Neuropsychiatric Issues in Parkinson's Disease

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Disclosures

- No conflicts of interest to disclose
- The content of this presentation does not represent the views of the U.S. Department of Veterans Affairs or the United States Government
- The following presentation may contain information including off-label use of medications

Learning Objectives

- Recognize common neuropsychiatric symptoms (NPS) experienced by PwPD
- Understand the role PD and its treatments may play in developing PD NPS
- Consider initial treatments for PD NPS
- Highlight the importance of coordinated, multi-disciplinary care in PD

1817- “the senses and intellects being uninjured.”

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ESSAY

ON THE

SHAKING PALSY.

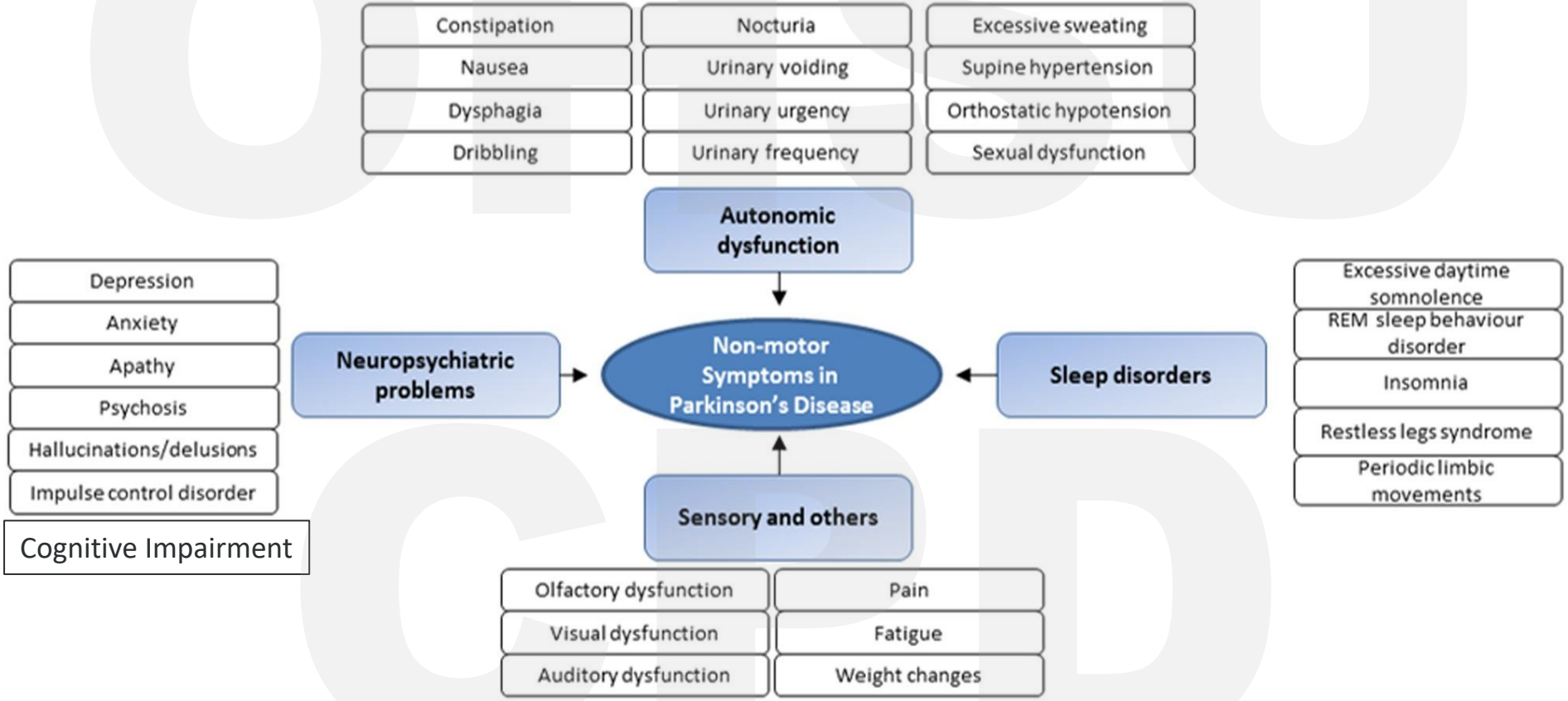
CHAPTER I.

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.

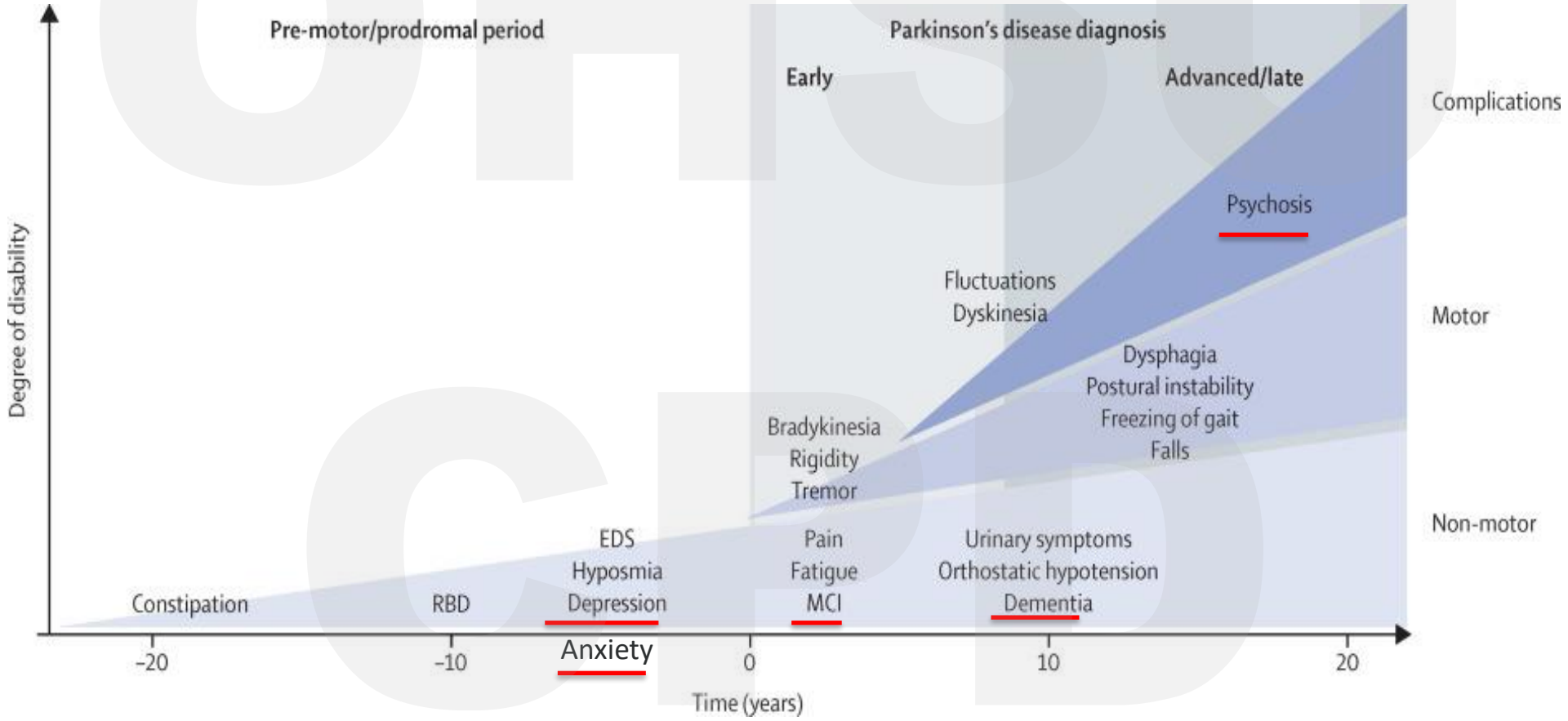
Non-motor symptoms in PD



PD: "THE QUINTESSENTIAL NEUROPSYCHIATRIC DISORDER"
- Weintraub, 2011

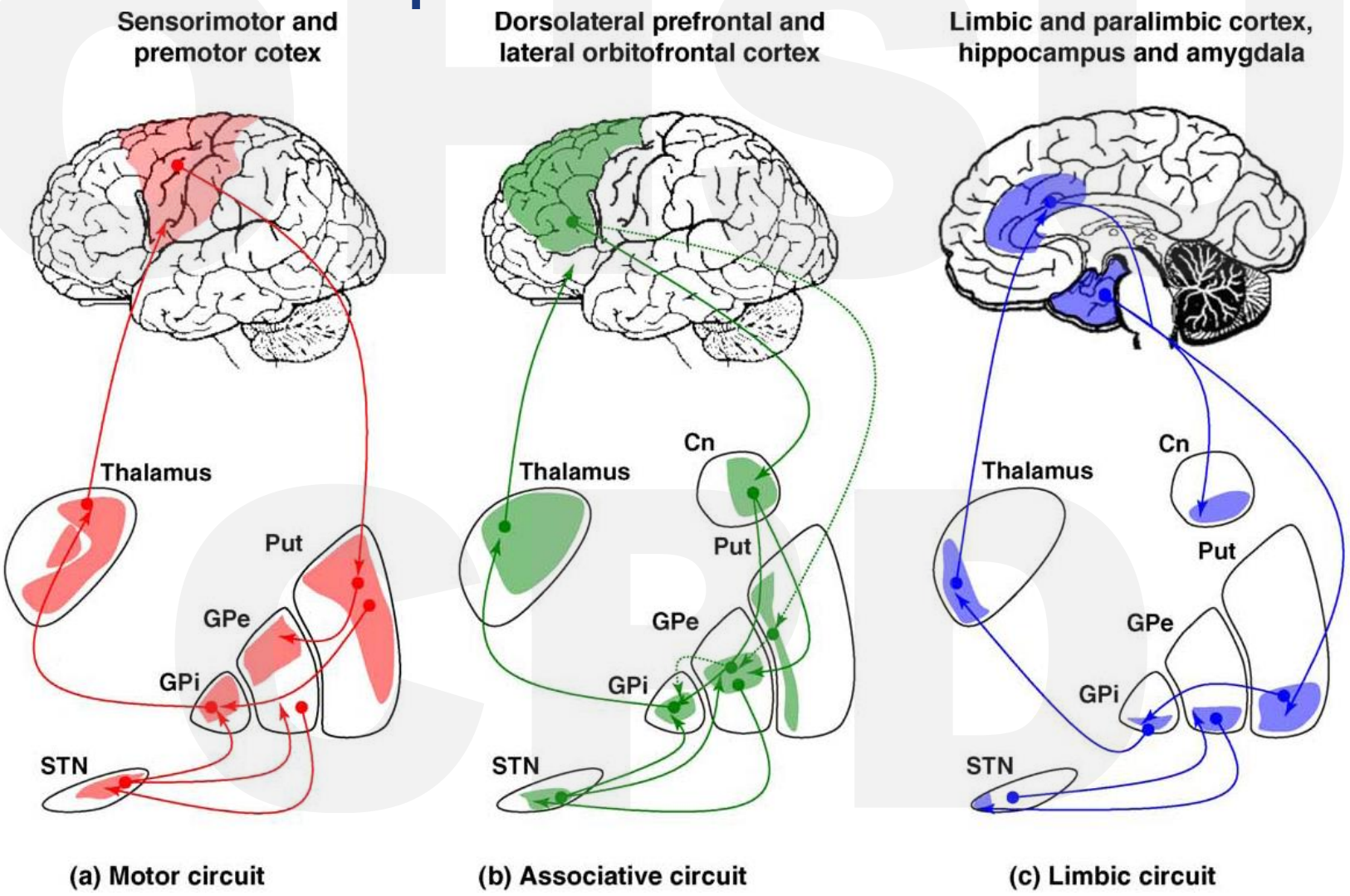
Qamar MA et al. npj Parkinson's Disease 2017;3:5

