

DRUGS IN MOVEMENT DISORDERS: TRUTHS, MYTHS AND MORE

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We will discuss commonly used medications in the movement disorder patient

- Who are our patients?
- What medications do we use?
- Why do we choose certain medications?
- What common side effects or interactions can occur?

Who are our patients?

Patients with:

- Parkinson's disease *
- Essential tremor *

- Atypical parkinsonism (vascular parkinsonism, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration)
- Tic disorders

- Ataxia or cerebellar disorders
- Myoclonic disorders
- Huntington's disease

What medications do we use?



Parkinson's disease medications

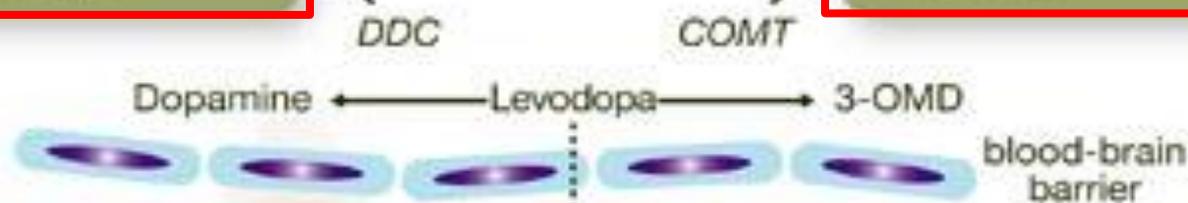
- Carbidopa/levodopa
- Dopamine agonists
- Monoamine oxidase B (MAO B) inhibitors
- Catechol-O-methyl transferase (COMT) inhibitors
- Anticholinergics
- Amantadine

