Parkinsonism Characteristics

Neurodegenerative Disease

Symptoms include: tremor, postural instability, slowed movement (bradykinesia), rigidity, shuffling

Combination of rigidity, bradykinesia, tremor, and postural instability

Non-motor symptoms: anxiety, depression, confusion, cognitive impairment, personality changes, apathy, fatigue, sleep disorders, autonomic function abnormalities, dysphagia, choking, sweating, sphincter dysfunction.

The disease is **incurable**, generally progressive, and increased disability with time.

**Pharmacologic treatment is used to treat symptoms and improve quality of life.

Importance of Tapering Off Therapy

Anti-Parkinson drugs must be tapered. Not tapering leads to a syndrome that resembles "neuroleptic malignant syndrome" due to sudden "dopamine antagonist effects"

A 4 week tape is suggested

Signs similar to NMS: fever, severe "pipeline" rigidity, tachycardia, sweating

Drug Categories/Mechanisms of Action

Periphery:	-COMT inhibition (Entacapone, Tolcapone, Opicapone) DOPA DC Inhibitors (Carbidopa) Levodopa
Brain:	-MAO-B Inhibitors (Selegiline, Rasagiline) COMT Inhibitors (Tolcapone) Dopamine Receptor Agonists (Pramipexole, Ropinirole non erogt) (Bromocriptine ergot not used)

Drug Categories/Mechanisms of Action (cont)

Other:	Amantadine (mechanism unknown) Antimuscarinics (benztropine, trihexyphenidyl, biperiden, ect)

Parkinson Dyskinesia

A complication of L-Dopa therapy is dyskinesias-abnormal, choreiform, and involuntary movements usually involving the neck, trunk, and upper extremities. Dyskinesias are often associated with peak antiparkinsonian benefit, although they can also develop during the rise and fall of L-dopa effects. They are too much movement secondary to the extension of pharmacologic effect or too much striatal dopamine receptor stimulation. They are much more likely to occur with L-dopa therapy than with dopamine agonist therapy.

Adenosine Antagonist

*Adenosine is a G protein receptor in the striatum that modulates the body's response to dopamine

Drug: Istradefylline (Nourianz)

MOA: adenosine antagonist interferes with GABA release and releases dopamine (gives patients a better voluntary movement capability)

Indications: adjunct to levodopa/carbidopa for treatment of "off episodes"

Formulation: oral

Side Effects: constipation, dizziness, nausea, little chance of insomnia, dyskinesia is the most common side effect even though the risk is relatively low

Adenosine Antagonist (cont)

Considerations: once daily dosing, reduces "off time" by an hour and seems to be better tolerated than COMT-I and DA agonists in regard to dyskinesias and compulsive behavior. Lower risk of psychotic symptoms reported.

Drug integrations with CYP3A4 inhibitors, dose adjustments required (max of 20 mg with from inhibitors)

Levodopa-Carbidopa (Dhivy)

MOA: Levodopa replenishes dopamine levels, carbidopa is a dopa decarboxylase inhibitor

Indications: Triple scored for ease of titration (IR product)

Side Effects: Dyskinesias, motor fluctuations, nausea, confusion, constipation, dry mouth, headaches, loss of appetite, orthostatic hypotension, discolored sputum and cough (Inbrija)

Contraindications: CI in patients with suspicious undiagnosed skin lesions or history of melanoma.

Dopamine Agonists

Drugs: **Pramipexole (Mirapex, MirapexER), Ropinirole (Requip, Requip XL), Rotigotine (Neupro)**

MOA: Agonists of dopamine

Indications: better for younger patients, first line in those less than 50 (still less effective than levodopa), can be added to levodopa to reduce off time and improve symptoms or to help with dyskinesias that are sometimes caused by levodopa

Formulation: Oral, Rotigotine is a skin patch (used for early Parkinson's more continuous DA stimulation)

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Dopamine Agonists (cont)

Side Effects: hallucinations, somnolence, may impair impulse control, other side effects are similar to levodopa-carbidopa

Contraindications: Avoid in patients with a history of addictions, impaired impulse control, psychosis, cognitive impairment, recent MI

Considerations: Lower risk of dyskinesias with these agents, Bromocriptine falls in this category, but is rarely used anymore (D2 agonist)-> it is an ergot. **DA agonists have higher risk of neuropsychiatric symptoms, BUT less risk of motor symptoms**.

Levodopa Inhaler (Inbrija)

Not for patients with lung disease

Onset in 10 minutes

Duration of 1 hour

Treatment of Essential Tremor

Dysfunction of beta receptors has been implicated in some instances of essential tremor and this is evident by the fact that they may respond well to beta blockers such as metoprolol and propranolol.

The most useful is propranolol, metoprolol can be used in patients with concomitant pulmonary disease that prevents them from using propranolol.

