

# THE ART OF MEDICATION MANAGEMENT IN PARKINSON'S DISEASE

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# DISCLOSURES



- I have no disclosures relevant to this presentation



## PARKINSON'S DISEASE 101

- First described by James Parkinson in his “Essay on the Shaking Palsy” in 1817
- A neurodegenerative condition of unknown cause with 4 cardinal features:
  - Bradykinesia – slow, clumsy movements
  - Resting tremor
  - Rigidity of the muscles
  - Balance problems



# PARKINSON'S DISEASE 101

- Brain cells (neurons) in a part of the brain called the substantia nigra are slowly lost
- These neurons make a neurotransmitter called dopamine
- Loss of dopamine leads to many of the symptoms of Parkinson's disease



# PARKINSON'S DISEASE 101



- In addition to the loss of dopamine, cells making other neurotransmitters are also lost:
  - Serotonin
  - Norepinephrine
  - Acetylcholine



## HOW IS PARKINSON'S DISEASE DIAGNOSED?

- To this day, the only test that can accurately establish a diagnosis of Parkinson's disease is an autopsy
- Diagnosis is made based on the symptoms and physical exam, with a limited role for diagnostic tests
- There are a number of conditions that can mimic Parkinson's disease, and at each visit, your neurologist will look for signs that point to one of these mimics as the cause of your symptoms.



# SYMPTOMS OF PARKINSON'S DISEASE

- Parkinson's disease has a large variety of symptoms that can be broken into 3 broad categories:
  - Pre-motor
  - Motor
  - Non-Motor
  
- It is important to keep in mind that no two people with Parkinson's disease are the same, and you will likely not experience many of the symptoms that I will describe



## PRE-MOTOR SYMPTOMS

- 5-10 years before the onset of tremor, walking problems or balance issues, many people experience one or more of the following symptoms:
  - Loss of sense of smell/taste
  - Constipation
  - Anxiety and/or depression
  - REM sleep behaviour disorder – vivid dreams, acting out dreams
- These symptoms are believed to be due to the presence of Parkinson's pathology in the olfactory nerves, gut, etc.





# MOTOR SYMPTOMS



- These are the classical symptoms of Parkinson's disease
  - Resting tremor – shaking when the arm or leg is totally at rest. This initially starts intermittently in one part of the body and then spreads and becomes more continuous
  - Rigidity – stiffness of the muscles. Because of this, it is harder to use the muscles and people often feel that their muscles are weak



# MOTOR SYMPTOMS

- Bradykinesia – slowness of movements. This can manifest as reduced swinging of the arms when you walk, soft speech, small handwriting, reduced facial expression and difficulty with fine motor skills
- Loss of balance



## NON-MOTOR SYMPTOMS



- Parkinson's disease is (unfortunately) more than just tremor! The pathology can be found throughout many parts of the nervous system and can cause many different symptoms.
- These can be broken down into several categories



## NON-MOTOR SYMPTOMS: AUTONOMIC

- The autonomic nervous system regulates the body’s “housekeeping” functions
- Constipation
- Delayed gastric emptying → bloating
- Increased frequency and urgency of urination
- Changes in sweating
- Lightheadedness when standing up



# NON-MOTOR SYMPTOMS: PSYCHIATRIC

- Depression
- Anxiety
- Apathy
- Hallucinations
- Paranoia



# NON-MOTOR SYMPTOMS: COGNITIVE

- Impaired planning and problem-solving
- Impaired visuospatial skills



# NON-MOTOR SYMPTOMS: SLEEP



- REM sleep behaviour disorder → vivid dreams, screaming, acting out dreams
- Sleep fragmentation
- Daytime sleepiness
- Fatigue
- Sleep apnea
- Restless leg syndrome



