# Non-Motor Symptoms of Parkinson's Disease

Kimmy G. Su, MD/PhD VA Puget Sound/University of Washington Movement Disorders Fellow



## **Talk Outline**

- Symptoms of Parkinson's disease (PD)
- History of PD
- Non-motor symptoms of PD



#### PD: The numbers

- Second most common neurodegenerative disorder after Alzheimer's disease
- Affects approximately seven million people globally and one million people in the United States
- Prevalence ~ 1-2% of 65+ year old population and 4% of 80+ year old population
- Average age of onset ~ 60 years, although 5– 10% of cases begin between the ages of 20 and 50 (classified as young onset PD)

#### **PD:** Features



Well, I ALWAYS WANTED TO BE ONE OF THE MOVERS AND SHAKERS--I'VE BEEN DIAGNOSED WITH PARKINSON'S

#### **PD:** Features

#### Tremor

- One-sided initially
- Resting
- "Pill-rolling"

#### **Rigidity** or stiffness

Cog-wheeling





#### **PD:** Features

#### Akinesia/Bradykinesia

- Fancy word for slowed movements
- Masked face
- Soft voice
- Drooling
- Shuffling
- Small handwriting

#### **Postural instability**

Balance issues







## PD: History

- First described by British physician James Parkinson in 1817
- Identified the major symptoms, calling it "the shaking palsy"



ESSAY

ON THE

#### SHAKING PALSY.

#### CHAPTER I.

#### DEFINITION-HISTORY-ILLUSTRATIVE CASES.

SHAKING PALSY. (Paralysis Agitans.)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

### PD: History



#### Jean-Martin Charcot

## PD: History

- French neurologist Jean-Martin Charcot aka "The Father of Modern Neurology"
- First to truly recognize James Parkinson's work and renamed the disease after him (1862)
- Refined Parkinson's earlier description, including noting that not all PD patients have tremors

#### PD: What causes the symptoms?

- Certain nerve cells in the brain produce a chemical messenger called dopamine.
- Some of these nerve cells in PD patients have died or have become impaired. Less dopamine is thus produced.





#### PD: What changes occur in PD?

- Frederic Lewy described microscopic particles in affected PD brains, later named Lewy bodies (1912)
- Lewy bodies are composed of accumulated protein called alpha-synuclein





#### PD: Lewy bodies



Lewy bodies in nerve cells affect proper cell function

#### PD: Loss of nerve cells



Substantia nigra means → "black substance"

#### PD: Loss of nerve cells



#### PD: Loss of nerve cells

- Not only in the substantia nigra (involved in motor control)
- There is also cell loss in other areas of the nervous system that control the non-motor symptoms



#### The Parkinson's Iceberg



### The Parkinson's Iceberg



## PD: Non-motor symptoms

- Often more troublesome than motor symptoms
- Often under-recognized and hence undertreated



## PD: Non-motor symptoms

- Pain
- Sleep disorders
- Constipation
- Bladder issues
- Orthostatic hypotension
- Drooling
- Mood issues
- Cognitive impairment

#### **Exercise challenge!**



#### **Exercise challenge!**

Everytime I mention **exercise** as a treatment option, we will get up and stretch!



- Common, but under-recognized symptom in PD
- Up to 85% of people with PD experience pain, and up to 63% of that pain is directly attributable to PD
- Many PD patients consider pain one of their top three most bothersome symptoms, significantly affecting quality-of-life



- Pain management is largely determined by the underlying cause of the pain symptoms
- PD pain can be divided into a few categories:
  - Muscle stiffness
  - Muscle cramping (dystonic)
  - Dyskinesia
  - Neuropathic
  - Musculoskeletal



Muscle stiffness Muscle cramping Dyskinesia

# Adjustment of PD medications



 Neuropathic 
Gabapentin, pregabalin, duloxetine, nortriptyline, topical creams etc.



