Parkinson’s Foundation

PD Expert Briefing:
Is It Related to PD?
Runny Noses, Skin Changes and Overlooked PD Symptoms

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Learning Objectives

• Appreciate non-motor and non-traditional symptoms of PD

• Appreciate variability of presentations among patients and guide therapy to most bothersome symptoms

• Recognize pharmacological and non-pharmacological treatments for these symptoms

• Review recent changes in the management of Parkinson disease
Off-Label Indications

• Many of the agents I will discuss will not have FDA indications for the symptoms or problems that they may treat

• When you see Miss Umbridge on a slide, one or more agents listed will be off-label and should be considered judiciously
Who Is This?
James Parkinson

AN 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 forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.
James Parkinson

• “a proneness to trembling in some particular part...most commonly in one of the hands”

• “the hand failing to answer with exactness to the dictates of the will”

• “less strict than usual in preserving an upright posture...legs are not raised to that height, or with that promptitude which the will directs”
James Parkinson

• “the sleep becomes much disturbed”

• “the bowels, which all along had been torpid, now, in most cases, demand stimulating medicines of very considerable power”

• “walking, a mode of exercise to which the sufferers of this malady are in general partial; owing to their attention being somewhat diverted from their unpleasant feelings”
What is PD?

- Fatigue
- Sleepiness
- Hyposmia
- Imbalance

- Tremor
- Bradykinesia
- Rigidity
- Gait disorder

- Dystonia
- Sleep Disorders
- Constipation
- Hypophonia

- Cognition
- Sexual dysfunction
- Restless legs

- Depression/anxiety
- Hallucinations
- Orthostasis
Most Troubling Symptoms - Early

1. Slowness
2. Tremor
3. Stiffness
4. Pain
5. Loss of smell/taste
6. Mood
7. Handwriting
8. Bowel problems
9. Sleep
10. Appetite/weight
Most Troubling Symptoms - Late

1. Fluctuations
2. Mood
3. Drooling
4. Sleep
5. Tremor
6. Pain
7. Bowel problems
8. Urinary problems
9. Falls
10. Appetite/weight
Treatment – Motor Symptoms

- Levodopa
- Oral Dopamine Agonists
- Rotigotine
- Apomorphine
- Anticholinergics
- Selegiline, Rasagiline (MAO-B inhibitors)
- Entacapone, Tolcapone (COMT inhibitors)
- Amantadine

Exercise!
Treatment of Parkinson’s

• Considerations
  – What symptoms are we treating?
  – What problems are we creating?
  – Age of the person with Parkinson’s
  – Medical comorbidities (especially orthostasis, depression, polypharmacy)
  – Goals of treatment (The perfect is the enemy of the good…)
MOUTH
Jaw tremor and/or rigidity can occur and produce tooth damage. Chewing may be impaired as well as the quality of ingested food.

PHARYNX
An abnormal oropharyngeal phase of swallowing increases the risk of aspiration. Dysphagia for liquids can cause dehydration that contributes to constipation. Saliva retention in the mouth is associated with drooling.

OESOPHAGUS
Motor involvement translates into altered peristalsis (achalasia, slow transit), spasms and gastro-oesophageal reflux. Dysphagia is for solids and is associated with reduced food intake and weight loss.

STOMACH
An abnormal emptying pattern produces early satiety, nausea, reduced food intake and weight loss. It also contributes to gastro-oesophageal reflux. Impairment of L-dopa pharmacokinetics and motor control can also occur.

COLON
Altered motility and prolonged transit result in constipation with discomfort and abdominal distension. Possible complications (e.g., megacolon, true or pseudo obstruction, perforation) should be considered.

SMALL INTESTINE
Altered motility and prolonged transit may cause abdominal distension and bloating. This, in turn, can be associated to bacterial overgrowth, malabsorption and weight loss.

Barichella et al., 2009
Major Nutritional Issues in PD Management

- **Food intake**: (hyposmia, gastrointestinal dysfunction, bradykinesia-related impairment in activities of daily living, depressive symptoms, neuroendocrine factors?)
- **Energy expenditure**: (rigidity, resting tremor)

- **Food intake**: ("honey-moon" well-being, improvement in swallowing and mood, compulsive eating)
- **Energy expenditure**: (decreased rigidity, resting tremor)

- **Food intake**: (hyposmia, oro-pharyngeal and gastrointestinal dysfunction, impairment in activities of daily living, depression, dementia)
- **Energy expenditure**: (rigidity, dopaminergic-induced dyskinesia)
- **Malabsorption**: (?)
Implications for Treatment

- **Exenatide (Byetta)**
  - Synthetic analog of exendin-4
  - Neuroprotective in cell cultures and animal models of PD
  - Clinical trial in people with PD produced symptomatic improvement (but poorly designed study)

Aviles-Olmos et al., 2013
The GI Tract in PD - Constipation

Heiko Braak\textsuperscript{a}, Rob A.I. de Vos\textsuperscript{b}, Jürgen Bohl\textsuperscript{c} and Kelly Del Tredici\textsuperscript{a}

