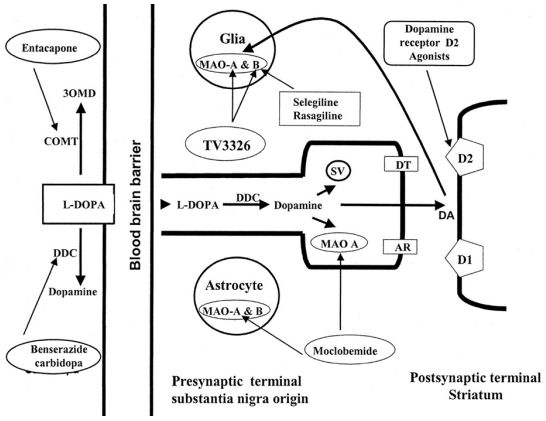
- Most effective drug for PD → If failure, challenge PD diagnosis!
- **Always combined with (1) Carbidopa or (2) Carbidopa + Entacarpone** (never given alone)
    - If given alone, it exacerbates the situation (does not work well) & ↑↑ risk of hypertensive crisis
    - Hypertensive crisis because Dopamine is the precursor of NE. By adding dopamine to the periphery = more NE synthesis = ↑ sympathetic activation= cardiac effects
- Therapeutic delay → Efficacy ↑ over first few months
- Therapeutic decline → Efficacy ↓ over time (≈5 years)
- 'Off Effect" → Loss of benefits despite high plasma levels
    - Usually lasts a few minutes to a few hours
    - Frequency and duration increases over time
    - *Manage with **Entacapone** or **Rasagiline***

Kinetics

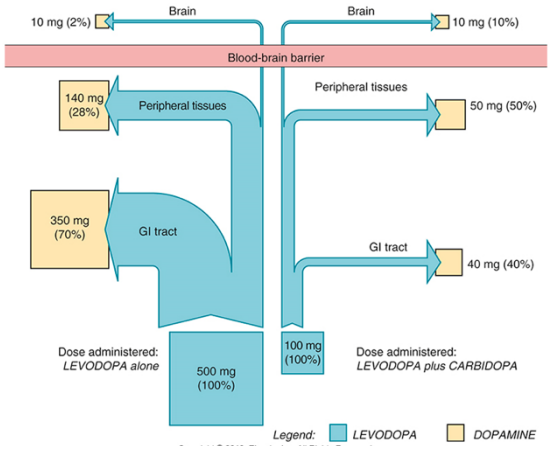
- PO available → However, alot of food Interactions
    - Meals delay absoprtion by slowing gastric emptying → should be taken on an empty stomach
    - Protein-rich food ↓ BBB X-ing
- Metabolism by DDC & COMT (at a lesser extent)
    - Peripheral DDC enzymes convert levodopa into dopamine (an active metabolite)
    - COMT enzymes converts Levodopa into an inactive metabolite.
- Alone, only 2% crosses BBB → Majority is metabolized in the periphery by DDC & COMT enzymes

(A) Levodopa + Carbidopa or (B) Levodopa + Carbidopa + Entacapone

- Carbidopa & Entacapone are used to enhance the effect of Levodopa.
    - Carbidopa inhibits metabolism of Levodopa by DDC whereas Entacapone inhibits metabolism of Levodopa by COMT enzymes → Making more levodopa available to the CNS.
- Since Carbidopa cannot cross the BBB, it does not suppress conversion of levodopa to dopamine by DDC enzymes in the brain.



- In the absence of Carbidopa, 98% of Levodoa is metabolized in intestinal and peripheral tissues (either by COMT or DDC), leaving only 2% for actions in the brain.
- By combining Levodopa/Carbidopa/Entacapone (thereby inhibiting DDC & COMT metabolism), it increases the percentage of levodopa available to the brain
    - To get the same effect, you can reduce initial Levodopa dose & reduce toxicity (in the GIT and Peripheral tissues)



Dose required to get 10mg in the brain

Adverse Effects

1. Nausea & Vomiting
    - ↑ DA activates CTZ (vomiting center in the brain)/ Intensity ↓ over time
    - Use low initial doses & increase carbidopa dose
2. Dyskinesia
    - Too much Levodopa = DA/ACh balance tilts the other way around (Dopamine > ACh)= Diskinesia
    - 80% of patients within the first year
    - **Amantadine** (DA-releasing agent) can alleviate
3. Cardiovascular effects
    - Orthostatic hypotension (conversion of Levodopa to DA in the periphery) → Fluid + Salt intake
    - ↑ peripheral Levodopa conversion into DA → ↑ NE → ↑ sympathetic response → Dysrhythmias
4. Psychosis (≈20% of patients)
    - Main Sx: Visual hallucinations & paranoid ideations
        - Positive symptoms associated with dopamine in psychotic attacks!
        - Manage with SGAs (**Quetapine or Clozapine**)
5. CNS effects
    - Any drgs that act in the CNS will lead to CNS effects (affecting other transmissions/pathways)
    - Main Sx: Anxiety + Agitation + Memory & cognitive impairments
    - Rare: Impulse control behavior changes (ex.: promiscuity; gambling)

Drug Interactions

Drug Category	Drug	Mechanism of Interaction
Drugs that *increase* beneficial effects of levodopa	Carbidopa	Inhibits peripheral decarboxylation of levodopa
	Entacapone, tolcapone	Inhibit destruction of levodopa by COMT in the intestine and peripheral tissues
	Rotigotine, apomorphine, bromocriptine, cabergoline, pramipexole, ropinirole	Stimulate dopamine receptors directly, and thereby add to the effects of dopamine derived from levodopa
	Amantadine	Promotes release of dopamine
	Anticholinergic drugs	Block cholinergic receptors in the CNS, and thereby help restore the balance between dopamine and ACh
Drugs that *decrease* beneficial effects of levodopa	Antipsychotic drugs[a]	Block dopamine receptors in the striatum
Drugs that *increase* levodopa toxicity	MAO inhibitors (especially *nonselective* MAO inhibitors)	Inhibition of MAO increases the risk of severe levodopa-induced hypertension

Extra dopamine produced is not degraded.

Use if too much Levodopa

Dopamine Agonists (Pramipexole)

- General Information:
  - 1st-line alternative to L-DOPA (especially young patients)
  - Beneficial effects result from direct activation of dopamine receptors in the striatum → Binds onto dopamine receptors as if it was dopamine.
  - Combine with L-DOPA in advanced stages of PD
- Prototype: **Pramipexole**
  - Nonergot derivative very selective for DA receptors
  - Mechanism of Action: Binds selectively to dopamine D2 & D3 DA receptors (agonists)
    - **Benefits from D2 agonisms**
- Kinetics: Available PO / Accumulates in RBC / Renal excretion
- Sepecific Toxicity:
  - Monotherapy: Nausea / Insomnia / Hallucinations
  - Combination: Dyskinesia / Orthostatic Hypotension / ↑ Hallucinations
  - Rare: Impulse control problems & Sleep Attacks (sudden falling asleep)
    - Because dopamine is associated with reward center → A lot of gambling & risky behaviors in individuals already prone to these types of behaviors.

Advantages over L-DOPA	Disadvantages over L-DOPA
1) No enzymatic conversion	1) ↑ Serious ADRs (Ex.: Hallucinations)
2) No food interaction	2) Postural Hypotension
3) ↓ risk of Dyskinesia	3) Daytime sleepiness
4) Slower therapeutic decline (can last longer)	**Younger pts tolerate these ADRs better vs older pts**

Other PD Drugs

1) MAO-B inhibitors: **Selegiline**
   - Modest motor Sx improvement (Not preferred over other 2 classes)
   - 1st-line Rx for mild impairements (keep best Tx for last restort)
   - Possible (unproven) neuroprotective actions

Actions:

- Inhibition of DA breakdown → ↑ DA transmission
- Selective for MAO-B:
- Weak antidepressant and hypertensive crisis risk

Adverse Effects:

- Main: Insomnia & Orthostatic Hypotension
- Hypertensive Crisis: only if overdose
- SSRIs Interaction: ↑ 5-HT syndrome
- L-DOPA Interaction: ↑ Action & Toxicity

2) COMT Inhibitors: **Entacapone**

- No direct therapeutic effects
- Benefits: ↓ peripheral L-DOPA conversion by DDC & COMT enzymes
- ↑ L-DOPA $T_{1/2}$ and BBB X-ing

Kinetics:

- PO Available / Hepatic metabolism
- Renal Excretion / $T_{1/2} \approx$ 1.5-3h

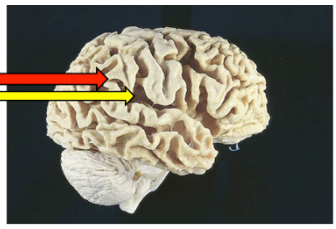
Adverse Effects:

