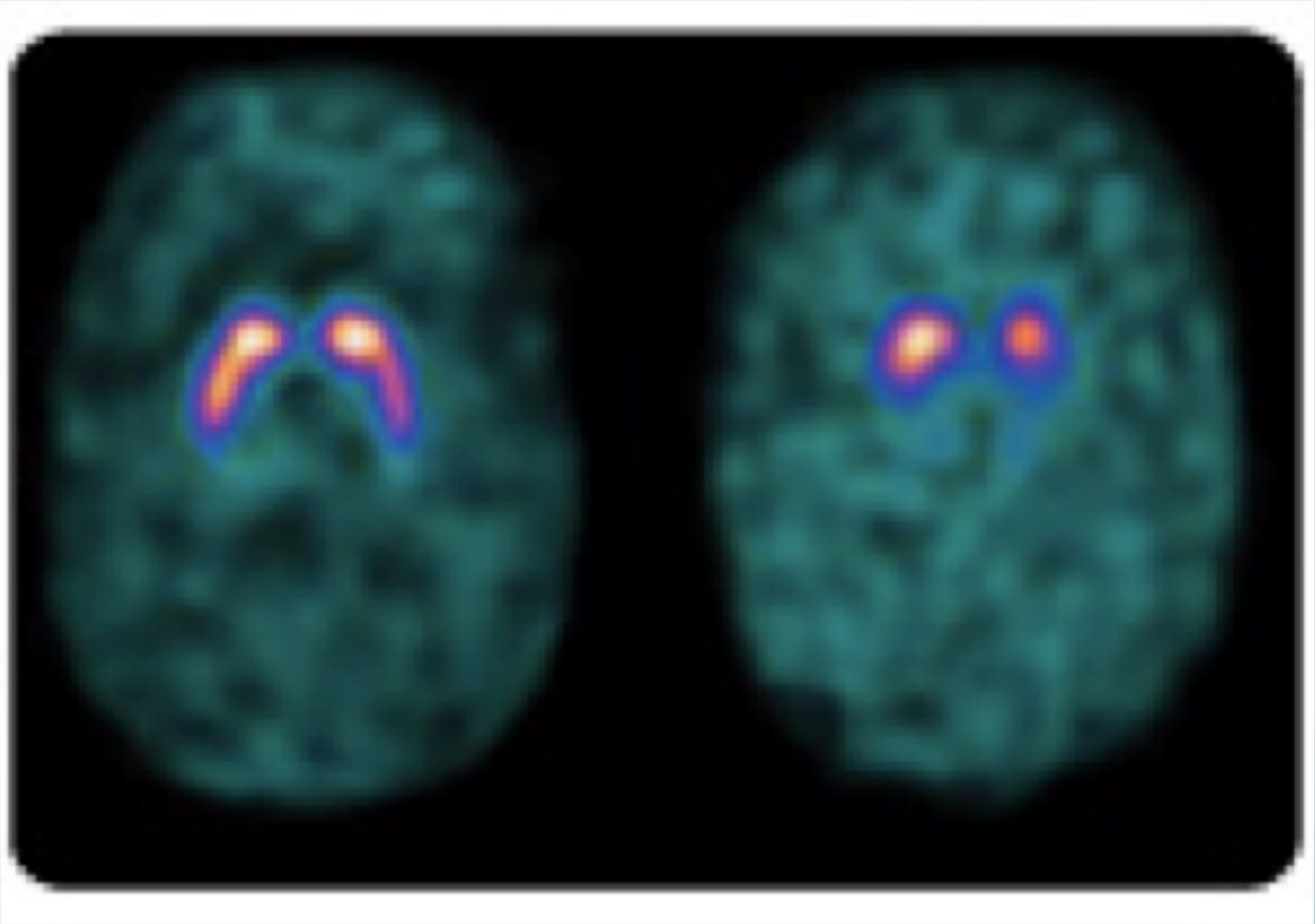
# Parkinson's Disease: Nonmotor Manifestations

Neal Hermanowicz, MD, FAAN
Parkinson's & Movement Disorders Program
Hoag Neurosciences
Newport Beach, CA

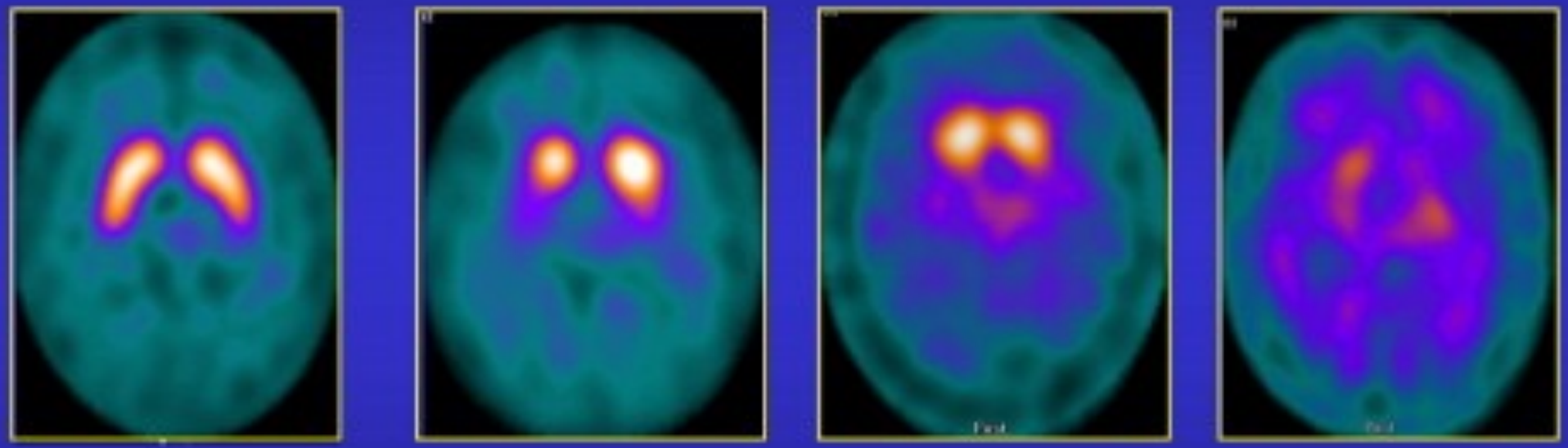
# Diagnosis of Parkinson's Disease (PD)

- PD Remains a clinical diagnosis
  - DaT scans, skin biopsies are not definitive and may be wrong in early, mild PD
- Symptoms
  - Described by the patient
  - Elicited by the examiner
- Examination findings (TRAP)
  - Tremor
  - Rigidity
  - Akinesia/bradykinesia
  - Postural instability/gait

# DaT Scan



# DATSCAN/SPECT as a Marker of Disease Progression



Healthy Control

PD H&Y I

PD H&Y II

PD H&Y IV

Antonini A, DeNotaris R. Sleep Med. 2004 Mar;5(2):201-6.

