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Saint John's Health Center
PROVIDENCE Health & Services

Update on medications for motor symptoms of PD

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apda AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Overview of talk

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- PD Motor Manifestations
- Medication options
- Early and Advanced Stages
- Tips / FAQs

PD: motor manifestations

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- **Bradykinesia**
  - Most characteristic clinical hallmark of PD
  - Slowness in ADLs, movement, reaction times
  - Impairment/breakdown of fine motor movement
  - Sialorrhea (reduced frequency of swallow)
  - Monotonic, hypophonic dysarthria
  - Facial Hypomimia
  - Reduction of armswing (loss of automatic movement)
  - Micrographia
  - Bradyphrenia
- **Rigidity**
  - Increased resistance throughout range of movement
  - Cogwheeling if underlying tremor
- **Rest Tremor**
  - Pill-rolling, 4-6 Hz; may experience an internal tremor
  - Though 32% of PD pts never manifest tremor
- **Postural Instability**
  - Common cause of falls, hip fractures
  - Festination – chasing center of gravity
- **Freezing**
  - Sudden, transient inability to move
  - Motor blocks, a form of akinesia

PD: basics of motor management

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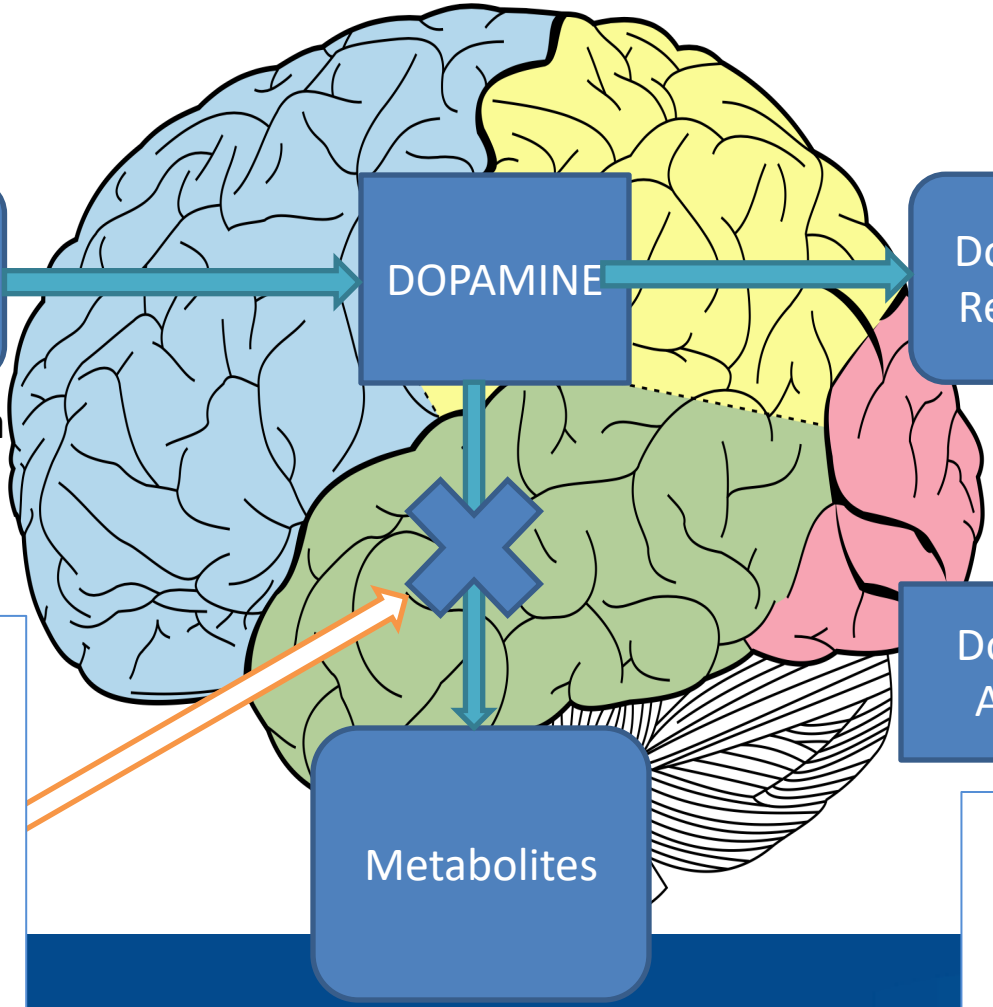