 Musculoskeletal → Analgesics (Tylenol, NSAIDs), topical creams



- Medications come with side effects!
  - Gabapentin → Drowsiness, dizziness, unsteadiness, cognitive impairment
  - NSAIDs → GI issues (stomach upset, ulcers)



- Exercise
- Massage
- Acupuncture
- Relaxation techniques (mindfulness, meditation, yoga, taichi)
- Heating pack
- Cold pack



#### INTERVAL TRAINING FOR PARKINSON DISEASE

#### AMERICAN PARKINSON DISEASE ASSOCIATION

**GREATER ST. LOUIS CHAPTER** 

Consult a physician before performing this or any exercise program. Any exercise program may result in injury. By voluntarily undertaking this exercise program, you assume the risk of any resulting injury. The American Parkinson Disease Association ("APDA") and its affiliates/chapters are not responsible for any loss or damage suffered by any person as a result of the use or misuse of any of the information or content in this program.

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#### TAI CHI FOR PARKINSON DISEASE

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## PD: Non-motor symptoms

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- Mood issues
- Cognitive impairment

## **Sleep disorders**

- Common complaints include:
  - Difficulties falling or staying asleep
  - Daytime sleepiness with sleep attacks
  - Sleep fragmentation
  - REM sleep Behavior Disorder aka RBD (acting out of dreams)
- REM sleep behavior disorder involves REM (aka Rapid Eye Movement) sleep
- Active dreaming occurs at this stage of sleep
- Happens several times a night
- Usually everything but the eyes and diaphragm do not move
- In patients with REM sleep behavior disorder (RBD) this paralysis is impaired, so patients will "act out their dreams"

#### Things to consider:

- Possible side effects from medications?
- Poor sleep hygiene?
- Other symptoms affecting sleep? (Ex: pain, urinary issues, psychosis, depression)
- Undiagnosed sleep apnea?

 PD medications can be adjusted or timed differently to optimize motor symptoms control and minimize side effects

Examples:

- Controlled-release carbidopa/levodopa at bedtime
- Selegiline to be taken in the morning
- Reduce daytime dopamine agonists due to sleep attacks

#### Ways to improve sleep hygiene:

- Avoid/limit daytime naps
- Exercise earlier in the day
- Avoid television, mobile devices, and other electronic screens in the bedroom
- Avoid caffeine and alcohol later in the day
- Avoid drinking too much water in the evening (to reduce number of bathroom trips in the middle of the night)

### Do you have sleep apnea?

#### STOP

S	So you <b>snore</b> loudly (louder enough to be heard through closed doors or louder than talking)?	Yes	No
Т	Do you often feel tired, fatigued or sleepy during the daytime?	Yes	No
0	Has anyone <b>observed</b> you stop breathing or choking or gasping during your sleep?	Yes	No
Р	Do you have or are you being treated for high blood pressure?	Yes	No

#### Bang

В	BMI more than 35?	Yes	No
а	Age - over 50 years old?	Yes	No
n	<b>Neck</b> circumference – is it greater than 17" if you are a male or 16" if you are a female?	Yes	No
g	Gender – are you a male?	Yes	No

**3 or more** = High risk of sleep apnea **Less than 3** = Low risk of sleep apnea

# Sleep apnea affects more than just sleep!









#### Many mask options!



- Medications to consider:
  - Melatonin (5–50 mg) can also be utilized to normalize circadian rhythm and to treat RBD (3-12 mg)
  - Clonazepam (0.5–1.0 mg) has been reported to be helpful for RBD treatment as well



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## Autonomic nervous system

- The involuntary part of the nervous system
- Includes the following systems:
  - Sympathetic (fight or flight)
  - Parasympathetic (rest and digest)
  - Enteric (gut)
- Affects the following functions:
  - Blood pressures
  - Heart rate
  - Breathing
  - Digestion
  - Urination
  - Salivation
  - Sexual function







**Rest-and-digest:** Parasympathetic activity dominates. Fight-or-flight: Sympathetic activity dominates

#### Constipation

- Often an early sign of PD before motor symptoms develop
- Around 50% of PD patients have issues with constipation
- Defined as less than 3 bowel movements a week

#### Constipation

- Non-pharmacologic treatments:
  - Exercise
  - Diet changes
    - Adequate hydration (~ 8 glasses of water a day)
    - Increasing fiber

#### "Keep it Moving Colon" Cocktail

#### Ingredients

- 1/2 cup bran
- 1/2 cup prune juice
- 1/2 cup applesauce

#### • Directions

• Mix together and refrigerate. Take 1 or 2

tablespoonfuls each evening. If needed,

you may increase dose by 1 tablespoon

each week. You can also add some extra

stewed prunes daily.