## OTHER NON-MOTOR SYMPTOMS

- Pain
- Sensory changes such as numbness and tingling





# PROGRESSION OF PARKINSON'S DISEASE

- Progression is highly variable from one person to the next
- Early in the course of the disease, it is impossible to predict how an individual will progress
- In general, for a given individual, progression tends to be fairly stable
  - If your symptoms worsen abruptly, it is usually a sign that something else is going on



## TREATMENT OF PARKINSON'S DISEASE

- There is no cure for Parkinson's disease and most available treatments focus on managing the symptoms
- Since the symptoms and response to treatment vary from person to person, there is no standard recipe for the treatment of the condition.
- Treatments must be tailored to each individual depending on the challenges they are facing



## SOME DEFINITIONS

- Kicking in – most people will eventually feel their medication start working anywhere from 15-60 minutes after taking a dose
- Wearing off – when the effect of a dose of medication starts to wane
- On – when your medication is working and your mobility has improved
- Off – when your medication has stopped working (e.g. first thing in the morning or between doses)



# TREATMENT OF PARKINSON'S DISEASE



- The only treatment that slows the progression of Parkinson's disease is physical activity
  - 30 minutes of moderate intensity exercise 5 times per week
  - Moderate intensity = enough to get your heart rate up a bit and be slightly short of breath, but still able to talk to a workout partner



# TREATMENT OF PARKINSON'S DISEASE



- There are a number of effective medications available to treat the motor symptoms of Parkinson's disease
- The goal of treatment is to allow you to live as normal a life as possible for as long as possible



# NON-PHARMACOLOGICAL TREATMENTS

- There is good evidence that mind-body techniques have benefit in PD:
  - Yoga
  - Tai Chi
  - Qigong
  - Mindfulness
  - Biofeedback
  
- Evidence for benefit of acupuncture is inconclusive



# PHARMACOLOGICAL TREATMENTS

- Monoamine oxidase inhibitors
- COMT inhibitors
- Dopamine agonists
- Levodopa
- Vitamins/Nutraceuticals/Supplements/Cannabis



# MONOAMINE OXIDASE INHIBITORS

- Work by preventing dopamine from being broken down by monoamine oxidase
- Selegiline, rasagiline
- Can be used alone in early disease, or to increase the effectiveness of levodopa in more advanced disease
  - Reduce off time by about 45 minutes per day
  - Offs are not as deep





# MONOAMINE OXIDASE INHIBITORS



- Minimal side effects – selegiline can cause insomnia if taken too late in the day
- Health Canada labeling includes some dietary restrictions that have been removed by the FDA
- Theoretical interactions with antidepressants



## COMT INHIBITORS

- Slow the breakdown of dopamine by COMT
- Entacapone
- Must be taken together with levodopa and extends the duration of effect by 15-30 minutes
- Main side effects are orange discolouration of the urine and diarrhea



# DOPAMINE AGONISTS

- Work by directly stimulating dopamine receptors in the brain
- Moderate benefit for symptoms
- Bromocriptine, pramipexole, ropinirole, rotigotine
- Similar side effects to levodopa, but tend to be a bit more severe with agonists



# DOPAMINE AGONISTS

- Compared to levodopa, there is a higher risk of developing impulse control disorders
  - 10% of people taking dopamine agonists, higher risk at higher doses
  - Compulsive gambling, shopping, eating, hypersexuality (including pornography), use of the internet
  - Increase in goal-directed (but purposeless) activity, such as collecting and sorting objects, rearranging furniture, cleaning, etc.
- Can be associated with changes in posture such as leaning to one side (Pisa syndrome) or extreme flexion at the waist (camptocormia)
- Reports of sleep attacks (caution regarding driving), though these are rare



# AMANTADINE

- Complex mechanism of action, working on multiple different neurotransmitters
- Originally developed to treat the flu in the 1960s
- Predominantly used to treat dyskinesias, but can also have some benefit for tremor and stiffness
- Side effects: constipation, dry mouth/eyes, rash, ankle swelling\*, hallucinations\*  
\* = need to stop the medication