- ↑ L-DOPA toxicity: (ex.: Dyskinesia) → Makes L-DOPA more potent
- Directly: GI disturbances (ex.: constipation)

DRUGS FOR ALZHEIMER'S DISEASE (CH. 22)

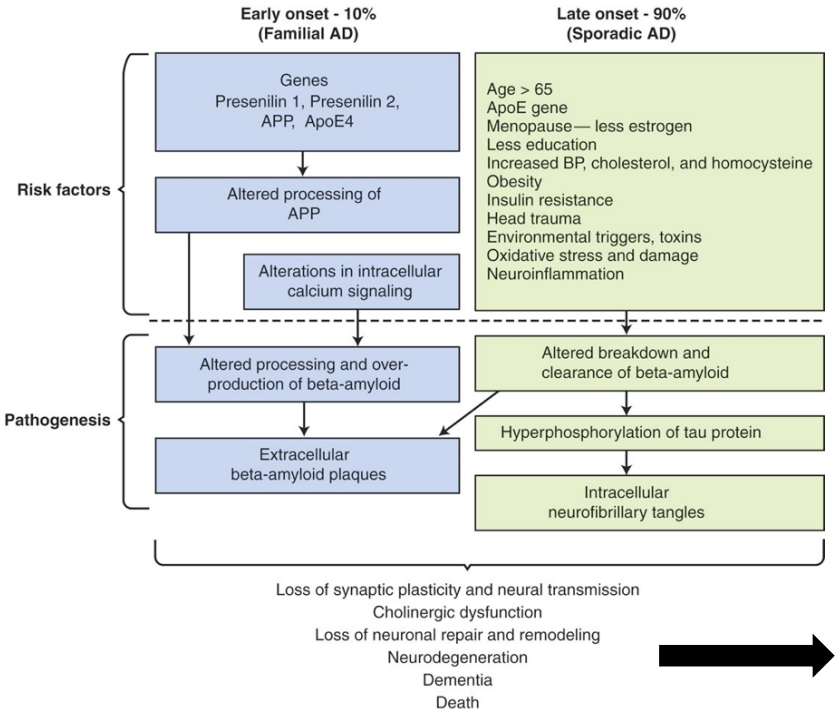
Pathophysiology review

Alzheimer's Disease (AD)



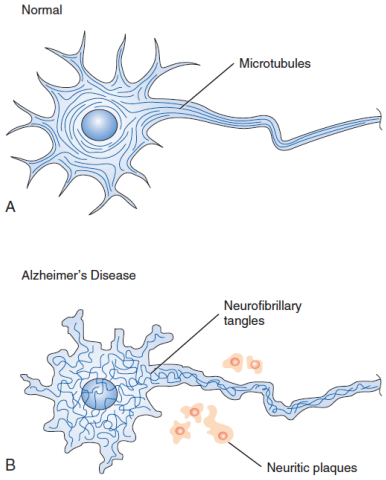
- In Alzheimer's disease, the major pathologic findings are (1) cerebral atrophy, (2) degeneration of cholinergic neurons, and the (3) presence of neuritic plaques and neurofibrillary tangles
  - Neuronal damage is irreversible
- Neuronal degeneration occurs in the hippocampus early in AD, followed later by degeneration of neurons in the cerebral cortex and subsequent decline in cerebral volume.
  - Hippocampus: Plays an important role in memory
  - Corte: Central to speech, perception, reasoning.
- In patients with advanced AD, levels of ACh are 90% below normal for 2 reasons:
  1. ACH is an important transmitter in the hippocampus and cerebral cortex (regions where neuronal degeneration occurs).
  2. ACh is critical to forming memories, and its decline has been linked to memory loss.

AD: Types & Risk factors



Loss of ACh Pathways
↓
Decline in memory & attention

B-Amyloid Plaques & Neurofibrillary (Tau) Tangles



Beta-Amyloid & Neuritic plaques

- Form outside of neurons (hallmark of AD).
- Composed of beta-amyloid (a protein fragment) surrounded by neuron remnants.
- In patients with AD, beta-amyloid is present in high levels and may contribute to neuronal injury.
- Accumulation of beta amyloid begins early in the disease process.

Neurofibrillary Tangles and Tau

- Prominent feature of AD (Formed inside neurons) → Intracellular
- Tau is found in healthy neurons. However, when the orderly arrangement of microtubules becomes disrupted, tangles form inside of the neurons = results in production of an abnormal form of tau.

Clinical Manifestations: → Gradual progression :

STAGE	MILD COGNITIVE IMPAIRMENT	EARLY STAGE	MIDDLE STAGE	LATE STAGE	END STAGE
Cognitive	Mild memory loss, particularly for recent event (episodic memory) and new information (semantic memory)	Measurable short-term memory loss; difficulty planning; disorientation to location	Significant forgetfulness; easy to get lost; may dress inappropriately; may have hallucinations	Little cognitive ability; language not clear; personality change; does not recognize family members; wandering; repetitive behavior	No significant cognitive function; loss of word speech
Functional	Possibly depression (vs. apathy); mild anxiety	Mild IADL problems	IADL-dependent; some ADL problems	ADL-dependent; incontinent; difficulty eating	Nonambulatory/bedbound; unable to eat

Cognitive Impairment Drugs

- Drugs for Alzheimer disease:
  1. Cholinesterase Inhibitors (**Donepezil, Rivastigmine**)
  2. NMDA antagonists (**Memantine**).
- Ideal Therapeutic Objective: Sx improvement + Cognitive decline reversal
- Actual Therapeutic Objective:Slow cognitive decline & Sx progression

Drugs for Alzheimer's Disease: Severity Indications

Drug	Indication (AD Severity)
CHOLINESTERASE INHIBITORS	
Donepezil [Aricept]	Mild to severe
Rivastigmine [Exelon]	Mild to moderate
Galantamine [Razadyne, Razadyne ER, Reminyl ER ♣]	Mild to moderate
NMDA ANTAGONIST	
Memantine [Namenda, Namenda XR]	Moderate to severe

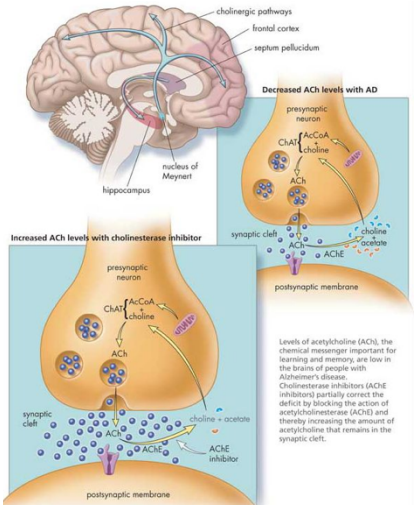
Drugs for Alzheimer's Disease: Pharmacokinetic Properties

Drug	Route	Peak	Half-Life	Metabolism	Excretion
Donepezil [Aricept]	PO	3 hr (8 hr for 23-mg tablet)	70 hr	Hepatic (CYP2D6, CYP3A4 and glucuronidation)	Urine (primary), bile
Rivastigmine [Exelon]	PO, transdermal	PO: 1 hr Transdermal: >8 hr	1.5 hr	AChE in the brain	Urine (primary), feces
Galantamine [Razadyne, Razadyne ER Reminyl ER ♣]	PO	IR tablet without food: 1 hr IR tablet with food: 2.5 hr ER tablet: 5 hr	7 hr	Hepatic (predominantly CYP2D6 and CYP3A4)	Urine
Memantine [Namenda, Namenda XR]	PO	3–7 hr	60–80 hr	Hepatic (primarily non-CYP450)	Urine

- All available PO, half-life either very short or fairly long
  - Long Half-Life → Nemantine & Donepezil
- Hepatic metabolism & urinary excretion

- Efficacy of Alzheimer's Rx:
  - Statistically significant vs. Clinically Irrelevant
    - The differences are significant (the drugs work), but clinically, the difference is not relevant to the life of the patient → Same as loosing ½ pound after 6 months diet…
- Official Guidelines
  - Individualised patient decision to initiate Tx
  - No evidence of one agent superior to others
  - Drug selection based on tolerability

Cholinesterase Inhibitors



<u>MOA</u>: Prevent the breakdown of ACh by acetylcholinesterase (AChE) → Increases the availability of ACh at cholinergic synapses that have not yet been destroyed.

- AChE: Enzyme that breaks down ACh to terminate the transmission.

