Managing Non Motor Symptoms of Parkinson's Disease

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Disclosures

- None

Non motor symptoms

- Present throughout the preclinical and clinical course of PD in the vast majority of patients.
- Hugely underrecognized and underreported.
- Impose a tremendous physical, psychosocial and financial burden on patients and families.
- May predominate in the early and late stages of the disease.
- Some are partially L-Dopa responsive, many are not.
- Appropriate management, to the degree possible, is of paramount importance.
- Discussion considered AAN, MDS and EAN guidelines.

DOMAINS

A. Sensory dysfunction

B. Mood disorders

C. Cognitive disorders

D. Sleep disorders

E. Autonomic nervous system dysfunction

F. Speech

A. Sensory dysfunction

- **Hyposmia/anosmia in up to 90% of PD patients**
- May precede motor features
- Likely due to a-synuclein deposition in the olfactory bulb and amygdala
- Typically does not get better with dopaminergic therapy
- Worth excluding other aggravating factors like vitamin deficiencies, viral infections, trauma

A. Sensory dysfunction

- Visual hallucinations: Associated with cognitive decline and sleep dysfunction, worsened by dopaminergic therapy.
- **Impaired color vision/low visual acuity: Degeneration of dopaminergic retinal cells, not well studied if and how much dopamine replacement therapy restores deficits.**
- **Pain: 30-85% of PD patients.** Various causes: Mostly musculoskeletal vs central, may or may not fluctuate with time of meds, OFF symptom, various neurotransmitters involved, beyond dopamine, like serotonin and noradrenaline.

A. Sensory dysfunction

- Pain: Optimization of dopaminergic therapy with reduction in OFF time, using extended release L- Dopa, rotigotine patch, levodopa or apomorphine pumps, **DBS (with long lasting effects).**
- Botulinum toxin injections in patients with painful dystonia.
- Combination with NSAIDS, pain modulating antidepressants like venlafaxine and duloxetine.
- Physical therapy.

B. Mood disorders

- **Anxiety disorders**: Up to 60%, may or may not be associated with depression.
- Often in the preclinical or early stages, more common in females, very common in the more advanced stages.
- Can be associated with OFF symptoms and improved dopaminergic therapy and/or DBS may help.
- Antidepressants, preferably SSRIs may help.

B. Mood disorders

- **Depression:** Clinically significant in 35% of the PD population, milder than depression seen in non-PD patients, more commonly associated with apathy.
- Due to PD, or reactive or separate or all of the above.
- Most neurotransmitter systems are involved like dopamine, noradrenaline, serotonin.
- Multidisciplinary approach.
- Rx: SSRIs, SNRIs, TCA (evidence that they may work well in PD, avoid amitriptyline), DOPAMINE AGONISTS, ECT, rTMS, CBT.
- **DBS may exacerbate depression.**

B. Mood disorders

- **Apathy**: Up to 60% of patients with PD, with or without depression and/or dementia.
- Can be an early manifestation of PD, sometimes out of proportion to motor symptoms.
- **Can be seen as a side effect of DBS.**
- Dopamine and acetylcholine are involved.
- Rx: Dopamine agonists (especially after DBS, also avid rapid L-Dopa reduction after DBS), cholinesterase inhibitors.

B. Mood disorders

- **Fatigue**: Up to 50% of the PD population, troublesome to treat.
- Not associated with duration or severity of PD.
- R/o: Depression, sleep disturbance (OSA), autonomic symptoms, like orthostatic hypotension.
- Side effect of L-Dopa and dopamine agonists, may have to lower individual doses.
- Can try: Coffee, **methylphenidate**, amantadine, modafinil.

B. Mood disorders

- **Psychosis**: Visual hallucinations and/or delusions. Up to 40% of PD patients.
- De novo or as a side effect of L-Dopa or dopamine agonists. AVOID anticholinergics.
- Vivid dreams and nightmares may predate or be more common in those who develop PD psychosis.
- Rx: AVOID typical neuroleptics, very cautious with atypicals, **clozapine**, **PIMAVANSERIN** (Nuplazid) ONLY

FDA approved medication, easy to dose.

B. Mood disorders

- **Impulse control disorders and obsessive/compulsive behavior.**
- **Common SE of dopamine agonists: appr. 15%.**
- Can occur as part of PD.
- D/c offending agents.
- DBS may help reduce DA dose and indirectly help ICD

  But ICD can also happen after DBS.
- Amantadine, neuroleptics.

B. Mood disorders

- Pseudobulbar affect: Inappropriate, emotionally incongruent laughter or crying.
- Consider dextromethorphan/quinidine (NUEDEXTA).
- AE: Patients with cardiac issues.
- Can consider the same drug for patients with agitation.