DDC inhibitors

- Prevent peripheral breakdown of levodopa

COMT inhibitors

- Prevent peripheral breakdown of levodopa



Levodopa

- Converted to dopamine within the brain

Levodopa

Dopamine

DOPAC

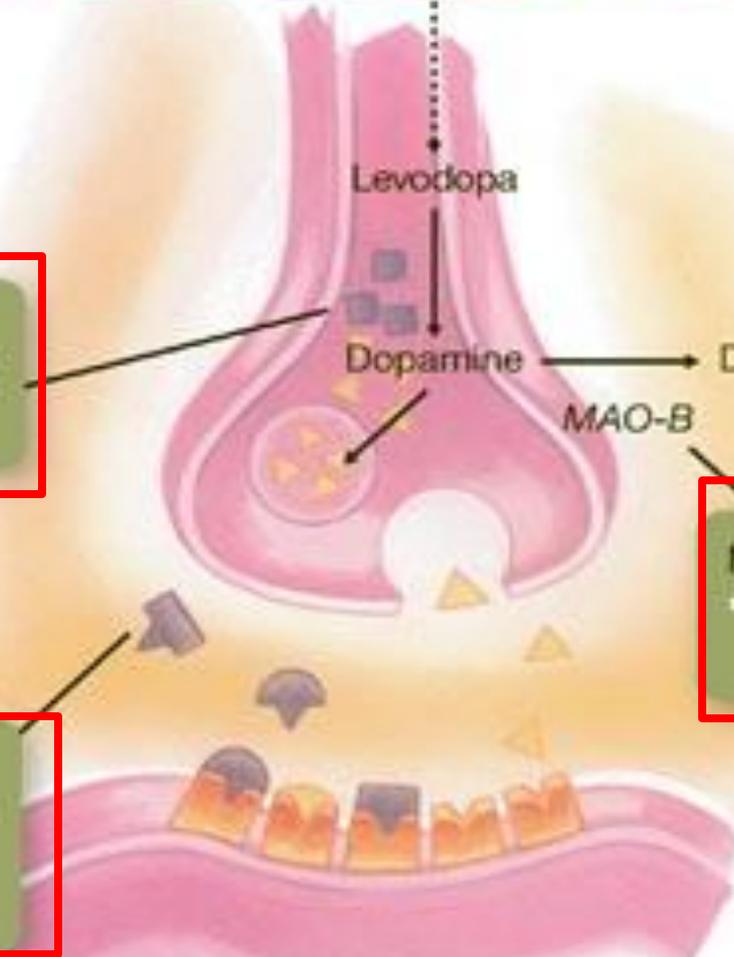
MAO-B

MAO-B inhibitors

- Prevent further breakdown of dopamine

Dopamine agonists

- Post-synaptic mimicry of naturally occurring dopamine



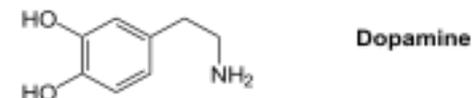
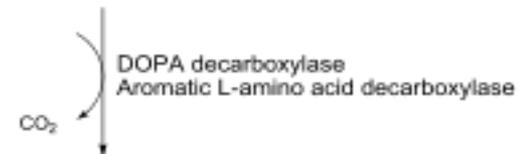
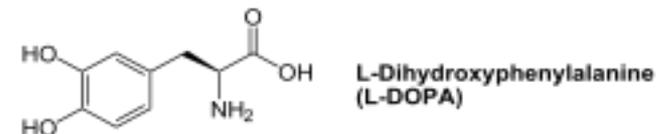
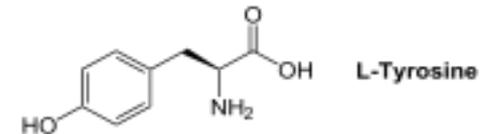
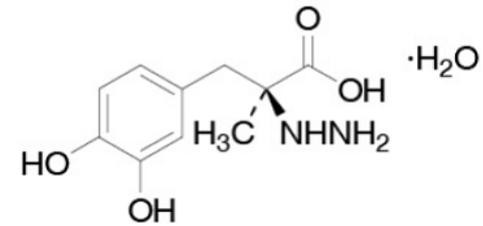
Carbidopa/Levodopa

- Carbidopa

- decarboxylase inhibitor (prevents breakdown of levodopa in extra-cerebral tissues)
- does not cross the blood brain barrier and therefore does not affect the CNS metabolism of levodopa
- decreases the amount of levodopa required to produce a response by 75% and increases the plasma half life of levodopa from 50 minutes to 90 minutes

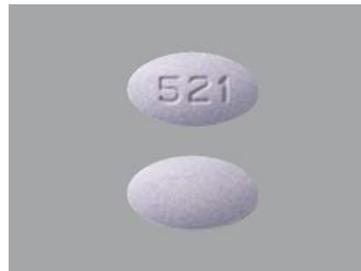
- Levodopa

- amino acid that becomes dopamine by removal of a carboxyl group



Formulations

- c/l 10/100 (IR)
- c/l 25/100 (IR)
- c/l 25/250 (IR)
- c/l CR/SA 25/100
- c/l CR/SA 50/200



Parcopa



- Orally disintegrating tablets – not really a true “sublingual” preparation as it is still absorbed in the lower GI tract and not through the oral mucosa
- Similar pharmacokinetics to IR c/l with a slightly shorter time to T_{max}
- c/l 10/100 mg, c/l 25/100 mg, c/l 25/250 mg
- Inactive ingredients include aspartame, phenylalanine and citric acid

Rytary



- Combination of IR and SA forms
- c/l 23.75/95 mg, c/l 36.25/145 mg, c/l 48.75/195 mg, c/l 61.25/245 mg
- Inactive ingredients include talc and gelatin
- Initial peak at 1 hour
- Plasma concentrations are maintained for 4-5 hours before declining
- Bioavailability of levodopa from Rytary is approximately 70% relative to IR c/l (dose conversion can be tricky)

- Caution in patients with cardiac history
 - Placebo controlled study in patients with early PD – percent who reported ischemic CV adverse reactions
 - 2.4% (7/289) Rytary treated patients
 - 1.1% (1/92) placebo treated patients
 - Active controlled study in patients with advanced PD – percent who reported ischemia CV adverse reactions
 - 0.7% (3/450) Rytary treated patients
 - 0% (0/471) of oral IR c/l treated patients

these patients all had a previous history of ischemic heart disease or CV risk factors

Duopa

- Enteral suspension of c/l (4.63 mg c/20 mg l per mL)
 - Maximum recommended dose is 2000 mg of levodopa over 16 hours (1 cassette)
 - Prior to initiating duopa, patients must be converted to IR c/l from all other forms of levodopa
 - Administered through a PEG-J tube (can be given short term through an NG tube if needed)
 - Peak plasma levels reached in 2.5 hours
 - Must be stored in freezer (-20 degrees C) and thawed in refrigerator (2-8 degrees C) prior to dispensing (12 week expiration after thawing)
 - Gastric emptying rate does not influence the absorption of duopa as it is administered by continuous intestinal infusion
 - 5% of patients (19/412) developed a generalized polyneuropathy – most often axonal sensorimotor polyneuropathy