<u>Benefits:</u>

- May slow down progression by few months (Does not cure)
- Only works in 1/12 patients
- Short-lasting, modest cognitive improvements

Adverse Effects:

- All caused by ↑ cholinergic transmission
- Ex.: GI disturbances / Headaches
- Bronchoconstriction → Caution with COPD patients (Risks outweigh any potential benefit in this case)
- Cardio effects: Bradycardia → Hypotension + Fainting
    - ACh is part of the parasympathetic innervation → May be boosting parasympathetic pathways = slowing down HR

Drug Interactions: Anticholinergic agents (ex.: TCAs/ Antihistamines) ↓ efficacy

Dosage & Tx Duration:

- Low dosage increased gradually until highest tolerable dose
- Continue until benefits fade or toxicity becomes unbearable

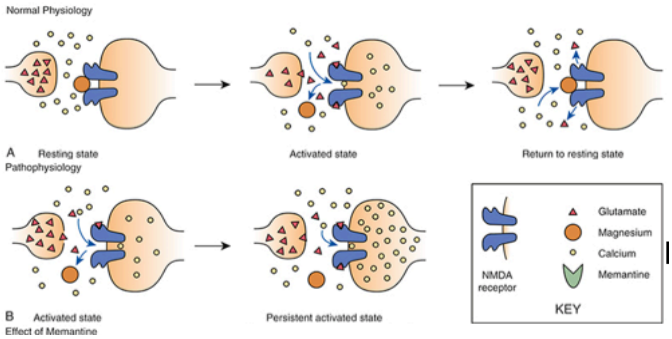
NMDA Antagonists: Memantine

Under healthy conditions:

1. An action potential (AP) releases a burst of glutamate into the synaptic space (when the neuron is activated).
2. Glutamate then binds with the NMDA receptor and displaces magnesium from the receptor channel, permitting Calcium entry.
3. Glutamate then quickly dissociates from the receptor, permitting Mg to reblock the channel, and thereby prevent further calcium influx.

Under pathological conditions (Alzheimers)

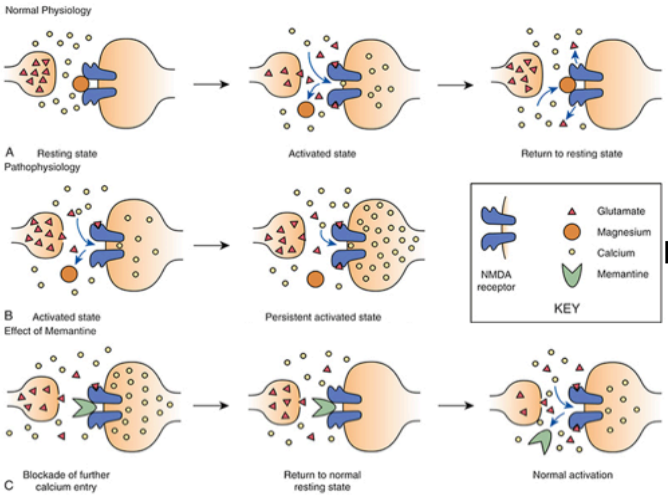
1. There is a slow but steady leakage of glutamate from the presynaptic neuron (persistent activated state)
2. The channel in the NMDA receptor is kept open, thereby allowing excessive influx of calcium
3. High intracellular calcium leads to
    - ↓ Learning & Memory processes
    - ↑ neurodegeneration (Neuron death due to toxicity)



MOA: Memantine modulates the effects of glutamate (major excitatory transmitter in the CNS) at NMDA receptors by blocking calcium influx when extracellular glutamate level is low and permitting calcium influx when extracellular glutamate is high.

a) When the glutamate level is low (during slow but steady leakage), Memantine is able to occupy the NMDA receptor channel, and thereby block the entry of calcium.
→ Level of intracellular calcium is able to normalize.

b) When a burst of glutamate is released in response to an AP (normal signalling), the resulting high level of extracellular glutamate is able to displace Memantine, causing a brief period of calcium entry.
    - Because intracellular calcium is now low, normal signaling can occur.
    - When glutamate diffuses away from the receptor, Memantine reblocks the channel, and thereby stops further calcium entry, despite continuing ow levels of glutamate in the synapse.



Adverse Effect & Interactions:

- Mild GI disturbances & headaches
- Other NMDA antagonists (ex.: amantadine & ketamine)
- Reduce dosage in renal impaired patients (high risk of toxicity)

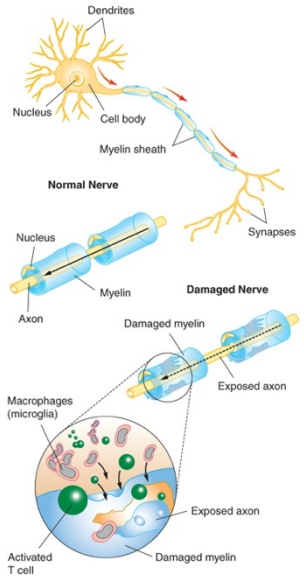
NMDA antagonists Vs. Cholinesterase Inhibitors:

- Unclear efficacy advantage
- Better tolerated (less toxicity)
- Combination of Donoezepil & Memantine seems to be better than Donezepil alone

Latest Research…Not much unfortunately…

- Vitamin E: Cochrane 2016 review debunked all positive effects claims
- No evidence of significant modifiable factor Ex.: exercise, diet, supplements, social interventions)
- 2 Antipsychotics (risperidone & olanzapine) can help with neuropsychiatric symptoms
    - ex.: Hallucinations, agitations, aggressions

DRUGS FOR MULTIPLE SCLEROSIS (CH. 23)



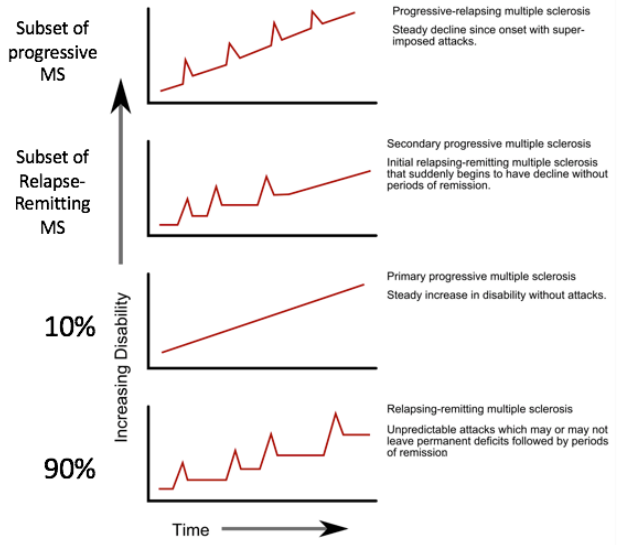
Pathophysiology review

Multiple Sclerosis (MS)

- Auto-immune disorder (Immune cells attacking your own neurons)
    - Chronic Inflammatory disease → Damages the myelin sheath of neurons in the CNS, causing a wide variety of sensory, motor, and cognitive deficits.
    - Plaque formation + Neuronal loss
    - Genetic vulnerability → Immune genes (HLA complex)
- 1st episode = Clinically isolated syndrome (CIS)
    - Neurological dysfunction < 24h

<u>MS: Pathophysiology</u>

- Event precipitates onset of MS in vulnerable individuals
    - Ex.: neuronal infection, pregnancy, brain trauma
- Autoreactive B & T-Cells attack myelin autoantigen → Myelin sheath destruction
    - Inflammation → ↓ neuronal connectivity + Neurodegeneration
- Inflammation involves:
    - Activated T-Cells (helper & cytotoxic) & Macrophage/Basophils/Eosinophils & Complement Recruitment
    - Anti-inflammatory cytokine < Pro-Inflammatory cytokines
    - Activated B-Cells + Antibodies in chronic cases
- Leads to ionic disruption + ROS + release of neurotoxins → Brain atrophy
- Multifocal MS Lesions
    - White & Gray Matter alike
    - Sx associated to the
- Major Hallmarks
    1) Substantial loss of gray matter over time
    2) Disability & Progression rate ∝ to Brain atrophy
    3) Oligodendrocytes dysfunction/loss



<u>MS: Types of Manifestations</u>

- Periods of remission = Remyelination
- symptoms progress & disease gets worse over time

