Fatigue in Parkinson's disease

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Financial disclosures

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Why is understanding fatigue important?

- May manifest even during premotor stages of disease and once present, may often persist or even worsen over time
- Leads to limited working hours, participation in social activities, hobbies and exercise, which have a negative collective impact on patients' quality of life
- Described as a sense of exhaustion or significantly diminished energy level or an increased perception of effort disproportionate to attempted activities
- Easy to understand, tough to conceptualize and measure. Heterogenous measurements.
- PRIAMO study on over 1000 patients with PD, fatigue in 58% (most common non-motor symptom)

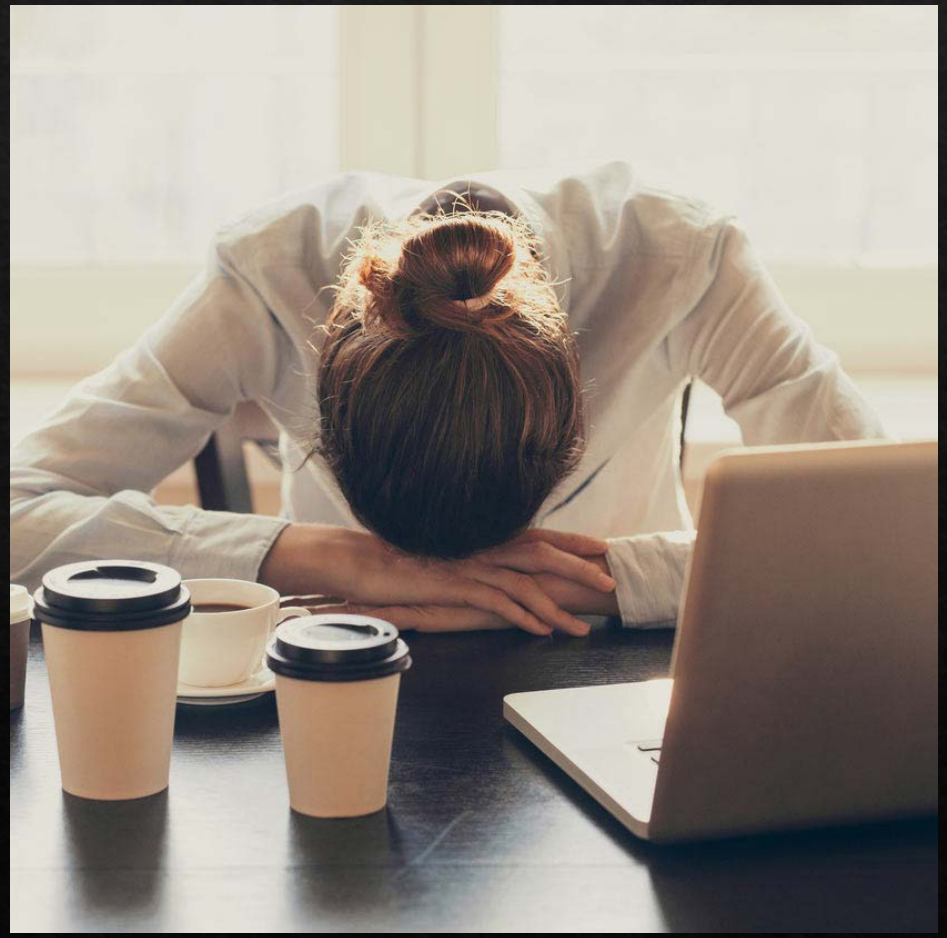
Sicilliano et al. Mov Dis. 2018, Barone et al. Mov Dis. 2009

What is fatigue in PD?

Thought to be an intrinsic symptom or independent manifestation of PD

While it appears to worsen with underlying disease progression, it may not correlate with duration or motor disability.

Important to differentiate subjective perception of fatigue and task-performance fatigability



Kostic et al. MDCP 2016, Pavese et al. Brain 2010, Image from Hopkinsmedicine.org

What is fatigue in PD?

Involvement of both serotonergic and dopaminergic circuits has been proposed.

Substantial overlap with depression, anxiety, sleep issues and apathy.

As such, an idea of primary and secondary fatigue has been proposed.

Kostic et al. MDCP 2016, Pavese et al. Brain 2010

Fatigue accompanying MOTOR-OFF

People report not feeling “energized”

Reward feedback: ease of completing a task

Optimal dose of dopamine replacement is key

Fatigue may present as an OFF phenomenon that may mirror motor symptoms

Franssen et al. Mov. Dis. 2014

Fatigue accompanying MOTOR-OFF

Difficult to compare dopaminergic drugs due to heterogeneity in outcome measures, drugs and dosages, duration of treatment, and control of other factors, such as depression.