Carbidopa/Levodopa (Sinemet, Stalevo, Rytary, Inbrija)

MAO-B inhibitors:
Rasagiline (Azilect)
Selegline (Eldepryl)
Safinamide (Xadago)
COMT inhibitors:
Entacapone (Comtan, Stalevo)

Pramipexole (Mirapex)
Ropinirole (Requip)
Rotigotine (Neupro patch)
Apomorphine

Levodopa

Aka L-dopa; carbidopa-levodopa; Sinemet; Rytary

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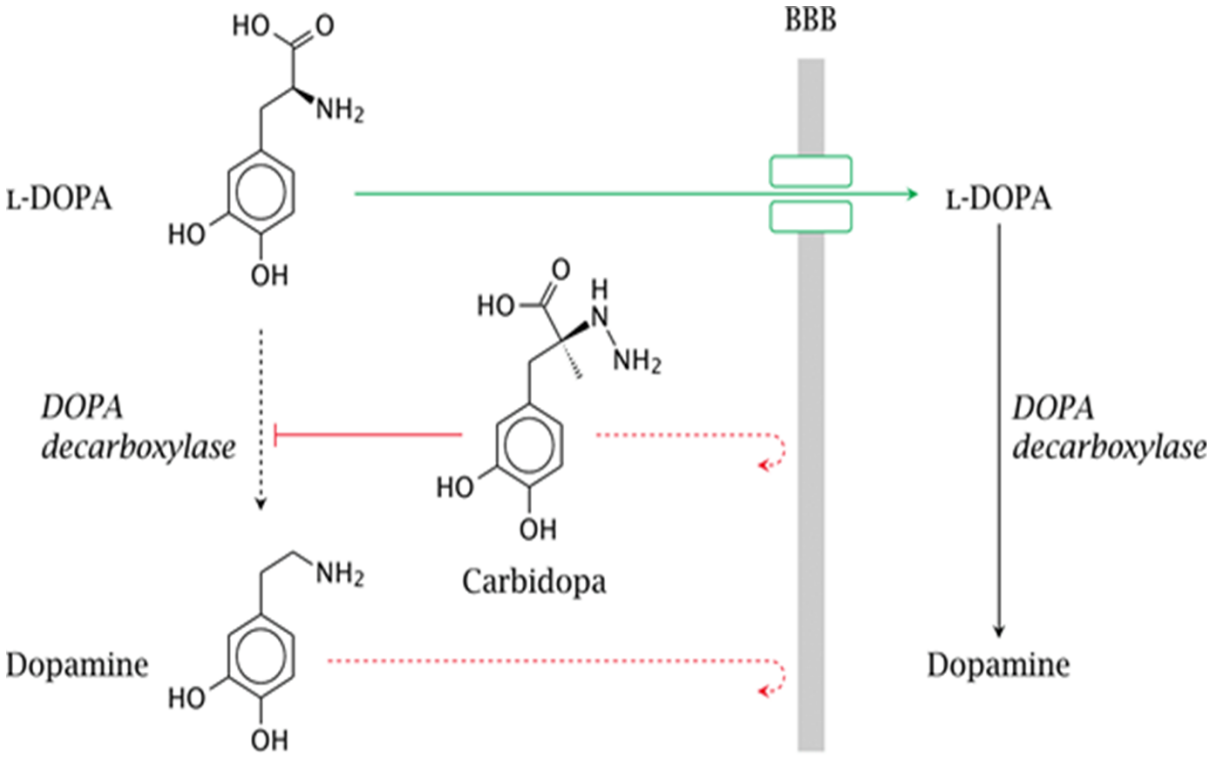

- Precursor to Dopamine

  Ratio of 1:4 typical (25 mg carbidopa: 100 mg levodopa)

  Formulations: Sinemet IR and CR, Parcopa (orally disintegrating), Rytary (capsules)