Clinical symptoms and time course of PD progression



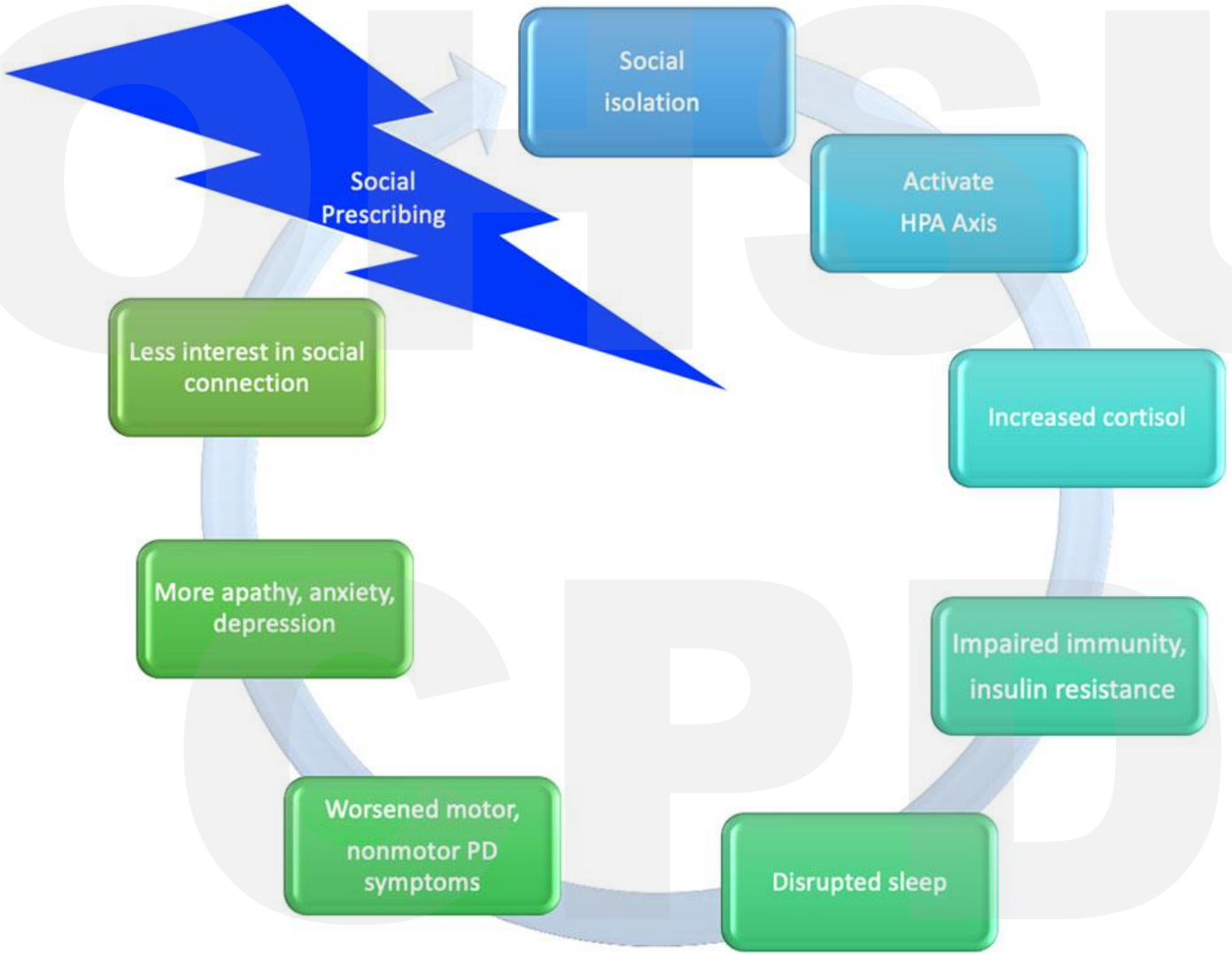
Kalia LV & Lang AE. *Lancet* 2015; 386: 896–912.

Cortico-Striatal-Pallido-Thalamo-Cortical Loops



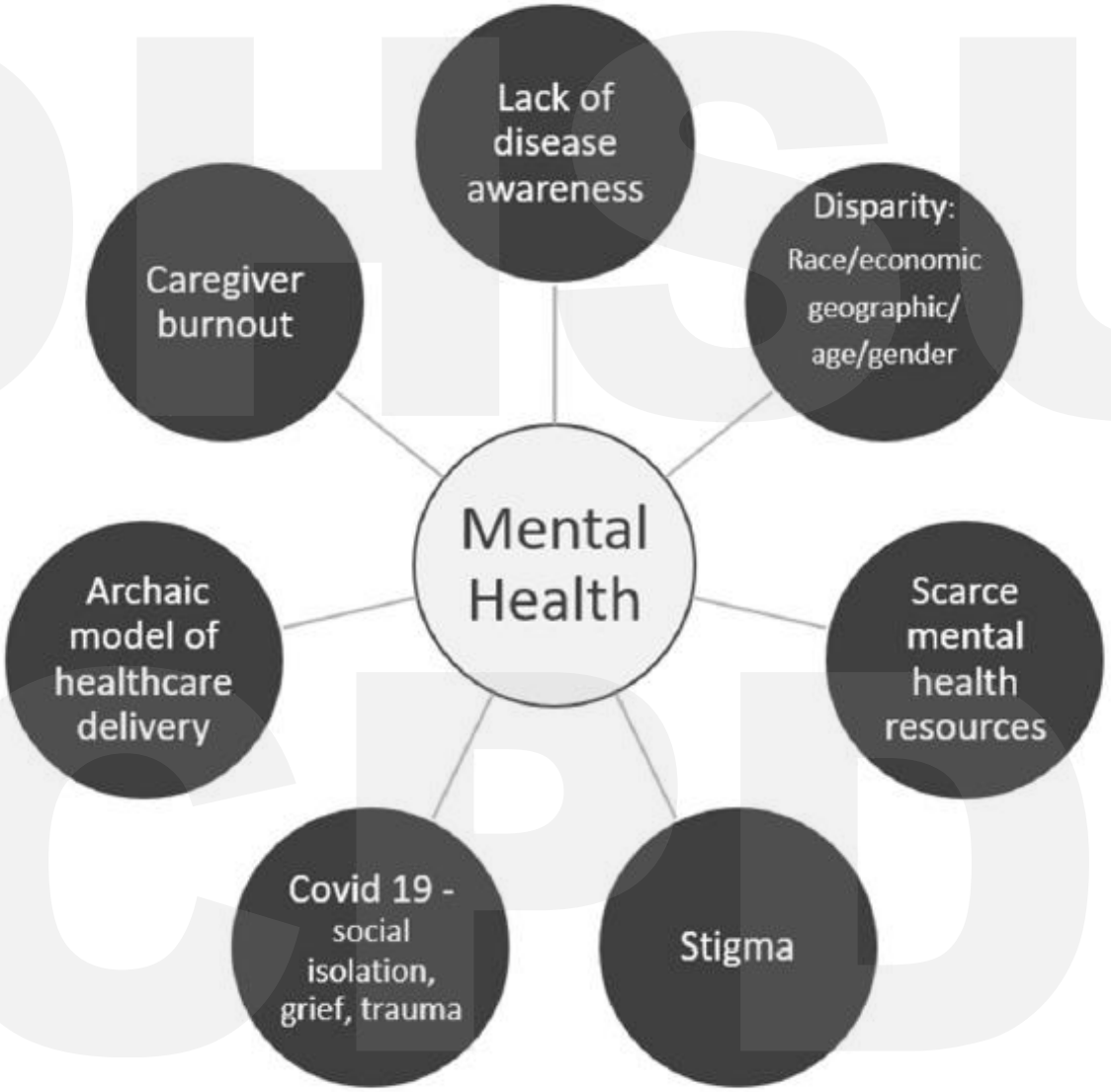
Krack et al, 2010, *Trends in Neuroscience*

Social Isolation, Stress, and PD Symptoms



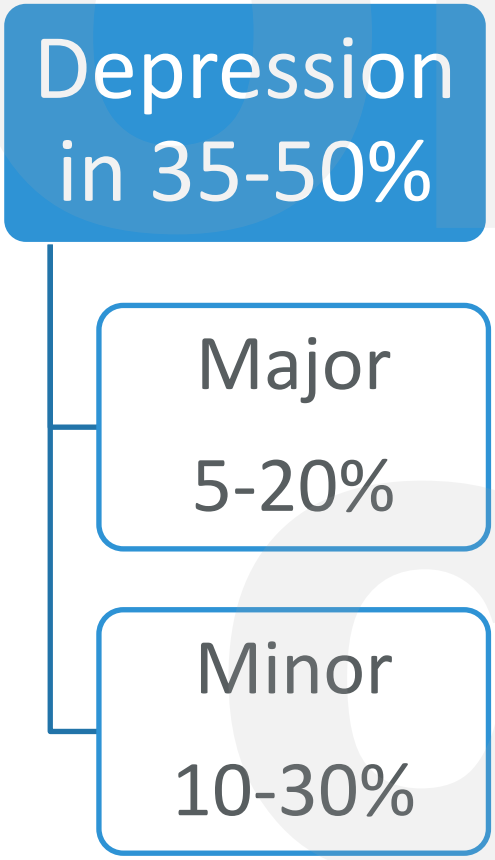
Subramanian et al. npj Parkinson's Disease (2020) 6:28.

Barriers to Mental Health and Wellness in PD



Subramanian et al. Parkinsonism and Related Disorders 93 (2021) 97–102.

