The Management of Non-Motor Symptoms of Parkinson Disease

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Cardinal Symptoms of Parkinson Disease

- Resting tremor:
  - 5Hz, pill-rolling, asymmetric
- Rigidity
  - increased resistance to passive movement, often w/cogwheeling
- Bradykinesia/Hypokinesia
  - Loss of automatic movements (i.e. armswing), masked facies, festinating gait, freezing
- Postural Instability
  - Difficulty rising from a chair
  - Falling backwards

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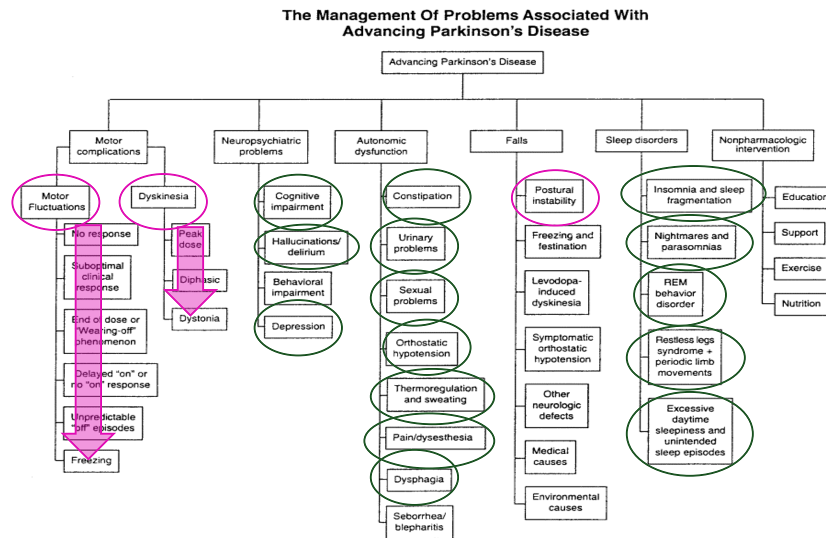
Parkinson Disease—What else?



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PD: Nonmotor Symptom (NMS) Burden

- Besides the classic motor symptoms, there are psychiatric, autonomic, sensory, and sleep issues
- Studies suggest an average of 8-13 NMS per patient, with some experiencing as many as 32 symptoms simultaneously
- <2.5% of patients have no NMS
- Quality of life of patients is more affected by NMS than motor, particularly as the disease progresses

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Why is the NMS Burden so High?

- Not looked for or recognized by physicians
- Not spontaneously reported by patients
- Our current PD medications, while fairly good for the motor symptoms, provide minimal if any relief for most of the NMS

Depression

- Depression is extremely common in PD
  - Approximately 60% of patients experience this during some part of the disease
  - ~ 30% experience depression prior to diagnosis
  - PD patients have the highest rates of depression by age for ANY disease
- It is more than just “woe is me”
  - Low dopamine can affect mood
  - Serotonin is also low in PD, and this chemical is highly implicated in depression

Treatment of Depression in PD

- Treating depression improves quality of life
  - It also improves movement and motor symptoms
  - Treating motor symptoms alone does not improve mood
- Many types of medication have good evidence
  - Pramipexole has very good evidence beyond its motor
  - Nortriptyline – TCA – good evidence
  - Sertraline – SSRI – good evidence
  - Venlafaxine – SNRI – good evidence
  - Paroxetine – SSRI – evidence is mixed

Suicide in Parkinson disease

- Suicide is rare in PD
  - This is not the case in all movement disorders. Huntington disease patients have high rates.
- Death and suicide ideation is relatively common
  - Death ideation rate ~ 28% ("Time when you felt that life was not worth living")
  - Suicide ideation rate ~ 11.2% ("Have you thought about taking your own life?")
- Number of patients who have attempted suicide is so small it has been difficult to study

Fatigue

- Extremely common in Parkinson's disease
- Most important reason cited for medical disability insurance claims in PD in the U.S.
- Not necessarily associated with depression
- Can try methylphenidate, amphetamine salts, modafanil, armodafanil. Results are mixed.
- One small positive study for sodium oxybate for fatigue and excessive daytime sleepiness

Apathy

- ~30% of patients have apathy and depression
- ~12% have apathy alone
- Study looking at rotigotine, a transdermal dopamine agonist, did not show benefit.
- No other trials published

Cognitive Impairment and Dementia

- Relative risk of developing dementia in Parkinson's disease is five times that of controls
- Mild cognitive impairment can be present in early stage non-demented Parkinson patients
- Bradyphrenia – the slowness of processing information – is extremely common
- Parkinson's disease dementia and Dementia with Lewy bodies are closely related

Cognitive Impairment Treatment

- Acetylcholinesterase inhibitors
  - Rivastigmine – FDA approved for Parkinson dementia
  - Donepezil – Appears to be effective
  - Galantamine – Insufficient evidence (but I would use it if there are problems with the others)
- Memantine – NMDA receptor antagonist – data is conflicting and uncertain
- Rasagiline – Trial for mild cognitive impairment was negative.