# LEVODOPA

- Converted to dopamine by the body and acts as a replacement for the dopamine that is no longer being produced in the brain
- Combined with another drug (carbidopa or benserazide) to prevent the conversion until it reaches the brain
- Still the gold standard for the treatment of the motor complications of Parkinson's disease



# LEVODOPA



- Side effects include nausea, fatigue, lightheadedness when you stand, hallucinations and problems with impulse control (the last two are less common than with dopamine agonists)
- Because it is the most effective treatment, almost everyone with Parkinson's disease will eventually need to go on levodopa



# ADVANCED THERAPIES



- For individuals who cannot achieve acceptable control of their symptoms with oral medications, two advanced therapies are available in Canada:
  - Levodopa/carbidopa intestinal gel (Duodopa)
  - Deep brain stimulation (DBS)





# SUPPLEMENTS

- The following supplements have been found to be ineffective in studies:
  - Creatine
  - Coenzyme Q10
  - Vitamin E
- Small trials of intranasal glutathione have shown a slight benefit on the motor symptoms of Parkinson's disease



# SUPPLEMENTS



- *Mucuna pruriens* extract contains levodopa and has demonstrated benefit for the motor symptoms of Parkinson's disease with fewer side effects
  - studies have all been short term (single doses) and involved small numbers of participants



# CANNABIS

- The available evidence is of poor quality
- The results are contradictory
- Currently, cannabis and its derivatives are not recommended in the treatment of Parkinson's disease, but research is ongoing



# MOTOR COMPLICATIONS OF PARKINSON'S DISEASE

- When treatment is first started for Parkinson's disease, people experience a so-called "honeymoon period" where response to treatment is smooth without any off time.
- As time passes, a combination of changes in the brain due to disease progression and the treatments for the disease, a number of motor complications arise
- Broken into two categories: fluctuations and dyskinesias



# MOTOR FLUCTUATIONS



- Wearing off
  - Sudden offs
  - Random offs
  - “Super” offs
- Delayed kicking in
- Dose failures
- Freezing of gait (FOG)
- Off dystonia



## WEARING OFF

- Generally begins as end-of-dose failure
- Practical definition → <4 hour duration of an adequate dose of levodopa
- Early in disease, healthy neurons are able to take up and store levodopa and release it later when it is needed, so the effect of each dose persists despite a drop in blood levels of levodopa



## WEARING OFF

- As the disease progresses, there are fewer healthy neurons left to store the drug, and this long-duration response is lost



- Each dose of levodopa only lasts 1.5 – 2 hours, so as the disease progresses, you need more doses of the medication

- This does not mean that the medication stops working, but is largely due to changes in the brain due to disease progression



## WEARING OFF

- Sudden offs are those that occur over a period of minutes, as opposed to the slow wearing off that is usually seen
- Random offs can occur at any time. Some people will kick back in again without having to take another dose of medication
- Super offs are periods when you feel worse than if you were not on any medication
- It is unknown how/why these occur





## WEARING OFF

- There are many options available to treat wearing off, each with their own advantages and disadvantages:
  - Higher doses of medication
  - More frequent doses of medication
  - Adding a medication to extend the duration of a dose (e.g. adding entacapone to levodopa)
  - Adding a different type of medication
  - Adding a longer-acting formulation of an existing medication (e.g. levodopa/carbidopa CR)



# OFF-PERIOD DYSTONIA



- Dystonia is a contraction of muscles leading to abnormal postures
- Commonly manifests as leg cramping or toe curling in the early morning when medication levels are at their lowest



## DELAYED KICKING IN

- Defined as taking >30 minutes for a dose of levodopa to start working
  - At its most extreme, the dose fails to kick in at all
- Especially common for the first AM dose
- Due to any or all of:
  - Delayed gastric emptying
  - Constipation
  - Poor absorption due to competition with dietary protein