# Neurological Examination

- Vital signs- BP and P (orthostatics), weight
- Speech
- Mental status (MoCA, MMSE)
- Cranial Nerves (especially eye movements)
- Motor
  - Muscle bulk
  - Tone
  - Presence or absence of adventitial movements
  - Power
  - Coordination
  - Reflexes, including plantar response
  - Sensation (pain, cold, vibration, proprioception)
  - Stance and gait

# Why is this important?

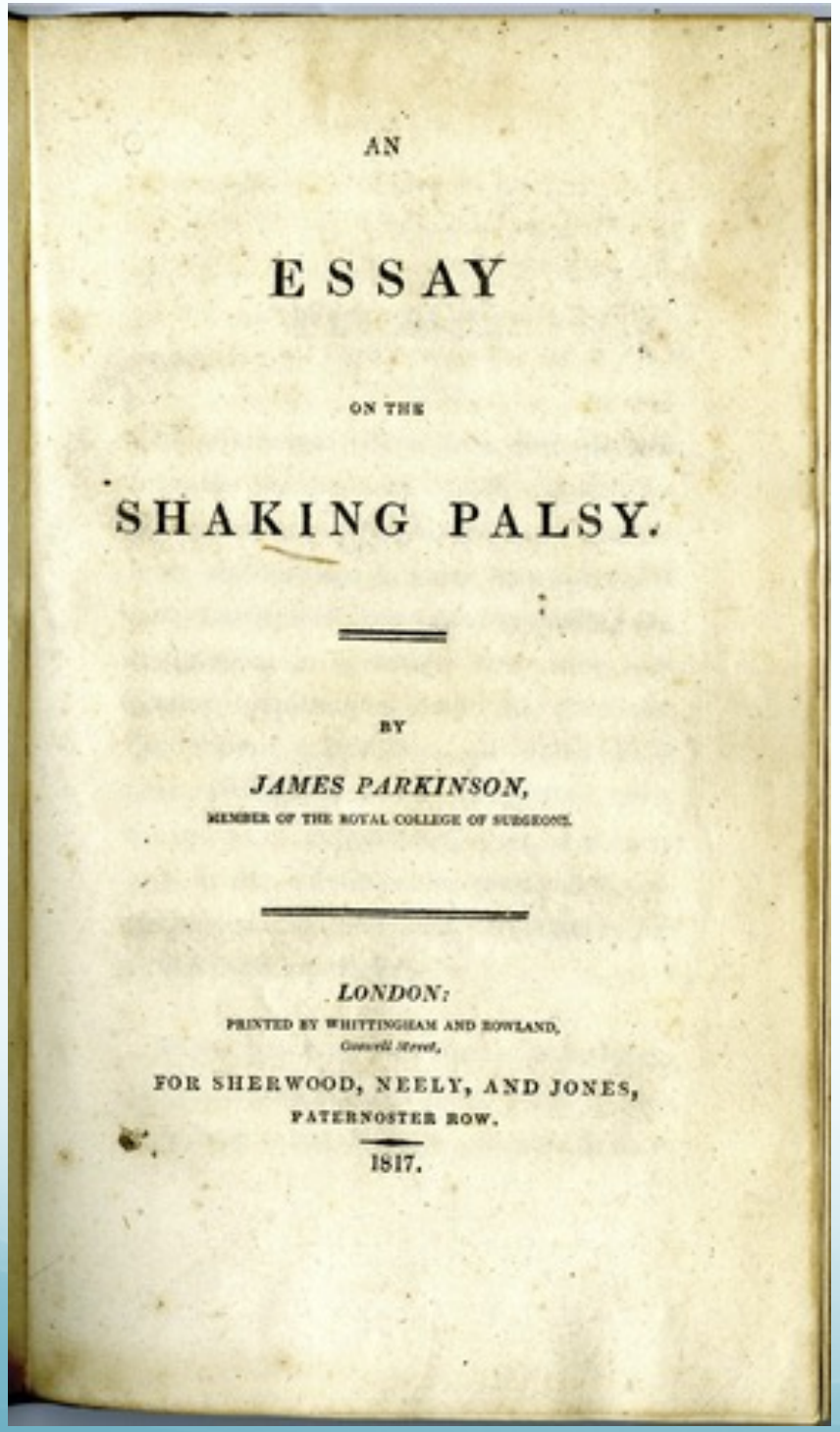
- Is it just normal ageing?
- Baseline
- There are other diagnoses that may be similar to PD but there are often clues from the symptoms and the examination regarding the correct diagnosis
- Incidentally, tremor is not normal ageing.