Propranolol (higher doses required at least 120 mg/daily divided) long acting version preferred with patients for less dosing.

CAUTION in patients with asthma, CHF, depression, or hypoglycemia (just due to BB side effects)

Amantadine (Symmetrel)

MOA: antiviral medication (not used for the flu anymore) also potentiates DA functionality by influencing synthesis/release and reuptake, also a NMDA receptor type antagonist (decreases glutamate, antidyskinetic effect)

Indications: can be used to target tremor, or added to levodopa in progressed disease for dykinesias

Formulations: Oral

Side Effects: confusion, insomnia, hallucinations, depression, dizziness, orthostatic hypotension, **livedo reticularis** (cosmetic problem only, due to spasms of blood vessels or blood flow problem near the surface of the skin)

Contraindications: CI in severe renal impairment, **caution in suicidal ideation** D/C at the first sign of psychotic symptoms

Considerations: Gocovri is the ER version. Efficacy may wane after weeks or months, only used for later disease for dyskinesia. Taken once at bedtime.

MAOIs

Drugs: Selegiline (zelapar), Rasagiline (Azilict), Safinamide (Xadago)

MOA: MAO-A breaks down NE, 5HT, and dopamine, MAO-B breaks down dopamine only. MAOIs stop the action of MAO A/B. This helps to preserve level of dopamine.

Indications: Mild benefit in early disease (must have DA left to worry about rate of breakdown), not beneficial as a monotherapy ->works best in combination (Safinamide is NOT effective alone at all, only in combo to reduce response fluctuations)

Formulations: Oral, Selegiline now has a transdermal patch (achieves higher plasma levels than oral)

MAOIs (cont)

Side Effects: hallucinations, orthostatic hypotension, nausea, HTN, dry mouth, vivid dreams, HA, insomnia. May worsen dyskinesias when used with levodopa. Agitation and insomnia are most common with selegiline, Safinamide has less nausea.

Considerations: can be added to levodopa to reduce off time, keeps DA around longer, increases duration of action of levodopa. **Drug interactions (antidepressants, tramadol, meperidine, dextromethorphan, amphetamines, and other MAOIs pose a risk for serotonin syndrome)** Selegiline is most "Activating" so consider taking in the morning first thing

Overall lower risk of neuropsychiatric effects compared to DA agonists, and less risk of dyskinesia compared to levodopa

Levodopa gel (Duopa)

Gel

Levodopa: Why can't we just give Dopamine

Tyrosine->L-Dopa->Dopamine

Dopamine is unable to cross the blood brain barrier by itselt.

However, the precursor levodopa crosses the BBB where it is then converted to Dopamine

There is also the peripheral inactivation of L-Dopa by COMT

So, Levodopa must be administered with Carbidopa (DDC Inhibitor) or Entacapone/Tolcapone (COMT Inhibitor) to prevent the breakdown in the periphery.

When levodopa is used alone, it has to be given in large doses to overcome metabolism.

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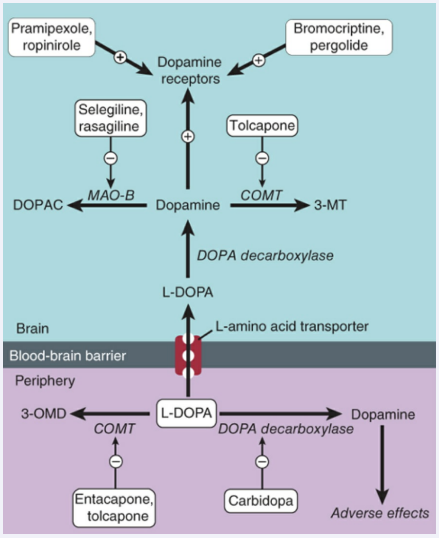
Levodopa: Why can't we just give Dopamine (cont)

This is why it is often given with another agent such as Carbidopa (a dopa decarb-oxylase inhibitor) or a COMT inhibitor to overcome its metabolism to DA so more is available to cross the BBB

Giving levodopa with carbidopa reduces the daily levodopa requirements by 75%

The goal is that Levodopa is converted to Dopamine once in the brain

Drug Categories/Mechanisms of Action



Tremor Types

Intention Tremor	Involuntary contractions that occur during voluntary movement. Most commonly affects the limbs and speech muscles. There is no real treatment, if drug induced then discontinue or reduce dose.

Tremor Types (cont)

Essential Tremor	A tremor without intentional movement. Happens all the time. Hands and upper limbs are most commonly affected. Can be worsened with anxiety or intentional movement.
Parkin-son's Tremor	Tremor at rest. Gone when moving.