  Pros:
  - Most effective PD med

  Cons:
  - Some patients may experience nausea, lightheadedness, dizziness, fogginess, which typically dissipate
  - Confusion, hallucinations can occur in older pts or those with dementia
  - As the disease progresses, dyskinesias and motor fluctuations are common

Dopamine agonists

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- Act on the same receptors as natural dopamine

- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro patch)
- Apomorphine (Apokyn, Kynmobi)

- Pros:
  - No dyskinesias or fluctuations
- Cons:
  - Less effective than levodopa
  - Some pts experience somnolence, edema, hallucinations
  - Impulse control disorders (compulsive eating, gambling, spending)
  - Potential withdrawal syndrome

MAO-B inhibitors

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- Reduce the breakdown of natural dopamine

- Rasagiline (Azilect)
- Selegline (Eldepryl)
- Safinamide (Xadago) (2017)

- Pros:
  - less dyskinesias or fluctuations
  - Fewer side effects
- Cons:
  - Less effective than levodopa
  - Can cause nausea, LH, insomnia, anxiety
  - Can interact with medications including OTC and supplements

Changes in levodopa responsiveness

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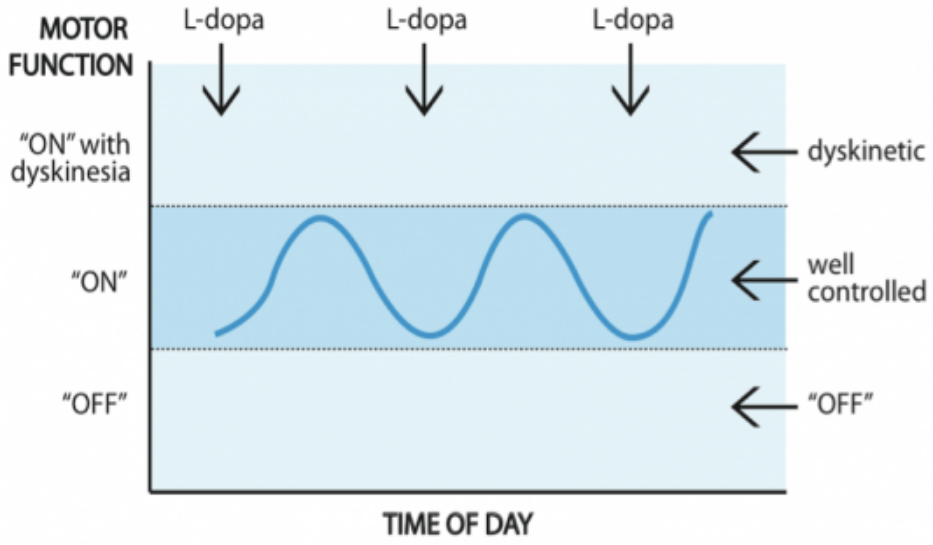