Drug Therapy Overview

2 main interventions

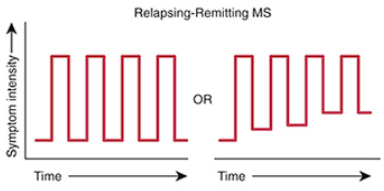
a) Disease Modifying Therapy:
   - ↓ Frequency & Severity of relapses & may prevent permanent axonal damage
     - Trying to change the course of the disease (long-term modification)
   - Relapse-remitting MS patients benefit the most
   - 2 main groups of disease-modifying drugs: Immunomodulators & Immunosuppressants
     - Immunomodulators > Immunosuppressants (better tolerability)
     - Immunomodulators are more powerful but are more toxic and take more time to act
       → Not good for acute attacks because of delayed therapeutic effects

b) Acute (Relapse) Episode Therapy
   - Stop whatever is going on (not thinking about the next attack, thinking about the one right now)
   - Immunomodulators < Immunosuppressants
     - Immunomodulators are more powerful but are more toxic and take more time to act
       → Not good for acute attacks because of delayed therapeutic effects
   - High-dose IV Glucocorticoid for 3-5 days = Best option
     - ↓ Duration & severity of attack
     - Avoid long-term and frequent use
       - Corticosteroids are very efficient and minimally toxicity when used short-term.
   - IV γ-Globulins for those unresponsive to Glucocorticoid

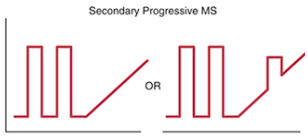
- Symptom Management: Depends on the symptoms!
  - Depression → SSRIs or Buproprion
  - Cognitive dysfunctions → Alzheimer's Rx
  - Neuropathic Pain → Carbamazepine (Anti epilectic drug) or TCAs (muscle spasticity drug)
  - Muscle Spasticity → Muscle relaxants or Benzodiazepines

Disease-Modifying Therapy

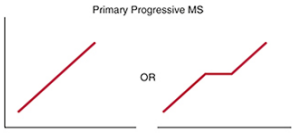
- Relapsing-Remetting MS : Progressively getting worse
  - All should receive 1 immunomodulator (next slide)
  - Initiate ASAP → To get potential neuroprotection effect
    - Prevention of further degradation of neurons= still debated
  - Continue until effects fade or toxicity unbearable
  - **Mitoxantrone** as last resort (more powerful)



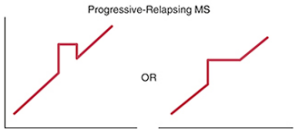
- Secondary Progressive MS
    - Mitoxantrone also effective but only short-term use
    - Interferon-β = Best option



- Primary Progressive MS
    - Mitoxantrone = Only approved option
    - Modest benefit & High toxicity



- Progressive-Relapsing MS
    - No evidence-base treatment yet
        - Rarest type = difficult to do research
        - Type that progresses the fastest → difficult to study the benefits/effects of the drugs.



    - Promising research with immunosuppressants (not yet confirmed)

Disease Modifying Drugs

- Toxicity increases proportionally with efficacy → So, drug selection should be based on individualised risk-benefit ratio at the moment
- They are all immunomodulators except **Mitoxantrone** (which is an immunosuppressant).
- Glatiramer Acetate (Copaxone): Only non-teratogen option → Used mostly for pregnant patient

Disease-Modifying Drugs for MS

Drug	Preparation	Route	Maintenance Dose	Administration and Storage	Adverse Effects
Interferon beta-1a [Avonex]	Pre-filled syringe: 30 mcg/0.5 mL Powder: 30 mcg, reconstitute with 0.5 mL sterile water	IM	30 mcg once a week	Rotate injection sites. Administer late in the day so that flu-like symptoms occur during sleep. Store both powder and pre-filled syringes at 36°F to 46°F (2°C to 8°C). If refrigeration is unavailable, store at or below 77°F (25°C) for up to 30 days.	Flu-like symptoms Liver injury Myelosuppression Injection-site reactions
Interferon beta-1a [Rebif]	Pre-filled syringe: 8.8 mcg/0.2 mL, 22 mcg/0.5 mL, or 44 mcg/0.5 mL	subQ	44 mcg 3 times a week at least 48 hours apart	Refrigerate at 36°F to 46°F (2°C to 8°C). If refrigeration is unavailable, store at or below 77°F (25°C) for up to 30 days.	
Interferon beta-1b [Betaseron, Extavia]	Powder: 300 mcg, reconstitute to 250-mcg/mL solution	subQ	250 mcg every other day	Rotate injection sites. Store powder at room temperature. May be refrigerated up to 3 hours following reconstitution.	
Dimethyl fumarate [Tecfidera]	ER capsule: 120, 240 mg	PO	120 mg or 240 mg twice daily	Administer with or without food.	Flushing GI discomfort Infections Rash
Glatiramer acetate [Copaxone]	Pre-filled syringe: 20 mg/mL glatiramer plus 40 mg of mannitol	subQ	20 mg once daily	Let syringe warm at room temperature for 20 minutes before administration. Refrigerate at 36°F to 46°F (2°C to 8°C).	Injection-site reactions Postinjection reaction
Natalizumab [Tysabri]	Concentrate: 300 mg/15 mL for dilution to 100 mL	IV	300 mg every 4 weeks	Infuse over 1 hour. Observe during administration and for 1 hour afterward. Stop infusion immediately if signs or symptoms of hypersensitivity develop.	Progressive multifocal leukoencephalopathy Liver injury Allergic reactions
Fingolimod [Gilenya]	Capsules: 0.5 mg	PO	0.5 mg once daily	Administer with or without food	Bradycardia Infections Liver injury Macular edema Fetal harm
Teriflunomide [Aubagio]	Tablets: 7, 14 mg	PO	7 mg or 14 mg once daily	Administer with or without food	Neutropenia Alopecia Infections Liver injury Fetal harm
Mitoxantrone [Novantrone]	Solution: 2 mg/mL in 10-, 12.5-, and 15-mL vials	IV	12 mg/m^2 every 3 months	Dilute with at least 50 mL NS or D_5W. Infuse over 15–30 minutes into a free-flowing IV line. Do not mix with other drugs.	Myelosuppression Cardiotoxicity Fetal harm

Interferon Beta

- Interferon Beta is a naturally occurring glycoprotein with antiviral, antiproliferative, and immunomodulatory actions (seen for Tx of hepatitis).
    - Natural interferon beta is produced in response to viral invasion and other biologic inducers.
- In patients with MS, Interferon-Beta is believed to help in 2 ways:
    1. Inhibit migration of proinflammatory leukocytes across the BBB, preventing these cells from reaching neurons in the CNS → preventing WBCs from killing your own cells
    2. Suppress T-helper cell activity → Suppresses immune system (drawback)

Adverse effects:

1) Flu-like symptoms Frequent but diminish over time → Mitigate with NSAIDs
2) Hepatotoxicity: Liver function Test montly → Decrease dosage if liver damage
3) Myelosuppression (Bone marrow suppression)Complete blood count montly
4) Injection-Site reaction: Mitigate with rotation of injection site & topical anti-inflammatory Rx

Interactions: Caution with other myelosuppressive & hepatotoxic agents

Dimethyl Fumarate (DMF)

Kinetics: Prodrug metabolised into active monomethyl fumarate (MMF); PO

Action:

- DMF is an immunomodulator that promotes apoptosis of activated T lymphocytes and inhibits migration of lymphocytes into the CNS by reducing BBB X-ing.
- Activates the Nrf2 antioxidant response pathway (which protects cells from oxidative stress and provides anti-inflammatory effects)

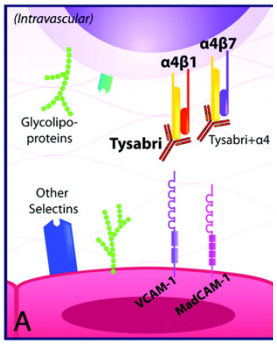
Adverse Effects:

1) Flushing & GI Discomfort:
    - Most common→ ↓ over time
    - Mitigate by administering Rx with food or transient dose reduction
2) Infection: Caused by ↓ WBC → Monitor blood count regularly
3) Alterations in Lab Analysis: ↑ Proteinuria & hepatic enzymes level without significant impacts on health
    - Not saying that MS is worse/better or that the drug is working (byproduct)

Interactions: ↓ Vaccine efficacy & ↑ risk of infection if live-attenuated vaccine → due to ↓ immune response

Natalizumab (Tysabri) (ends in -mab = monoclonal antibody)

MOA: In patients with MS, Natalizumab prevents circulating leukocytes (T cells and monocytes) from leaving the vasculature, and thereby prevents these cells from migrating to sites where they can do harm.



- Tysabril (trade name) → binds onto alpha4B1 and work as VCAM- inhibitors.
  - VCAM are molecules found on blood vessels cells (endothelial cells) → Act like Velcros
  - Blood cells need to bind to VCAM molecules (on endothelial cells) to stop moving and then diffuse across out of the vessel to the site of injury.
  - If you inhibit the interaction with VCAM & RBCs, blood cannot slow down = WBCs trapped in the blood vessels (where they don't do much).