Levodopa may reduce fatigue, although the degree of benefit varies, depending on the severity of PD. It may help task-performance fatigue but not otherwise.

Data on DA agonists in modulating fatigue associated with PD are not consistent. Benefit reported may be due to improvement in other motor and non-motor features.

TABLE 1. Outcomes studies

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Franssen et al. Mov. Dis. 2014

Fatigue and night-time sleep

Difficulty falling asleep

Leg cramps, difficulty rolling over, frequency/ noctiuria, difficulty going back to sleep

Snoring, apneic spells, early morning bifrontal headaches, day-time fatigue or irritability

Movement in sleep

Table 1. Problems falling asleep

Not sleepy when lights go off
Nursing home, early bedtime
Caretaker, early bedtime
Out of phase with spouse, family
Daytime naps
Medication effect (alcohol; stimulants; SSRI antidepressants)
Discomfort
Cannot find comfortable position
Annoying tremor
Anxiety
Restless legs syndrome
Depression
Akathisia
Illusions, hallucinations
Delusions
Back pain
Painful leg cramps

Table 2. Problems maintaining sleep

Bladder
Anxiety
Depression
Sleep apnea
Tremors during sleep
Nightmares
REM sleep behavior disorder
Vocalizations during sleep
Periodic leg movements
Respiratory disorders due to PD
Inability to turn over/difficulty getting in/out of bed
Fragmentary nocturnal myoclonus

Freidman and Chou. PRD 2004

Sleep apnea and PD

Anecdotally, OSA and PD are common in the same age group. Mixed evidence about co-prevalence in literature

OSA has been proposed as a risk factor for PD (aHR 1.84), especially with insomnia (aHR 1.97)

OSA associated with worse motor and cognitive symptoms in PD

CPAP use may improve motor features in PD

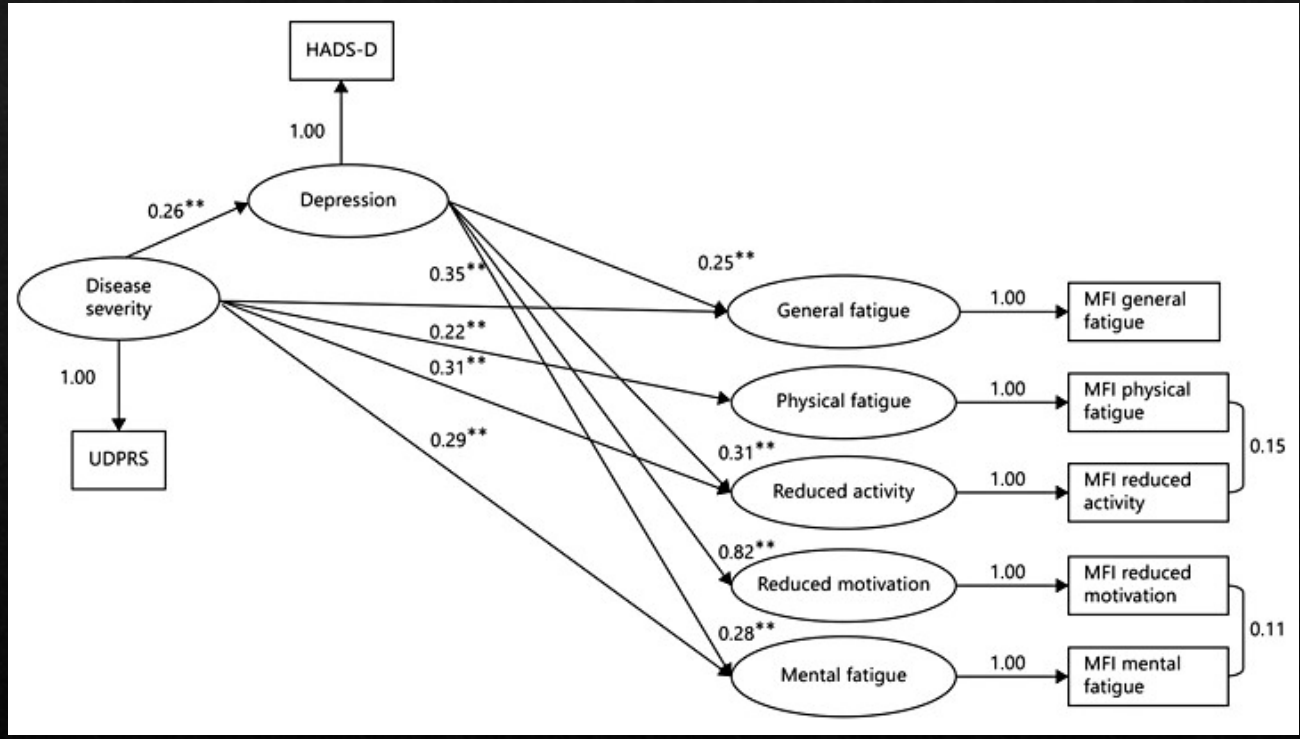
Chen et al. J Sleep Res. 2015, Meng et al. PRD 2020, Elfil et al. Mov. Dis. 2021