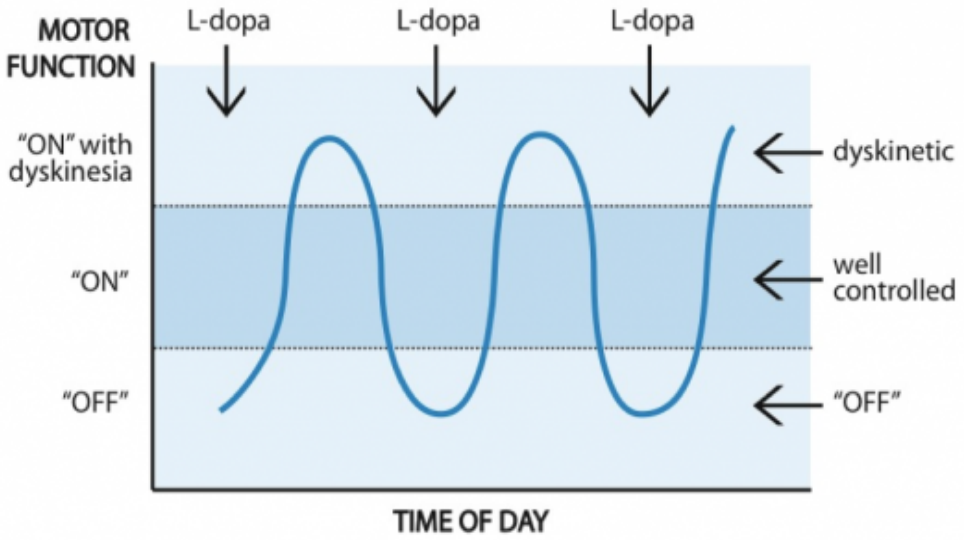

Changes in levodopa responsiveness

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- ON time = feeling well, muscles are loose, movements are smooth
- OFF time = feeling stiff, rigid, stuck, frozen, slow, fatigued
- DYSKINESIAS = abnormal involuntary movements (does not include tremor)
- Non-motor fluctuations
- Within 5 years of treatment with levodopa:
  - 50% of patients experience dyskinesias, but only 20% find them troublesome
  - About 40% of patients experience troublesome on-off fluctuations

Longer acting levodopa

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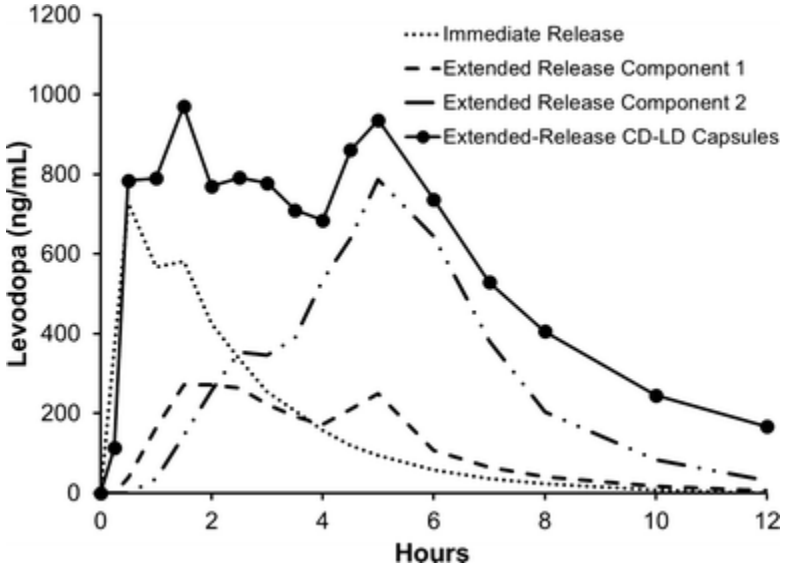
- Controlled release (CR) carbidopa/levodopa: 25/100; 50/200
- Extended release carbidopa/levodopa: Rytary
  - 23.75/95
  - 36.25/145
  - 48.75/195
  - 61.25/245
  - Combination of two components with different time release
  - Can be opened and sprinkled onto applesauce



Mittur et al., 2017

Even longer acting levodopa

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- Duopa (levodopa intestinal gel infusion)
  - Reduces OFF time ~ 2 hours vs placebo
  - 16-hour administration via a cartridge into a PEJ tube
  - Bypasses the stomach
  - Same benefit as levodopa, but a smoother concentration over the course of the day
  - Complications include tube malfunction, ileus, pulled tube, neuropathy, usually only in the first 2 weeks

Future options

Non-oral formulations of levodopa

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- Subcutaneous levodopa (ND0612, Neuroderm and ABBV-951, Abbvie)
  - Pump/Patch form of carbidopa/levodopa
  - Both are recruiting phase 3 trials now
    - ABBV-951 enrolling at UCLA, Cedars, Pasadena
    - BouNDless enrolling in Reseda and Long Beach
  - Met primary and secondary endpoints of pharmacokinetics

Future options

oral formulations of levodopa

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- Accordion Pill (Intec)
- Meant to make it last longer in the GI tract
- Phase 3 trial did not meet primary end point
  - Secondary analysis found higher doses were effective
- New phase 3 trial being planned
- Next generation 24-hour medication being developed

Olanow/Intec Pharma, 2019

COMT inhibitors

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- Reduce the breakdown of levodopa
- Only work when given with levodopa

- Entacapone (Comtan, Stalevo)
- Opicapone (Ongentys)

- Pros:
  - Can improve “ON” time
- Cons:
  - Can exacerbate dyskinesias and other levodopa side effects (hypotension, hallucinations, impulse control issues)
  - Can cause somnolence