Depression in PD



- Underrecognized and undertreated

(Weintraub D et al. *J Geriatr Psychiatry Neurol* 2003; 16:178-183)

- Poorer functioning and quality of life

(Schrag A et al. *Journal of Neurology, Neurosurgery & Psychiatry* 2000;69:308-312)

- Increases difficulty for caregivers
- May be prodromal (~5 years pre-PD Dx)
- Not just a normal reaction to PD Dx

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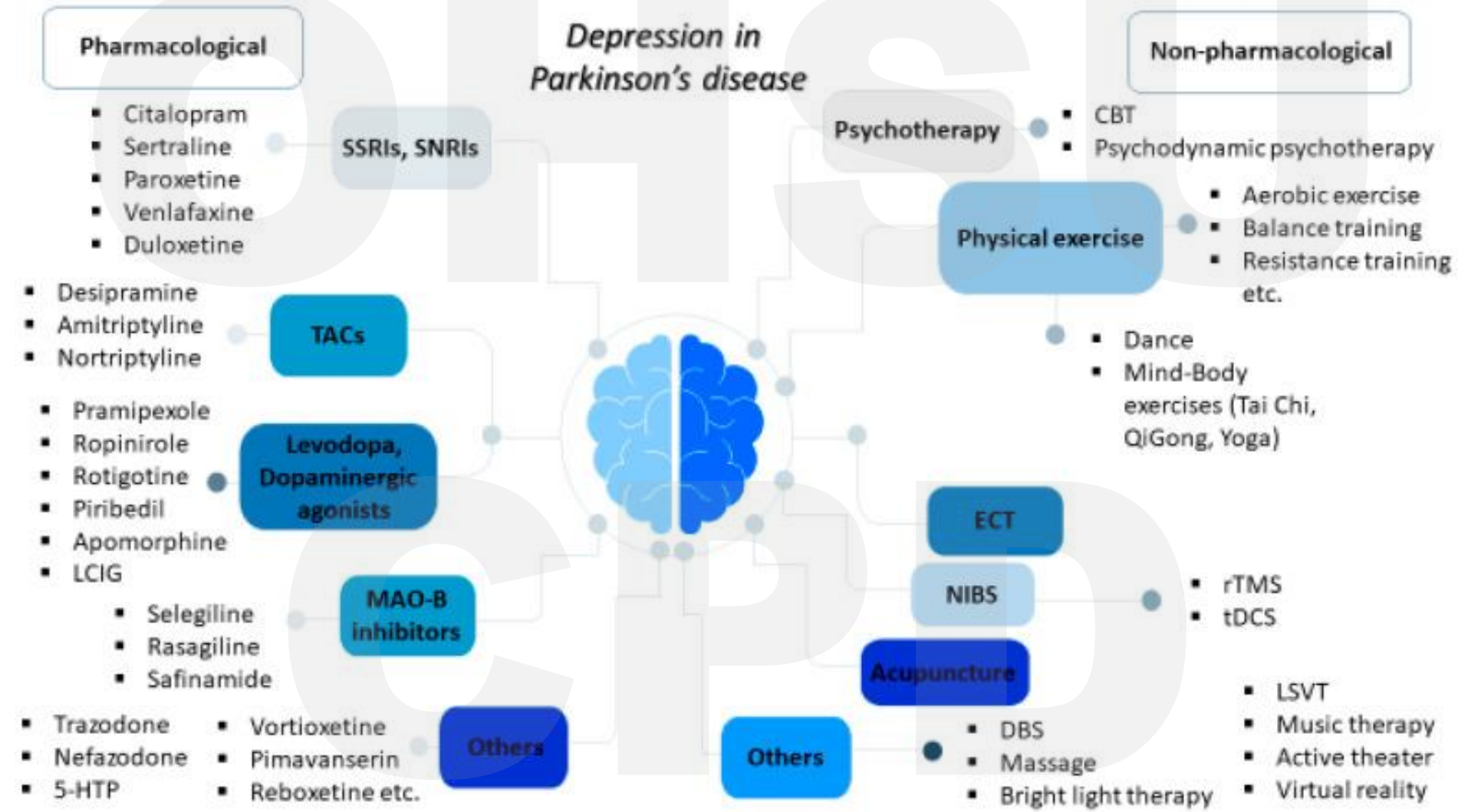
Overlapping Symptoms of PD and Depression

	MAJOR DEPRESSION	*PARKINSON DISEASE*
MOTOR PHENOMENA	Psychomotor retardation, stooped posture, restricted/depressed affect, agitation	Bradykinesia, stooped posture, masked face/ hypomimia, tremor
OTHER SOMATIC COMPLAINTS	Physical complaints, muscle tension, gastrointestinal symptoms, sexual dysfunction	
VEGETATIVE CHANGES	Decreased energy, fatigue, sleep and appetite changes	
COGNITIVE DISTURBANCES	Poor concentration, decreased memory, impaired problem-solving	

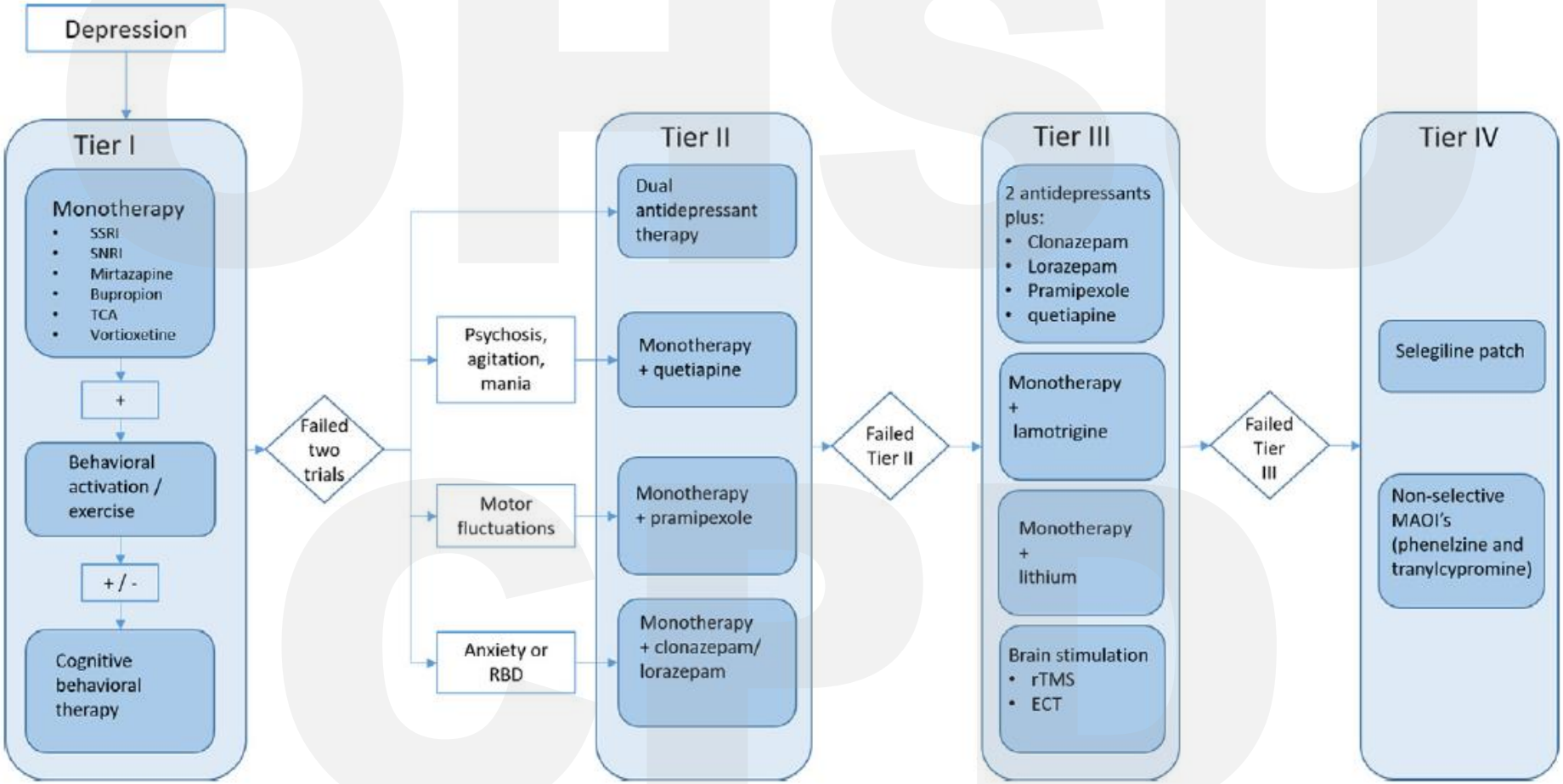
Marsh L. *Current neurology and neuroscience reports*. 2013;13(12):409.

Overview of PD Depression Tx Options



Angelopoulou et al. Medicina 2023, 59, 1454.

Algorithm for Tx of PD Depression



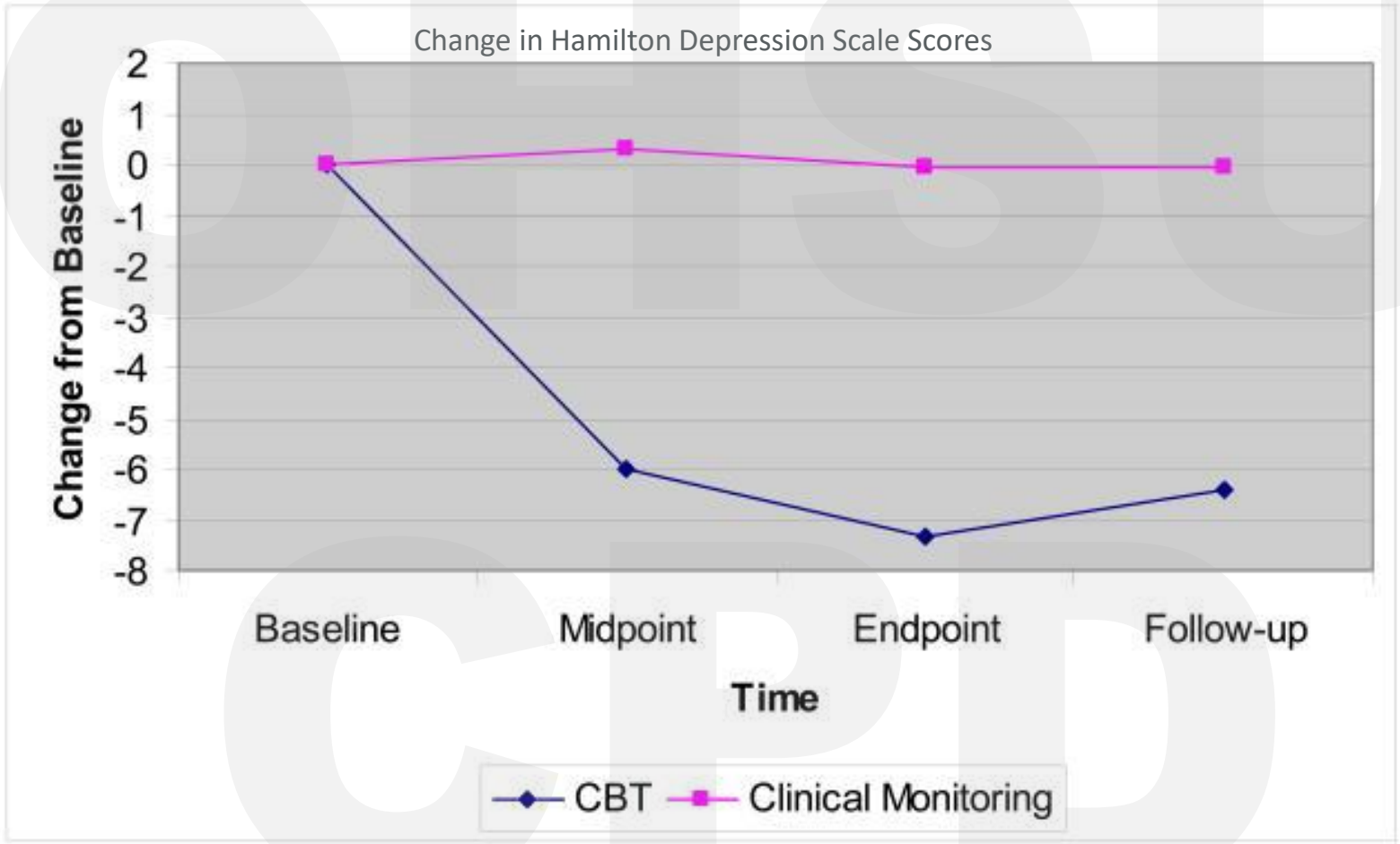
Pontone et al. Am J Geriatr Psychiatry. 2021 Feb 9:S1064-7481(21)00204-9.