Fatigue and mood

Fatigue more common in people with depression across many disorders

The greater the depression and/ or disease severity, the greater the fatigue

Treatment of depression improved general fatigue, mental fatigue, motivation and activity but not physical fatigue



Van Dijk at al. Eur Neurol 2013

Orthostatic hypotension in PD

Defined as a reduction of systolic BP ≥20 mm Hg or diastolic blood pressure ≥ 10 mm Hg within 3 minutes of standing up

Updated in 2011 to include a fall in SBP of ⩾30 mm Hg for patients with an elevated baseline BP including those with supine hypertension (SH)

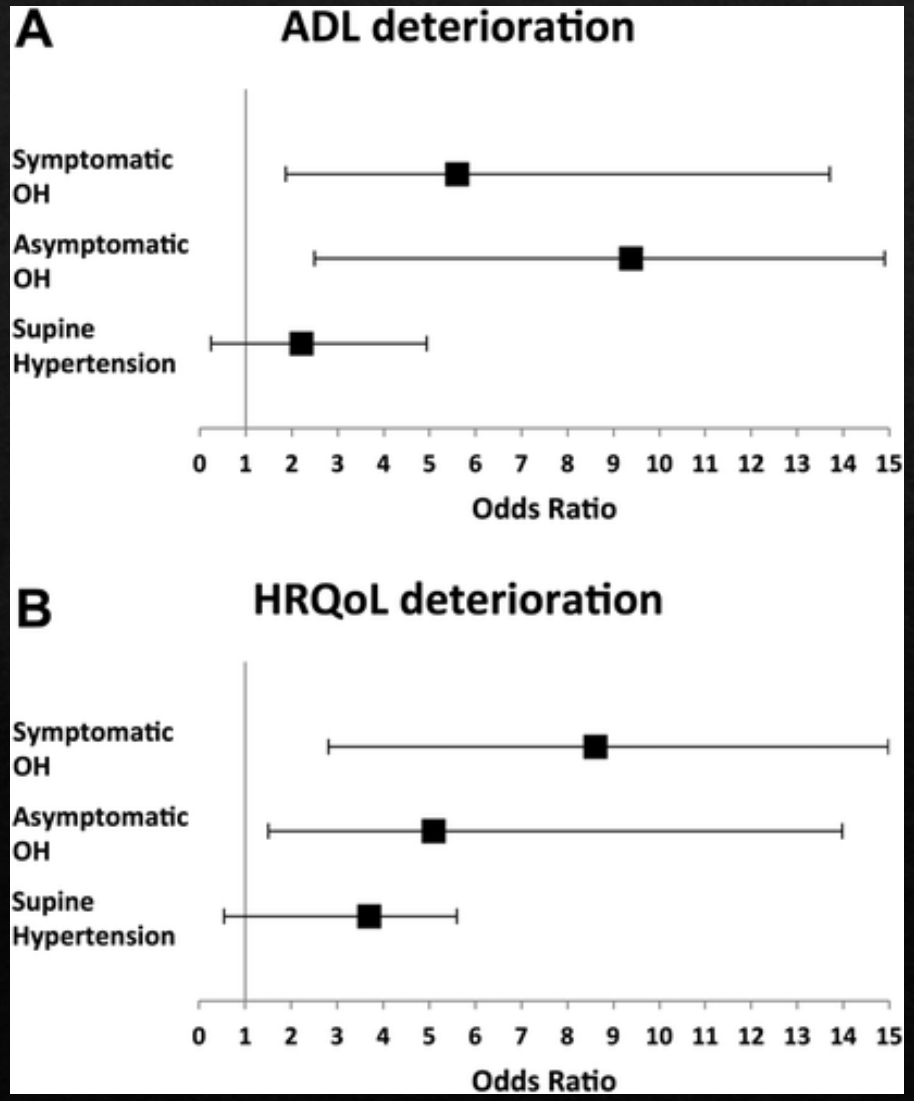
Prevalence of orthostatic hypotension in certain settings

