



PARKINSON'S DISEASE

SPOTLIGHT ON PARKINSON'S DISEASE: INNOVATIONS IN OFF THERAPY

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PRESENTATION



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MOTOR MANIFESTATIONS OF PARKINSON'S DISEASE (PD)

Bradykinesia

- Most characteristic clinical hallmark of PD
- Slowness in ADLs, movement, reaction times
- Impairment/breakdown of fine motor movement
- Soft, hoarse, monotone voice
- Masked facies
- Reduction of armswing (loss of automatic movement)
- Reduced stride length (dragging foot)
- Micrographia (small handwriting)

Rigidity

- Increased resistance throughout range of movement
- Cogwheeling if underlying tremor

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Rest Tremor

- May begin in one finger then gradually spread to the hand; 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
- "stutter steps"















EVALUATING FOR MOTOR FLUCTUATIONS









EVEN LONGER ACTING LEVODOPA

- 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

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- Complications include tube malfunction, ileus, pulled tube, vitamin deficiency, neuropathy, usually only in the first 2 weeks
- Has been studied for 24-hour infusion











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COMT INHIBITORS

- Reduce the breakdown of levodopa
- Only work when given with levodopa
- Entacapone (Comtan, Stalevo) 200 mg per dose of levodopa
- Opicapone (Ongentys) 50 mg once nightly

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Pros:

- Can improve "ON" time 2 hours
- Ongentys may be more effective than entacapone
- Ongentys can reduce early morning "OFF" time, more so than entacapone

Cons:

- Can exacerbate dyskinesias and other levodopa side effects (hypotension, hallucinations, impulse control issues)
- Can cause somnolence and constipation
- Entacapone can cause discoloration of urine
- Cost







DOPAMINE AGONISTS

Act on the same receptors as natural dopamine

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

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Pros:

 Reduces off time 2.7 hours (neupro patch)

Cons:

- Less effective than levodopa
- Some pts experience somnolence, edema, hallucinations
- Impulse control disorders (compulsive eating, gambling, spending)
- Potential withdrawal syndrome







ADENOSINE A2A ANTAGONISTS

- Istradefylline (Nourianz)
- Can reduce off time by 1.2 hours with once daily dosing
- · Can exacerbate dyskinesias and hallucinations









HELPFUL HINTS FOR MEDICATION CONSISTENCY

- Taking medications on an empty stomach
- Taking medications at consistent times every day
- · Preventing fluctuations of dopamine levels in the brain
 - Reduce risk of developing dyskinesias

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Reduce risk of ON/OFF fluctuations





- Medication sets
 - Fill once a week
 - Help to verify that pills have or have not been taken but do not remind patients
- **Medication alarms**
 - Available as a watch or on a smart phone
 - Will not verify that the med has been taken if patient silents an alert without taking the medication.

MedReady

Alerts a family member or caregiver when medications have not been taken within a certain amount of time.

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LIFESTYLE CHOICES Exercise Adequate Sleep Resilience techniques for stress Mindful awareness Mindset / counseling Water intake • Management of constipation • **ISON DISEASE** ASSOCIATION ngth in opt m. Hope in progress





GUT BACTERIA INHIBITS LEVODOPA ACTION









WHAT AFFECTS LEVODOPA METABOLISM?

- · Levels of specific bacteria:
 - Enterococcus faecalis and Eggerthella lenta
- · Levels of specific enzymes:
 - tyrosine decarboxylase from E. faecalis
- Specific SNPs (gene variant) from *E. lenta* gene that codes for a specific enzyme (dopamine decarboxylase, *dadh*)

Maini Rekdal et al., Science 2019 AMERICAN PARKINSON DISEASE ASSOCIATION Strength in optimism. Hope in progress.

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PROLONGED USE OF LEVODOPA AND DISEASE DURATION ARE ASSOCIATED WITH INCREASED *TDC* GENE-CARRYING BACTERIA



- Altered levels of gut dopamine → Impaired GI motility → SIBO → worsening of motor fluctuations → higher doses → vicious cycle
- In small intestinal bacterial overgrowth (SIBO) associated with PPI use, *Enterococcus* tends to dominate
- Prolonged use of levodopa appears to favor growth of *tdc* bacteria, further lowering efficacy of levodopa
- May identify biomarker for proper levodopa dose
- Some Probiotics contain *tdc* genecarrying *Enterococcus*Van Kessel et al., Nature Communications 2019



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Serum L-dopa

15 30

60 90 120

Time (minutes)



CARBIDOPA DOES NOT BLOCK BACTERIAL METABOLISM

Carbidopa blocks human peripheral decarboxylase enzyme

- · Making levodopa more present in serum and thus brain
- BUT NOT BACTERIAL decarboxylase!

Alpha-fluoromethyl-tyrosine (AFMT), an amino acid, can block bacterial tyrosine decarboxylase

Making levodopa more avail in mice serum

• potential rx for managing motor fluctuations Maini Rekdal et al., Science 2019



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SUMMARY

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









CLOSING REMARKS



Rebecca Gilbert, MD, PhD Vice President, Chief Scientific Officer American Parkinson Disease Association



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