Dopamine agonist

- Ropinirole (Requip)
 - Agonist at D₂ and D₃ receptors, stimulates postsynaptic D₂ receptors in basal ganglia
 - Rapidly absorbed, peak concentration in 1-2 hours with a half life of 6 hours
 - Inactive ingredient: anhydrous lactose
- Pramipexole (Mirapex)
 - Same mechanism of action as above
 - Peak concentration in 2 hours, half life 8-12 hours (12 hours in elderly population)
- Rotigotine (Neupro)
 - Same mechanism of action as above
 - Patch form, continuous 24 hour delivery of medication
 - Contains sodium metabisulfite – can cause allergic reactions in patients with sulfite sensitivity





- Apomorphine
 - Injectable form (subcutaneous)
 - Rapid absorption, peak concentration in 4-12 minutes, half life of 30 minutes
 - Need to used in conjunction with antiemetic – trimethobenzamide (Tigan)
 - Cannot use with ondansetron – several reports of profound hypotension and LOC
 - Caution in patients with sulfite sensitivity – contains sodium metabisulfate
- Pergolide, bromocriptine (rarely used)

MAO-B inhibitor

- Rasagiline (azilect)
 - Irreversibly inhibits the action of MAO-B enzyme -- decreases the breakdown of dopamine in the brain and inhibits the reuptake of dopamine at the presynaptic receptor
 - 5 times more potent than selegiline
- Selegiline
 - Amphetamine metabolite – can have a stimulant effect causing insomnia, anxiety and hallucinations



COMT inhibitor



- Entacapone/Tolcapone
 - Reversible, peripherally acting COMT inhibition -- decreases the breakdown of dopamine
 - Increases the half life of levodopa by 30-50% (from 1.5 to 2.5 hours)
 - Rapidly absorbed, T_{max} of 1 hour. Bioavailability not affected by food
 - Used mostly for patients with “wearing off” prior to next dose
 - Not used alone must be given with levodopa
 - Can cause increased dyskinesias, diarrhea, abdominal pain
 - Tolcapone with 3 patients deaths due to development of fulminant hepatitis

Anticholinergics

- May be of benefit for “tremor predominant” PD
- Trihexyphenadyl (Artane), benztropine (Cogentin)
- Side effects:
 - Dry mouth
 - Blurred vision
 - Constipation
 - Urinary issues
 - Memory issues/confusion
 - Hallucinations



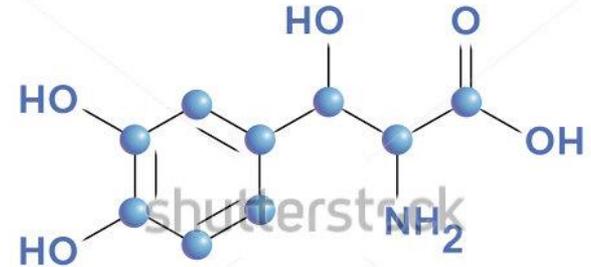
Amantadine

- Antiviral drug originally developed to prevent influenza but was found to improve mild motor symptoms in PD patients
- May help to reduce dyskinesias secondary to levodopa use, but benefit if transient
- Side effects:
 - Hallucinations
 - Confusion
 - LE edema
 - Livedo reticularis



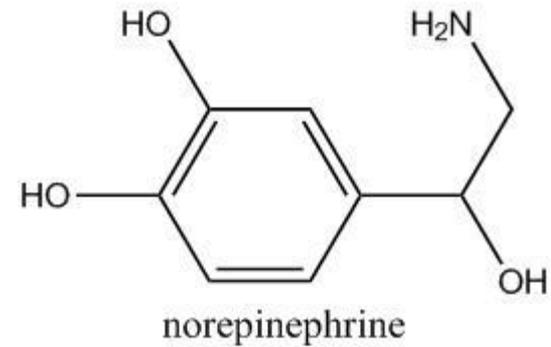
Droxidopa

- Synthetic amino acid precursor which acts as a prodrug to norepinephrine
- Unlike NE, droxidopa can cross the BBB
- Used for neurogenic orthostatic hypotension
- Used in Asia since 1989, FDA approved here in February 2014
- Inactive ingredient: gelatin
- Caution when used in combination with other agents that increase BP (midodrine, triptans)
- Caution in patients with pre-existing CHF, ischemic heart disease or arrhythmias