\textsuperscript{a} Parkinson’s Disease Foundation

A division of the Parkinson’s Foundation
Constipation - Rx

• Three W’s
  – Water
  – Walking
  – Wegetables

• Rancho recipe
  – 1 cup bran cereal
  – 1 cup prune juice
  – 1 cup applesauce
Constipation

- Probiotics - Lactobacillus
- Fiber + Water
- Coffee!
- Abdominal Exercises
- Stool Softeners
- Senna
- Laxatives (Miralax et al.)
- Glycerin suppositories
- Pyridostigmine (Mestinon)
- Lubiprostone (Amitiza)
- Linaclotide (Linzess)
- Enemas
Delayed Gastric Emptying and Bloating

- Domperidone (Motilium)
- Baclofen
- Nizatidine (Axd)
- **NOT** metaclopramide (Reglan)
Sialorrhea

- Botulinum toxins
- Rimabotulinumtoxin B and incobotulinumtoxin A in clinical trials
- Oral glycopyrrolate (Cuvposa)
- Atropine drops
- Amantadine
- Anticholinergic agents
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- Sleep disorders
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- Cognition
- Sexual dysfunction
- Restless legs
- Depression/anxiety
- Fatigue
- Sleepiness
- Orthostasis
- Drenching sweats
Sleep Disorders

- Insomnia
  - Initiation, maintenance, terminal

- REM Sleep Behaviour Disorder

- Restless Legs

- Stridor, Apnea (MSA)
Sleep and Parkinson’s

• About 60% of people with PD report problems with sleep (compared to 33% of age-matched controls)

• Frequent (40%) or early (25%) awakenings are twice as common in PD

• May be more severe in atypical parkinsonisms, especially MSA
• Active movements during REM (dreaming) sleep

• RBD may precede motor/cognitive symptoms by >10 years

• Conversion to neurodegenerative disease 23% at 3 years and 41% at 5 years

• Pedunculopontine nucleus?

• Clonazepam, Melatonin, Ramelteon
Sleep Disorders

• Initiation Insomnia
  – Hypnotics?
    • Associated with increased risk of RBD, including suvorexant (Belsomra)
  – Ramelteon (melatonin agonist, Rozerem)

• Nocturnal ‘wearing off’
  – Dopamine agonist, Carbidopa/levodopa CR, Rytary at bedtime
Sleep Hygiene

- Consistent bedtime AND awakening time
- No alcohol or caffeine after supper
- The bed is only for sleeping and sex
- Avoid exercise within three hours of bedtime
- No long daytime naps (30 minutes)
- Wear socks!
Fatigue/Sleepiness

- Sleep and mood history!
- Exercise
- Methylphenidate (Ritalin)
- Caffeine (Failed in clinical trial)
- Modafinil (Provigil)
- Armodafinil (Nuvigil)
Caffeine

Hernán et al., 2001; Morozova et al., 2008; O’Reilly et al., 2009; Thacker et al., 2007

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Hallucinations

- Visual hallucinations most common
- People, furry animals, and insects
- 25-30% of people with PD will develop hallucinations after some years; 10% will develop paranoid delusions
- May be associated with worsening cognition and risk of dementia
  - Attention, frontal executive function, visuospatial abnormalities, language and verbal memory
Hallucinations

- PD medications may cause or worsen
- Illness (UTI!!) may cause or worsen
- Cholinesterase inhibitors
  - Quetiapine, clozapine
  - **Nuplazid (pimavanserin)** only FDA-approved agent
  - **NOT** risperidone, haloperidol, olanzapine, aripiprazole, lurasidone
Depression in PD

• Depression occurs in 45% of people with PD
• Psychiatrist experienced in PD
• Depression (and anxiety) correlated with leaving work and poor quality of life
• Mood disorders are more common in early PD than in the general population, but may remain stable for years

Armstrong et al., 2014; Weintraub et al., 2004
Depression in PD

- Tricyclic antidepressants
  - Amitriptyline, nortriptyline
- Serotonergic antidepressants
  - Escitalopram, other SSRIs
- Mirtazapine, venlafaxine
- Exercise, yoga, acupuncture
Anxiety in PD

• Dopaminergic medications for ‘off’ anxiety
• Cholinesterase inhibitors for anxiety and attention
• Mirtazapine, venlafaxine, SSRIs
• PRN Benzodiazepines
Apathy, Fatigue and Sleepiness

- 75% of people with PD suffer from one or more of these symptoms
- Difficult to define and difficult to measure
- Difficult to study!
- Strong association between fatigue and depression; also between apathy and depression
- Apathy may predict dementia

Skorvanek et al., 2014; Dujardin et al., 2009
Apathy, Fatigue and Sleepiness

- May respond to dopamine (and apathy may worsen after DBS, if medications are lowered)
- Serotonin and other neurotransmitters may be involved
- Ensure good sleep at night!
- Exercise
- Mood evaluation by psychiatrist
- ‘Alerting’ antidepressants
- Methylphenidate