PD Depression: Treatment

Medication Class	Dose Range (mg/day)	Side Effects for Medication Class
Selective serotonin reuptake inhibitors	Sertraline 25–200 mg/day; Fluoxetine: 10–60 mg/day; *(Es)Citalopram: 10–40; Escitalopram 5-20 mg/day *Paroxetine 10–50 mg/day	*Common*: GI side effects, sexual dysfunction, insomnia vs sedation. Low risk of worsening motor sx. QTc issue with Citalopram.
Serotonin norepinephrine reuptake inhibitors	*Venlafaxine: 37.5–225 mg/day; *Duloxetine: 20–120 mg/day Desvenlafaxine 50-100 mg/day	Same as SSRIs; also dose-dependent increased blood pressure with venlafaxine
Tricyclic antidepressants	Amitriptyline: 25–300 mg/day; *Desipramine: 25–200 mg/day; *Nortriptyline: 25–150 mg/day	*Common*: Anticholinergic (cognitive) side effects, weight gain, dizziness, orthostatic hypotension, sexual dysfunction; *Rare/serious:* QTc prolongation, cardiac arrhythmias, sudden death
Other	*Mirtazapine: 7.5–45 mg/day	*Common:* Sedation, increased appetite, weight gain
Other	Bupropion: 100–450 mg/day	*Common:* Nausea, weight loss, anxiety, agitation, insomnia; Rare/serious: Seizure
Dopamine Agonist	*Pramipexole: 1–3 mg/day	*Common:* Nausea, somnolence, dizziness; *Rare/serious:* Impulse control disorders, paranoia, hallucinations, confusion

*Supported by studies
~Rare complications of serotonergic agents: serotonin syndrome; induction of mania

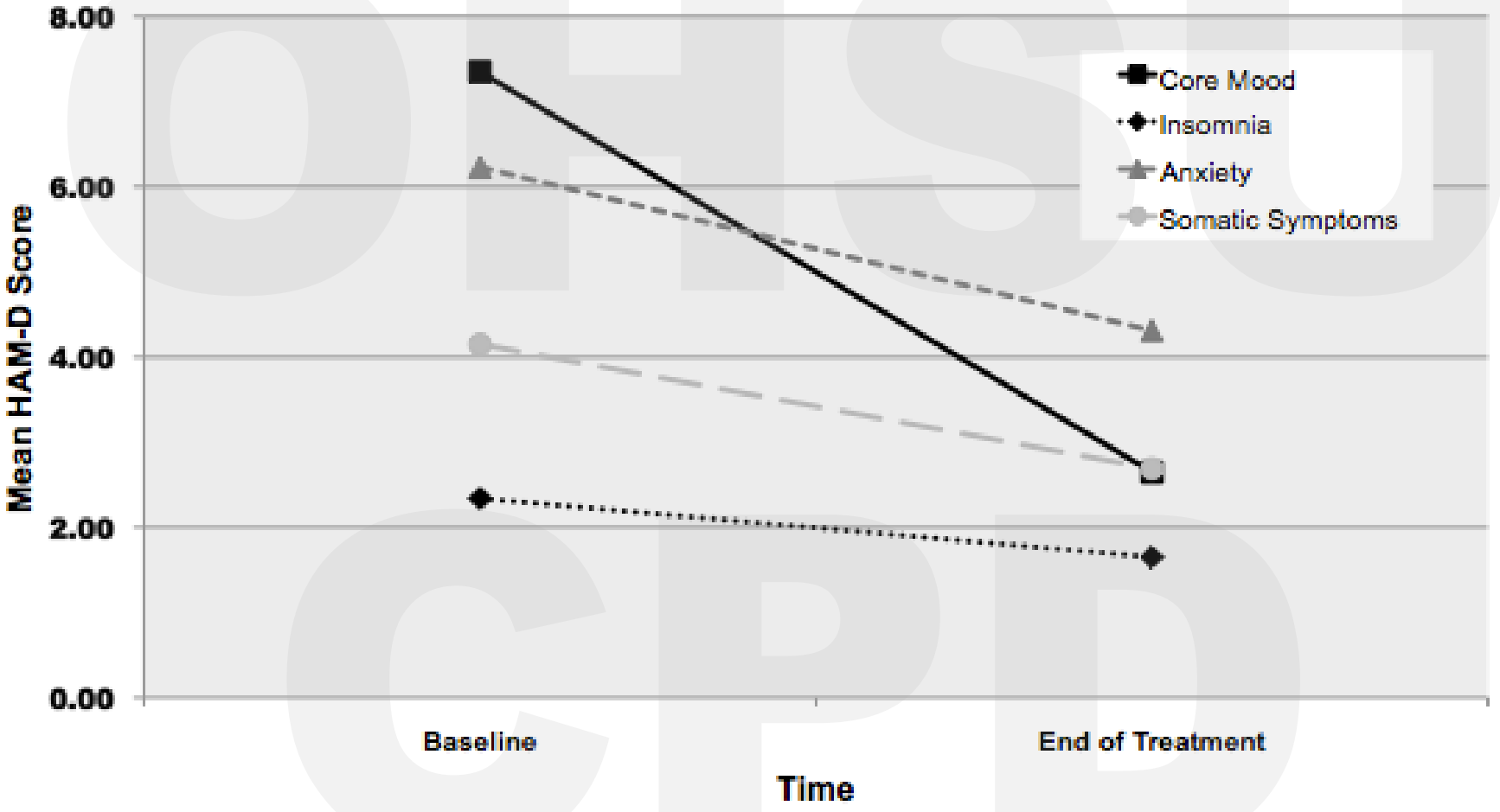
CBT for PD Depression



5 (midpoint), 10 (end of treatment), and 14 weeks (follow-up evaluation)

Dobkin et al, Am J Psychiatry. 2011 October; 168(10): 1066–1074.

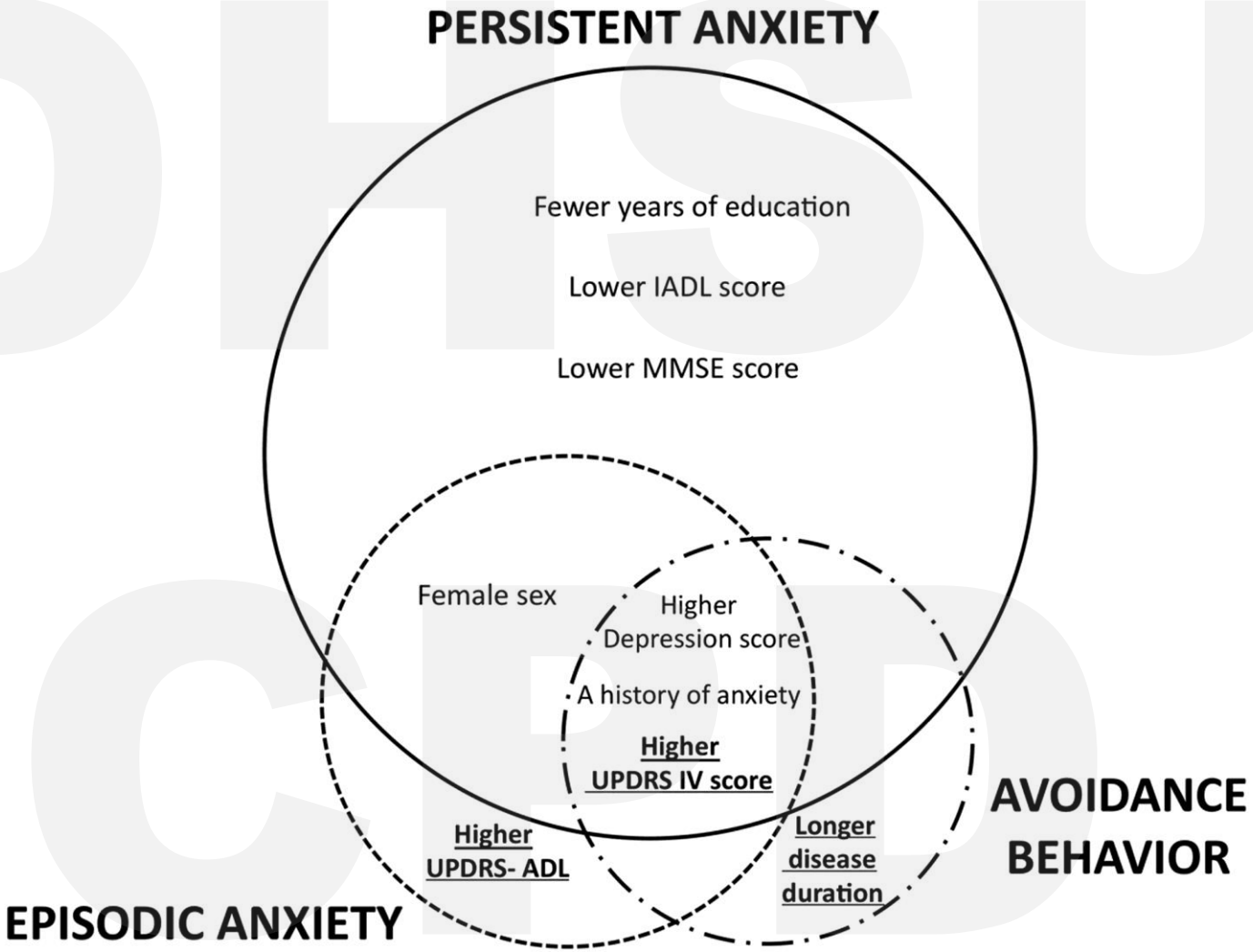
Figure 1. Change in HAM-D Symptoms



Dobkin et al. *Int J Geriatr Psychiatry*. 2019 May;34(5):722-729.