**Table 2** Clinical features of the most common differential diagnoses of the syndrome.[27–32]

| | PD | DIP | VP | PSP | MSA-P | LBD | CBD |
|---|---|---|---|---|---|---|---|
| **Mean age of onset (SD)** | 59.4 (11.5) | 60.6 (13.4) | 70.6 (6.4) | 66.9 (7.6) | 55.5 (6.5) | 67.8 (9.2) | 63 (7.7) |
| **Tremor** | Pure rest (30%), pure action (20%), mixed (20%) | Pure rest (35%), pure action (10%), mixed (30%) | Pure rest (4%), pure action (10%), mixed (2%) | Pure rest (10%)[a], pure action (20%), mixed (20%) | Rest (5%), Action (80%)[f], mixed (10%)[f] | Pure rest (3%), pure action (7%), mixed (24%) | Rest (2%), Action (10%)[g], mixed (55%)[g] |
| **Postural instability** | Common but late feature | Rare | Prominent / early or presenting sign | Prominent / early or presenting sign | Prominent / early | Prominent / early | Prominent / early |
| **Asymmetry** | +++ | 0 | + | 0[a] | + | 0 | +++ |
| **Survival – Mean (SD)** | Variable[b] | N/A | 8 (4.1) | 8.6 (5.7) | 7.5 (4) | 4.1 (4.1) | 8 (0.7) |
| **Levodopa response** | Marked / sustained | None to moderate[c] | None to moderate[c] | Mild to moderate[d] | Mild to moderate[d] | Mild to moderate[d] | Mild[d] |
| **LID[e]** | ++++ | 0 | + | +[a] | ++ | + | + |
| **Dementia** | Common in advanced stages | 0 | Very common, presenting as VD | Very common, early, fast decline | Less common than PD | Part of diagnostic criteria; may fluctuate | Common, may be early, fast decline |
| **RBD** | Very common | 0 | 0 | Unusual | Very common | Very common | 0 |
| **Additional clinical features** | Slower progression compared to other degenerative forms. | Onset during treatment with offending drug; improvement / resolution after withdrawal. | Pyramidal and pseudobulbar signs; lower body predominant. | Supranuclear gaze palsy; disproportional axial (nuchal) rigidity; photophobia / blepharospasm; | Profound early dysautonomia; antero-collis; pseudobulbar affect; pyramidal signs. | Early well-formed visual hallucinations; neuroleptic sensitivity; dysautonomia. | Limb dystonia; apraxia; cortical sensory loss; alien limb phenomena. |
| **Brain MRI findings** | No specific findings on standard imaging. | No change | Periventricular white matter lesions, lacunar infarcts in BG, ventricular dilation. | Predominant midbrain atrophy; superior cerebellar peduncle atrophy. | Putaminal atrophy; OPCA and "hot cross bun sign" in advanced stages. | Global atrophy. | Asymmetric fronto-parietal atrophy. |

Abbreviations: PD, Parkinson's disease; DIP, drug-induced parkinsonism; VP, vascular parkinsonism; PSP, progressive supranuclear palsy; MSA-P, Parkinsonian form of multiple system atrophy; LBD, Lewy body dementia; CBD, corticobasal degenerartion; SD, standard deviation; LID, levodopa-induced dyskinesia; RBD, REM-sleep behavior disorder; MRI, magnetic resonance imaging; BG, basal ganglia; OPCA, olivo-ponto-cerebellar atrophy.
Notes: a) PSP-P variant presents with asymmetric features, rest tremor, levodopa response and LID; b) widely dependent on age of onset, ranging from 38 (5) years for early onset (25-39 years old) to 5 (4) for late onset (≥ 65 years old); c) may be sustained in responders; d) typically in early stages, not sustained; e) in levodopa responders under long term treatment; f) jerky postural tremor / polyminimyoclonus; g) jerky action tremor / myoclonus.

Munhoz RP, et al. Arq Neuropsiquiatr. 2024 Jun;82(6):1-10.



AN

# ESSAY

ON THE

# SHAKING PALSY.

BY

*JAMES PARKINSON,*

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

*LONDON:*

PRINTED BY WHITTINGHAM AND ROWLAND,

*Goswell Street,*

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

‘the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth’

‘The bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power: the expulsion of the faeces from the rectum sometimes requiring mechanical aid…’

# Why Do Nonmotor Symptoms Matter?

- They are very troubling to people, sometimes more so than motor symptoms
- They sometimes precede the motor manifestations by a decade or more and may be indicators of trouble brewing
- There is great interest in identifying PD early, and intervening early