C. Cognitive disorders

- **PD related cognitive impairment and dementia**: May affect up to 80% of PD after 20 years of disease.
- PD dementia: Degree correlates with the density of Lewy bodies in the cortex.
- Drugs: RIVASTIGMINE, donepezil, galantamine, then consider adding memantine, or as a first choice if the above are contraindicated.
- Benefit varies, may help visual hallucinations in DLB
- OFF label: Consider pimavanserin in PD patients with dementia and psychosis

D. Sleep disorders

- Sleep and wakefulness commonly disrupted in PD, more prevalent as the disease progresses, up to 90% of patients affected.
- Include: Insomnia, REM sleep behavior disorder, excessive daytime sleepiness (EDS), sleep disordered breathing (SDB) and obstructive sleep apnea (OSA), restless legs syndrome (RLS), periodic limb movements in sleep (PLMS) and circadian disruption.
- Significantly affect quality of life, mood and cognitive performance.

D. Sleep disorders

- Insomnia and sleep fragmentation: Up to 80% of PD patients.
- May be due to the PD process, as a side effect of medications, psychiatric issues or all of the above.
- Small studies to support evidence.
- Better sleep hygiene (minimize daytime napping, increase physical activity, light exposure).
- Light therapy.
- Benzodiazepines, quetiapine, doxepin.
- Melatonin.
- Extended release L-Dopa, DBS, Duopa pump may help, although not intended for that purpose.

D. Sleep disorders

- REM sleep behavior disorder (RBD): Precedes PD in more than 80% of patients and affects up to 50% of them.
- Patients with more severe PD, rigid/akinetic subtype and higher L-Dopa needs are more likely to have RBD.
- Risk factor for cognitive decline.
- Implement safety measures to avoid accidents in the bedroom.
- Eliminate aggravating medications like antidepressants.
- **Clonazepam (0.25mg-2mg), Melatonin 3-12mg, first line**
- Small trial: Rivastigmine patch, helped RBD!
- Dopamine agonists may help but effect not consistent.

D. Sleep disorders

- Restless legs syndrome (RLS): 20% of PD patients, associated with greater severity of PD, depression and low iron levels.
- Rx: Dopamine agonists (low doses), pregabalin, gabapentin, clonazepam, opioids.
- Avoid L-Dopa, if possible due to the effect of augmentation.
- Avoid dopamine blocking meds/anticholinergics/antihistamines.
- Replenish iron if needed.
- Pregabalin may be preferable to pramipexole due to less risk for augmentation.
- DBS may improve but also aggravate RLS

D. Sleep disorders

- PLMS: L-Dopa may help.
- SDB-mainly OSA: weight loss, CPAP, mandibular advancement devices.
- Extended release dopaminergic medications may help.
- Circadian disruption: Light therapy.

D. Sleep disorders

- Excessive daytime somnolence (EDS): Up to 50% of PD patients.
- Assess for OSA, improve sleep hygiene, light therapy, minimize aggravating meds, like dopamine agonists
- **Modafinil: 100-400 mg/d.**
- Caffeine: 200 mg twice daily.
- Methylphenidate.
- Atomoxetine.
- Counsel against driving.

D. Sleep disorders

- New evidence suggests that deep sleepers may progress more slowly in their PD.
- Possible opportunity for therapeutic intervention by sleep restoration strategies.

E. Autonomic nervous system (ANS) dysfunction

- 1. Urinary dysfunction
- 2. Erectile dysfunction
- 3. Gastrointestinal dysfunction
- 4. Cardiovascular dysfunction
- 5. Other

1. Urinary dysfunction-I

- Includes frequency, urgency and nocturia, all parts of detrusor muscle hyperreflexia.
- Loss of inhibitory role of the basal ganglia.
- Dopaminergic medications like L-Dopa, dopamine agonists may help.
- Anticholinergics, like oxybutynin, may have adverse cognitive effects.
- Newer medications like mirabegron (b3-agonist) do not affect cognition and have other potentially beneficial side effects (hypertension).

1. Urinary dysfunction-II

- Intranasal desmopressin may help nocturia.
- **DBS (STN) may also help bladder capacity and voiding.**
- Intra-detrusor injection of botulinum toxin A may help.
- Sacral and percutaneous posterior tibial nerve stimulation, neuromodulation approaches.

2. Erectile dysfunction (ED)

- Rule out other reversible causes of ED.
- Sildenafil (Viagra) approved for ED.
- Evaluate for cardiac issues before starting sildenafil.
- Side effects: Headache, hypotension.