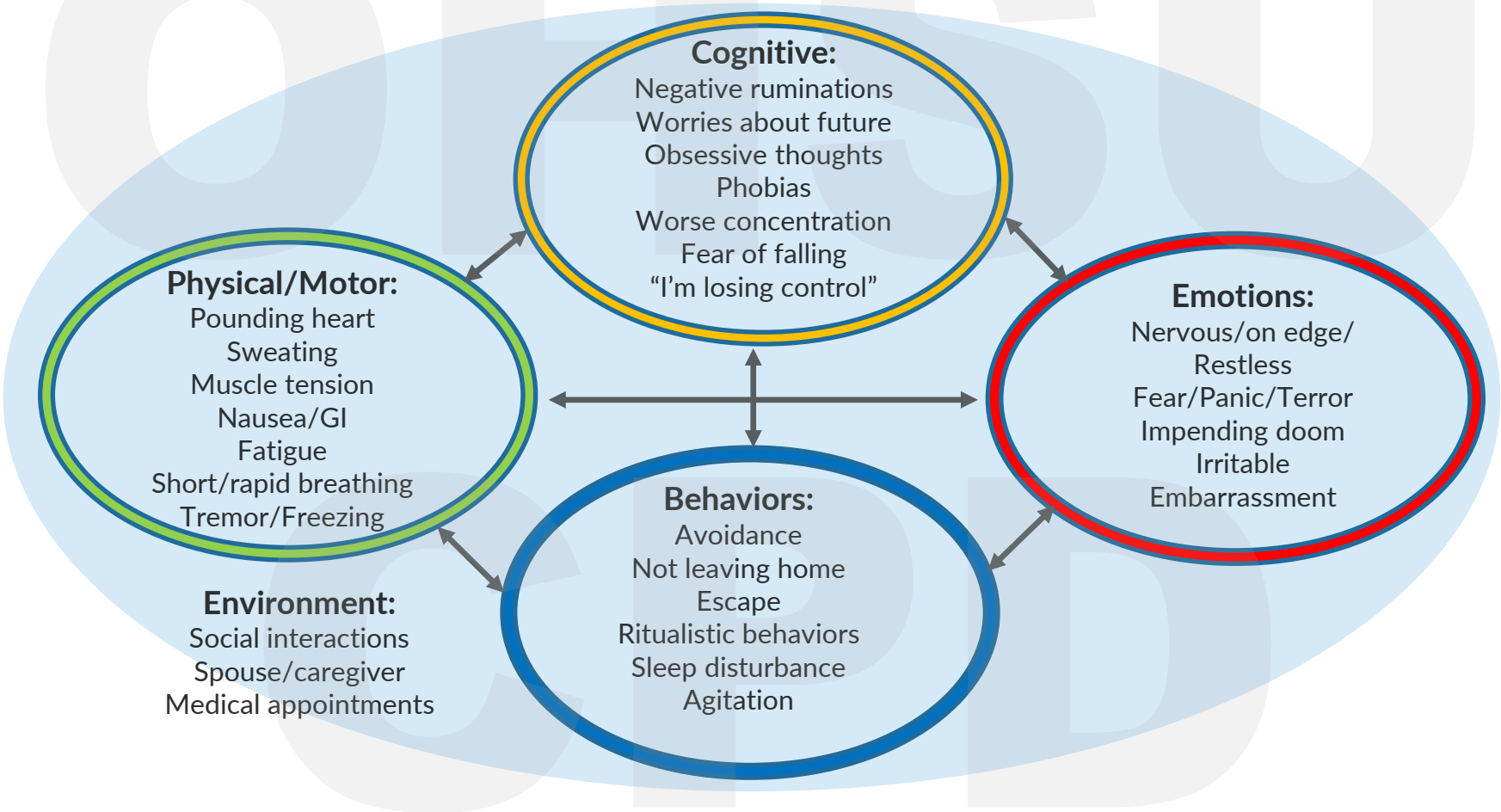
PD Anxiety

- Prevalence: ~30-40%

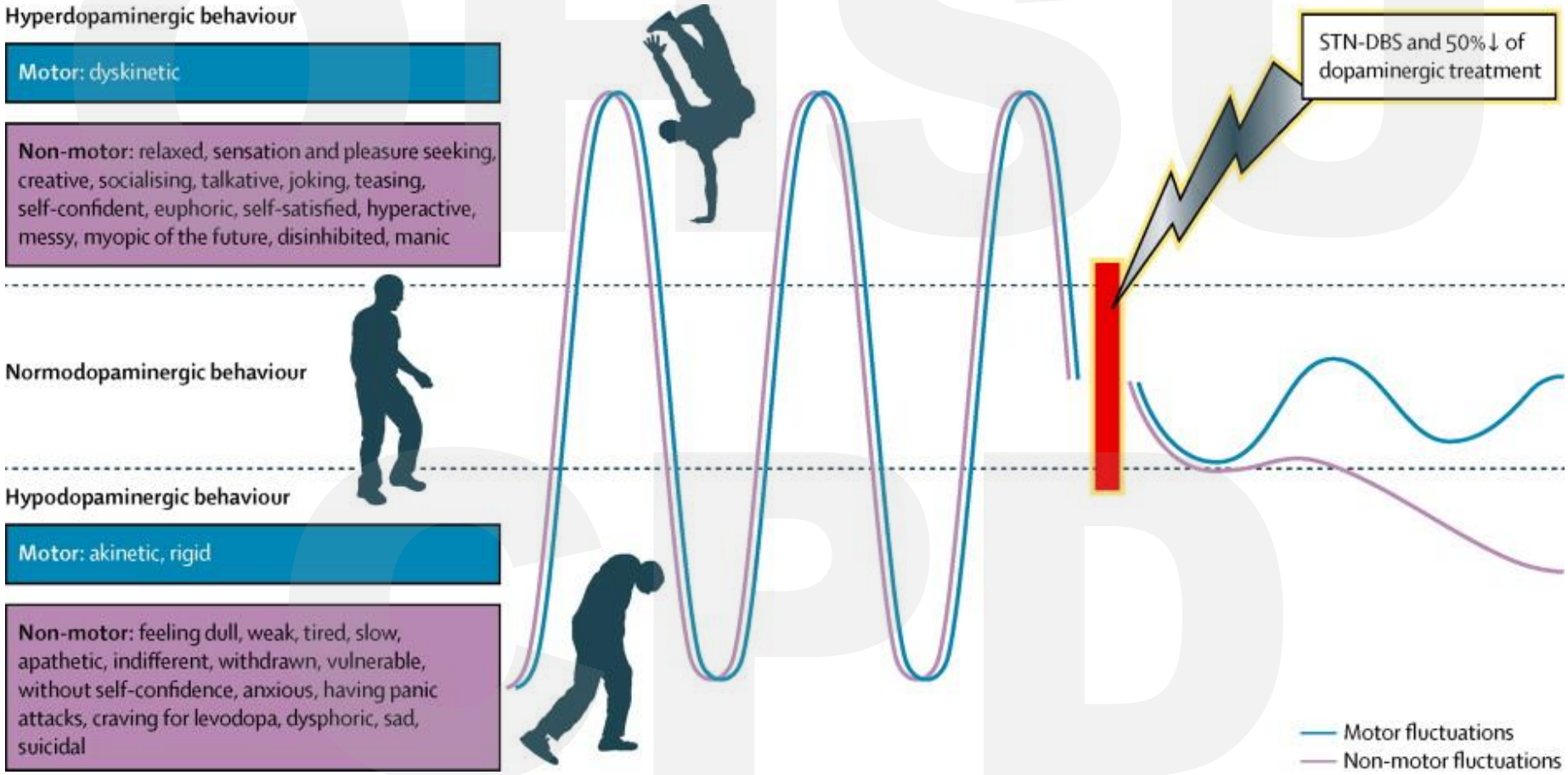


Broen et al. *Journal of Geriatric Psychiatry and Neurology*. 2018;31(2):55-62.