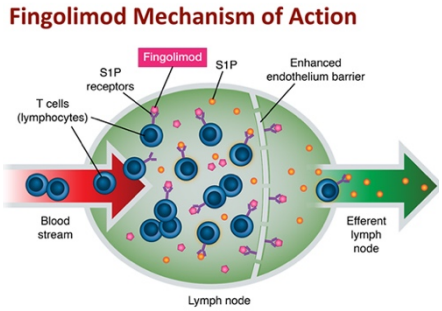
Adverse effects
Possibly the most efficient immunomodulator → But possibly the most toxic

1) Progressive Multifocal Leukoencephalopathy (PML)
   - Serious oppotunistic infection → Death or severe debilitation
     - Virus that needs important immunosuppressants to be activated.
   - Risk ↑ over time → Rx is only available through the *TOUCH Prescribing Program*
   - Main PML Sx: Progressive one-sided weakness + confusion & vision disturbances
2) Hepatotoxicity: Even more than IFN-B → Discontinue if liver damage
3) Neutralizing antibodies & Allergic Reactions:
   - Develop in ≈6% of patients → ↓↓ Efficacy
   - Also ↑↑ risk of allergic reactions

Interactions: Immunossuppressants ↑ PML Risk

Fingolimod

MOA:



- Normally, B-Cells & T-Cells hang out in the lymph nodes when they are not required (Waiting…) → They only come out when they get a call
- In order to get out, immune cells need to interact with S1P (S1P travels in the blood and binds onto S1P receptors on lymphocytes to call immune cells out).
- Fingolimod blocks S1P receptors on lymphocytes, causing their sequestration in lymph nodes → Traps leukocytes within lymph nodes.
- As a result, there are fewer lymphocytes in peripheral blood, → fewer lymphocytes enter the brain.

Kinetics :

- High efficacy + High toxicity → Usually a last resort when others failed.
- Metabolised into active and inactive compounds by P450 enzymes
- Long Half-life (6-9 days) → It takes months to reach plateau or to wash out (Nonitor even post Tx)

Adverse effects:

1) Bradycardia: Greatest within 6h of 1st dose → ↓ over time thereafter
2) Macular Edema
    - Swelling of the eye → Ophtalmic screening if vision changes
    - Generally, resolves on its own with or without discontinuing the Rx
3) Infection: ↑ risk of infections + ↓ Vaccine efficacy

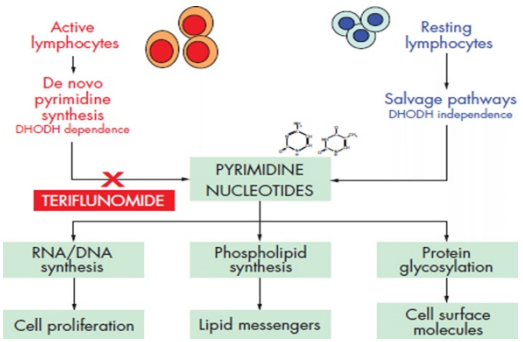
Interactions:

- Ketoconazole (Antifungal) → CYP450 inhibition → ↑ Fingolimod toxicity
- HR modifying drugs (ex.: β-blocker, CCBs) → ↑ risk of bradycardia

Teriflunomide

MOA:

- Teriflunomide is a de novo pyrimidine synthesis inhibitor
    - Pyrimidine is one of the building blocks of DNA
- By inhibiting pyrimidine synthesis, it decreases T-cell and B-cell proliferation and activation.



Kinetics:

- 99% protein bound
- It undergoes enterohepatic recycling → Which contributes to its long half-life (15-20 days)

Adverse Effects:

- Fetal & Infant Harm → Causes serious birth defects if taken by pregnant women
    - Also Impairs quality of sperm in males

Contraindications: Pregnancy & sever liver impairment

Interactions:

- Leflunomide → ↑↑ Toxicity
- Bile Acid Sequestrant or Activated charcoal → ↓ Teriflunomide levels

Monitoring: Monitor regularly: Liver function test / Complete blood count / Signs of infections

Mitoxantrone → (immunosuppressant)

MOA:

- Mitoxantrone is a cytotoxic drug that binds with DNA and inhibits topoisomerase II.
    - Inhibits DNA & RNA synthesis and promotes cross-linking and breakage of DNA strands.
- In patients with MS, mitoxantrone suppresses production of immune cells (B lymphocytes, T lymphocytes, and macrophages) → Which decreases autoimmune destruction of myelin.
- Also ↓ immune response by reducing production of cytokines (interleukin-2, tumor necrosis factor TNF-a, interferon gamma).

Kinetics Wide distribution / Extensive hepatic metabolism (mandatory Pre-Tx liver function test)

Adverse effects:

1) Fetal harm: Not proven in humans but YES in animals and similar Rx in humans (try to avoid it)
2) Cardiotoxicity:
    - ↓ Left Ventricular Ejection Fraction (LVEF) & possible Heart Failure (HF)
    - Risk ↑↑↑ if cumulated lifetime dose > 140mg/m^2
3) Myelosuppression: ↑ infection risks & ↓ vaccine efficacy → Regular CBC
4) Other ADRs: Anticancer-like ADRs: GI disturbances / Nausea & Vomiting / Urine & skin color changes

Monitoring

- CBC: Baseline + Before each dose + 10-14 days afer each dose
- LFT: Baseline + Before each dose
- Determine LVEF before each dose & anytime if there are signs of HF developing (Signs of cardiotoxicity)

DRUGS FOR SEIZURE DISORDERS (CH. 24)

Pathophysiology review

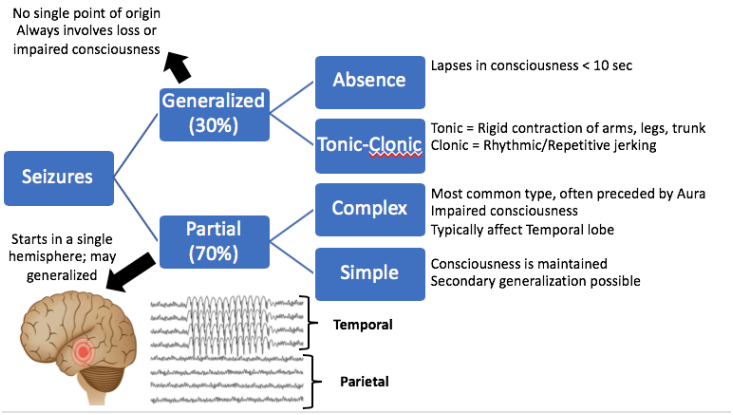
Seizure disorders

- Manifestation of a disease → not a disease in itself
- Seizure = Disruption of brain electrical function
    - Common etiology = 1) Cerebral Lesions or Trauma; 2) Biochemical alterations; 3) Epilepsy
- Epilepsy = Recurrent seizures without underlying cause
- Convulsion = Type of seizure (Clonic phase) strongly associated with Epilepsy

TABLE 17-18 TERMINOLOGY USED TO DESCRIBE A SEIZURE

TERM	DEFINITION
Aura	A partial seizure experienced as a peculiar sensation preceding the onset of a generalized seizure or complex partial seizure that may take the form of gustatory, visual, or auditory experience; a feeling of dizziness or numbness; or just "a funny feeling"
Prodroma	Early clinical manifestations, such as malaise, headache, or a sense of depression, that may occur hours to a few days before the onset of a seizure
Tonic phase	A state of muscle contraction in which there is excessive muscle tone
Clonic phase	A state of alternating contraction and relaxation of muscles
Postictal state	The period immediately following the cessation of seizure activity

Types of Seizure



Seizure Pathophysiology

Excitation-Inhibition Imbalance → ↑↑ Excitation → Glutamate via NMDA receptors → Ca^{2+} influx → ↑ Muscle Contraction (OR) ↓↓ Inhibition → Defective GABA receptors → Ca^{2+} influx → ↑ Muscle Contraction

- Seizure Initiation = ↑ AP frequency + Hypersynchronization
    - Leads to excessive neuronal activity → Tonic phase & Impaired consciousness
    - Inhibitory pathways try to block excitation → Clonic Phase occurs
    - ↑↑ Muscle activity → Drastic ↑↑ in ATP, O_2, Glucose consomption → Exhaustion
- Status Epilepticus = Seizures longer than 5 mins or Very short post-ictal phases (post convulsion)
    - No time to rest between seizures = depletion of energy store → Potentially lethal