#### Constipation

	Example	How It Works	Time to Relief
Stimulant Tablet (taken by mouth)	Dulcolax® Laxative Tablets Dulcolax Pink® Laxative Tablets	Speeds up stool movement by stimulating the bowel muscles	Works overnight
Stimulant Suppository (inserted rectally)	Dulcolax <sup>®</sup> Laxative Suppository	Speeds up stool movement by stimulating the bowel muscles	Works in minutes
Stool Softener	Dulcolax <sup>®</sup> Stool Softener DulcoEasePink <sup>®</sup> Stool Softener	Softens the stool in the intestine, making it easier to pass	Works gradually
Osmotic	Miralax®	Draws water into the bowel, providing softer stools and increases frequency of bowel movements	Works in 1 to 3 days
Bulk-Forming	Metamucil®	Absorbs more fluid in the intestines, making the stool bigger, giving the urge to pass	Works in 12 to 72 hours
Lubricant	Mineral Oil	Coats the wall of the intestine so that stools can pass through more easily	Works in 6 to 8 hours

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#### **Bladder issues**

- Present in about 50% of all PD patients
- Can be caused by PD or by by other conditions associated with aging
- Further medical workup to rule out other causes of bladder dysfunction may be warranted (ex: diabetes, prostate enlargement, gynecological disorders, medications, infection)

#### **Bladder issues**

- Non-pharmacologic treatments:
  - Timed voiding
  - Incontinence briefs
  - Bedside commodes
  - Limiting/avoiding caffeine and alcohol
  - Pelvic floor physical therapy exercises
  - Percutaneous posterior tibial nerve stimulation (PTNS)

#### **Pelvic Floor PT Exercises**



Lie down and spread your legs equivalent to shoulder width apart. Relax your buttocks and lower stomach, and then squeeze your pelvic muscles for 5 seconds. Repeat.



Put your knees and palms on the ground. While inhaling, bend your back and squeeze your pelvic floor muscles for 5 seconds. Release and repeat.



Lie down, bend your knees and inhale. Contract your pelvic floor muscles while lifting the buttocks. Release the contraction while pulling down your shoulders, back and buttocks. Repeat.



Sit down and stretch your feet. Then squeeze your pelvic floor muscles for 5 seconds while rotating your feet outward. Repeat.



Sit down and cross your legs. Squeeze your pelvic floor muscles slowly for 5 seconds. Repeat.

Stand firmly and balance your body using a table or chair. Lift your heels while squeezing your pelvic muscles for 5 seconds. Relax your heels back on the ground. Repeat.

#### PTNS

- Stands for "percutaneous posterior tibial nerve stimulation"
- Indirect stimulation of bladder nerves via tibial nerve (located in lower leg)
- Weekly treatments for 12 weeks, 30 minutes per session
- Patients who respond to treatment may require occasional treatments (~ once every 3 weeks) to sustain improvements

#### PTNS



#### PTNS





#### **Bladder issues**

- Pharmacologic treatments:
  - Commonly used medications such as oxybutynin (reduces bladder contraction) can cause cognitive issues
  - Mirabegron (Myrbetriq) → Relaxes urethral smooth muscle using a different mechanism that doesn't affect cognition (main side effect is high BP)



#### **Bladder issues**

 Can also consider Botox injection into the bladder wall muscle (detrusor muscle)



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- Aka positional hypotension
- Normally when we change positions (from lying down to sitting up, from sitting down to standing up), our blood vessels will contract to maintain blood pressure to the brain as gravity is pulling the blood downwards
- This reflex can be impaired in PD patients

