




2019 PFNCA Annual Symposium

Symptom Fluctuations

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Disclosures

I served as a paid consultant for Acorda Therapeutics at an advisory board meeting.

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I will not be discussing the use of off-label products or services or will point out any off-label uses



Overview

- Define symptom fluctuations, ON and OFF states
- Motor and Non-motor OFF symptoms
- Dyskinesias
- Management options and strategies
- Future options



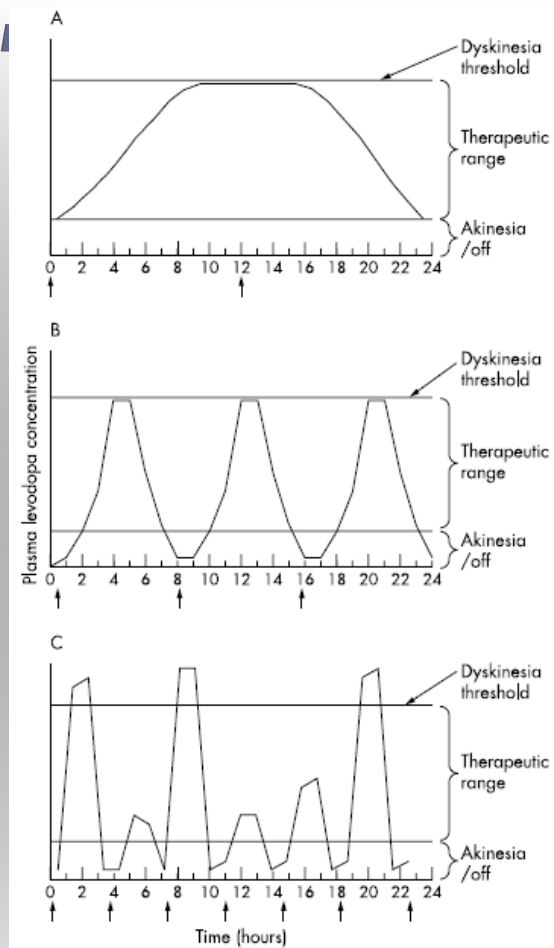
Definitions

- **ON period:** time period when symptoms are controlled
- **OFF period:** time period when symptoms are evident
 - NOTE: there can be MOTOR and NON-MOTOR symptoms
- Fluctuation Types
 - **Wearing off:** re-emergence of symptoms prior to the next scheduled PD medication dose
 - **Delayed ON:** medication onset of effect takes longer than expected
 - **Dose failure:** medication effect fails to occur
 - **Sudden OFF:** medication effect cuts off abruptly and unexpectedly
 - **Morning OFF:** significant OFF symptoms due to lack of medications overnight

Why do fluctuations develop?



- Result of continued degeneration of dopamine-producing cells, leading to a decline in the brain's ability to process external sources of dopamine
- Changes in intestinal motility and absorption
 - Protein effect



Thanvi BR, Lo TCN. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. Postgrad Med J. 2004, 80.

Motor OFF Symptoms

- Rest tremor
- Slowness of movement (bradykinesia)
- Rigidity
- Gait difficulty
 - shuffling
 - freezing of gait
 - postural instability
- Reduced facial expression, softer volume of voice

Non-Motor OFF Symptoms

- Anxiety, panic attack
- Depressed mood
- Shortness of breath, “gasping”
- Pain/discomfort
- “weakness” and/or fatigue
- “feeling poorly”
- Flushed, sweaty
- Slower mental function

Why is this important?


- > 90% respondents to a 2014 MJFox Foundation survey of ~ 3000 reported at least one OFF period/day (~ 30-60 minutes)
 - 65% reported ≥ 2 hours of OFF time/day
 - 50% reported moderate to severe OFF periods – had to stop or avoid activities that they could do when ON
- PD ≤ 5 years: **50%** experienced OFF symptoms vs PD at 15 years: **96%**
- Significant negative impact on QoL and ADLs



Dyskinesias

- Involuntary movements that develop over time with PD medication treatment
 - chorea or dystonia
 - can affect limbs, body, head-neck, face
 - most commonly occurs in ON period
 - initially mild, intermittent; person may be unaware
 - worsens over time, can become intrusive and disabling
- Related to both progression of PD and qualities of PD medications