3. Gastrointestinal dysfunction

- Drooling, Dysphagia, Impaired gastric emptying, Constipation.
- Drooling: Due to impaired swallowing in PD, associated with increased risk of respiratory infection
- 10-81% of PD patients.
- May coexist with dry mouth as saliva secretion is actually REDUCED in PD.
- Dry mouth present in 60% of PD patients.
- Aesthetically disturbing and bad for oral hygiene.

Drooling

- Chewing sugarless hard candy or gum.
- Glycopyrrolate 1-2 mg BID or TID either swallow or crush in mouth (low dose to avoid cognitive side effects, constipation).
- Atropine drops (similar SE as glycopyrrolate).
- Scopolamine patch (similar SE).
- Botulinum toxin injections in the parotid and rarely necessary in the submandibular glands.

Dysphagia

- Common in advanced stages but also in early ones.
- Subjectively in 35% of PD patients, objective findings

  in as many as 82%.
- Aspiration present in 15-56% of PD patients.
- Speech and language evaluation necessary, as early as possible, rehabilitative approaches, diet modification, evaluation by GI with invasive testing if needed.
- Expiratory muscle strength training and video-assisted swallowing therapy.

Impaired gastric emptying and GI motility

- 70-100% of PD patients.
- May result in delayed or complete loss of benefit from L-Dopa.
- H. Pylori infection may play a role in motor fluctuations by interfering with gut motility and L-Dopa absorption.
- Small intestinal bacterial overgrowth (SIBO) syndrome may also be associated with more (severe) motor fluctuations.

Impaired gastric emptying and GI motility

- No really good studies and no universally acceptable approaches.
- Remove/optimize exacerbating factors.
- Prokinetics (NOT METOCLOPRAMIDE aka REGLAN): Domperidone, Cisapride (cardiac side effects), Erythromycin.
- Consider eradication of H.Pylori and antibiotic cycles for SIBO syndrome.
- Consider orally disintegrating L-Dopa, rotigotine patch, apomorphine, DBS to reduce OFF time.

Constipation

- Most common GI symptom in PD.
- Reported in 80-90% of PD patients.
- Can be present well before the onset of motor symptoms.
- Can also be a side effect of PD (and many other) medications like L-Dopa and dopamine agonists.

Constipation

- ADEQUATE WATER INTAKE!!!
- Increase dietary fiber, fruits and vegetables.
- Fiber supplements (psyllium).
- Increase physical activity.
- Avoid prolonged periods without any BM.
- Macrogol (polyethyleneglycol) AKA Miralax: Helps retain water in the GI tract.
- Lactulose syrup (and other osmotic laxatives).
- Lubiprostone AKA Linzess (secretagogue).

4. Cardiovascular symptoms

- Cardiac autonomic dysfunction in up to 80% of PD patients.
- Orthostatic hypotension AND/OR labile hypertension.
- OT is 30-58% of PD patients.
- Hypertension may be associated with OFF state and hypotension exacerbated by PD meds.
- Increased HR and supine hypertension in PD patients may cause end organ damage.
- Reduced maximum heart rate during exercise in PD patients.

Orthostatic Hypertension (OH)

- Only FDA approved drugs are midodrine (watch for supine hypertension) and the newly approved droxidopa AKA Northera (can titrate slowly).
- Other medications commonly used are fludrocortisone and pyridostigmine.
- Can use is combination if response is suboptimal like midodrine and fludrocortisone.
- ADEQUATE WATER INTAKE!!!
- May have to resort to a combination of low dose BP meds and the above.
- Rationalize pre-existent BP med regimen. Think whether PD meds make OH worse.

5. Other

- Polyneuropathy: Mostly sensory, perhaps associated with vitamin deficiencies, can be exacerbated by L-Dopa or Duopa pump. Check and correct B12, B6, folate, homocysteine, methylmalonic acid.
- Rhinorrhea: Up to 33% of PD patients, may not be associated with disease duration. More common in men. Consider atropine spray.
- Dysfunctional sweating: Poorly understood phenomenon, dry hands and sweaty body, optimize dopaminergic therapy, can be caused by DBS.

F. Speech

- Up to 90% of PD patients affected.
- Both dopaminergic and non-dopaminergic pathways involved.
- Highest level of evidence suggest benefit from LSVT-LOUD with improvements lasting up to 2 yrs.
- Other approaches like surface electrical stimulation (Vital-Stim) need to be validated.

Valuable Resources

Websites:

Davis Phinney Foundation
www.davisphinneyfoundation.org

The Michael J. Fox Foundation
https://www.michaeljfox.org

Michigan Parkinson's Foundation
www.parkinsonsmi.org

National Parkinson's Foundation
www.parkinson.org

Thank you for your attention

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