Setting	Number	Age (years)	Prevalence (%)	Reference
Nursing home	250	61-91	11	Rodstein and Zeman[29] (1957)
Outpatients	494	≥65	24	Caird et al.[30] (1973)
VA geriatric unit	319	50-99	10.7	Myers et al.[31] (1978)
Outpatients	186	≥65	22	MacLennan et al.[32] (1980)
Geriatric unit	272	Mean age 83	10	Lennox and Williams[33] (1980)
Geriatric unit	247	≥60	33	Palmer[34] (1983)
Outpatients	300	Mean age 70	6.4	Mader et al.[35] (1987)

Freeman et al. 2011, Low and Tomalia, 2015

OH and PD

- 131 patients prospectively followed over 12 months
- Orthostatic Hypotension Symptoms Assessment (OHSA) total score, worsened by 20% over 12 months
- Overall increase in OH prevalence from 31.1% to 46.7%
- Independently associated with deterioration in ADLs and health-related QoL
- Regardless of symptoms, affected ADLs, HR-QoL and falls



Merola et al. Mov Dis. 2018

OH in PD: impact on cost of care

A total of 317 PD patients

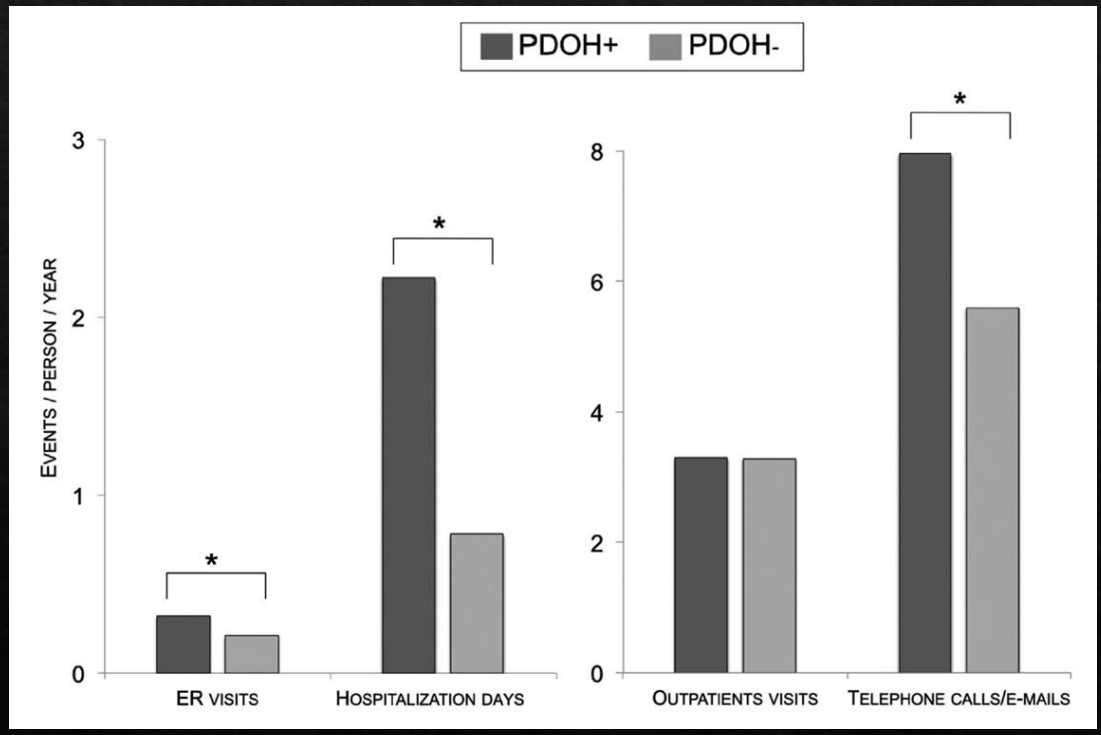
- 29.3% classified as PDOH+
- 30.2 ± 11.0 months
- 247 hospitalizations, 170 ER visits, 2386 outpatient evaluations, and 4747 telephone calls/e-mails.

OH associated with more hospitalization days (+285%), ER visits (+152%), and telephone calls/e-mails (+142%).

OH led to 2.5-fold higher health care related cost.