# FREEZING OF GAIT



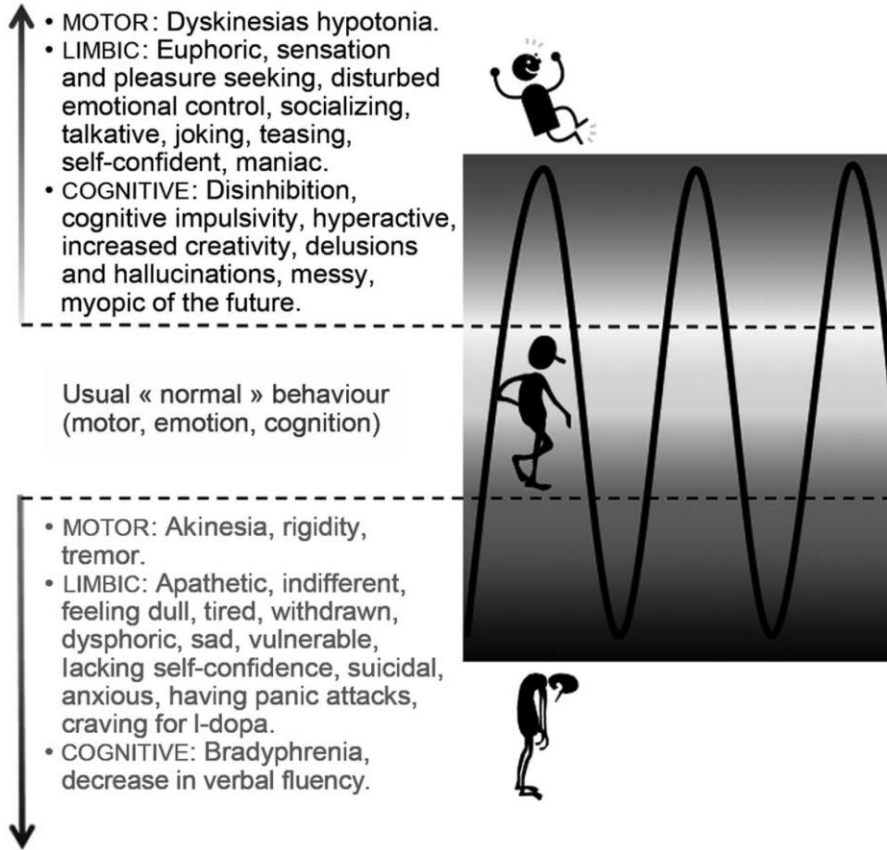
- The inability to move your feet to start walking despite the attempt to do so
- Usually begins with start hesitation – freezing when you first start to walk
- More common in narrow spaces and when under stress



# NON-MOTOR FLUCTUATIONS

- As with the motor symptoms, almost any of the non-motor symptoms of Parkinson's disease can fluctuate with the level of your medication
- For example, some people become very anxious a short time before a dose of medication is due, with the anxiety improving when the next dose kicks in
- Non-motor symptoms can fluctuate even if the motor symptoms don't





# DYSKINESIAS

- Involuntary fidgety movements related to medication
- Can be caused by almost any of the medications used to treat Parkinson's, but more likely with levodopa
- Can occur in two patterns:
  - Peak dose: when the blood levels of the medication are their highest
  - Diphasic: as the medication is just kicking in or wearing off



## “THE DRUGS DON’T WORK”

- Some symptoms may take higher doses of medication to treat than others
- Tremor and freezing can be particularly resistant to medication, so it can seem like the medication isn’t doing anything
- Medications are best for muscle rigidity and slowness and clumsiness of movements (bradykinesia)
- Increasing medications to treat the symptoms may worsen others and increase side effects





# RISK FACTORS FOR FLUCTUATIONS AND DYSKINESIAS

- Even though these problems are common, there is not much research on how common they are or what factors may contribute to developing them
- The available evidence suggests that after 5 years of treatment for Parkinson's disease:
  - Around 52% of people have fluctuations (42%), dyskinesias (24%), or both