Manifestations of PD Anxiety

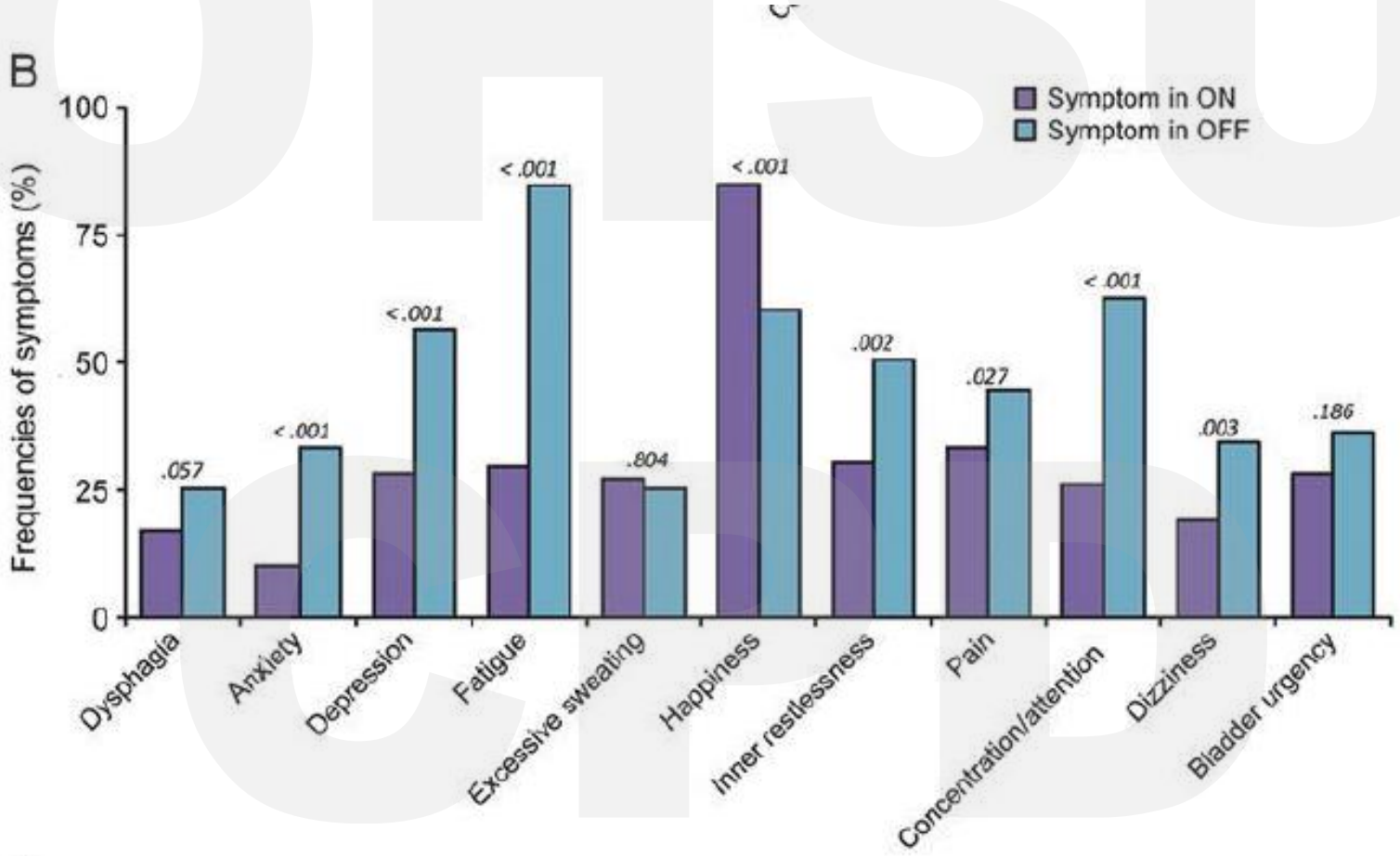


Non-Motor “off” symptoms



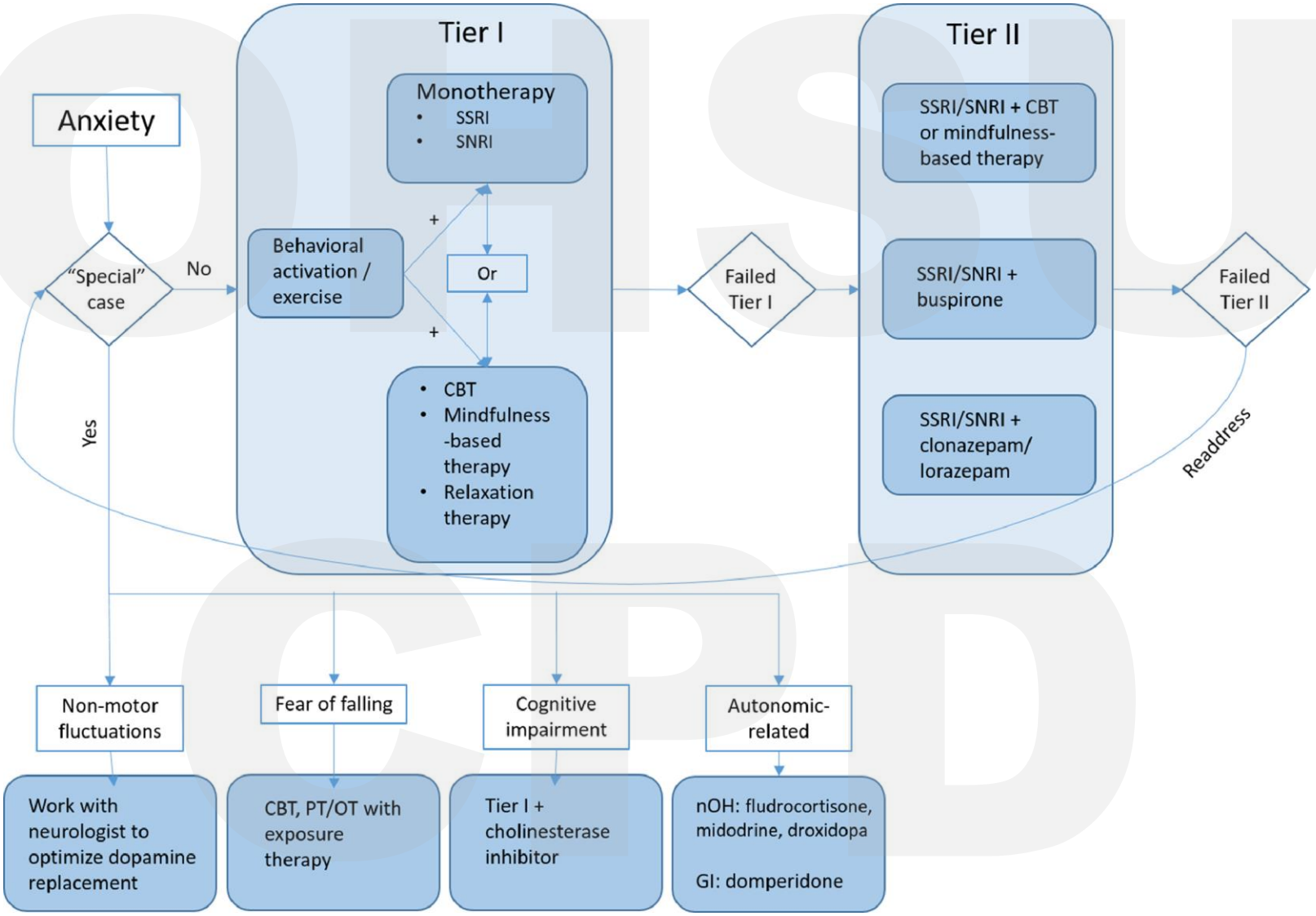
Castriata et al. *Lancet Neurol* 2014; 13: 287–305.

Frequency of nonmotor symptoms in on and off states



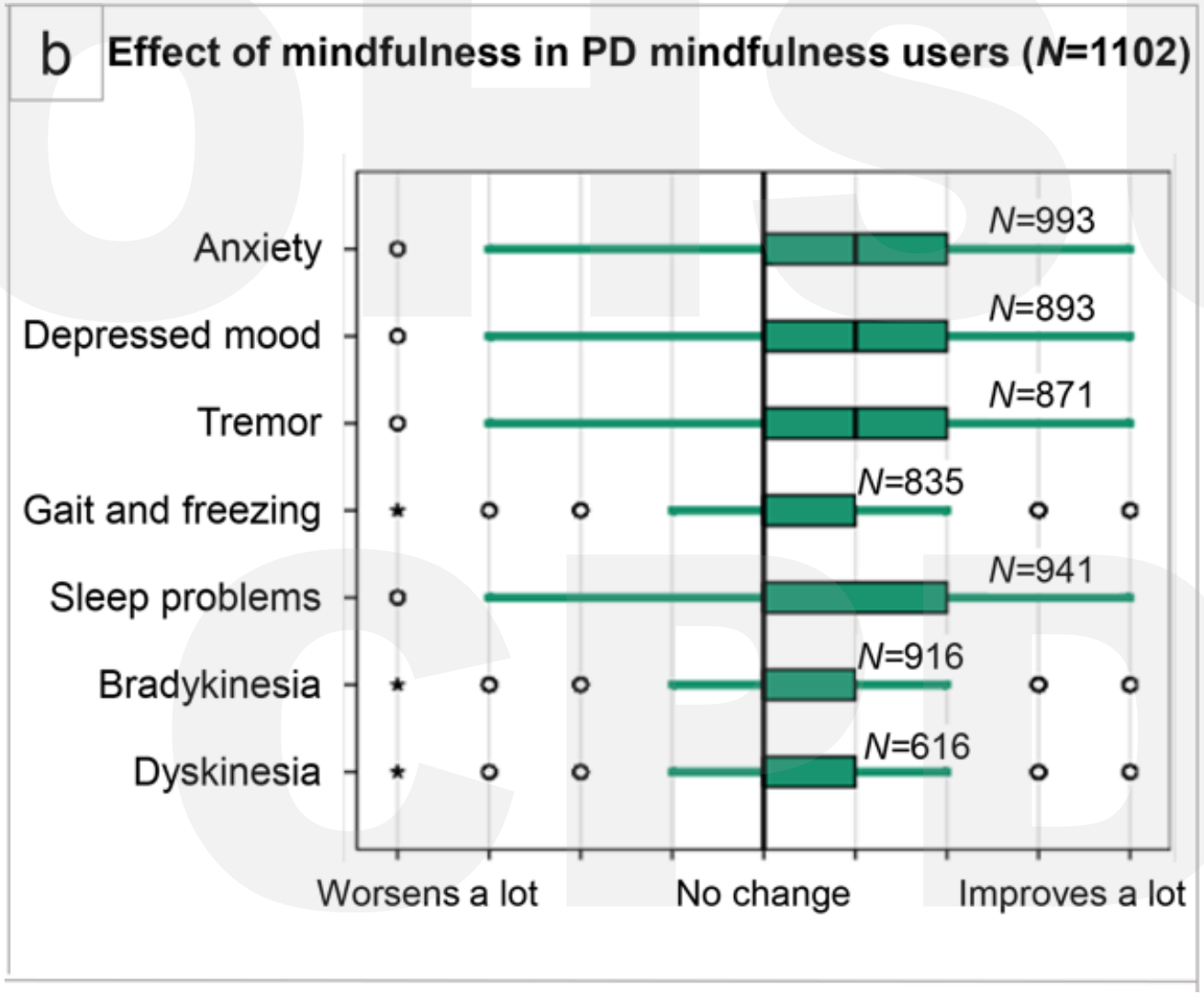
Storch et al. Neurology 2013;80:800-809

Management of PD Anxiety



Pontone et al. Am J Geriatr Psychiatry. 2021 Feb 9:S1064-7481(21)00204-9.

Perceived effect of mindfulness to reduce stress in PD patients



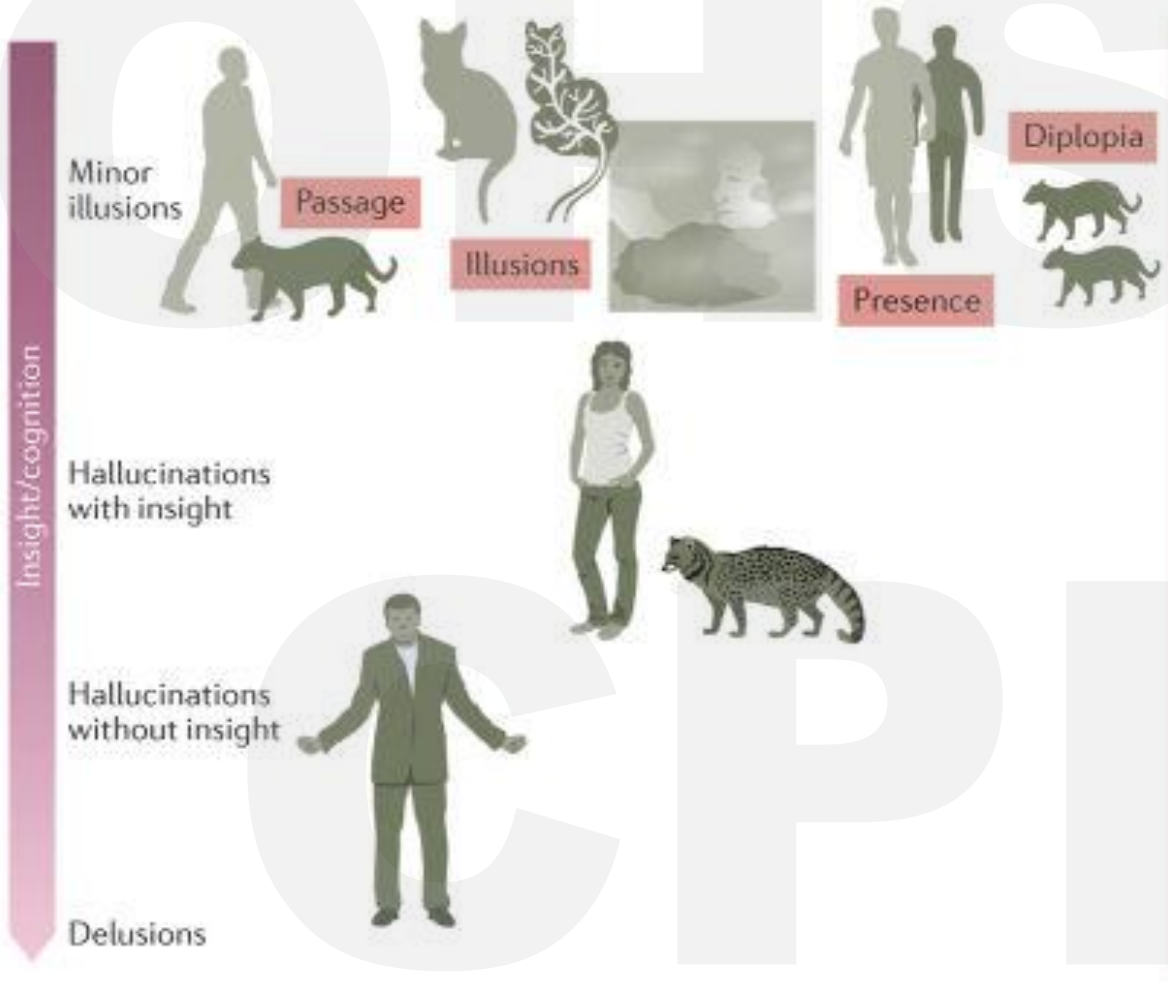
Adopted from:van der Heide et al. *npj Parkinsons Dis.* **7,** 7 (2021).