Psychosis

- May affect up to 20% of PD patients. Some trials suggest more.
- Primarily visual hallucinations. Usually not threatening – i.e. small children, animals
- Can also be auditory, tactile, olfactory, gustatory
- Can also be delusional (i.e. spouse is cheating)
- Early on there is insight
- In later disease, there can be paranoid delusions
- Can be exacerbated by dopaminergic medicines

Psychosis Treatment

- Pimvanserin – $5\text{-}HT_{2A}$ inverse agonist – FDA approved for hallucinations and delusions in PD
- Antipsychotic agents
  - Clozapine – strong data, but specialized monitoring required
  - Quetiapine – open label trials all show good benefit, blinded trials do not
  - Olanzapine – not helpful and PD motor symptoms worsened
  - Typical agents – i.e. haloperidol – should not be used since they will worsen the Parkinson's disease
- Acetylcholinesterase inhibitors – can be very useful for the hallucinations

Orthostatic Hypotension

- Patients with PD get low blood pressure
- Symptomatic OH may be as high as 20%
- This can be caused by PD itself
- Dopaminergic medications also cause OH
- First treatment is to eliminate anti-hypertensives

Orthostatic Hypotension Treatment

- Droxidopa – FDA approved on February 18, 2014
  - Norepinephrine precursor
  - Thought to work by its conversion into norepinephrine, causing peripheral vasoconstriction
- Fludrocortisone – synthetic adrenocortical steroid
- Midodrine – vasopressor/antihypotensive agent
- Main side effect of all three is supine hypertension

Sexual Dysfunction

- Some of this can be associated with the motor symptoms of PD or other NMS (i.e. depression)
- Increase in libido can occur with levodopa
- Compulsive sexual behaviors have been seen in about 3.5% of patients on dopamine agonists
- In management, don't forget about non-PD issues (i.e. enlarged prostate)
- Sildenafil has been shown in a clinical trial to be effective in erectile dysfunction. Other PDE_5 inhibitors also likely work

GI – Constipation

- Frequently occurs in PD patients (>60%), often years before diagnosis
- Many non-medicinal recommendations:
  - Increase water intake (6-8 glasses daily)
  - Increase fiber intake
  - Raw fruits and vegetables
  - Daily exercise
  - Reduce/Eliminate dairy

GI – Constipation – Medications

- Polyethylene Glycol – Osmotic laxative
  - causes water to be retained to help constipation
  - strong evidence that it can be helpful
- Lubiprostone – Chloride channel protein 2 activator on GI epithelial cells
  - fluid secretion that increases motility and promotes spontaneous bowel movements
  - evidence for this is medium
- Tegaserod – very small study, medication pulled from market and markedly restricted

GI – Nausea

- Usually this is a result of side effects of levodopa and dopamine agonists
- Also a result of reduced gastric motility
- Taking the dopamine agonist with food can help
- Avoid taking levodopa with protein as that can lessen its effect. Taking it with orange juice can be very effective at speeding up absorption
- Levodopa can be liquefied allowing a small dose more frequently

GI – Nausea - Medications

- Metoclopramide – very potent dopamine antagonist – DO NOT USE! Can greatly exacerbate Parkinson's disease symptoms
- Domperidone – dopamine antagonist
  - Highly effective. Does not cross blood-brain barrier
  - Not available in the United States
  - Be aware of QT prolongation. Need an EKG.
- Serotonin 5-HT_3 receptor antagonists – Ondansetron, Granisetron – non-dopaminergic
- Don't forget about adding extra carbidopa

Sialorrhea (Drooling)

- ~70% of PD patients have abnormal salivation
- It is not from excess production of saliva
- It is likely from reduced spontaneous swallowing
- Flexed head position lets saliva out of the mouth
- Can sometimes use non-pharmacologic techniques
  - Chewing gum or hard candy
  - More saliva is produced, but pt. swallows more frequently

Sialorrhea Treatment

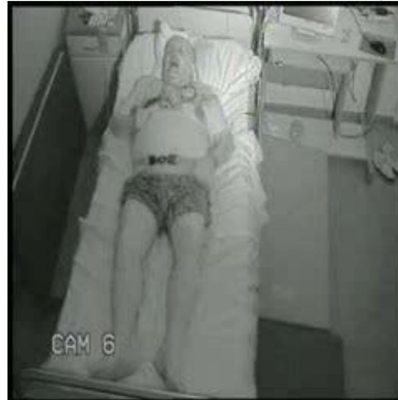
- Glycopyrrolate – anti-cholinergic – good evidence, at least for short-term
  - Does not cross blood-brain barrier
  - Dry mouth, urinary retention, constipation, etc.
- Sublingual atropine – anti-cholinergic
  - Helpful, but problems with delirium, hallucinations
- Botulinum toxin – injection into salivary glands
  - Inhibits cholinergic parasympathetic, postganglionic sympathetic activity
  - Benefit with both types A and B

Hyperhidrosis (Excessive sweating)

- Decreased activation of sweat glands in the hands
- Increased in the face, head, and trunk
- Can cause drenching of clothes
- Often an “off” symptom, so increasing frequency of levodopa can help this
- There are no other known good therapies

REM Sleep Behavior Disorder (RBD)

- Normally people are paralyzed in REM sleep
- RBD patients lose this
- Patients act out dreams
- Can occur prior to diagnosis
- Often affects bed partner more than the patient
- Not the same as RLS; it does not respond to RLS drugs
  - Clonazepam has strongest evidence, but it can adversely affect fatigue and/or dementia
  - Melatonin may be helpful with fewer side effects



Summary

- Parkinson's disease is more than than just a motor disease of tremors and rigidity
- We have good medicines for the motor symptoms
- We are beginning to have better medicines for the non-motor symptoms
- Don't forget to ask about – and treat – the NMS

Thank you!

“Mr. Osborne, may I be excused? My brain is full.”