Inhalable levodopa (Inbrija)

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- Pros
  - Good for unpredictable or sporadic “OFF” time
  - Rapid and predictable onset, lasting 1-4 hours
- Cons
  - Pure levodopa so pts still have to take oral carbidopa
  - Side effects of cough / URI (improved with having water prior to and after medication and taking slower breath)
  - Does not prevent “OFF” time

Sublingual apomorphine (Kynmobi)

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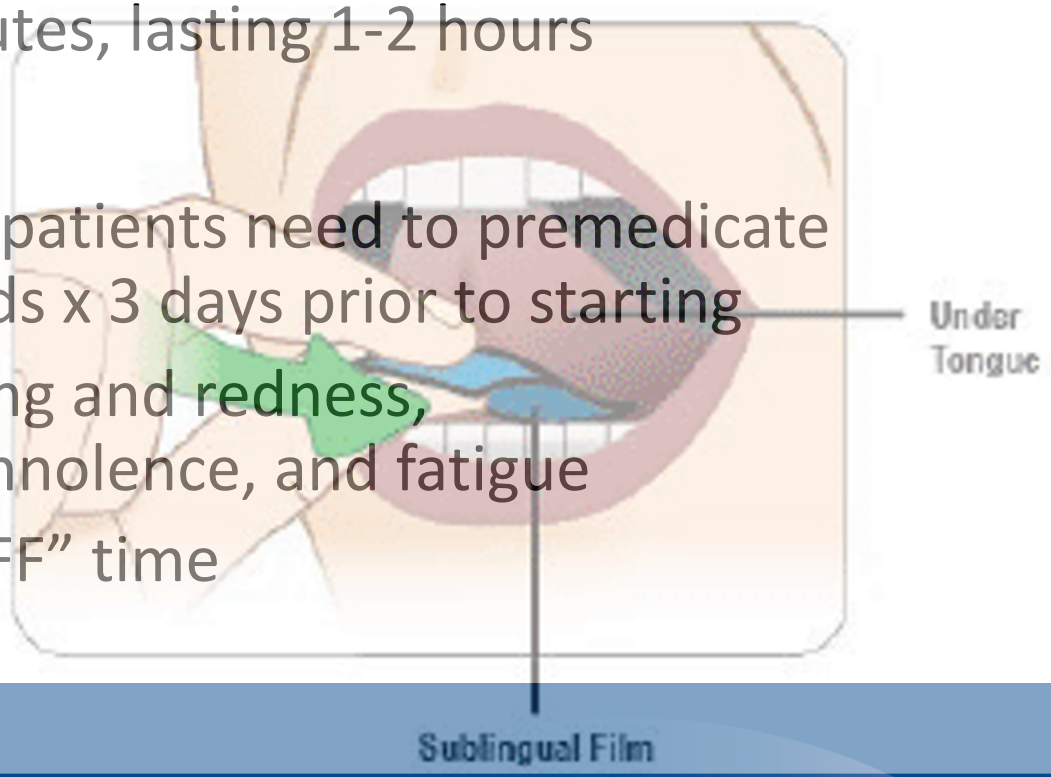
- Pros
  - Good for unpredictable or sporadic “OFF” time
  - Onset within 30 minutes, lasting 1-2 hours
- Cons
  - Can cause nausea so patients need to premedicate with anti-nausea meds x 3 days prior to starting
  - Can cause oral swelling and redness, lightheadedness, somnolence, and fatigue
  - Does not prevent “OFF” time



Adenosine A2A antagonists: Istradefylline (Nourianz)

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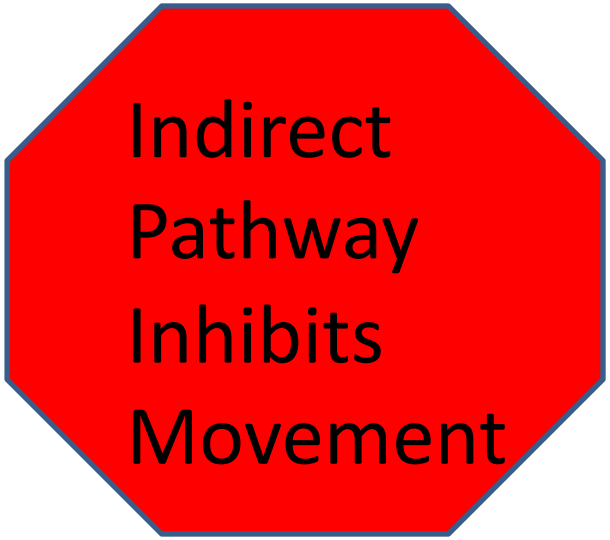