Integrative Mind-Body Interventions for PD-NPS

Intervention	Improvements
Mindfulness	anxiety; depression; QoL
Tai Chi	sleep; QoL
Dance	cognition; apathy; QoL
Yoga	QoL; anxiety; depression
Acupuncture	depression; QoL; sleep
Exercise/PT/OT	QoL; sleep; fatigue; depression; subsets of cognition; apathy; anxiety

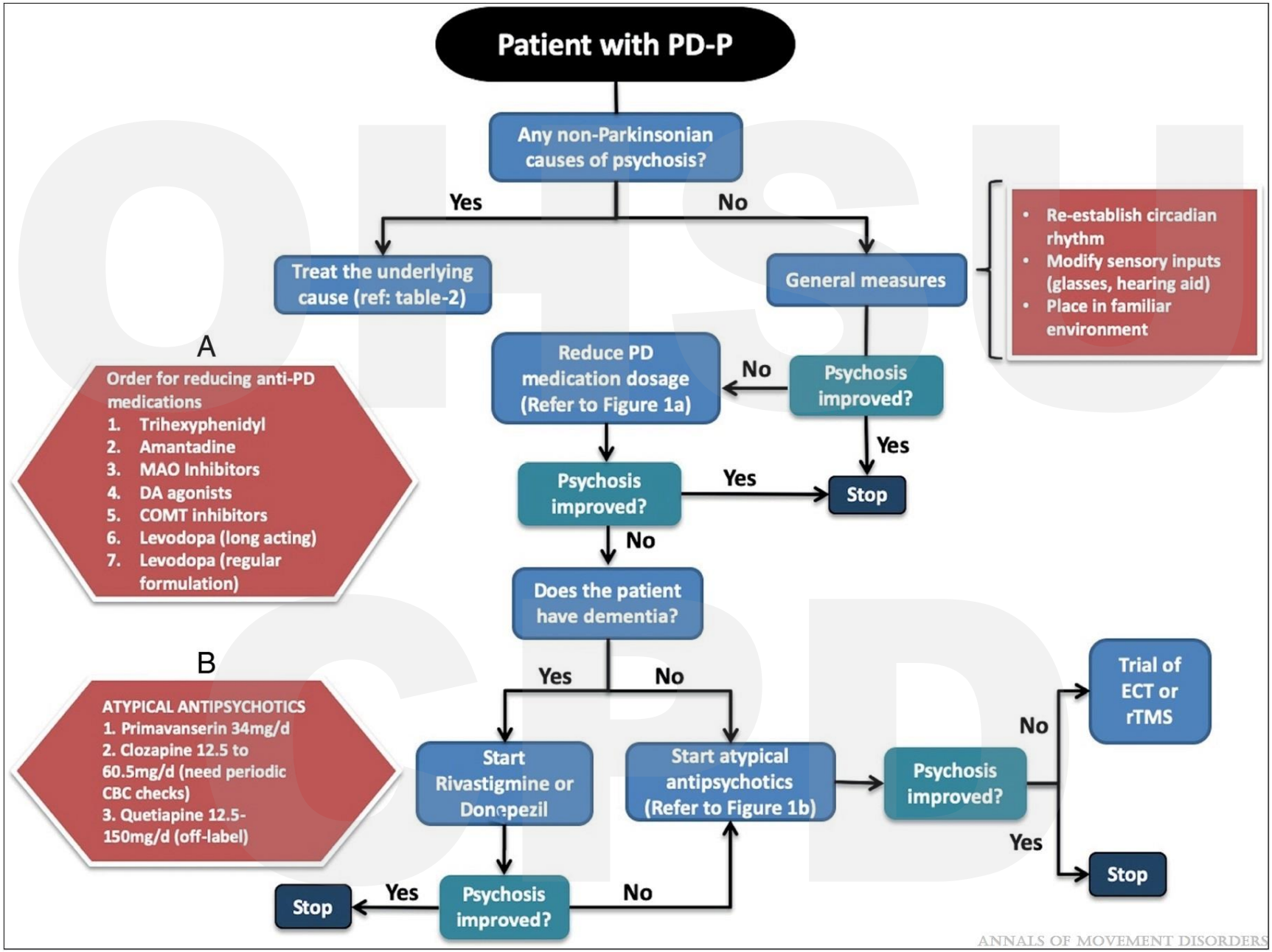
Adopted from Subramanian I. International Review of Neurobiology. Vol 134, 2017, pp 1163-1188.(with updates)

The Psychosis Spectrum in PD



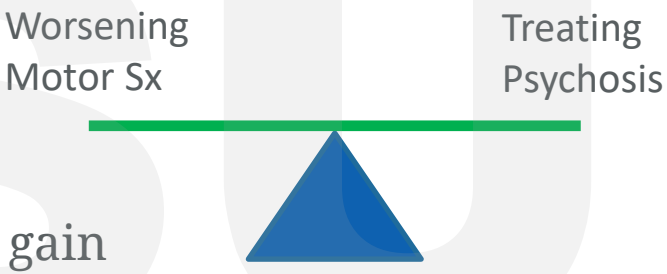
- Seen in >50% of PD patients over course of illness
- Persists & worsens over time
- Increased caregiver burden, nursing home placement, and mortality

Ffytche et al, *Nat Rev Neurol*. 2017 Feb;13(2):81-95.



Lenka et al. *Annals of Movement Disorders*, 2(3):83-90, Sep-Dec 2019.

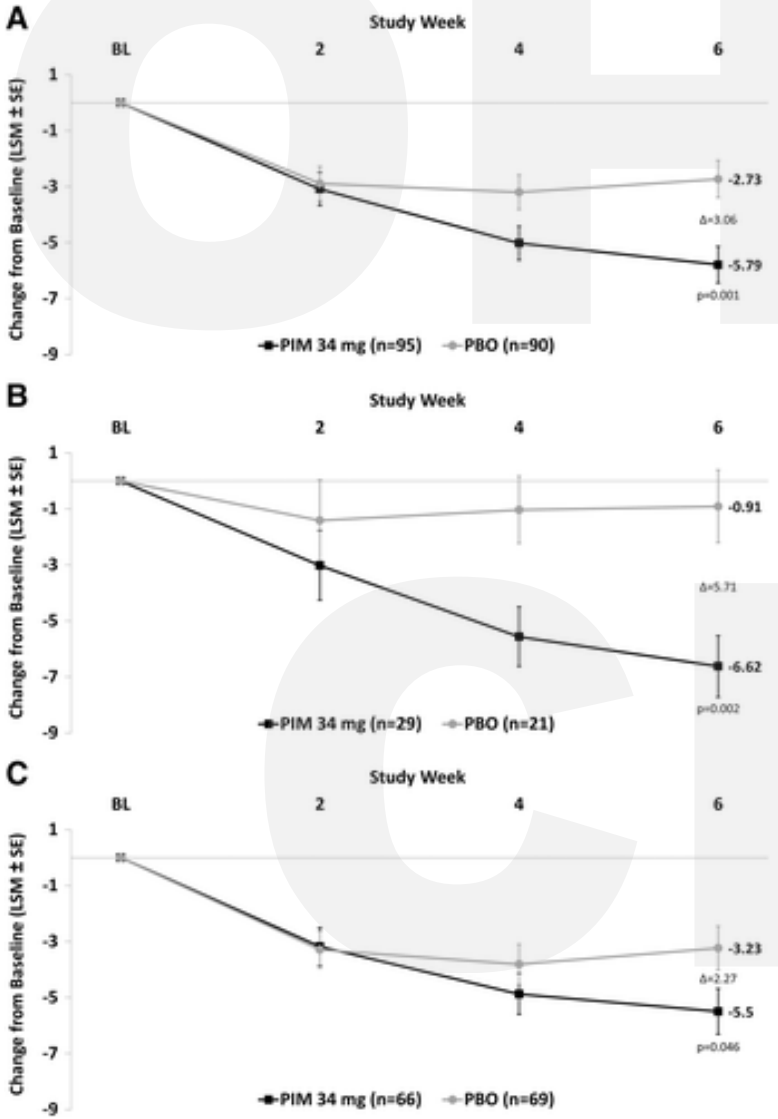
PD Psychosis: Treatment



- Cholinesterase inhibitors
- Quetiapine 12.5-200 mg/day
  - Orthostatic hypotension, drowsiness, weight gain
- Clozapine 6.25-50+ mg/day
  - Drowsiness, sialorrhea, constipation/GI, seizures, *agranulocytosis, orthostatic hypotension, myocarditis/cardiomyopathy
    - * Requires weekly blood draws to monitor CBC
- Pimavanserin, 34 mg/day
  - Two-week bridge from quetiapine
  - Confusion, hallucinations, nausea, peripheral edema, constipation

Black Box warning for all antipsychotics:
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death (cardiovascular, pneumonia).

Pimavanserin effects stratified by baseline cognition



SAPS-PD change from baseline stratified by baseline MMSE score. (A) overall population, (B) MMSE 21 to 24, and (C) MMSE ≥ 25. LSM, least squares mean; SE, standard error; PBO, placebo.