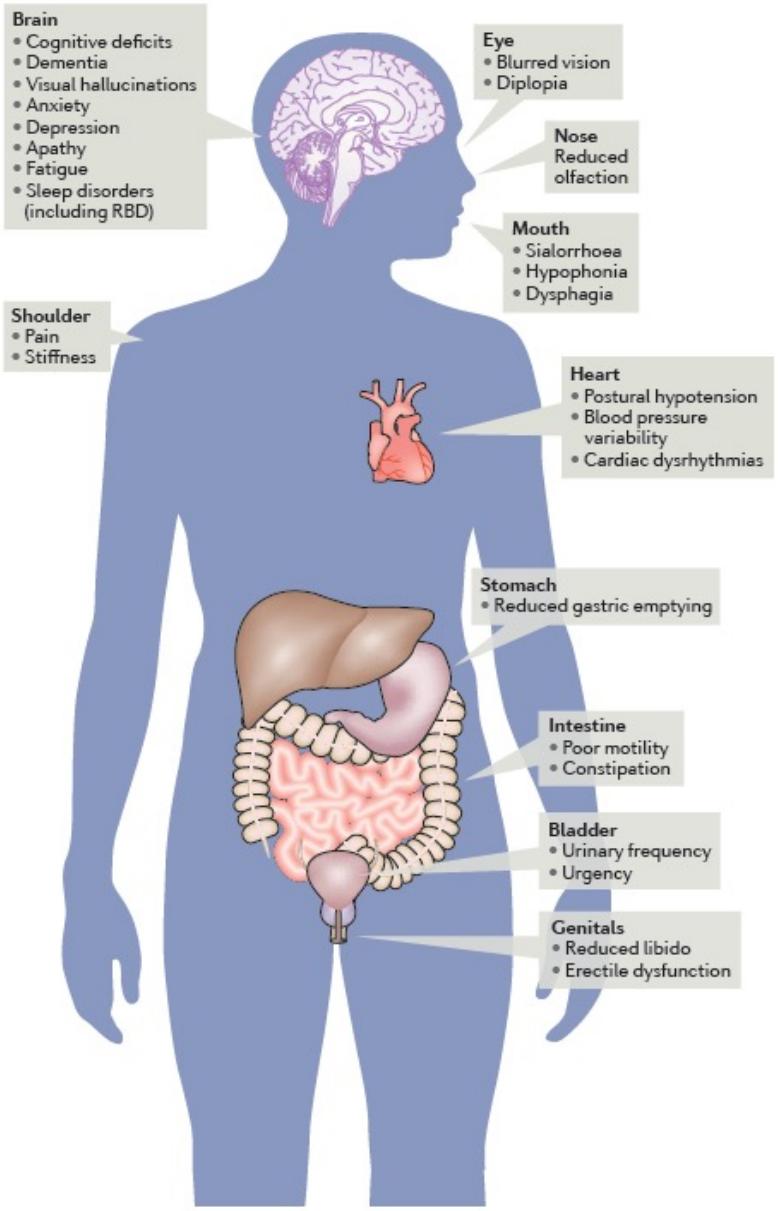



Figure 2 | **Potential non-motor features in Parkinson disease**. The non-motor features of Parkinson disease reflect deficits in various functions of the CNS and autonomic nervous system. Multisystem involvement develops to varying levels of severity and in a variable sequence in different patients. Although some non-motor impairments precede motor abnormalities (for example, cardiac, bowel and olfactory deficits), most develop over time with progression of the underlying disease. Cognitive dysfunction usually appears late in the course of Parkinson disease, although visual hallucinations may appear earlier and are a risk factor for subsequent dementia. RBD, REM sleep behaviour disorder.

Schapira AHV et al. Non-motor features of Parkinson disease..Nat Rev Neurosci. 2017 Aug;18(8):509.

**TABLE 1.** Indications of nonmotor symptoms covered by this review

- Neuropsychiatric symptoms
  - Depression and depressive symptoms
  - Anxiety and anxiety symptoms
  - Apathy
  - Psychosis
  - Impulse control and related disorders
  - Dementia
  - Cognitive impairment (other than dementia; mainly mild cognitive impairment)
- Autonomic dysfunction
  - Drooling
  - Orthostatic hypotension
  - Urinary dysfunction
  - Erectile dysfunction
  - Gastrointestinal dysfunction
  - Excessive sweating
- Disorders of sleep and wakefulness
  - Sleep fragmentation and insomnia
  - Rapid eye movement sleep behavior disorder
  - Excessive daytime sleepiness
- Others
  - Pain
  - Fatigue
  - Olfactory dysfunction
  - Ophthalmologic dysfunction

Seppi K et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord. 2019 Feb;34(2):180-198.

# Nonmotor PD

## What I commonly hear from patients

- Fatigue
- Sleep
  - Early waking
  - Daytime somnolence
  - REM Sleep Behavior Disorder
- Constipation
- Overactive bladder
- Drooling
- Dizziness/low blood pressure

## What I find especially concerning

- Hallucinations/delusions
- Impulse control disorder
- Depression
- Cognitive impairment without insight

# Fatigue

**TABLE 9.** Interventions to treat fatigue in PD

| Intervention | | | | |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| Monoamine oxidase B (MAO-B) inhibitors | **Rasagiline** | *Efficacious* | *Acceptable risk without specialized monitoring* | *Possibly useful* |
| Psychoactive drugs | **Methylphenidate** | Insufficient evidence | Insufficient evidence | Investigational |
| | **Modafinil** | Insufficient evidence | Insufficient evidence[a] | Investigational |
| Nonpharmacological interventions | **Acupuncture** | *Insufficient evidence* | *Acceptable risk without specialized monitoring* | *Investigational* |

# Fatigue

Rasagiline (Azilect)?

# Sleep

**TABLE 7.** Drugs to treat disorders of sleep and wakefulness in PD

| Intervention | | | | |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| **Insomnia** | | | | |
| Levodopa | Controlled-release formulation of levodopa/carbidopa | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| Dopamine agonists | Pergolide | Insufficient evidence | Acceptable risk with specialized monitoring | Not useful |
| | Piribedil | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| | Rotigotine | Likely efficacious | Acceptable risk without specialized monitoring | Possibly useful |
| Hypnotics | Eszopiclone | Insufficient evidence | Acceptable risk without specialized monitoring[1] | *Possibly useful*[a] |
| Melatonin | 3-5 mg | Insufficient evidence | Acceptable risk without specialized monitoring | *Possibly useful*[b] |
| | 50 mg | Insufficient evidence | Insufficient evidence | Investigational |
| Nonpharmacological interventions | **Continuous positive airway pressure**[c] | *Likely efficacious* | *Acceptable risk without specialized monitoring* | *Possibly useful* |
| **Excessive daytime somnolence and sudden onset of sleep** | | | | |
| Psychoactive drugs | Modafinil | Insufficient evidence | Insufficient evidence[d] | *Possibly useful*[e] |
| | **Caffeine** | *Insufficient evidence* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Nonpharmacological interventions | **Continuous positive airway pressure**[c] | *Likely efficacious* | *Acceptable risk without specialized monitoring* | *Possibly useful* |

# Sleep

- Insomnia- Rotigotine (Neupro)
- Excessive daytime sleepiness
  - Caffeine
  - Modafanil (Provigil)
- Snoring?
  - Consider sleep study

# Constipation

- Polyethylene glycol (Miralax, Macrogol)
- Probiotics and prebiotic fiber
- Lubiprostone (Amitiza)
- Prucalopride (Motegrity)
- Linaclotide (Linzess)

# Overactive Bladder

- ?Solifenacin (Vesicare)
- Mirabegron (Myrbetriq)
- Virabegron (Gemtesa)

# Drooling

- Botulinum toxin (Botox, Myobloc) injected into salivary glands
- Atropine 1% solution (prescription)

# Hallucinations/Delusions

**TABLE 6.** Interventions to treat psychosis in PD

| Drug | Efficacy | Safety[a] | Practice Implications |
|---|---|---|---|
| Clozapine | Efficacious | Acceptable risk with specialized monitoring | Clinically useful |
| **Olanzapine** | *Not efficacious* | Unacceptable risk | *Not useful* |
| Quetiapine | Insufficient evidence | Acceptable risk without specialized monitoring | *Possibly useful*[b] |
| **Pimavanserin** | *Efficacious* | *Acceptable risk without specialized monitoring*[c] | *Clinically useful* |