Adenosine A2A receptors

Dopamine

Adenosine A2A antagonists: Istradefylline (Nourianz)

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- Pros
  - Once a day medication to reduce “OFF” time
- Cons
  - Can exacerbate dyskinesias and hallucinations

Current management of dyskinesias

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- Reduce levodopa dose
- Amantadine (NMDA receptor antagonist)
  - Long-acting amantadine:
  - Gocovri, FDA approved August 2017
  - Osmolex, FDA approved February 2018
  - Can cause insomnia, hallucinations, and edema
- Advanced treatment options (DBS)
  - Especially GPi

Early stages of PD: When to start medication?

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- Levodopa does not delay the progression of PD but also does not accelerate progression
- Complications of levodopa treatment ("off" time and dyskinesias) are related to the dose and the duration of the disease, not the timing of when levodopa was started
- Current consensus is that patients should start on medication at the lowest dose without unnecessary delay

Tips on taking meds

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- Levodopa should typically be taken on an empty stomach to improve absorption
- Take medications at the same time of day on a set schedule; set recurring alarms
- Keep a log of the medications you try, including the dose, time of day, improvement or side effects, and dates
- If you are taking newer medications (e.g., Rytary, Nourianz, Xadago) and you need to be hospitalized, bring your medications from home to be administered
- Medications are not enough! Lifestyle factors such as exercise, sleep, diet, social engagement, cognitive stimulation are vital to combine with medications

PD: Meds to avoid

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	Safe Medications	Medications to Avoid:
Antipsychotics	pimavanserin (NuplazidTM, *FDA approved to treat Parkinson's disease psychosis*), quetiapine (Seroquel®), clozapine (Clozaril®)	avoid all other typical and atypical anti-psychotics
Pain Medication	most are safe to use, but narcotic medications may cause confusion/ psychosis and constipation	if patient is taking MAOB inhibitor such as selegiline or rasagiline (Azilect®), avoid meperidine (Demerol®)
Anesthesia	request a consult with the anesthesiologist, surgeon and Parkinson's doctor to determine best anesthesia given Parkinson's symptoms and medications	if patient is taking MAOB inhibitor such as selegiline or rasagiline (Azilect®), avoid: meperidine (Demerol®), tramadol (Rybix®, Ryzolt®, Ultram®), droperidol (Inapsine®), methadone (Dolophine®, Methadose®), propoxyphene (Darvon®, PP-Cap®), cyclobenzaprine (Amrix®, Fexmid®, Flexeril®), halothane (Fluothane®)
Nausea/ GI Drugs	domperidone (Motilium®), trimethobenzamide (Tigan®), ondansetron (Zofran®), dolasetron (Anzemet®), granisetron (Kytril®)	prochlormethazine (Compazine®), metoclopramide (Reglan®), promethazine (Phenergan®), droperidol (Inapsine®)
Anti-depressants	uoxetine (Prozac®), sertraline (Zoloft®), paroxetine (Paxil®), citalopram (Celexa®), escitalopram (Lexapro®), venlafaxine (Effexor®)	amoxapine (Asendin®)

Caution with anticholinergics such as oxybutynin in patients with confusion or elderly patients; caution with alpha blockers in patients with orthostatic hypotension (prazosin, tamsulosin)

Summary

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- Nine new meds for motor symptoms since 2014:
  - Rytary 2014
  - Duopa 2015
  - Xadago 2017
  - Gocovri 2017
  - Osmolex 2018
  - Inbrija 2019
  - Nourianz 2019
  - Kynmobi 2020
  - Ongentys 2020

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- Next month:
- February 1st at noon PST
- Lifestyle Treatment Options
  - Giselle Tamula, NP