# RISK FACTORS FOR FLUCTUATIONS AND DYSKINESIAS



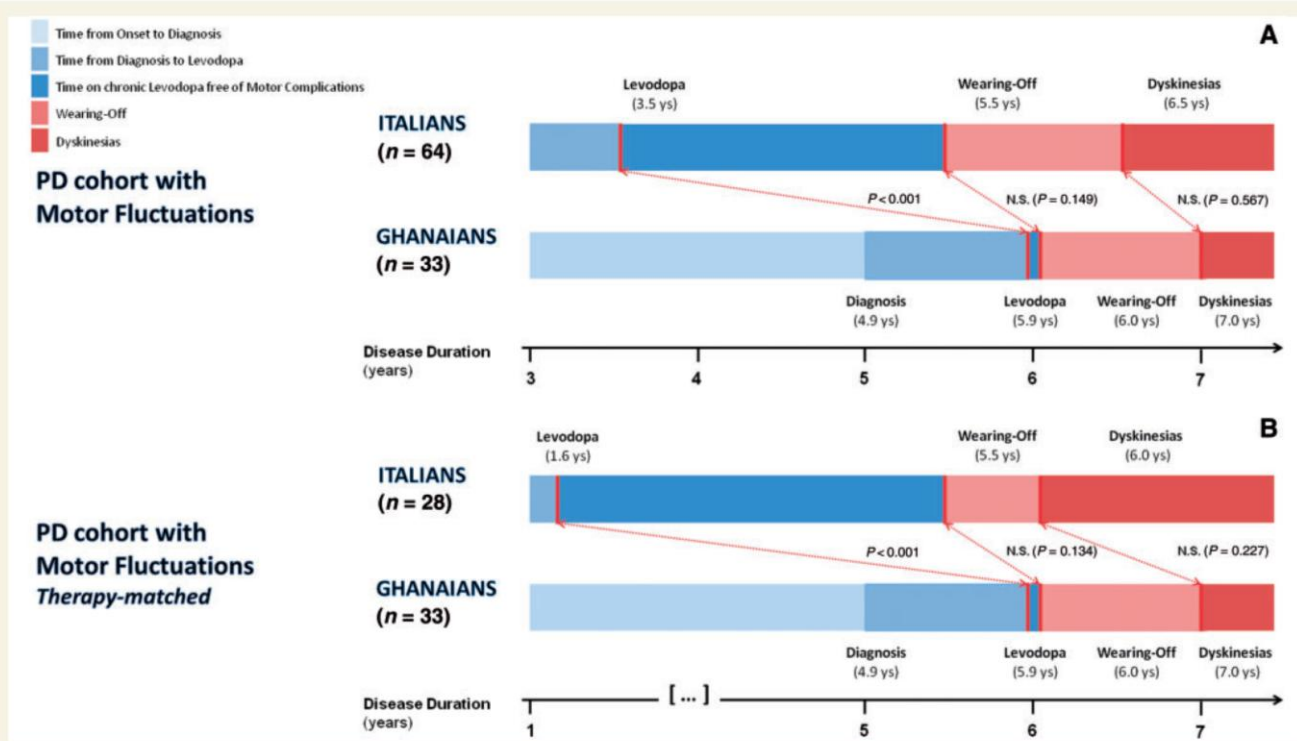
- Known risk factors for fluctuations and dyskinesias include:
  - Younger age at diagnosis
  - Being a woman
  - Longer duration of Parkinson's disease
  - More severe disease
  - Higher total daily dose of levodopa



## THE ROLE OF LEVODOPA

- In the past, we used to avoid using levodopa for as long as possible because it was felt to delay the onset of the motor complications
- In recent years it has become clear that the risk of complications is related to higher total daily doses of levodopa, and delaying treatment does not significantly delay the onset of the complications as long as the dose of medications is kept as low as possible





**Figure 2** (A) Relationship between initiation of levodopa therapy and onset of motor fluctuations, and between initiation of levodopa therapy and onset of dyskinesias in Ghanaian patients with Parkinson's disease and Italian Parkinson's disease control subjects with motor fluctuations (Supplementary Table 1). (B) The Parkinson's disease control group has been additionally matched for therapy regimen (Table 3).

# WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- In general, Parkinson's disease progresses slowly without significant changes in symptoms over the short term (though there will be good days and bad days)
- Symptoms that worsen fairly suddenly over a couple of days are an indicator that something else is going on
  - Poor sleep
  - Bladder or other infection
  - Interaction between your Parkinson's medications and a new drug
  - Other medical issues
- Worsening of Parkinson's symptoms may be the only symptom of the other problem
  - See your family doctor!



## WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- Exercise is an effective treatment for Parkinson's disease and many of the symptoms that are associated with it:
  - Fatigue
  - Depression and anxiety
  - Prevention of cognitive/memory problems
  - Prevention of falls
- Consider a Parkinson's-specific exercise program or see a trainer or physiotherapist to tailor an exercise program to your needs



# WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- We still do not know what the “best” exercise is or how long or how hard to do it for
- The current recommendation is 30 minutes of moderate intensity activity, 5 times per week
- Try to incorporate some stretching, core strengthening and balance exercises into your routine



# WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?



- It remains to be seen if there is a “best exercise” for Parkinson’s disease
- Even if there is, if you don’t like the “best exercise”, you won’t do it, so find something that you enjoy and do that





# WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- If you are experiencing delayed kicking in:
  - See if spacing your medication 30-60 minutes from high-protein food helps
    - This includes dairy products, eggs, soy products like tofu, peanut and nut butters in addition to meat and fish
  - Take your medication with an acidic beverage, like orange juice or club soda
  - If you are on levodopa, you can try chewing  $\frac{1}{2}$  - 1 tab and swallowing the rest
    - NB chewing CR levodopa changes it to IR, so it may not last as long



# WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- Managing constipation can make a big difference in how long your medication lasts and how long it takes to kick in
  - you can't absorb your medication as well when you are constipated
- Stay hydrated (2 L of water per day, mostly between waking up in the morning and supper)
- Exercise! (Core exercises help too)
- Coffee
- Take a daily laxative (or two): senna tea, PEG, magnesium citrate, etc
- Aim for a soft bowel movement without straining every time you go



## WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- If you are having dyskinesias, keep track of when they occur in relation to your medication times
  - As mentioned, there are two types of dyskinesias
    - Peak dose
    - Diphasic
    - You may have both types
  - They may look the same, but the treatment is different, so the timing matters!



## WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- With any bothersome symptom, it is worthwhile keeping a diary for a week or two, noting what time the symptom occurs, when you take your medications, when you eat your meals, and any other relevant details (were you sick? Did you sleep poorly the night before?)
- As mentioned, some symptoms can be related to Parkinson's disease OR the medications used to treat it
  - The timing is important in helping your doctor figure out which it is



## WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- If you are experiencing freezing of gait, keep track of whether it is occurring when you are on or off
- Often physiotherapy is more effective than medications for this problem
- When you freeze, stop and take a deep breath and try again
- Counting or singing in your head, trying to step over a line on the floor, your partner's foot or other obstacle can help overcome the freeze



# WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- If you are falling, what is making you fall?
  - Freezing?
  - Are you feeling lightheaded?
  - Are you falling while turning or backing up?
  - Are you losing your balance?
  - Do you fall more when you are on or off?
  - Are dyskinesias throwing you off balance?



## WHAT CAN YOU DO ABOUT BOTHERSOME SYMPTOMS?

- Parkinson's disease is complicated and can affect multiple organ systems, and it is often unclear whether symptoms that you experience are related to Parkinson's, your medication, or something else entirely
- Non-motor symptoms are treated the same as they would be if you didn't have Parkinson's disease. Your family doctor is often better qualified to manage these than your neurologist