Antiepileptic Drugs (AEDs) Actions

5 Mechanisms that decrease Action Potential:

1) ↓ Na^+ Influx (need sodium for AP)

2) ↓ Ca^{2+} Influx

3) ↑ K^+ Efflux (By promoting exit= inhibit AP)

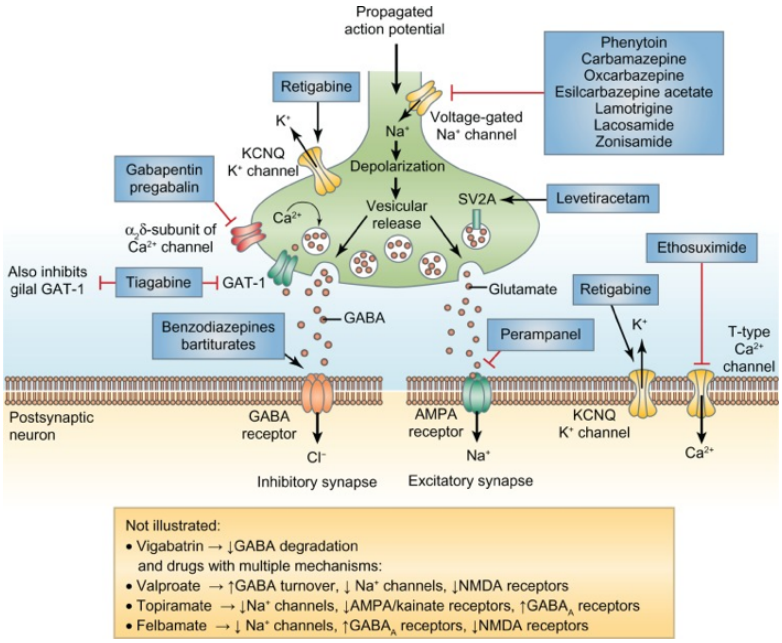
4) Glutamate Antagonism (Gas pedal: By blocking, AP is blocked)

5) GABA Potentiation (Break pedal: By potentiating, AP is blocked)

Beneficial Activity:

1) They all ↓ neuronal discharge within seizure focus

2) Suppress propagation of seizure discharge



Basic Therapeutic Considerations

- Therapeutic Goal & option
  - Drug therapy helps 60-70% patients (pretty good) → Reduce seizures as much as possible
  - Nondrug Tx: Neurosurgery/Vagus Nerve Stimulation/Ketogenic Diet
- Diagnosis & Rx selection
  - Most AEDs are selective against certain seizure types only
    - Need to determine which type of seizure patient has!
    - Ex.: **Ehosuximate** → Absence Seizures / **Phenytoin** → Tonic-clonic & partial seizures
  - Monotherapy preferred over combination (No chance of resistance → Decrease toxicity)
- Drug Evaluation
  - Try Rx at different dosages and significant amount of time before ruling failure
  - Seizure chart maintenance → determine Rx effectiveness
- Monitering Plasma Drug levels
  - Well documented data regarding safest & most effective drug levels.
  - Plasma drug levels most useful for tonic-clonic seizures (to prevent Sx) > absence seizures
    - For absence seizures, symptoms is more difficult to detect and less harmful

- Promoting patient adherence
    - Nonadherence accounts for 50% of Tx failure
    - Monitoring plasma levels & seizure charts ↑ adherence
- Withdrawing Anti-Epileptic Drugs :
    - Over a minimum of 6 weeks & sequentially (if 2+ Rx) to ↓ Status Epilepticus risk (sustained seizure)
- Suicide Risk with AEDs
    - Conflicting data and possibly only a few AEDs are concerned
    - Monitor & inform family and patients about possible warning signs
- Interaction with Oral contraceptives → ↓ Efficacy & potential fetal harm

Management of Pregnancy & Status Epilepticus (SE)

- Status Epilepticus = Tonic-Clonic seizures for 20+ minutes
    - Early Sx: Tachycardia / Loss of consciousness / Hypoglycemia / Acidosis
    - If it goes beyond 20 minutes → Permanent neurological damages → Coma → Death
- Medical Emergency in hospital setting: Need to administer glucose & Benzodiazepine IV
    - Glucose because all systems of the body will be deprived due to muscle contractions
    - Benzodiazepine: To cam & relax (GABA potentiator) → Mechanism #5
    - Lorazepam or Diazepam = 1st-line choices → Lorazepam preferred because $T_{1/2}$ > Diazepam
- Medical Emergency out-of hospital setting: Diazepam 10mg rectal gel → Administer no more than 2x before hospital to prevent toxicity (& Bring patient to the hospital after)
    - Rectally because the patient is having a seizure → Cannot swallow anything
- Once seizures are controlled : Long-term suppression with AEDs (Phenytoin or Fosphenytoin)

<u>Pregnancy Interventions</u>

1) Monotherapy lowest effective dose
2) 2mg/day folic acid supplements
3) 10mg Vitamin K injections last few weeks and at birth

Traditional vs. New AEDs

- The AEDs can be grouped into 2 major categories (1) Traditional AEDs and (2) Newer AEDs.
    - No group is considered superior yet
    - Drug selection should consider all options available

Comparison of Traditional and Newer Antiepileptic Drugs

Area of Comparison	AED Group	
	Traditional AEDs[a]	Newer AEDs[b]
Efficacy	Well established	Equally good (probably), but less well established
Clinical experience	Extensive	Less extensive
Therapeutic niche	Well established	Evolving
Tolerability	Less well tolerated	Better tolerated (usually)
Pharmacokinetics	Often complex	Less complex
Drug interactions	Extensive, owing to induction of drug-metabolizing enzymes	Limited, owing to little or no induction of drug-metabolizing enzymes
Safety in pregnancy	Less safe	Safer
Cost	Less expensive	More expensive

Traditional AEDs

1) Phenytoin

Action & Uses

- 1st Rx to ↓seizures without depressing the entire CNS (Better than previous Tx with anesthetics)
- Action: Inhibition of Na^+ channels on hyperactive neurons
- Uses: All types of seizure except absence seizures (Also used as an Antidysrhythmic drug)

Kinetics

- **Tricky Kinetics: Difficult to maintain therapeutic range** → More toxicity associated to it
- Significant absorption variations between patients
- Very limited hepatic metabolism capacity → Dosage affect $T_{1/2}$
- At low dose $T_{1/2}$: 8h = (1st-order kinetics) → Constant percentage of elimination
- At High dose $T_{1/2}$: 60h = (0-order kinetics) → Constant amount over time

Preparations & Dosage

- Available IV & 3 PO formulations
- Many safety concerns when administering IV (due to ↑ Toxicity risks)
- Switching between manifacturers used to be a kinetic concern
- Dosage is highly individualised
- Monitor plasma levels for optimal range: **10-20mcg/mL**
- **High Toxicity if above 20mcg**

ADRs & Interactions

Most adverse effects occur when plasma levels ≈ or > 20mcg/mL

- CNS effects : Sedation / Visual impairments / Cognitive impairments
- Gingival Hyperplasia: ≈ 20% of patients → Reduce via folic acid supplements + dental hygiene
- Dermatologic effects
    - Risk of severe rash (Steven-Johnson Syndrome or Toxic Epidermal Necrolysis)
    - SJS & TEN associated with **HLA-B*1502 genetic polymorphism**
        - If you have this gene → At greater risk of severe rash & skin reactions
- Pregnancy Effects
    - Serious teratogen → Fetal hydantoin syndrome (FHS)
    - ↓ vitamin K-dependent clotting factors → ↑ newborn bleeding tendencies
- Cardiovascular effects
    - Cardiac hypotension & dysrhythmias risk during IV administration
    - Minimize risk via: Slow admin + diluted in saline

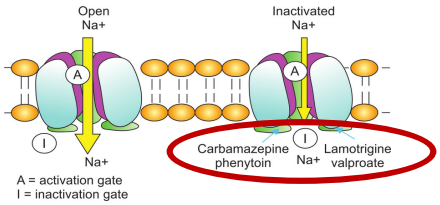
Drug interactions

- CYP450 induction: ↓ efficacy of oral contraceptives / warfarin / glucocorticoids
- Rx that ↑ Phenytoin levels: Valproate / Alcohol (acute intake) / Diazepam / Isoniazid
- Rx that ↓ Phenytoin levels: Carbamazepine / Phenobarbital / Alcohol (chronic intake)
- Additive CNS depression with other CNS depressants

2) Carbamazepine

Action & Uses :

- MOA: Identical to phenytoin Blocks sodium channels
- Also used for Bipolar Disorder & Cranial Nerve Neuralgias
- **Epilepsy:** Better safety profile → Preferred over phenytoin



MOA: Carbamazepine suppresses high-frequency neuronal discharge in and around seizure foci.