# Hallucinations/Delusions

- All of these medications have a boxed warning about increased risk of death in the elderly with cognitive impairment
- Quetiapine (Seroquel) is widely used but has neither supportive evidence or FDA approval for PD
- Clozapine can work quickly but requires a weekly blood test (No FDA approval for PD)
- Pimavanserin (Nuplazid) takes 4 to 6 weeks to work

# Hallucinations/Delusions

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS**

***See full prescribing information for complete boxed warning.***

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. SEROQUEL is not approved for elderly patients with dementia-related psychosis (5.1)**

**Suicidal Thoughts and Behaviors**

- **Increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants (5.2)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.2)**

# Impulse Control Disorder

- A side effect of dopamine medications
- Not newly recognized
- May be associated with all PD medications but especially dopamine agonists
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)
  - Rotigotine (Neupro)
  - Bromocriptime (Parlodel)
- Treatment
  - BE AWARE AND ON GUARD!
  - Reduce/eliminate medication

# Impulse Control Disorder Examples

- Shopping/spending
- Eating
- Gambling
- Cleaning
- Baking
- Hobbyism
- Driving
- SEX
- Similar to PUNDING (repetitive useless tasks- arranging items, taking things apart…)

BE AWARE AND ON GUARD!

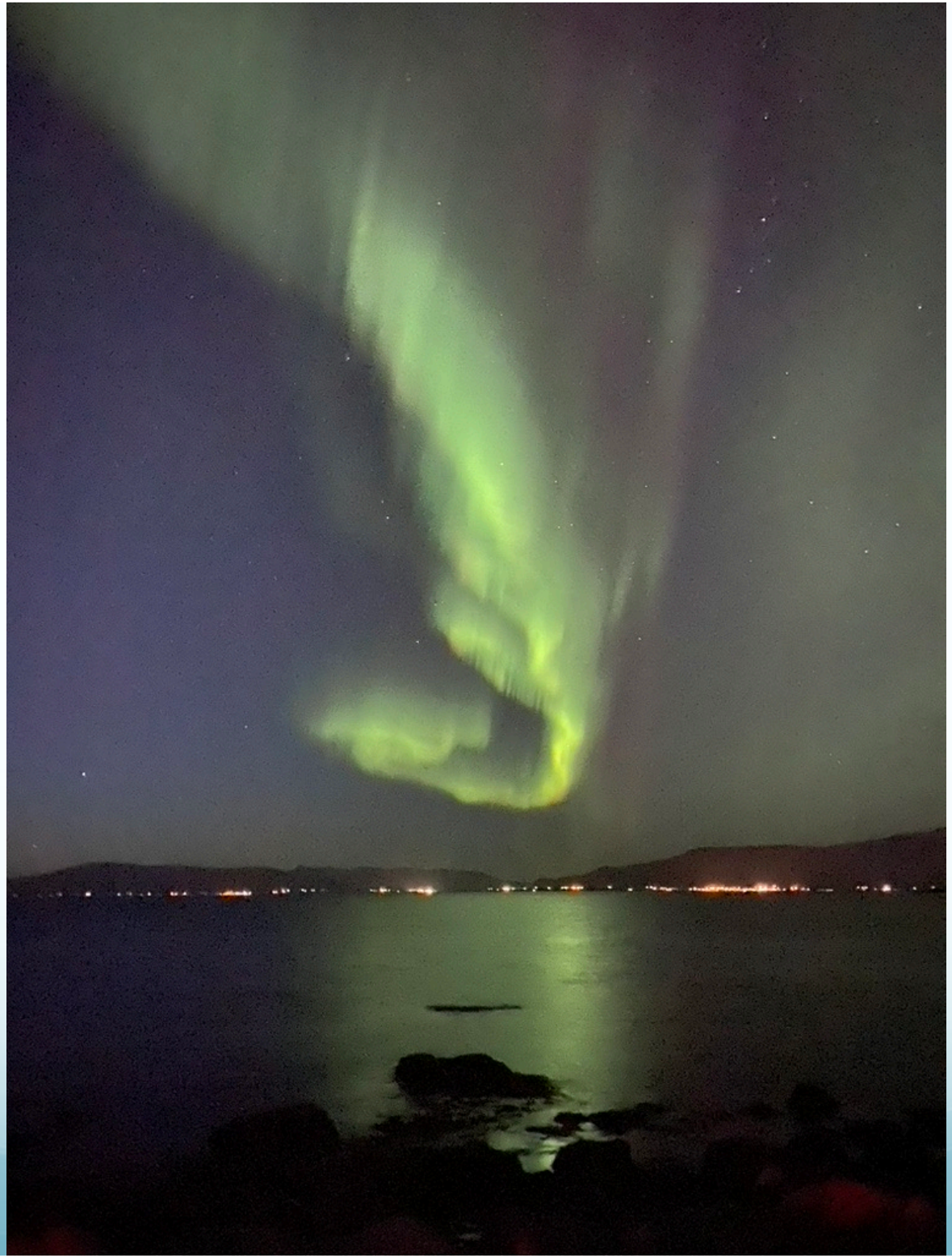
# Depression

**TABLE 2.** Interventions to treat depression, including depressive symptoms in PD

| Intervention | | | | |
|---|---|---|---|---|
| Drug class/ intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| Dopamine Agonists | Pramipexole | Efficacious | Acceptable risk without specialized monitoring | Clinically useful |
| | Pergolide | Insufficient evidence | Acceptable risk with specialized monitoring | Not useful |
| | **Rotigotine** | *Unlikely efficacious* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Monoamine oxidase B (MAO-B) inhibitors | **Rasagiline** | *Insufficient evidence* | *Acceptable risk without specialized monitoring* | *Investigational* |
| | Selegeline | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| | Moclobemide | Insufficient evidence | Acceptable risk with specialized monitoring[a] | Investigational |
| Tricyclic antidepressants | Nortriptyline | Likely efficacious | Acceptable risk without specialized monitoring[b] | Possibly useful |
| | Desipramine | Likely efficacious | Acceptable risk without specialized monitoring[b] | Possibly useful |
| | Amitriptyline | Insufficient evidence | Acceptable risk without specialized monitoring[b] | *Possibly useful*[c] |
| Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors | Citalopram | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | Sertraline | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | **Paroxetine** | insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | Fluoxetine | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[c] |
| | **Venlafaxine** | *Efficacious* | *Acceptable risk without specialized monitoring*[e] | *Clinically useful* |
| Other antidepressants | Atomoxetine | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| | Nefazodone | Insufficient evidence | Unacceptable risk | Not useful |
| Alternative therapies | 'Ω-3 fatty acids | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| Nonpharmacological interventions | **rTMS** | *Insufficient evidence* | *Acceptable risk without specialized monitoring*[f] | *Possibly useful (short term)* |
| | **CBT** | *Likely efficacious* | *Insufficient evidence*[g] | *Possibly useful* |

# Depression

- Pramipexole (Mirapex)
- Venlafaxine (Effexor)
- Nortriptyline (Pamelor)
- Desipramine (Norpramin)
- Others “possibly useful”
  - Citalopram (Celexa), sertraline (Zoloft), fluoxetine (Prozac)
- AVOID
  - Aripiprazole (Abilify), olanzapine (Zyprexa)



# Cognitive Impairment

**TABLE 5.** Interventions to treat dementia and nondementia cognitive impairment in PD

| Intervention | | Efficacy | Safety | Practice implications |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | | | |
| **Dementia** | | | | |
| Acetylcholinesterase inhibitors | **Donepezil** | Insufficient evidence | Acceptable risk without specialized monitoring[a] | *Possibly useful*[b] |
| | **Rivastigmine** | Efficacious | Acceptable risk without specialized monitoring[a] | Clinically useful |
| | Galantamine | Insufficient evidence | Acceptable risk without specialized monitoring[a] | *Possibly useful*[c] |
| N-methyl-D-aspartate (NMDA) antagonists | Memantine | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| **Nondementia cognitive impairment** | | | | |
| Acetylcholinesterase inhibitors | **Rivastigmine** | *Insufficient evidence* | *Acceptable risk without specialized monitoring*[d] | *Investigational* |
| Monoamine oxidase B (MAO-B) inhibitors | **Rasagiline** | *Insufficient evidence* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Nonpharmacological Interventions | **Transcranial direct-current stimulation (T-DCS)** | *Insufficient evidence* | *Insufficient evidence* | *Investigational* |
| | **Cognitive rehabilitation** | *Insufficient evidence* | *Insufficient evidence* | *Investigational* |

# Cognitive Impairment

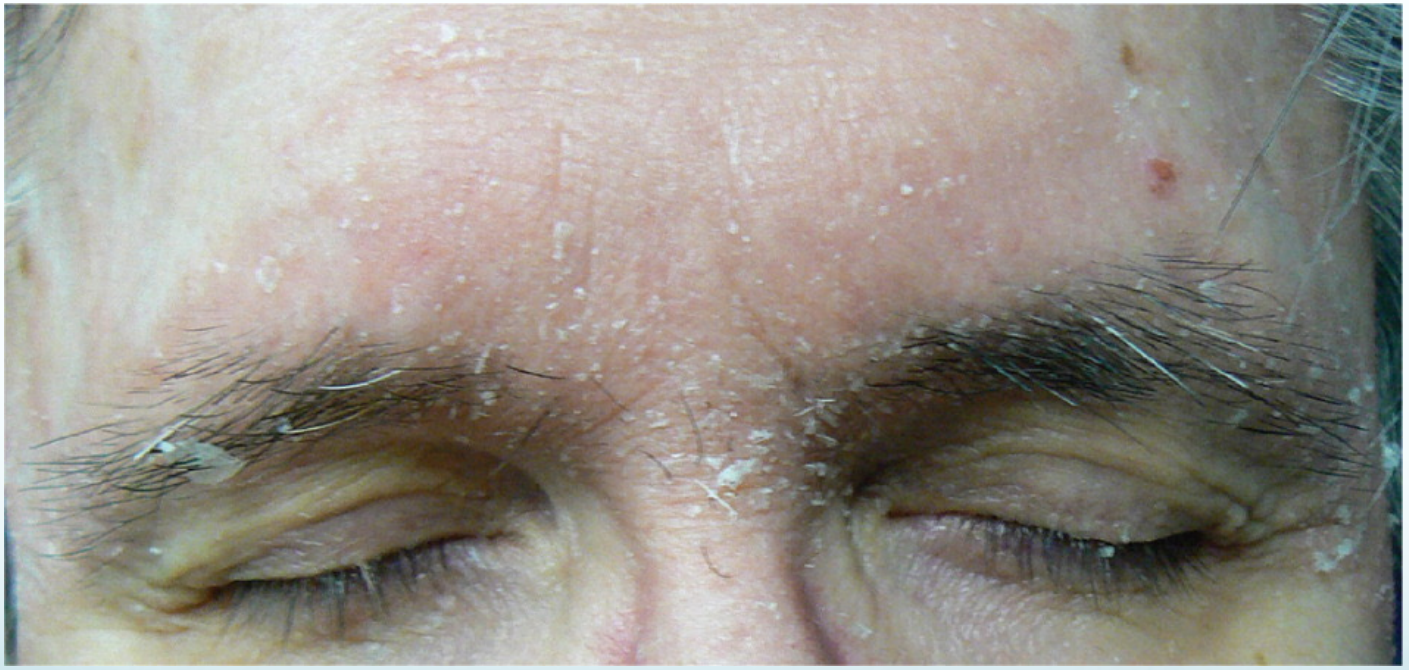
- Rivastigmine (Exelon), capsule twice a day, patch once a day
- Donepezil (Aricept) possibly useful

These medications can increase urinary symptoms and drooling.  Drooling more with donepezil.