Droxidopa

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New drugs in development

- New COMT inhibitors
- New MAO-B inhibitor
- New dopamine agonists
- Adenosine A (2A) receptor antagonists (proposed to block unwanted activity of receptors in the BG)
- Alpha-adrenergic receptor antagonists (proposed to help balance the GABA activity in the BG)
- Serotonergic agonists (proposed to enhance the transmission of serotonin)
- Neuroprotective medications
- Pioglitazone (DM drug)
- Isradipine
- Glutathione
- Growth Factor Neurturin

Essential tremor medications

- Topiramate (topamax)
- Primidone (mysoline)
- Propranolol (nderal)
- Clozapine
- Metoprolol
- Mirtazapine
- Atenolol
- Gabapentin
- Zonisamide
- Pregabalin
- Alcohol
- Benzodiazepines
- Botulinum toxin

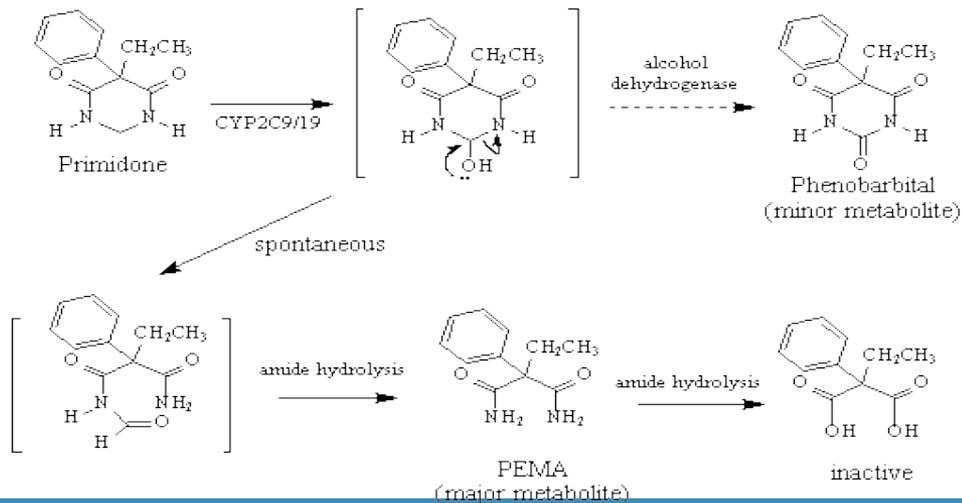
Topiramate



- Exact mechanism of action unknown for tremor control but blocks voltage-dependent sodium channels, augments GABA activity and antagonizes glutamate
- Rapid absorption, peak plasma concentration within 2 hours
- Not extensively metabolized, 70% is excreted unchanged in the urine
- Inactive ingredient: lactose monohydrate

