

Beyond the Tremor

Non-motor Symptoms of Parkinson's Disease

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DISCLOSURES

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- I am not a patent holder, shareholder or financially invested in any of the pharmaceutical products discussed in this presentation, and I am not receiving financial support in the form of research grants from industry or commercial supporters.

WHAT IS PARKINSON'S DISEASE

- A. A disease which makes you tremor?
- B. A disease which makes you stiff and slow?
- C. A disorder which affects multiple systems and leads to dysfunction in thinking, memory, and problems with sleep and mood control of bladder function, control of blood pressure, and constipation?
- D. All of the above

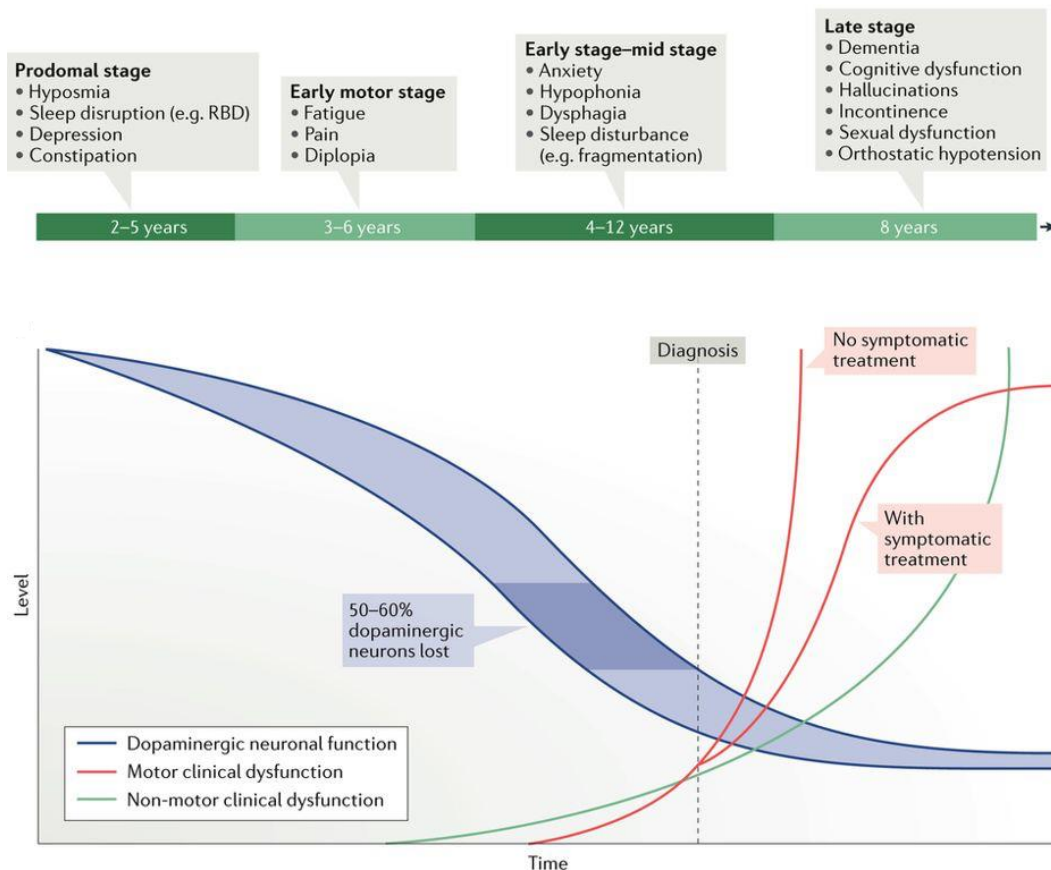
INTRODUCTION

- Non-motor symptoms may appear *during* the course of Parkinson's disease, but are also common before motor features and progress in both severity and diversity as the disease evolves
- They are often misdiagnosed and untreated.
- If untreated, they may impair quality of life and represent a major cause of hospitalization and institutionalization.