- Memantine (Namenda) inadequate evidence

# Skin

- Increased risk of skin cancer, including melanoma
- Seborrheic dermatitis



Clark GW, et al. Am Fam Physician. 2015 Feb 1;91(3):185-90.

# Prodromal PD

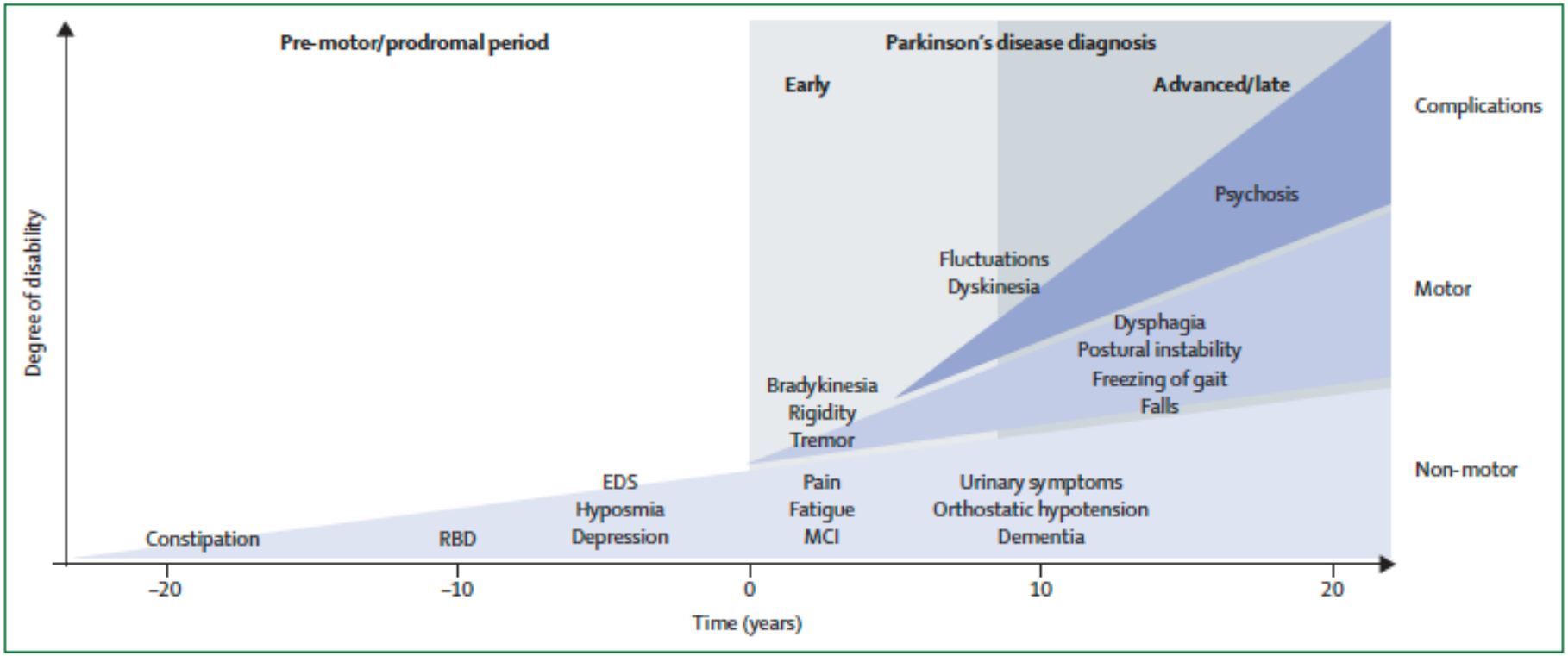



***Figure 1:*** **Clinical symptoms and time course of Parkinson's disease progression**
Diagnosis of Parkinson's disease occurs with the onset of motor symptoms (time 0 years) but can be preceded by a premotor or prodromal phase of 20 years or more. This prodromal phase is characterised by specific non-motor symptoms. Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability. Axial motor symptoms, such as postural instability with frequent falls and freezing of gait, tend to occur in advanced disease. Long-term complications of dopaminergic therapy, including fluctuations, dyskinesia, and psychosis, also contribute to disability. EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behaviour disorder.