OH causes an extra cost increase of $15,000 per patient per year.

The higher health care burden is represented by neuropsychiatric problems and falls.



Merola et al. PRD. 2018

OH and fatigue in PD

Cardiac sympathetic nerves have an important role in increasing the heart rate and blood pressure during exercise

Autonomic dysfunction, including cardiac sympathetic denervation, associated with fatigue in PD

Clinical manifestations may not be obvious in patients with PD

Home blood pressure diary

Name: .... Date of birth: .... height: .... cm weight: .... kg

Date	Fluid intake (liters)	Measurements	In the morning (before breakfast)				After lunch				In the evening (before going to bed)			
			systolic	diastolic	HR	Symptoms*	systolic	diastolic	HR	Symptoms*	systolic	diastolic	HR	Symptoms*
....	__ l	5' min supine												
		3' min standing												
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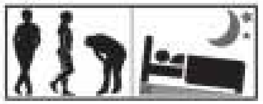
* X = postural dizziness | O = no complaints; HR = heart rate

TREATMENT

1. Correct non-neurogenic causes of OH and exacerbating factors

2. Lifestyle measures

DOs



DON'Ts

3. Non-pharmacological measures

4. Pharmacological measures

- Midodrine 3x 2.5-10 mg/d
- Fludrocortisone 0.1-0.3 mg/d
- Droxidopa 3x 100-600 mg/d
- In anemic patients: erythropoietin

5. Treatment of post-prandial hypotension

Before main meals:

- Acarbose 50-100 mg
- Octreotide 1 μg/kg of body weight s.c.
- Caffeine 250 mg

TREATMENT

1. Preventive measures

Avoid:

- the supine position during daytime
- offending agents (NSAIDs, SNRI, domperidone)
- long acting pressor agents
- bolus water drinking near bedtime

2. Non-pharmacological measures

- 10-20° head-up tilt over night
- Small snack at bedtime
- If alcohol, small amount at bedtime

3. Pharmacological measures

Bedtime administration of:

- Losartan 50 mg
- Eplerenone 50 mg
- Sildenafil 25 mg
- Clonidine 0.1 mg
- Nitroglycerin patch 0.1 mg/h

Kostic et al. MDCP 2016, Fanciulli et al. JPD 2020

Management of primary fatigue

Amphetamines: some evidence for methylphenidate?

Exercise, CBT, Caffeine: no consistent benefit

One meta-analysis: no drug or non-drug approach works for everyone

Another meta-analysis: Doxepin and rasagiline may work (is it primary?)

Anecdotally, naps for the win!

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Franssen et al. Mov. Dis. 2014

Medications causing fatigue

Peripheral	Central	
	Decreased Excitatory Activity	Increased Inhibitory Activity
Aminoglycosides	Anticholinergics	Anesthetics
Antiarrhythmics	Anticonvulsants	Antiemetics
Antidepressants	Antipsychotics	Barbiturates
Antiepileptics	Sympathomimetics	Benzodiazepines
Antifungals		opioids
Antigout agents		Skeletal muscle relaxants
Antihelmintics		
Antineoplastics		
Antipsychotics		
Antivirals		
Biologic agents		
Carbonic anhydrase inhibitors		
DMARDs		
Neuromuscular blocking agents		