INTRODUCTION

The sequence and timing of the development of non-motor symptoms can vary between patients

- The rate of decline depends on genetic and non-genetic factors
- Prodromal stage: non-motor symptoms develop insidiously years before onset of motor features
- Early motor stage: It is estimated that 50-60% of dopaminergic neurons have been lost *before* motor features appear



Schapira AHV et al., *Nat. Rev. Neurosci.*, 2017 | Nature Reviews | Neuroscience

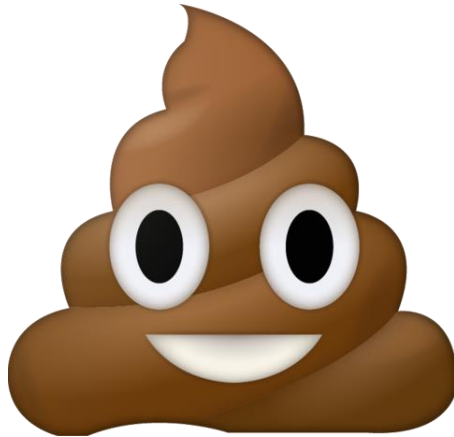
INTRODUCTION

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INTRODUCTION

- Today we will focus on some of the non-motor symptoms of Parkinson's disease, with the focus on how these symptoms can be better managed through conservative approaches via the aid of our multi-disciplinary care team, which includes physiotherapy, occupational therapy, speech and language pathology, dieticians and social work
- And when necessary ... how medical treatments can also help to alleviate these symptoms
- Topics to be discussed include:
 - Constipation
 - Urinary frequency and urgency
 - Low blood pressure
 - Pain
 - Speech and swallowing difficulties
 - Drooling
 - Sleep
 - Mood
- There are other symptoms of Parkinson's disease we won't have time to discuss today, including dementia and psychosis

Constipation



CONSTIPATION

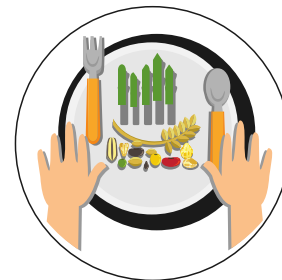
- Occurs in 58% of people afflicted with Parkinson's disease [Magerkurth C et al., *Clin. Auton. Res.*, 2005]
- Thought to result from a combination of neurodegenerative process affecting gastrointestinal motility coupled with the effects of dopaminergic medications
- **Delayed gastric emptying**
 - Occurs in nearly 70%
 - Can lead to feeling early satiety ("fullness") → reduction in calorie intake and weight loss
 - Can alter/reduce the absorption of Parkinson's medications, making them less effective



CONSTIPATION



CONSTIPATION REMEDIES



Eat foods high in fiber



Drink a lot of water



Avoid tea, coffee, alcohol



Routine stool

- Prunes
- Bran buds with psyllium
- Flax seed
- Fruit
- High fiber cereals and bars (e.g. Red River cereal)
- And reduce low fiber foods (e.g. fried foods, baked goods)

CONSTIPATION



CONSTIPATION REMEDIES



- Stool softeners (DAILY) – Metamucil, Docusate (Colace)
- Bowel stimulants – used if no bowel movements occur for 3 days or more
 - Senokot (suppository, syrup, tablets)
 - Dulcolax (bisacodyl)
- Laxatives
 - Restorolax
 - Lactulose
- Suppositories and digital disimpaction

Urinary Frequency and Urgency



URINARY FREQUENCY AND URGENCY

- Most people with Parkinson's disease will develop hyperactivity of the bladder wall muscle, which causes urinary urgency, frequency and nocturia (night-time urination) → can increase the risk of falls
- **Management:**
 - Urological evaluation and formal urodynamic testing are indicated for accurate diagnosis of the nature of the problem → referral to a Urologist
 - *Conservative measures*
 - No fluids 1 hour before bedtime
 - Scheduled bathroom breaks during the day
 - Incontinence pads/diapers
 - Bedside commode
 - Condom catheter

URINARY FREQUENCY AND URGENCY

- **Management:**
 - *Medical treatments*
 - Oxybutynin and tolterodine can be used, although no controlled clinical trials in PD populations have been performed, and possible side effects, such as memory loss and constipation, must be taken into consideration
 - Mirabegron (Myrbetriq®) → proven to reduce urinary urgency/frequency/nocturia
 - Botulinum toxin injections into the bladder wall can also improve bladder urine storage capacity and control

“Dizziness”



ORTHOSTATIC HYPOTENSION

- Low blood pressure upon standing → feeling dizzy or faint when you stand
- A very frequency but undertreated complication of early Parkinson's disease [Hiorth et al, *Neurology*, 2019)
 - Occurs in 65% of people with Parkinson's disease
 - Only 0.5% receive treatment
- **Management**
 - *Conservative measures*
 - Behavior modification – get up slowly
 - Increase hydration and dietart salt intake, compression stockings and abdominal binder
 - Use a cane or walker
 - Elevate head of bed to 30 degrees → increases renin secretion → increased BP