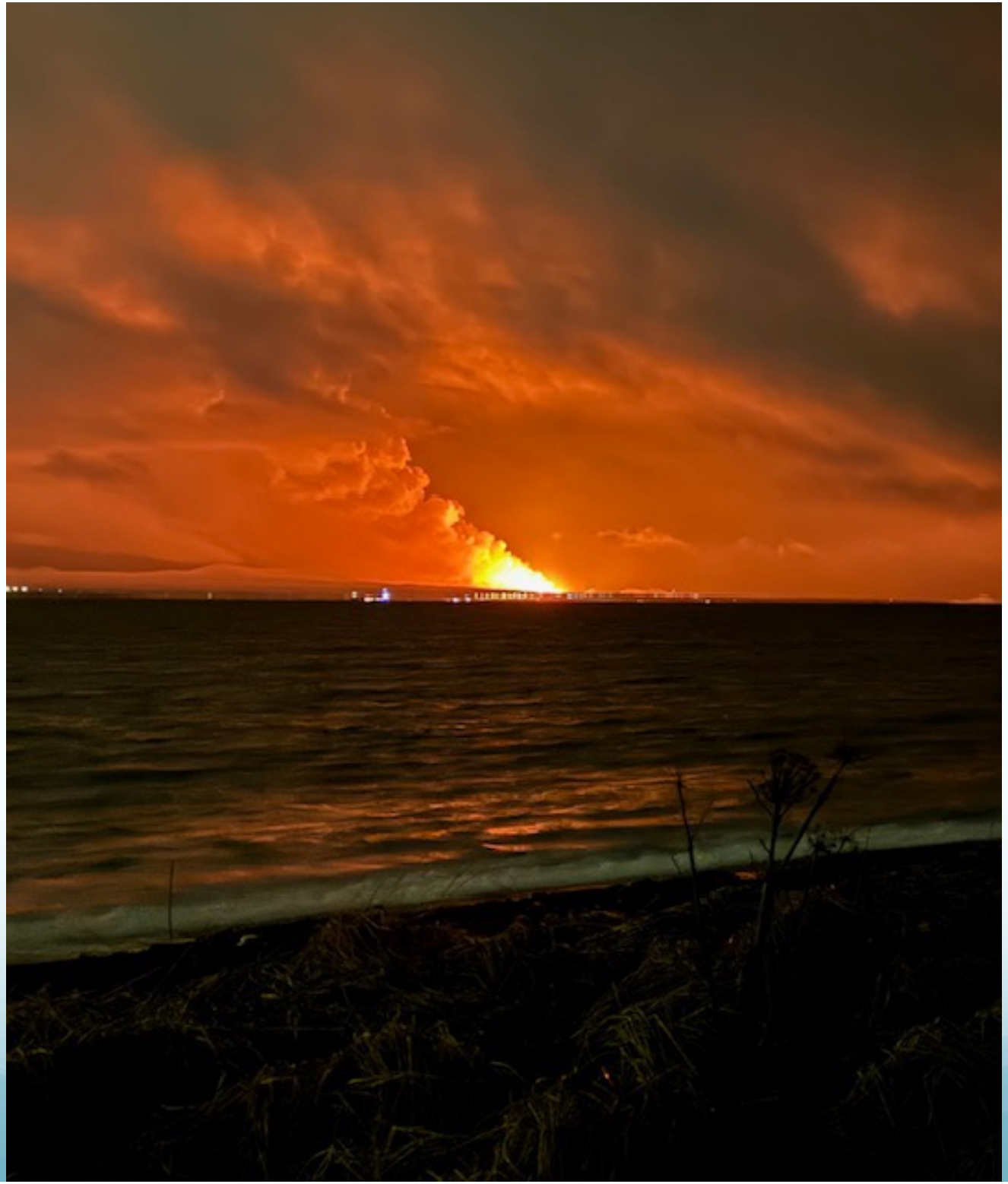
Kalia LV, Lang AE. Parkinson's disease. Lancet. 2015 Aug 29;386(9996):896-912.

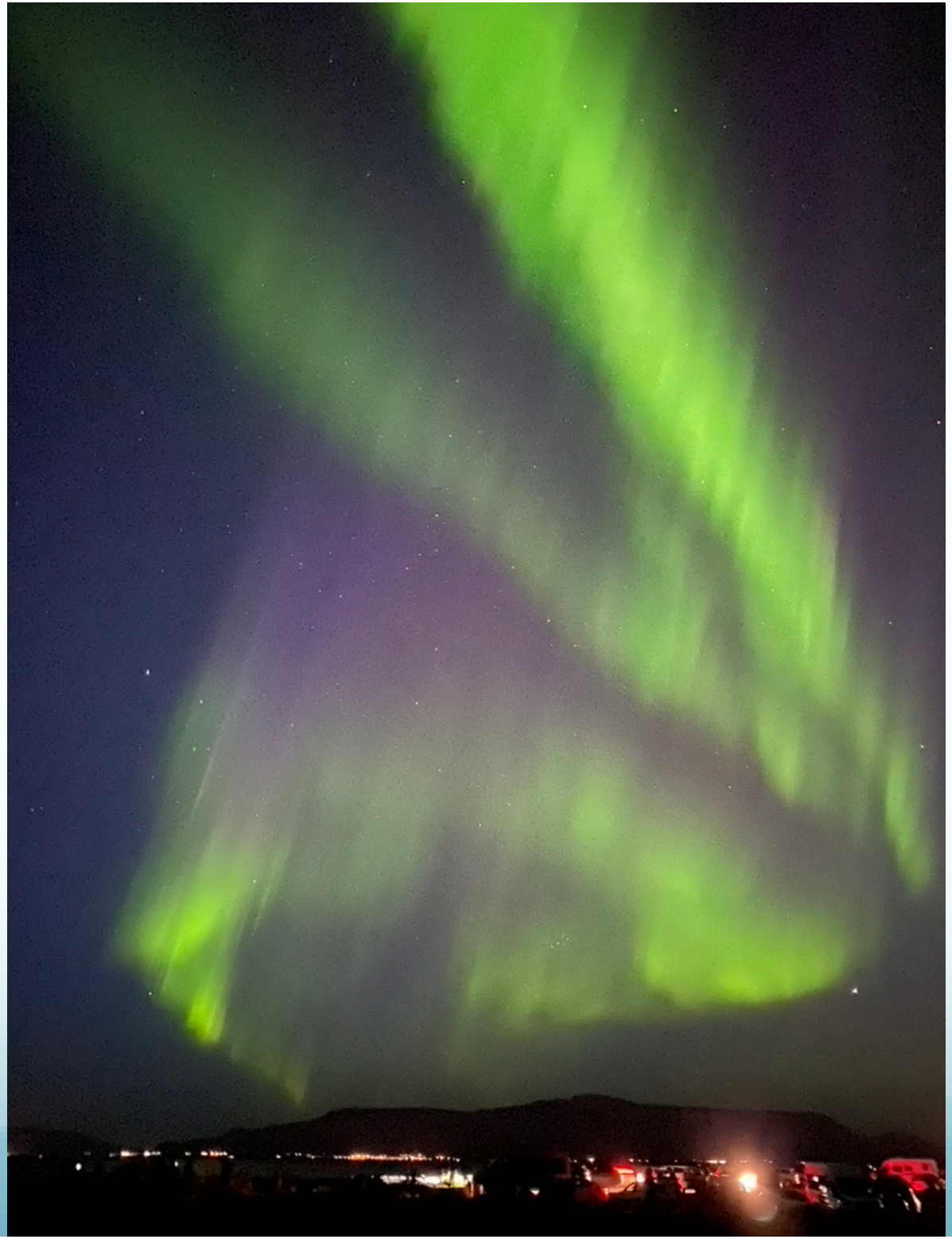
If you take levodopa:

Take a supplement with B12, B6 and Folic Acid (Folbee, Folbic, Folgard)

If your GFR is less than 50 you will need to take B12 as methylcobalamin

# Iceland





# Thank You

# Questions, Comments