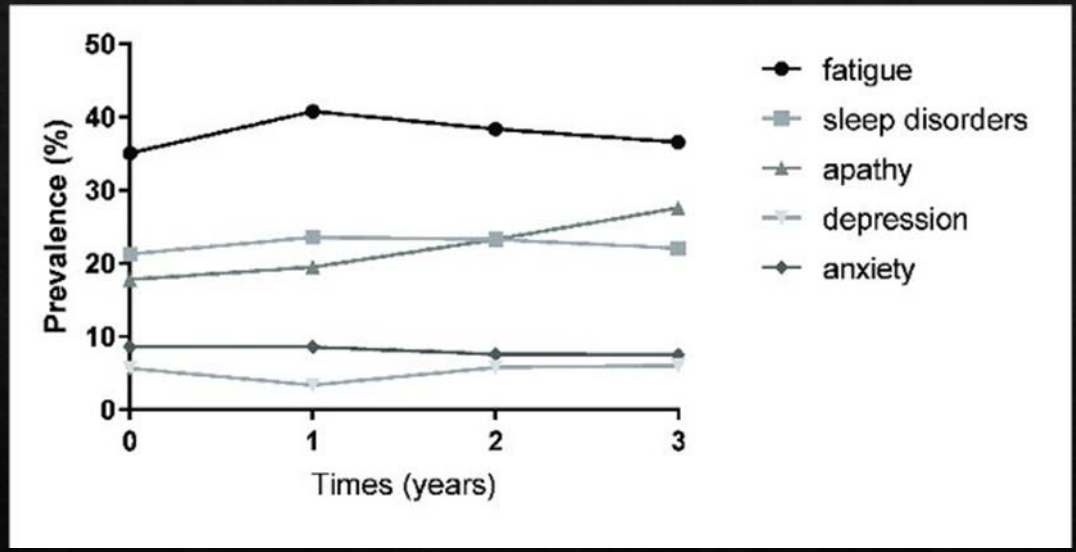
Zlott and Byrne. PM&R 2010

Approach to management

Table 1

Possible Algorithm for the Treatment of Fatigue in Parkinson's Disease

1. Screening and identifying fatigue
2. Is fatigue primary or secondary? Identify contributing treatable factors (depression, anxiety, apathy, sleep alterations, orthostatic hypotension, anemia…)
3. Explain nature of fatigue to a patient and caregiver
4. Nonpharmacological treatment like physical exercise[a]
5. Medication[a]
a. Methylphenidate (level C)
b. Dopaminergic drugs: dopaminergic agonists (pramipexole, rotigotine, rasagiline), optimization of levodopa
c. Antidepressant drugs (nortryptyline, doxepin, SSRI…)
d. Modafinil



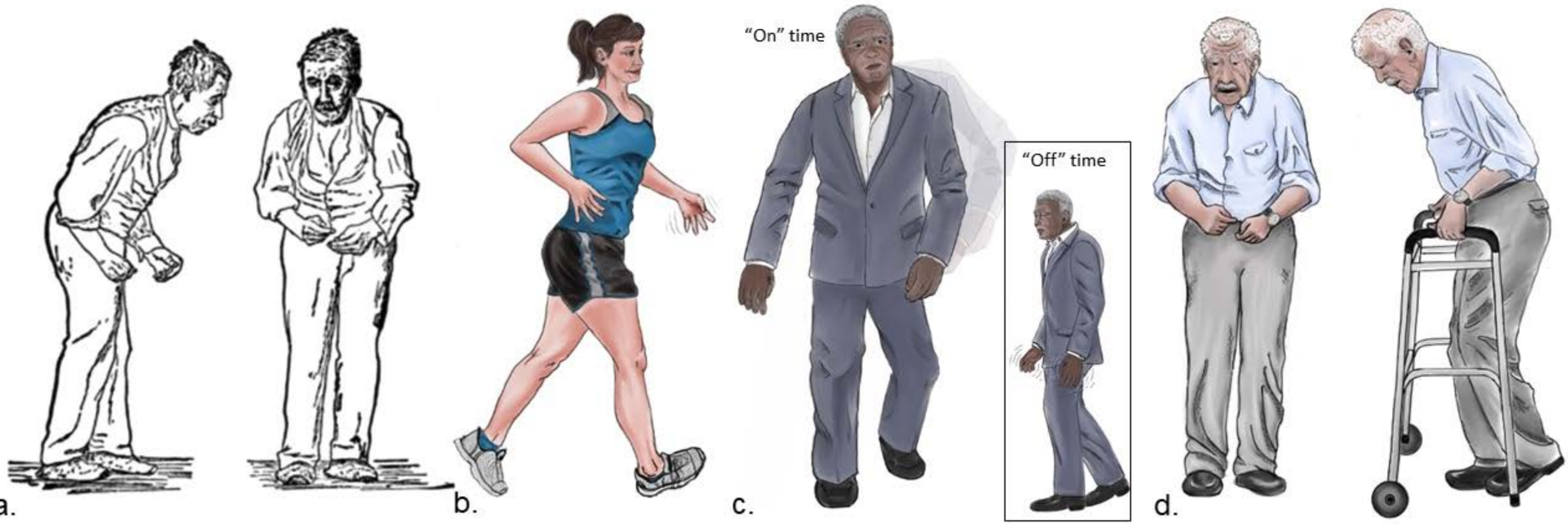
Kostic et al. MDCP 2016, Ou at al. Front Aging Neurosci. 2021

Motor and Non-Motor Parkinson Disease Symptoms

Fewer ← → **More**

Tremor, rigidity, bradykinesia, dystonia and/or gait issues

Autonomic, psychiatric, and/or cognitive symptoms



Armstrong et al. JAMA Neurol 2020