ORTHOSTATIC HYPOTENSION

- *Medical treatments*

- **Domperidone** – peripheral dopamine receptor blocker which counteracts the side of some anti-Parkinson's medications
- **Fludricortisone and midodrine** ... but people with Parkinson's can also present with supine hypertension [Schmidt C et al., *Mov. Disord.*, 2009]

Pain



Myth: “Parkinson’s is not a painful disease”

- Pain is a common feature of Parkinson’s disease and is under-reported
 - Often worsens in the OFF state [Storch A et al., *Neurology*, 2013]
- The basal ganglia is involved in sensory function through the modulation and integration of information from the primary pain processing structures of the brain (cortex, thalamus, trigeminal system)
 - The loss of dopamine signaling to the basal ganglia is thought to alter sensory perception and changes pain thresholds
- However, anti-Parkinson’s medications do not always eliminate pain people with Parkinson’s disease

PAIN

Types of pain experienced by people with Parkinson's disease:

- Dystonia – involuntary over-activation of muscles causing twisting of a body part around a joint
 - Frozen shoulder
 - Toe curling
 - Foot turning (inversion)
- Peripheral neuropathy
- Carpal tunnel syndrome (median nerve compression) is more common

PAIN

- OFF period pain → optimization of anti-Parkinson's medications
 - Consider rotigotine patch (Neupro®), Duodopa® intestinal pump or Deep Brain Stimulation (DBS)
- Painful rigidity → regular stretching
- Painful dystonia → **botulinum toxin injections** for people who do not respond to anti-Parkinson's medications
- Peripheral neuropathy → gabapentin, lyrica, amitriptyline/nortriptyline, topiramate
- Carpal tunnel syndrome → splinting, carpal tunnel release surgery

Swallowing difficulties



DYSPHAGIA

- More than 80% of people develop problems swallowing during the course of their disease
 - Can complicate medication intake
 - Lead to malnutrition
 - Aspiration pneumonia
- The underlying mechanisms are poorly understood
- Clinical assessment is often challenging and delivers unreliable results → referral to SLP (swallowing therapists) is strongly recommended to identify patients at risk for aspiration events
 - Video-fluoroscopic swallowing study
 - Fiberoptic or endoscopic evaluation of swallowing

DYSPHAGIA

- **Management**

- Fluctuating dysphagia with deterioration during the OFF-state should be treated by optimizing anti-Parkinson's medications
- Changing to softer textured foods or a minced diet and thickened fluids
- Swallowing therapy by SLP is the gold-standard treatment of Parkinson's disease-related swallowing problems but high quality studies are rare:
 - Expiratory muscle strength training (EMST) – 5 days/week, 25 breaths/day
 - 3 month follow-up did not demonstrate significant improvement of swallowing safety in a blinded RCT [Troche et al., J Rehabil Res Dev, 2014)
 - Video-assisted swallowing therapy (VAST) – visual biofeedback cueing to improve the coordination of a person's swallow
 - Patients mild to moderate dysphagia demonstrated a significant reduction in food residue after swallowing, and improvement in quality of life [Manor et al., Parkinsonism Relat Disord, 2013]

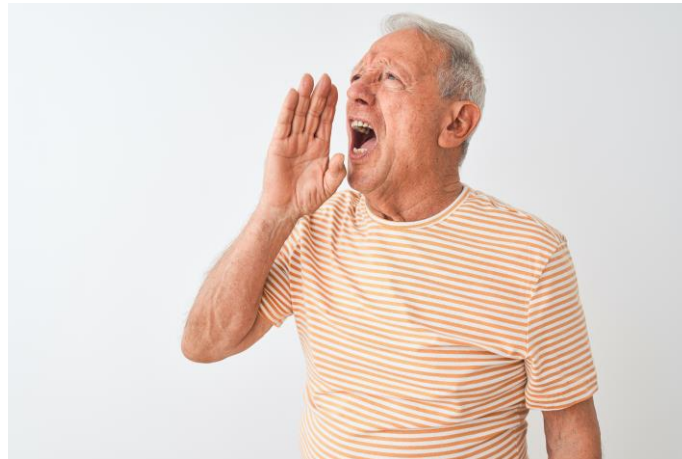


DYSPHAGIA

- Very few people with Parkinson's disease will develop difficulties swallowing severe enough to require a gastric feeding tube



Speech difficulties



HYPOPHONIA

- "Soft voice" ... to the person afflicted with Parkinson's disease, their voice may sound normal in their own ears
 - Alterations in muscle tone and control affect the muscles which underlie speech
 - Occurs in over 90% of people afflicted with Parkinson's disease
- **Management**
 - Anti-Parkinson's medications do not improve speech
 - Referral to speech therapy (SLP) for **Lee Silverman Voice Treatment** → an intensive speech therapy program, which focuses on maximizing vocal effort ("think loud, think shout") and maximizing sensory perception of vocal effort/loudness via biofeedback techniques
 - Speech aid devices (e.g. SpeechVive®) - plays background sounds in your ear while you're talking and turns off as soon as you stop talking → makes the person speak louder, slower, and more clearly.