General Principles of Treatment

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- No clear single, “right” way to treat
 - differences in opinion
 - Important to have a dialogue
 - pros & cons of options
 - Not all treatment options are applicable to all:
 - older age
 - medication sensitive
 - those with dementia
 - A “cocktail” of medications is not uncommon



Medication Options for OFF Symptoms

- Depending on what you are on, consider adding:
 - carbidopa-levodopa (IR tablets)
 - a dopamine agonist (ropinirole, pramipexole, rotigotine/Neupro)
- Add a MAOB inhibitor (selegiline, rasagiline, safinamide/Xadago)
- Add a COMT inhibitor (entacapone, tolcapone)
- Switch to extended release levodopa formulations
 - ER tablets (50/200 mg)
 - ER capsules/Rytary (95 mg, 145 mg, 195 mg, 245 mg capsules)
- Reduce interval between doses of medications
- Increase doses of medications



Pearls in the Use of Levodopa

- Delayed ON:
 - chewing carbidopa-levodopa tablets, take it with carbonated beverage or orange juice
 - avoid taking it with foods heavy in protein
 - take carbidopa-levodopa 30 minutes before full meals, or at least 60 minutes after meals
- Morning OFF: use ER tabs/capsules at bedtime, or take overnight
- Use different doses at different times
- Spot treat w/ extra carbidopa-levodopa doses



Advanced Medication Options


- Use Rytary capsules + carbidopa-levodopa IR tablets in combination
- ER + IR carbidopa-levodopa tablets in combination
- Apomorphine injection (Apokyn)
 - Injected subcutaneously
 - Rapid onset of effect
 - Up to 5X/day
 - Requires pre-medication w/ anti-nausea medication



New and on the Horizon

- Levodopa inhalation powder (Inbrija)
 - Inhaled, pulmonary route bypasses GI tract
 - 84 mg dose (2 capsules) per OFF period, up to 5X/day
 - Onset of effect as early as 10 minutes, full effect by 30 minutes
 - Duration: at least 60 minutes
 - Side effects: cough (15%), UR infection, nausea, discolored sputum
- Apomorphine Sublingual Film (APL-130277)
 - FDA was unable to approve in its present form.
 - FDA requested additional information and analyses, but no new clinical studies are required

Fluctuation Diary

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- Recording/charting your response to medication over the course of the day
 - Time wake up, go to sleep
 - Timing of doses
 - Speed of onset
 - Dyskinesias
 - Meal times
 - Can assist your neurologist in adjusting your medication regimen



Surgical Treatment Options

- Deep brain stimulation (DBS) surgery
 - Medtronic
 - Abbott-St. Jude
 - Boston Scientific
- Duopa – carbidopa-levodopa enteral suspension
- Future: (available in UK/Europe)
 - apomorphine infusion pump

When to consider surgical options?

- Symptom fluctuations that are inadequately managed by medications
- Significant number and duration of OFF periods/day
- Significant/disabling dyskinesias
- Early vs Delaying surgery



Surgical Considerations


- Most helpful for symptoms that respond to oral medications (levodopa)
- Realistic goals: improving ON time, reducing dyskinesias, smoothing out fluctuations
- Contraindications for DBS: dementia, poorly controlled depression
- Mentor programs for Duopa: speak to patients and caregivers who have gone through the process



Past Disappointments, Possible Future

- Adenosine A_{2A} receptor antagonists
 - Tozadenant – Phase III trial shut down in Nov 2017 due to agranulocytosis & sepsis
 - Istradefylline – available in Japan, re-submitted to FDA in Fall 2017
- Subcutaneous delivery of carbidopa-levodopa
 - via small belt-worn pump
 - ND0612L: for moderate Parkinson's disease patients
 - ND0612H: for severe Parkinson's disease patients
- Gene therapy (adeno-associated virus)
 - VY-AADC

Final Thoughts

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- Awareness of fluctuations can lead to better symptom control & QoL
 - There are many management options, but some may not be appropriate for all patients
 - Important to have a dialogue with your neurologist



Thank You!