- Mechanism is identical to Phenytoin: Delayed recovery of sodium channels from their inactivated state.

Adverse effects

1. CNS effects
    - Minimal cognitive effects vs. Phenytoin
    - Some sedation & visual disturbances → ↓ over time
2. Hematologic effects
    - Rare risk of severe bone marrow suppression
    - Monitor baseline and periodic CBC
3. Dermatologic effect (Same as phenytoin)
    - Also SJS & TEN associated with **HLA-B*1502 genetic polymorphism**
    - 5% of patient of Asian descent → Recommended pre-Tx testing
4. Electrolyte imbalance: due to ↑ ADH secretion → ↑ Water retention → Hyponatremia & osmolarity
5. Birth defects : ↑ risk of spinal tube defect → Minimize with folic acid supplement

Interactions:

- CYP450 induction: ↓ efficacy of oral contraceptives / warfarin / glucocorticoids
- Phenytoin & Phenobarbital: Additive CYP450 induction
- Grapefruit Juice: ↑ peak & trough levels by 40%

3) Valproate

Action & uses

- Uses: **Only AED effective against all types of seizures (including absence seizure)**
    - Effective against all types because it has 3 mechanisms of action (including ↓ T-type Ca^{2+} channels influx)
    - Absence seizure is related to calcium channels influx (Valproate targets this)
- Epilepsy**:** 1st-line Rx option
- Also used for Bipolar Disorder & Migraines

3 mechanisms of action:

1) Same as Phenytoin & Carbamazepine
2) ↓ T-type Ca^{2+} channels influx
3) GABA inhibition

Adverse effects

1. GI disturbances: Very common → Mitigate with enteric-coated formulation
2. Hepatotoxicity:
    - Rare fatal liver failures but high risk in children < 2 years old (1 in 500)
    - Monitor LFT & do not combine with other Rx in high risk patients
3. Pancreatitis: Potentially fatal bleeding → Patient education on early symptoms
4. Hyperammonemia
    - Risk of ↑ ammonia when combined with Topiramate (new AED) → Monotherapy preferred
    - Monitor for hyperammonemia encephalopathy
5. Pregnancy-related effects:
    - Highly teratogenic during 1st trimester (still teratogenic after)
    - ↑ risk of neural tube defects & cognitive impairment

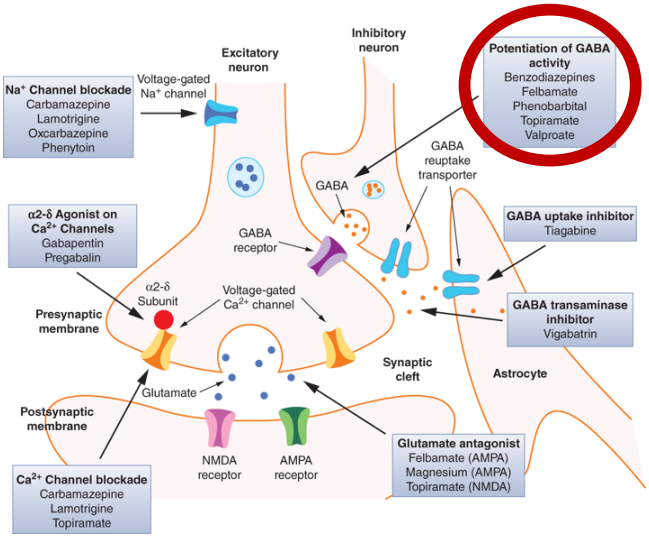
Interactions:

- Phenytoin: Displaces phenytoin from plasma proteins → ↑ activity
- Phenobarbital: ↓ metabolism → ↑ phenobarbital concentration
- Carbapanem antibiotic: ↓ valproate plasma levels → ↑ seizure risks

4) Phenobarbital

Action & Uses

- Action: Barbiturate → It potentiates ↑ GABA opening
- Uses: (1) Status Epilepticus management + (2) All seizures except absence → 2nd-line option after safer Rx have failed



Main Adverse Effects:

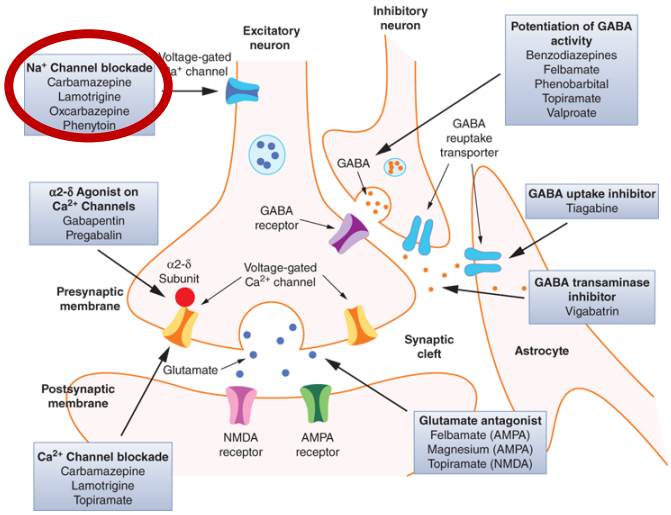
1. CNS depression: Sedation & drowsiness
2. Physical dependence → risk of withdrawal & overdose
3. Highly teratogenic

Main Interactions:

- CYP450 Induction: See phenytoin & carbamazepine
- CNS depressant: Additive effects
- Valproate increases phenobarbital levels by 40% → adjust dosage if combined

Newer AEDs

1) Oxcarbazepine



Action & uses

- Action: Same as carbamazepine: Blocks sodium channels
- Uses: Partial seizures in patients 6 years old and older
  → Similar safety profile to the older AEDs

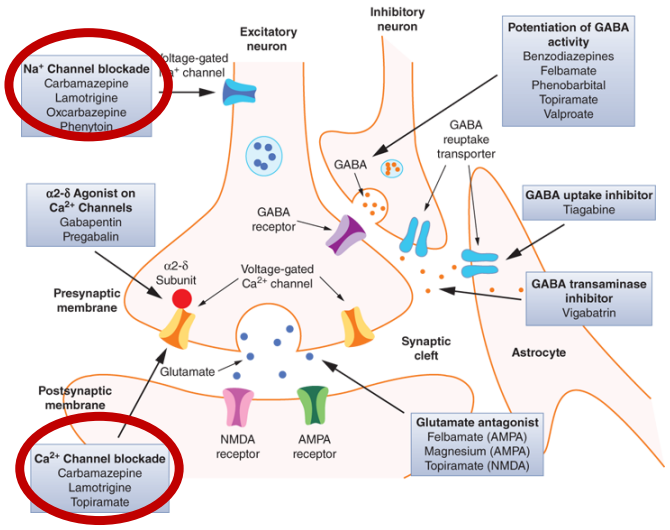
Main Adverse Effects:

1. CNS depression: Sedation & drowsiness
2. Significant hyponatremia
3. Hypothyroidism → Discontinue Rx (do not supplement)
4. Less bone marrow suppression vs. Carbamazepine
5. Risk of SJS or TEN skin rashes
6. Risk of multiorgan hypersensitivity reactions
7. Teratogenic risk

Main Interactions:

- Phenytoin: ↑ Phenytoin toxicity + ↓ Oxcarbazepine efficacy
- CYP450 Induction: ↓ Oral contraceptive efficacy
- Valproate & Phenobarbital: ↓ Oxcarbazepine levels

2) Lamotrigine



MOA: Action: ↓ Na^+ & Ca^{2+} influx

- Blocks sodium channels and (2) blocks calcium channels.
- Both actions decrease release of glutamate (an excitatory neurotransmitter).