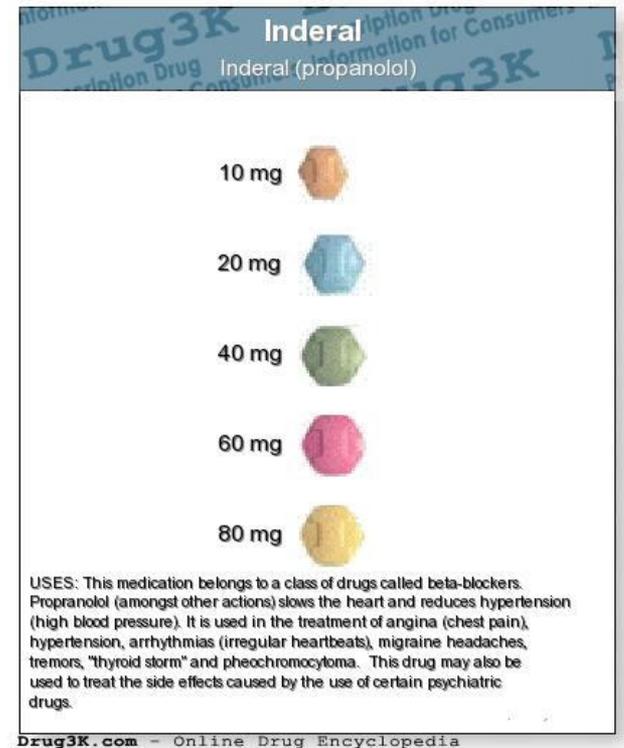
Primidone

- Exact mechanism of action unknown for tremor control
- Metabolized to phenobarbital which acts as a GABA_A receptor agonist and antagonist at some subtypes of glutamate receptors
- Phenobarbital is metabolized by the liver and induces many P₄₅₀ isozymes (especially CYP2B6)
- Inactive ingredients: lactose monohydrate, sodium lauryl sulfate, talc



Propranolol

- Non-selective beta-adrenergic receptor blocking agent
- Rapidly absorbed with peak plasma concentration from 1-4 hours after oral dose
- High first pass metabolism by the liver (P₄₅₀ system), only approximately 25% of propranolol reaches the systemic circulation
- Inactive ingredient: gelatin



Why we choose certain medications...

What common side effects or interactions
can occur?

PD

- There is no “correct” starting medication – this will vary by providers and depending on patient profile
- Often use dopamine agonists first for younger patients
- Need to take into account co-morbidities and side effects

ET

- Guidelines from the AAN 2011
 - Propranolol (regular or long acting) or primidone (Level A)
 - Topiramate, atenolol, gabapentin, sotalol (Level B)
 - Insufficient evidence for amantadine, clonidine, clozapine, pregabalin, zonisamide, metoprolol, nicardipine (Level U)

Side effects/interactions

Carbidopa/levodopa

- Nausea
- Mood/behavioral changes
- Daytime somnolence
- Orthostatic hypotension



- Dark urine or sweat due to increased urinary excretion of dopamine (more commonly seen in patients also taking entacapone)
- High protein diet may delay the absorption of levodopa due to competition for binding as both are transported across the small intestine by the same amino acid transport system
- Excessive stomach acidity may also delay the absorption of levodopa due to a delay in stomach emptying into the small intestine
- Iron salts (often a part of a multivitamin) also may reduce the amount of levodopa available to the body by forming chelates with the carbidopa and levodopa

- Good initial choice for ???
 - “Older” patients with suspected PD
 - Patients with significant mood disorder (other than depression or anxiety)

Dopamine agonists

- Mood/behavioral changes (more common in DA than with levodopa)
 - obsessions, compulsions, impulse control disorders – sexual, gambling, shopping...
 - hallucinations
- Daytime somnolence (sleep attacks)
- Leg edema
- Orthostatic hypotension



- Ropinirole is metabolized by P₄₅₀ enzyme system (CYP_{1A2})
- Drug level altered by enzyme inducers (smoking, omeprazole) and inhibitors (ciprofloxacin, verapamil, grapefruit juice, cumin, tumeric)
- Hormone replacement therapy also reduces clearance (estrogen effect)

- Pramipexole is not metabolized by P₄₅₀ enzymes (90% of drug excreted in urine unchanged)
- For renal impairment
 - Cr clearance 30-50 mL/min -- maximum dose is 0.75 mg tid
 - Cr clearance 15-30 mL/min – maximum dose is 1.5 mg daily

- Rotigotine patch has aluminum backing – must be removed before cardioversion or MRI
- Heat may increase drug absorption – avoid direct heat source (heating pads, electric blankets, heat lamps, hot tubs, hair dryers, prolonged direct sunlight)

- Good initial choice for ???
 - “younger” patients with PD symptoms
 - Patient with mild PD symptoms
 - Patient with restless legs syndrome

Topiramate

- Cognitive slowing
- Numbness and tingling of fingers and toes
- Weight loss (average of 5 lbs – mechanism unclear)
- Metallic taste with drinking “dark sodas”



- Decreased sweating and hyperthermia
- Reduce dose in patients with renal impairment (Cr clearance <70 mL/min)
- Risk of secondary angle closure glaucoma (myopia, eye pain, ocular redness) and visual field deficits
- Risk for metabolic acidosis – caused by renal bicarbonate loss
 - Caution in conditions which would predispose patients to acidosis – renal disease, severe respiratory disorders, diarrhea, ketogenic diet, some drugs – metformin – can lead to fatigue, renal stones, altered mental status, weakness
- Kidney stones (occurs in approximately 1.5% of patients) – suspected due to inhibition of carbonic anhydrase which reduces urinary citrate excretion and increases urinary pH