- Defined as drop in blood pressure within 2-5 minutes of standing up
  - Systolic BP (top number) drops by 20
  - Diastolic BP (bottom number) drops by 10

- Can contribute to falls
- Risk factors include medications, dehydration, heat exposure, prolonged bed rest, age
- Symptoms include lightheadedness or faintness that occurs with upright position

- Medications that can cause or worsen orthostatic hypotension include:
  - Alcohol
  - Anti-depressants
  - Blood pressure medications
  - PD medications
  - Anti-psychotics
  - Diuretics
  - Muscle relaxants
  - Sedatives

- Non-pharmacologic treatments:
  - Get up slowly
  - Physical counter maneuvers
  - Wearing elastic stockings and/or abdominal binders
  - Exercising
  - Increasing salt/water intake
  - Avoid over-heating
  - Avoid alcohol
  - Eat smaller meals

#### **Counter maneuvers**



Counter maneuvers that can help raise orthostatic blood pressures: (A) Leg-cross (B) Toe-raise (C) Squat (D) Forward lean\* • Use with some caution

Also clenching thigh, abdominal and buttock muscles can help

#### **Compression stockings**


#### **Abdominal binders**



# Orthostatic hypotension

- Pharmacologic options:
  - Note: They can worsen supine hypertension (aka blood pressures when lying down)
  - Fludrocortisone
  - Midodrine
  - Droxidopa (Northera)

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- Caused actually by impaired or infrequent swallowing rather than making too much saliva
- Very common in PD patients (~80%)
- Can be very frustrating socially for patients
- Can cause fungal infection at the corners of the mouth



- Non-pharmacologic treatment:
  - Tactics to encourage swallowing, such as chewing on gum or sucking on hard candy



- Pharmacologic treatments:
  - Medications such as glycopyrrolate tablets and atropine drops under the tongue
  - Reduce saliva production



- Pharmacologic treatments:
  - Issues with atropine and glycopyrrolate = potential undesirable systemic side effects



- More invasive treatment:
  - Botox injections into salivary glands







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#### **Mood issues**

- Prominent mood disorders in PD include depression, anxiety, apathy, and psychosis
- Can have a significant impact on quality of life for both patients and their caregivers
- Affects sleep, worsens fatigue, and limits socialization



#### Depression

- Is it a reaction to having an incurable disease or is it actually intrinsic to PD?
- Higher prevalence of depression in PD compared with other chronic conditions with comparable disability
- Lack of clear relationship between presence of depression and severity of PD symptoms
- Depressive symptoms can sometimes precede motor symptoms

#### Depression

- Non-pharmacologic options:
  - Psychotherapy
  - Light therapy
  - Exercise

#### Depression

- Pharmacologic options:
  - Some mood issues are suggested to be associated with OFF periods of PD
  - Can try adjusting dopaminergic medications to minimize these periods
  - Pramipexole has been compared to fluoxetine and sertraline for depression treatment, found to be superior to both

#### Anxiety

- Anxiety (often coinciding with depression in PD) can potentially improve with medication adjustments to stabilize motor symptoms and reduce OFF periods (can manifest as "panic attacks)
- Serotonergic medications such as sertraline, citalopram, fluoxetine, and venlafaxine can be useful for depression and anxiety management

- Hallucinations:
  - Seeing or hearing things that are not there
  - Sensations such as smell and touch
  - Usually benign
- Illusions:
  - Misinterpreting things that are there
- Delusions:
  - False unshakeable beliefs not based on reality, usually paranoid in nature
  - Can be more problematic

- Cognitive status can determine how severely patients are affected
- Less cognitively impaired patients may realize that the hallucination/illusion is not real
- More cognitively impaired patients may feel more threatened
- Can have an impact on family and caregivers

- Non-pharmacologic options:
  - Hallucinations and illusions that are not bothersome to patients do not need to be treated
  - Reassurance
  - Turning on the lights
  - Focusing on a different object