Uses: Partial & Tonic-Clonic seizures in 16+ patients

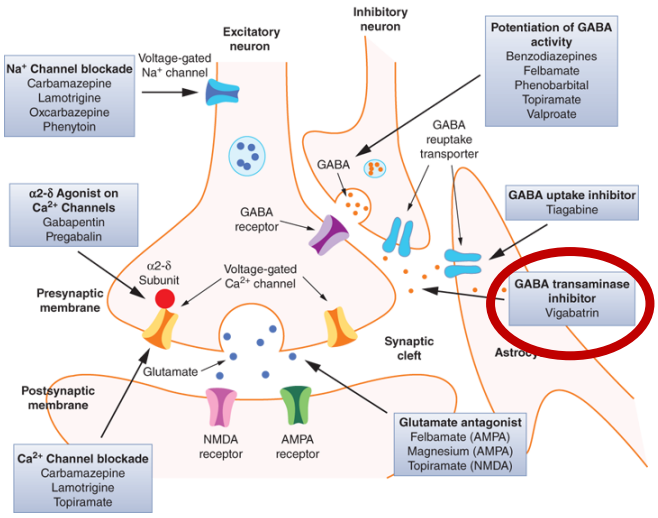
Main Adverse Effects:

1. Most common: GI disturbances & headaches
2. Risk of SJS or TEN skin rashes → Greatest if under 16yo
3. ↑ aseptic meningitis & suicide risk
4. Unclear teratogenic action

Main Interactions:

- CYP450 Inducers: ↓↓ Ora Lamotrigine's $T_{1/2}$
- Valproate: ↑↑ Lamotrigine $T_{1/2}$ & risks of SJS/TEN (skin rashes) → avoid combination
- Estrogens: ↓ levels of both Lamotrigine & oral contraceptives

3) Vigabatrin → Act on GABA



Action & uses

- Action: Inhibition of GABA breakdown → ↑ GABA inhibition
- Uses: Partial seizures adjunct & infantile spasms
    - Only option for infantile spasms (severe seizure disorder in infants)

Main Adverse Effects:

- Most common: Drowsiness & Headaches
- Most serious: Irreversible vision loss in 30% of patients
    - Loss of peripheral vision or retinal damage
    - Baseline and every 3 months vision tests
    - Discontinuing does not reverse present damage
- Other serious ADR: ↑ depression suicide risk

Main Interactions:

- Retinal damage: ↑ risk wth Rx promoting glaucoma (Ex.: Glucocorticoids & TCAs)
- CYP2C9 induction: ↓ Phenytoin levels

DRUGS FOR SPASMS & SPASTICITY (CH. 25)

Muscle Spasticity vs. Spasms

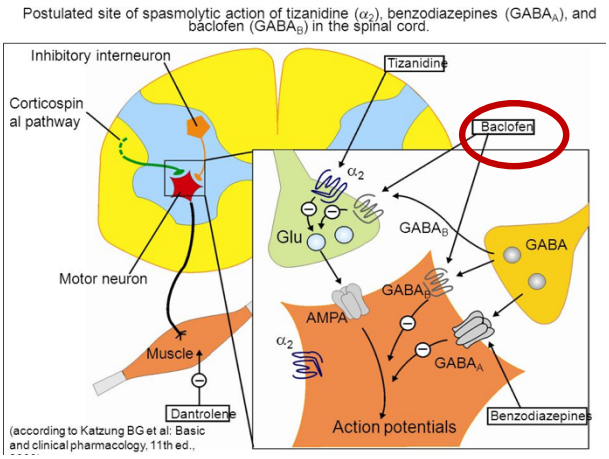
Spasticity	Spasms
- ↑ Muscle tone, spasms & ↓ dexterity - Common causes: MS & cerebral palsy - Tx: CNS-acting (change the transmission in the brain going to the muscles) & direct muscle relaxants	- Involuntary muscle contractions - Causes: Epilepsy, Trauma, Hypocalcemia - Nondrug Tx: Physical therapy, heat application - Drug Tx: CNS-acting muscle relaxants & NSAIDs

Muscle Relaxants

Drug	Indication	Common Adverse Effects	Notes
Centrally Acting Muscle F			
Baclofen [Lioresal, Gablofen]	Spasticity due to spinal cord injury or CNS condition	CNS depression, dizziness, headache, nausea, vomiting, constipation, urinary retention	Abrupt withdrawal can cause seizures and hallucinations. Taper slowly over at least 1–2 weeks.
Cyclobenzaprine [Fexmid, Amrix]	Musculoskeletal pain and muscle spasms	CNS depression, dizziness, anticholinergic effects (dry mouth, blurred vision, photophobia, urinary retention, constipation)	Administration with food increases bioavailability.[b] Contraindicated for patients taking MAO inhibitors. May cause serotonin syndrome in patients taking SSRIs and related antidepressants
Dantrolene [Dantrium, Revonto, Ryanodex]	Spasticity due to spinal cord injury or CNS condition	Muscle weakness, drowsiness, dysphagia, hoarseness, nausea, erectile dysfunction, diarrhea. Flushing with IV administration.	IV formulation is used for malignant hypothermia. Hepatic toxicity can be life-threatening.

Spasticity Agents

1) Baclofen



MOA

- Baclofen acts centrally within the brain or spinal cord to suppress hyperactive reflexes involved in regulation of muscle movement.
    - Acts on GABA receptors to (1) block glutamate release and to (2) decrease activation of the receiving neurons (acts on both sides of the synapse)
    - Action: ↑ GABA → ↓ spinal cord hyperactive muscle reflexes
- You want to stop the AP from going to the muscle → to stop muscle contraction (resolve spasticity)

Uses:

- No direct muscle-relaxant action → No ↓ in muscle strength
    - Preferred over Dantrolene when significant muscle weakness (bcs you don't want to further exacerbate that)
- Muscle spasticity associated to MS & spinal cord injuries

Kinetics: Minimal hepatic metabolism / Urine excretion / $T_{1/2}$ = 4h

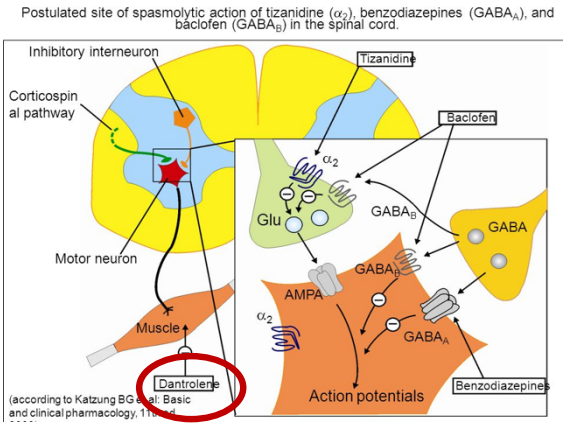
Adverse Effects:

- CNS Depression: Drowsiness & fatigue → ↓ over time (Related to inhibition of NT transmission)
- GI Disturbances: Constipation & urinary retention in 8-10% cases
- Withdrawal: Intrathecal withdrawal > PO withdrawal (Hallucinations /seizures/ organ failure/ death

Contraindications/Interactions:

- Other CNS Depressants: Additive effects
- Anticholinergic drugs: ↑ Urinary retention

2) Dantrolene



MOA: Acts directly on skeletal muscles → Direct muscle relaxant

- Relieves spasm by suppressing release of calcium from the sarcoplasmic reticulum → Muscle is less able to contract.
    - Direct muscle action → Significant ↓ in muscle strength
    - Minimal effects on smooth & cardiac muscle contraction
        - These muscles do not rely as much on Calcium storage (uses calcium as it goes) vs muscles.

Uses: Muscle spasticity associated to MS, SCI & Cerebral palsy

- Also used vs. Malignant Hyperthermia (excessive muscle contractions that lead to drastic increase (↑) in Temperature

Kinetics: Prodrug → Hepatic activation / Feces excretion / $T_{1/2}$ = 4-11h

Adverse Effects:

- Hepatotoxicity: 1:1000 risk / especially in women over 35
  - Baseline and periodic LFT / Short-term lowest effective dose
- Other ADRs: Muscle weakness, Drowsiness & GI disturbances

Drug for Muscle Spasms

Cyclobenzaprine

Action & Uses

- Action: CNS acting → Inhibits brainstem motor activity
- Uses: Best drug for acute muscle spasm and associated pain
  - Inefficient vs. Spasticity

Kinetics:

- Extensive hepatic metabolism: healthy $T_{1/2}$ ≈ 8-37h / $T_{1/2}$ ≈ 1 week with hepatic impairment
  - CYP3A4 / 1A2 / 2D6
  - Extensive enterohepatic cycling further ↑ $T_{1/2}$
    - When the drug is reabsorbed in the bile → Stays in the system longer

Adverse Effects:

- CNS Depression: Drowsiness & fatigue → ↓ over time
- Anticholinergic effects: dry mouth / blurred vision / urinary retention
- Cardiac rhythm disturbances: Similar to TCAs → ↑ HR & conduction delays (due to activity of NE)
  - Contrindications/Interactions:
  - Antidepressants: MAOIs contraindication & ↑ risk of 5-HT syndrome with SSRIs & TCAs
  - Alcohol & other CNS depressants: Additive effects

Legend

5HT : Serotonin

ADR: Adverse drug reaction

CNS: Central nervous system

LFT: Liver function test

MOA: Mechanism of action

NE: Norepinephrine

NT: Neurotransmitter

Pt: Patient

Rx: Drug

Tx: Treatment