Primidone



- Sedation
- Ataxia
- Vertigo
- Use with caution in patients on other sedative drugs (muscle relaxants, benzodiazepines, opiates) or with chronic ETOH use
- Phenobarbital is metabolized by the liver and induces many P₄₅₀ isozymes (especially CYP_{2B6}) therefore dosage adjustments need to be made for patients with hepatic failure

Notify other providers when starting this medication as it may alter the levels of other medications (statins, mental health medications...)

Propranolol

- Fatigue
- Bradycardia
- Hypotension
- Worsening of depression
- Worsening of asthma
- Use with caution in diabetics on insulin (may mask symptoms of hypoglycemia)
- SJS
- SLE-like reaction



- Chronic renal failure has been associated with a decrease in propranolol metabolism via downregulation of P₄₅₀ activity resulting in a lower "first-pass" clearance = higher peak plasma levels in patients with renal failure as well as in patients with hepatic failure
- P₄₅₀ inhibitors increase plasma levels of propranolol (amiodarone, cimetidine, fluoxetine, paroxetine, ciprofloxacin, fluconazole)
- P₄₅₀ inducers decrease plasma levels of propranolol (phenytoin, phenobarbital, cigarette smoking)

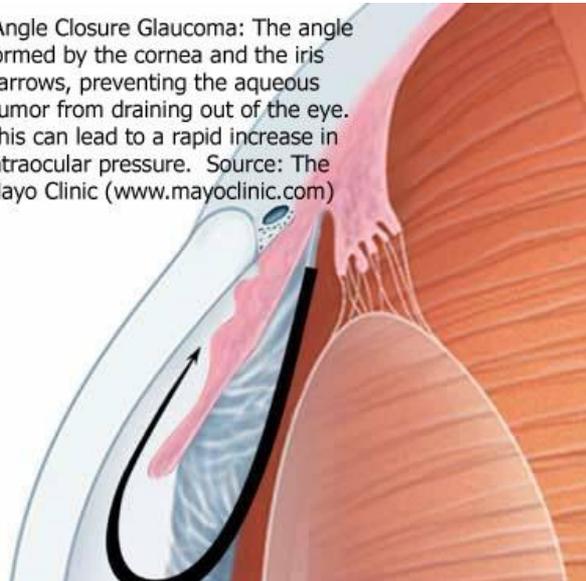
Other interesting facts...



Glaucoma

- Levodopa therapy is contraindicated in patients with narrow/closed angle glaucoma
- While levodopa primarily is a dopaminergic agent, there may be cross-over onto cholinergic receptors
- These receptors are generally responsible for pupil dilation which can cause narrowing of the angle which can increase eye pressure.

Angle Closure Glaucoma: The angle formed by the cornea and the iris narrows, preventing the aqueous humor from draining out of the eye. This can lead to a rapid increase in intraocular pressure. Source: The Mayo Clinic (www.mayoclinic.com)

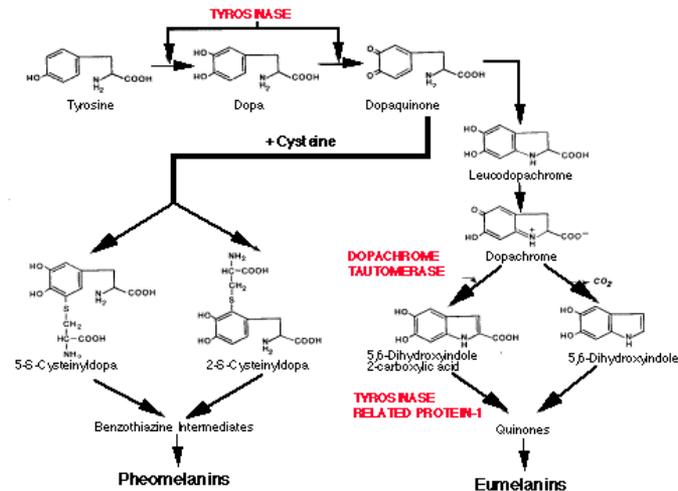


Narrow/closed angle glaucoma

Melanoma

- Overall risk for cancer in patients with PD is lower but risk for malignant melanoma is higher (4x increased risk)
- Unclear etiology – initially suspected due to relationship between dopamine and melanin (dopamine is precursor of melanin), but more complex than that – new genetic studies going on as studies finding early PD patients with melanoma (not treated with levodopa)