Drooling



DROOLING

- Due to stooped posture, resulting in pooling of saliva near the front of the mouth
- The back of the throat needs to be wet to stimulate involuntary swallowing
- **Management**
 - *Conservative measure*
 - Suck on a hard candy or chew gum
 - *Medical treatments*
 - Atropine 1% ophthalmic 1-2 drops under the tongue
 - Botulinum toxin injections into the the submandibular and parotid glands

Sleep difficulties



SLEEP DIFFICULTIES

- Occur in 75 to 98% of people with Parkinson's disease [Lees AJ et al., *Neuropharmacol.*, 1998; Olanow CW et al., *Neurology*, 2001]
 - Disorders of sleep initiation and maintenance are more prevalent in people with Parkinson's disease compared with the healthy population and are characterized by either a reduction in the stages III/IV of sleep or a decrease in REM sleep [Adler CH and Thorpy CJ, *Neurology*, 2005]
- REM sleep behavior disorder
 - Is a preclinical marker of Parkinson's disease [Postuma RB et al., *Neurology*, 2006]
 - Prevalence of 33 to 60% in people with Parkinson's disease [Cornella CL et al., *Neurology*, 1998; Gagnon JF et al., *Lancet Neurol*, 2006]
 - Treatment of choice is **clonazepam** – but may make daytime somnolence worse and should be avoided in patients with obstructive sleep apnea
 - 2nd line treatments include: **melatonin**
 - Often responds to increasing the dose of anti-Parkinson's medications

SLEEP DIFFICULTIES

- Other issues with sleep that can occur in people with Parkinson's disease include:
 - **Sleep fragmentation** → may be due to the motor manifestations of PD (e.g. OFF periods, dystonic movements and cramps), as well as nocturia
 - **Insomnia**
 - **Restless Legs Syndrome**
 - **Akathisia** (motor restlessness)
 - **Obstructive sleep apnea**
- **Excessive daytime sleepiness** - occurs in up to 50% [Hobson DE et al., *JAMA*, 2002], and does not correlate with the degree of nocturnal sleep impairment [Arnulf I et al., *Neurology*, 2002]
 - **Sleep attacks** have also been described with both DA agonists and Levodopa [Frucht SJ et al., *Neurology*, 1999]
 - **Modafanil** - generally safe and well tolerated by people with Parkinson's, but the data in support of its use is controversial

EXCESSIVE DAYTIME SLEEPINESS

- Caffeine ??
 - A possible protective effect was demonstrated in a large prospectively followed group of men
 - A 5-fold reduction in risk of developing Parkinson's disease in men who drank more than 4 cups of coffee a day [Ross et al., *JAMA*, 2000]
 - A robust neuroprotective effect was not seen in women [Ascherio, *Ann Neurol*, 2001]
 - Canadian Multi-center RCT to assess effects of caffeine on Parkinson's disease [Postuma, *Neurology*, 2017]
 - Caffeine tablets vs placebo
 - Participant had Parkinson's disease on stable medical treatment
 - Followed for 6 months
 - Results:
 - No improvement in motor symptoms
 - Slight improvement in daytime fatigue, which attenuated over time



Mood



DEPRESSION

- Meta-analysis of depression in Parkinson's disease demonstrated a prevalence of major depression of 17% and of minor depression and dysthymia of 22% and 13%, respectively [Reijnders JS et al., *Mov. Disord.*,2008]
- Depression may represent the first manifestation of PD years before the onset of motor symptoms. [Shiba M et al., *Mov. Disord.*,2000]
- Depression is often under-recognized as it may be masked by motor symptoms (i.e., bradykinesia and hypomimia) and frequently co-occurs with other neuropsychiatric conditions (i.e., cognitive impairment and anxiety).
- The symptom profile of depression in PD patients is different in comparison with patients without PD:
 - they have higher rates of anxiety, pessimism, irrationality, suicidal ideation without suicidal behavior, and less guilt and self approach. [Slaughter JR et al., *Neuropsychiatry Clin. Neurosci.*,2001]