Schifitto et al., 2008; Friedman et al., 2011; Devos et al., 2013
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Sexual Dysfunction - Men

- Phosphodiesterase inhibitors
- Dopaminergic meds
- Vasodilator injections
- Prosthetics
- Apomorphine
- Alternatives to intercourse
  - www.hotoctopuss.com
Sexual dysfunction - Women

- Dopaminergic meds
- Testosterone
- Flibanserin (Addyi)
- PDIs failed in clinical trials
- Alternatives to intercourse
  - [www.lelo.com](http://www.lelo.com)
Orthostatic Hypotension

- Iatrogenic
- Cold fluids, salt compression stockings
- Caffeine at meals
- Low glycemic index diet
  - Acarbose
- Fludrocortisone
- Midodrine
- Droxidopa
- Methylphenidate, ibuprofen, pyridostigmine

Exercise!
Autonomic failure as the initial presentation of Parkinson disease and dementia with Lewy bodies.

Kaufmann, Horacio; Nahm, Kirsty; Purohit, Dushyant; Wolfe, David

DOI: 10.1212/01.WNL.0000138500.73671.DC

Figure. [alpha]-Synuclein-positive inclusions in neuronal perikarya ("Lewy bodies," single arrows) and neurites ("Lewy neuritis," double arrows). (A, B) Case 1. (A) Thoracic sympathetic chain. (B) Substantia nigra. (C, F) Case 2. (C) Thoracic sympathetic chain. (D) Substantia nigra. (E) Frontal cortex. (F) Cingulate cortex.
Droxicdopa

- Brand name Northera
- Prodrug of norepinephrine
- Approved in 2014 for symptoms of neurogenic orthostatic hypotension
- No contraindications, but concomitant use of midodrine not allowed in clinical trials
- FDA proviso that efficacy beyond 2 weeks not established
- Supine hypertension warning (all hypertensive agents), so head of the bed at 30 degrees
- Approved in Japan for NOH and for freezing of gait
Rhinorrhea

• Occurs in 33-35% of people with PD compared to 10-12% age-matched controls
• If an ‘off’ phenomenon, then try to stay ‘on’
• Usually not responsive to levodopa
• Antihistamines (off-label)

Chou et al., Mov Dis, 2011; Sedig et al., Int J Neurosci, 2010
Skin

• Seborrheic dermatitis
  – Often between eyebrows
  – Soap and water
  – Anti-dandruff shampoos (Off Label)

• Sweating (covered later)
Skin Changes

- Melanoma in PD
- Elevated risk of melanoma and possibly breast cancer in people with PD
- Everyone with PD should have a skin check by a dermatologist at the time of diagnosis, and then as recommended by dermatologist

Disse et al., Dermatol Surg, 2016
Skin Changes Due to Medications

• Livedo due to amantadine
  – Disappears with discontinuation of the drug

• Erythema due to dopamine agonists
  – Disappears with discontinuation of the drug

• Nodules due to apomorphine injections or infusion
  – Small granulomas reported in about 4% of people with PD

Sladden et al., 2003; Borovac, 2016 Apokyn Prescribing Information
Drenching Sweats

- Uncommon, but extremely bothersome
- Poorly understood
- Cool environment and showers
- Loose fitting clothing
- Topical antiperspirants
- Botulinum toxin injections if sweating confined to axillae or palms
Balance and Falls

• No medications or surgical treatments for PD improve balance

• Poor balance and falls are a major cause of morbidity and mortality in people with PD

• Urgently need interventions that improve balance with minimal side effects

• Balance-centered Physical Therapy can improve postural instability and reduce falls

• Cholinesterase inhibitors may reduce the chance of falling as well
Exercise
PD - not just a dopamine disease any more...

- Dopamine
  - Motor control, mood, attention
- Acetylcholine
  - Cognition, anxiety
- Norepinephrine
  - Orthostatic hypotension, freezing of gait
- Serotonin
  - Tremor, dyskinesias, depression, weight loss
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Thank You!

“Since my Parkinson’s diagnosis in 2013, I have learned to doodle. Creativity keeps my mind and body focused on something besides Parkinson’s and my tremors make my art more interesting. Doodling has become a thirst that must be quenched.”

March Texas Spring Color, Sharon Skindell
Creativity and Parkinson’s Project
Questions and Discussion
Resources

Parkinson’s HelpLine
- Available at (800) 457-6676 or info@pdf.org
- Monday through Friday
- 9:00 AM – 5:00 PM ET

Centers of Excellence
- Worldwide network of 42 leading academic medical centers
- Search for one near you at www.parkinson.org/search

Fact Sheets and Brochures
- Parkinson’s Q&A
- Seeking Out a PD Specialist
- Secrets, Myths & Misconceptions

Video
- Diagnosis Parkinson’s Disease: You are Not Alone