The Melanin Chemical Pathway



- From the current literature there is :
 - Consistent data supporting an association between cutaneous melanoma and PD
 - A possible association between non-melanoma skin cancers and PD
 - Insufficient data to conclude on the association between L-dopa and melanoma in PD patients
 - Insufficient data to conclude on the association between MAO-B inhibitors, DA or other anti-parkinsonian drugs and melanoma or other skin cancers in PD patients
 - Insufficient data about the risk factors for skin cancer in PD patients and therefore no EBM recommendations regarding the need for periodic dermatological screening

- When you order carbidopa/levodopa a box pops up that says “ok to take pyridoxine with this combination”what is this all about?
 - Pyridoxine (B6) may reverse the effects of levodopa by increasing the rate of decarboxylation, but carbidopa inhibits this action



- To eat or not to eat....

- Protein competes with levodopa for transport across the small intestine and can decrease its absorption/plasma concentration
- Protein rich foods increase the bioavailability of propranolol by about 50%
- Patients who take levodopa on an empty stomach will often complain of nausea, can add additional carbidopa 25 mg to each dose or instruct patients to take with carbohydrate meal

- Can these medications be stopped abruptly or do they need to be tapered?
 - There is a risk of neuroleptic malignant syndrome with abrupt discontinuation of sinemet or a dopamine agonist, but this is rare
 - Primidone must be tapered off as metabolite is phenobarbital – increased risk of seizures with abrupt discontinuation
 - Propranolol must be tapered off due to risk of rebound hypertension if abruptly stopped

Conclusions...

- Variability in medication and dosing regimen between providers
- No “one correct” starting medication for all patients
- New medication trials currently underway
- Providers need to be aware of side effects, inactive ingredients and pharmacology/pharmacokinetics of medications

Questions?

References:

- <https://www.aan.com/Guidelines/Home/GetGuidelineContent/493>
- <http://www.uptodate.com/contents/parkinson-disease-treatment-options-medications-beyond-the-basics>
- <http://www.uptodate.com/contents/pharmacologic-treatment-of-essential-tremor>
- <http://www.rxlist.com/duopa-drug/indications-dosage.htm>
- <http://www.rxlist.com/rytary-drug.htm>
- <http://www.rxlist.com/northera-drug.htm>
- <http://www.rxlist.com/mysoline-drug.htm>
- <http://www.essentialtremor.org/treatments/medication/>
- Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology*. 2011;76(23):2002-2009. doi:10.1212/WNL.0b013e31821e554e
- Yacoubian TA, Standaert DG. Targets for Neuroprotection in Parkinson's Disease. *Biochimica et biophysica acta*. 2009;1792(7):676-687. doi:10.1016/j.bbadis.2008.09.009.
- Ondo WG, Shinawi L, Moore S. Comparison of orally dissolving carbidopa/levodopa (Parcopa) to conventional oral carbidopa/levodopa: A single-dose, double-blind, double-dummy, placebo-controlled, crossover trial. *Mov Disord*. 2010; 25(16):2724-7. doi:10.1002/mds.23158
- Fullerton T. Levodopa pharmacodynamics. *Neurology*. 1994; 44(2)365-6
- Topiramate induced sudden loss of vision. Baloch M, Siddiqui MA. *J Pak Med Assoc*. 2012; 62(10):1092-3
- Hammerstad JP, Woodward WR, Nutt JG, Gancher ST, Block GA, Cyhan G. Controlled release levodopa/carbidopa 25/100 (Sinemet CR 25/100): pharmacokinetics and clinical efficacy in untreated parkinsonian patients. *Clin Neuropharmacol*. 1994; 17(5):429-34
- Kestenbaum M, Fahn S. Safety of IPX066 , an extended release carbidopa-levodopa formulation, for the treatment of Parkinson's disease. *Expert Opin Drug Saf*. 2015; 14(5):761-7. doi: 10.1517/14740338.2015.1015986