DEPRESSION

- **Medical Management**

- It is still controversial whether depression/anxiety is related to ON-OFF fluctuations → anxiety and depression may fluctuate during the day
 - But the use of levodopa generally does not alleviate depressive symptoms [Sethi K et al., *Mov. Disord.*, 2008]
- However, dopamine agonists may reduce depression in Parkinson's disease → this effect may be explained by the stimulation of D3 receptors in the mesolimbic (reward) pathways of the brain
 - A multi-center randomized, double-blind placebo controlled trial showed a significant improvement of depressive symptoms in people treated with pramipexole, when compared with those given a placebo [Barone P et al., *Lancet Neurol.*, 2010]
 - Monoamine oxidase (MAO)-B inhibitors (selegiline, rasagiline) can have modest mood elevating properties [Cummings JL, *Am. J. Psychiatry*, 1992]
- Because of the lack of anticholinergic and sedative side effects, SSRIs are generally preferred
 - Several recent studies have demonstrated that paroxetine, sertraline, fluvoxamine and citalopram improve depression in PD without worsening motor function [Ceravolo R et al., *Neurology*, 2000; Hauser RA et al., *Mov. Disord.*, 1997; Montrastruc JL et al., *Mov. Disord.*, 1995; Rampello L et al., *Clin. Neuropharmacol.*, 2002]

APATHY

- “A lack of interest, enthusiasm or motivation”
- Occurs in 60% of people afflicted with Parkinson’s disease [Marin RS et al., *J. Neuropsychiatry Clin. Neurosci.*,1995]
 - May coexist with depression and dementia
 - BUT can also occur independently of both
- **Medical Management**
 - Rivastigmine (Exelon®) → 6 month multicenter double-blind placebo controlled RCT [Devos D et al., *J. Neurol. Neurosurg. Psychiatry*, 2014]



ANXIETY

- Anxiety affects nearly 40% of people with Parkinson's disease [Richard IH et al., *Adv. Neurol.*, 2005]
 - Can be an off-period related phenomena and can respond to anti-Parkinsonian medications
 - But can also predate motor symptoms by several years
- No high quality assessments of anti-anxiety treatments have been performed in Parkinson's disease
 - If the anxiety occurs solely in off periods, adjustment of anti-Parkinsonian medication to improve/resolve motor fluctuations is usually successful.
 - Benzodiazepines should be used cautiously because they may increase adverse effects, such as confusion or autonomic disorders.
 - SSRIs are useful for the treatment of anxiety disorders but their therapeutic efficacy is yet to be demonstrated in Parkinson's.



WHAT ABOUT ?



CONSERVATIVE MANAGEMENT OF MOOD DISORDERS

- In most head-to-head studies, Cognitive Behavioral Therapies have proven to be as effective or more so than pharmacological treatments in the treatment of less severe forms of depression [Gartlehner et al., *BMJ Open*, 2017]
 - Focuses on challenging and changing thoughts, beliefs, attitudes and behaviors, along with improving emotional regulation and developing personal coping strategies that target solving current problems
- Can be accessed via a therapist (Psychiatrist or Psychologist), group therapy or even online
- These resources are also available for free through Parkinson BC





Take Home Messages



TAKE HOME MESSAGES

- People afflicted with Parkinson's disease are affected by both motor AND non-motor symptoms
- Non-motor symptoms include but are not limited to problems with constipation, urinary urgency and frequency, low blood pressure, pain, speech and swallowing difficulties, drooling, sleep and mood, along with cognitive decline and even psychosis
- Medical management is available to help alleviate many of these difficulties ... but treatments need to be individualized for every individual with Parkinson's disease
- Many non-motor symptoms can be effectively managed by conservative measures guided by trained allied health care professionals in physiotherapy, occupational therapy, speech/swallowing therapy, as well as by dietitians, social workers and psychologists
- New therapies are emerging which hold the promise of improving the quality of life of people with Parkinson's disease by improving both motor and non-motor symptoms

THANK YOU

- **Fraser Health Movement Disorder Clinic Team**

- Neurologists: Dr. Claire Hinnell, David Rydz and Anish Kanungo
- Clinical nurse: Robinder Bal
- Physiotherapy: Marilyn Aruujo
- Occupational therapy: Lisa Wechselberger
- Speech/swallowing therapy: Jamie Russell
- Social Work: Baljit Chhokar



Coastal Specialty Clinics