Levodopa-Carbidopa-Entacapone (Stalevo)

MOA: Levodopa replenishes dopamine levels, carbidopa is a dopa decarboxylase inhibitor

Indications: COMPT inhibitor added

Formulation: Oral

Side Effects: Dyskinesias, motor fluctu-ations, nausea, confusion, constipation, dry mouth, headaches, loss of appetite, orthos-tatic hypotension, discolored sputum and cough (Inbrija)

Considerations: Tolcapone better penetrates the BBB and can act both peripherally and centrally

Levodopa-Carbidopa (Sinemet, Rytary)

MOA: Levodopa replenishes dopamine levels, carbidopa is a dopa decarboxylase inhibitor

Indications: First line choice, good for elderly patients

Formulation: Oral

Side Effects: Dyskinesias, motor fluctu-ations, nausea, confusion, constipation, dry mouth, headaches, loss of appetite, orthos-tatic hypotension, discolored sputum and cough (Inbrija)

Contraindications: CI in patients with suspicious undiagnosed, skin lesions, or history of melanoma

Levodopa-Carbidopa (Sinemet, Rytary) (cont)

Considerations: Most effective drug for Parkinson's motor symptoms, but it has the highest risk for dyskinesias and motor fluctuations. Take 30 minutes before eating to enhance absorption because food can decrease absorption. "Off episode"=s-ymptoms like tremor return between carbo/levo doses, this becomes more prominent as the disease progresses. There is a lower risk of neuropsychiatric side effects compared with DA agonists. Usually choose IR product for initial therapy due to ease of titration. *Patients should **NOT** take large doses of B6 because it will cause peripheral conversion of L-dopa to DA

COMT Inhibitors

Drugs: Entacapone (Comtan), Opicapone (Ongentys), Tolcapone (Tasmar)

MOA: Inhibit COMT to prevent the breakdown of Dopamine in the periphery

Indications: used as an adjunct to levodo-pa-carbidopa for "wearing off" NEVER as a monotherapy

Formulation: Oral

Side Effects: **discolored urine** (reddish brown), nausea, diarrhea, liver toxicity (TOLCAPONE- requires monitoring), low blood pressure/dizziness (Opicapone) weight loss (opicapone)

Considerations: when added to levodopa to reduce off time, it prolongs the action of levodopa by diminishing its peripheral metabolism . Combo product **stalevo (levo--carbi-entracpone)**, Entacoapone taken at the same time as levodopa-carbidopa (up to 6x per day)

Entacapone is generally preferred because it has not been associated with hepatotox-icity.

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Anticholinergics

Drugs: Trihexyphenidyl, Benztropine

MOA: antagonist at M receptor in basal ganglia, help antagonize M receptors to help with rigidity and tremors (ensure smooth motor action) Helps to restore balance of ACh and DA.

Indications: Used to target tremor (because unopposed ACh release), especially those <60 years of age

Side Effects: dry mouth, constipation, urinary retention, drowsiness, confusion, blurry vision, mydriasis

Contraindication: CI in glaucoma, BPH, and dementia. Caution in the elderly (increased anticholinergic effects)

Apomorphine (Apokyn)

MOA: non-selective dopamine agonist

Indications: used for acute treatment of "off episodes" in advanced disease, rapid onset. Can reverse "off episode" in 10 minutes, used for rescue therapy

Formulation: oral, SQ

Side Effects: runny nose, yawing, edema, mouth tissue swelling (SL film), nausea often a complaint (can pre-treat with antiemetic, not 5HT antagonist) **Warning: hypotension, syncope, QT prolongation, psychosis, hallucinations, impulse control, excessive sleepiness**

Considerations: short duration of action, average SQ dosing was TID in trial, SL can be given 5 times per day (2 hours apart). Can pre-treat with anti-emetic to prevent N/V (do not use 5HT antagonist med for this like ondansetron due to increased hypotension risk) Requires initial titration to check BP/pulse because HUGE risk of hypotension/syncope

Pathophysiology of Parkinson's

In Parkinson's disease there is **loss of the dopamine-containing neurons in the substantia nigra** (A progressive degeneration of the Nigro-Striatal tract). DA in normal physiology is present in the brain help to coordinate movement.

These neurons normally project tot he caudate putamen (one piece of the basal ganglia) where the **dopamine inhibits firing of the cholinergic neurons**. These cholinergic neurons form excitatory synapses onto other neurons that project out of the basal nuclei. **The result of the loss of dopamine-containing neurons is that the cholinergic neurons are now free to fire without their normal inhibition. This is like a car going down a hill without any brakes.**

Striatum-> receives information from Neocortex and Substantia Nigra (sends DA to coordinate)

Without DA, there is more GABA resulting in increased action of GABA which leads to inhibition of the motor cortex

Without dopamine, there is decreased inhibition of ACh so there is an increase in cholinergic activity.

This imbalance between inhibition and excitation leads to the manifestation of symptoms.

Over all the goal, pharmacologically is to replenish dopamine levels, mimic action of dopamine, and to antagonize the excitatory action of ACh on GABA.

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