- Pharmacologic options:
  - Medications to be tapered and eliminated if possible
    - Dopamine agonists
    - Anti-cholinergics
    - Amantadine
    - MAO-B inhibitors
    - COMT inhibitors
  - Medications to be continued but may need to be adjusted:
    - Carbidopa/levodopa

- Atypical anti-psychotic medications can be used (though judiciously, as they can also worsen motor symptoms)
  - Clozapine
  - Quetiapine
  - Pimavaserin

- Pimavaserin (Nuplazid)
- Only FDA-approved medication for PD hallucinations and delusions (April 2016)





- Common side effects of Nuplazid:
  - Leg swelling
  - Confusional state
  - Nausea
  - QTc prolongation (heart rhythm change)

# Nuplazid

Health » FDA worried drug was risky; now reports of deaths spark concern

# FDA worried drug was risky; now reports of deaths spark concern

U.S. Edition +  $\mathcal{P}$ 

Live TV

#### By Blake Ellis and Melanie Hicken, CNN Investigates

Updated 6:00 AM ET, Mon April 9, 2018

**(CNN)** — Two years ago, Brendan Tyne pleaded with the Food and Drug Administration to approve a drug that he was hopeful could finally bring his mother some peace.

She could no longer move without assistance and had fallen victim to the debilitating and frightening psychosis that haunts many people with Parkinson's disease.

# Nuplazid

Medication Errors

U.S. Department of Health and Human Services															
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Drugs															
Drug Safety and Availability Drug Alerts and Statements FDA analysis finds no new or unexpected s risks associated with Nuplazid (pimavanse												safety erin), a			
Medication Guides						me deli	dicati usion:	on to s of Pa	treat arkir	t the Ison <sup>:</sup>	hallı 's dis	ucinatior sease ps	is and ychos	l sis	
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Postmarket Drug Safety Information for Patients and Providers						Health care providers reminded to follow prescribing information [09-20-2018] The U.S. Food and Drug Administration (FDA) has completed a review of all postmarketing reports of deaths and serious adverse events (SAEs) reported with the use of Nuplazid (pimavanserin). Based on an									
	Infor	mation by	y Drug C	lass		analysis of all available data, FDA did not identify any new or unexpected safety findings with Nuplazid, or									

findings that are inconsistent with the established safety profile currently described in the <u>drug label</u>. After a thorough review, FDA's conclusion remains unchanged that the drug's benefits outweigh its risks for patients with hallucinations and delusions of Parkinson's disease psychosis.

#### PD: Non-motor symptoms

- Pain
- Sleep disorders
- Constipation
- Bladder issues
- Orthostatic hypotension
- Drooling
- Mood issues
- Cognitive impairment

- Can present in around 20% of PD patients at initial diagnosis
- Main cognitive areas affected include:
  - Executive function → Difficulty with multitasking, planning and organizing, problem solving
  - Visuospatial → Where things are in space, navigation

Non-pharmacologic treatments include:

Non-pharmacologic treatments include:



**Exercise!** 

- Pharmacologic treatments include:
  - Donepezil
  - Galantamine
  - Rivastigmine
  - Memantine
- Movement Disorders Task Force 2011 →
  - Rivastigmine clinically useful
  - Donepezil, galantamine, memantine data insufficient
- Rivastigmine is the only FDA approved medication for PD dementia

- Cholinesterase inhibitors may improve cognition to a certain degree, but will not stop cognitive decline
- Patients may experience worsening of motor symptoms
  - Example: Tremor may increase or become bothersome, commonest cause for discontinuation of rivastigmine

# Final key points

- PD includes both motor AND non-motor symptoms
- Let your doctor know if you are having any bothersome non-motor symptoms
- There are non-medication ways to manage most non-motor symptoms
- Sometimes changing PD medications can improve the non-motor symptoms
- Additional medications may be used if necessary – be mindful of possible side effects
- EXERCISE, EXERCISE, EXERCISE!

#### **Questions?**



"I'm sorry. It appears Mr. Mitchell won't be accepting any more information today."