Espay et al., Movement Disorders 33(11):1769-1776

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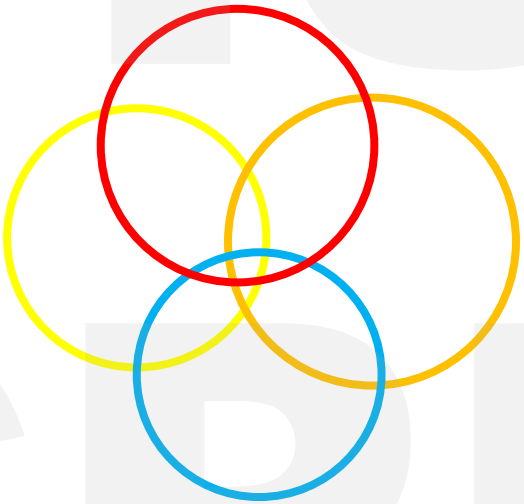
Impulse Control Disorders (ICDs)

Prevalence of ICDs-13.6%

Pathological Gambling- 5.0%



Compulsive Eating- 4.3%

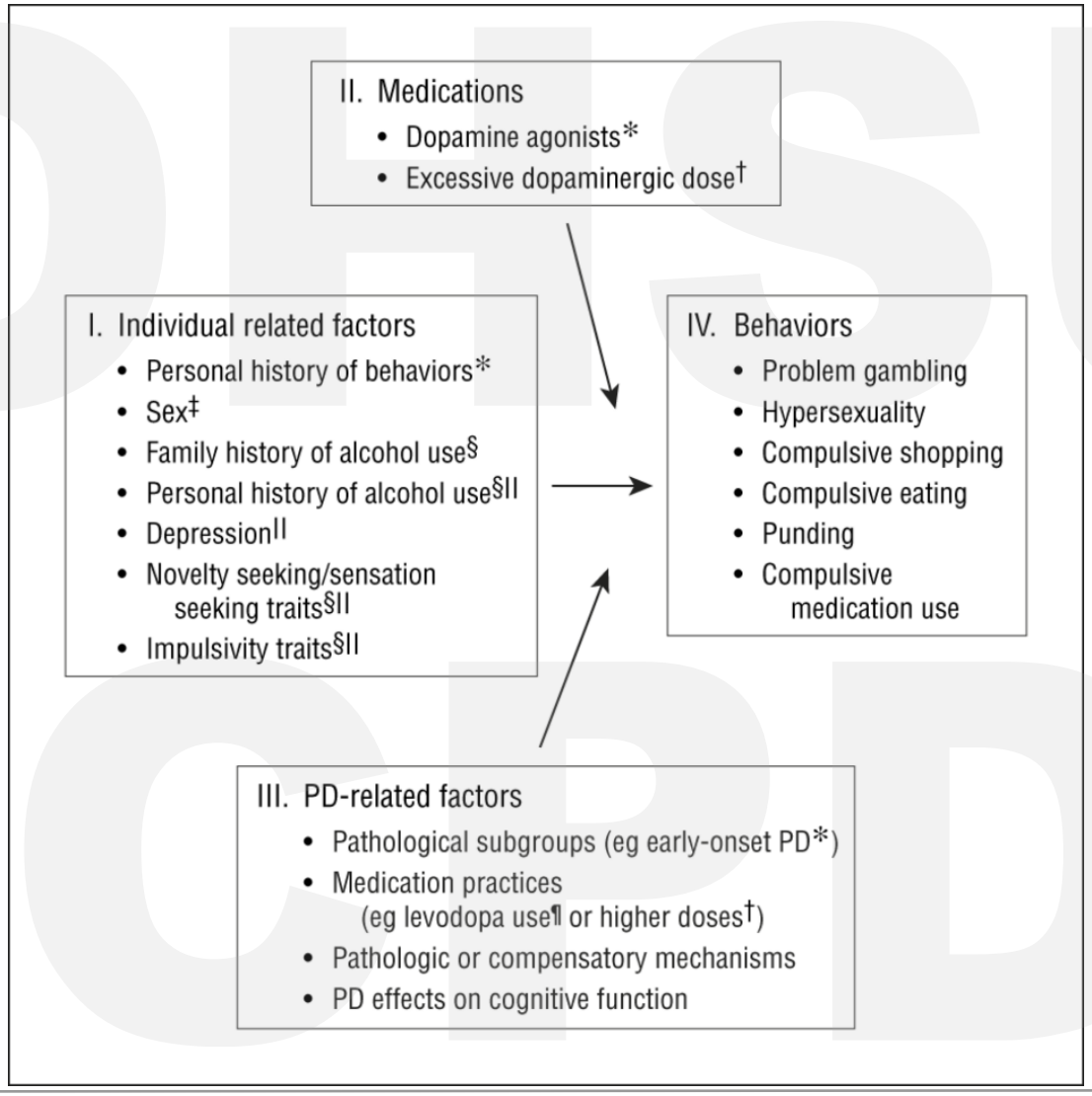
Compulsive Buying- 5.7%

More than one ICD- 3.9%

Compulsive Sexual Behavior- 3.5%

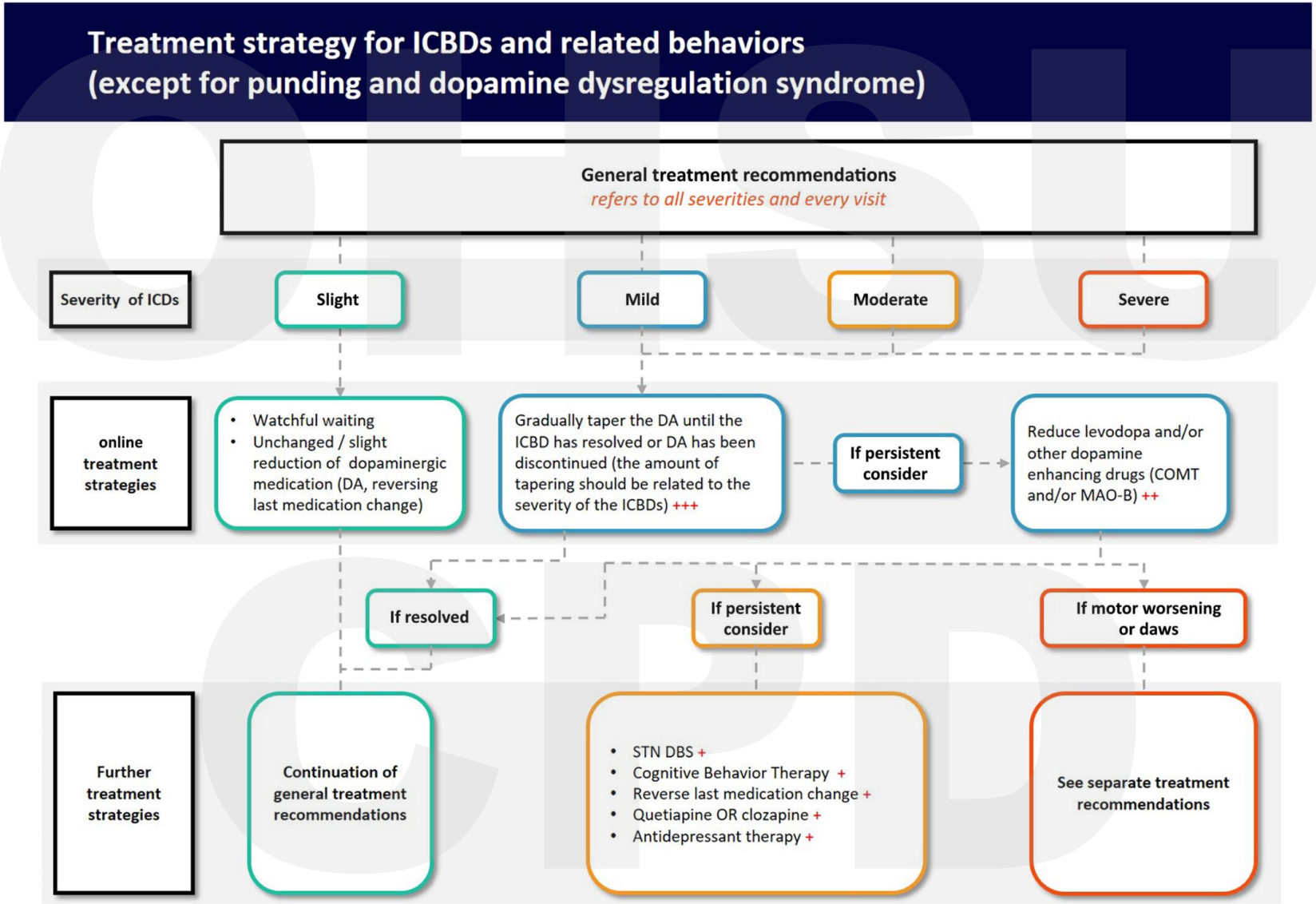
Weintraub et al, 2010, *Arch Neurol.* 2010 May;67(5):589-95

PD-ICD Risk Factors



Voon V & Fox S. Arch Neurol. 2007;64(8):1089-1096.

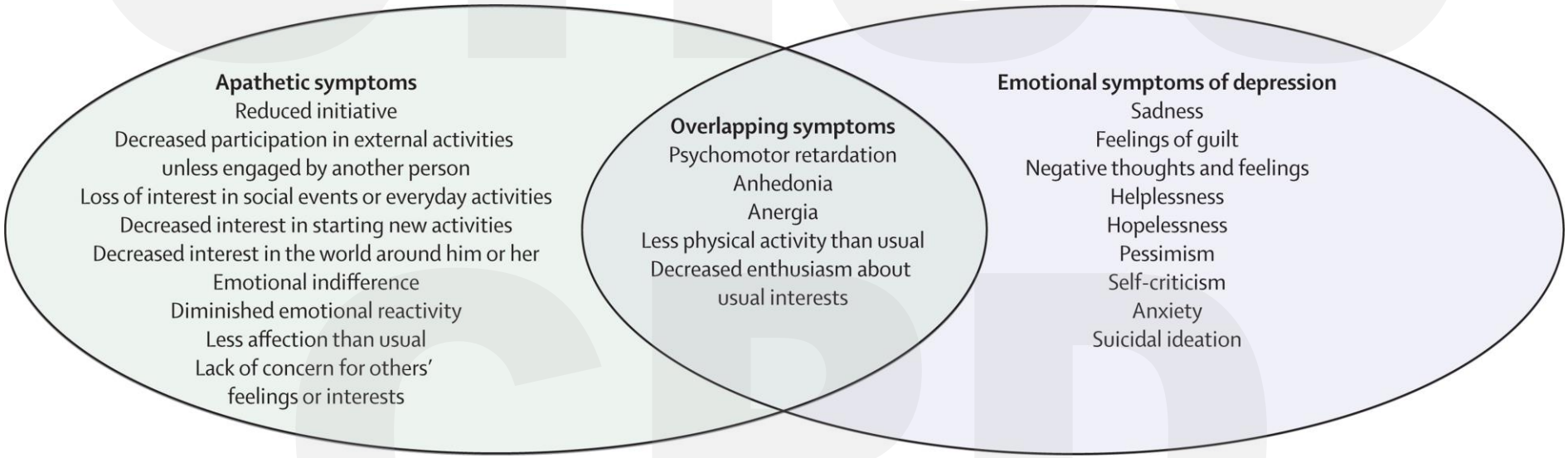
Management of ICDs in PD



Debove et al. *Mov Disord*, 39: 235-248.

Apathy vs Depression in PD

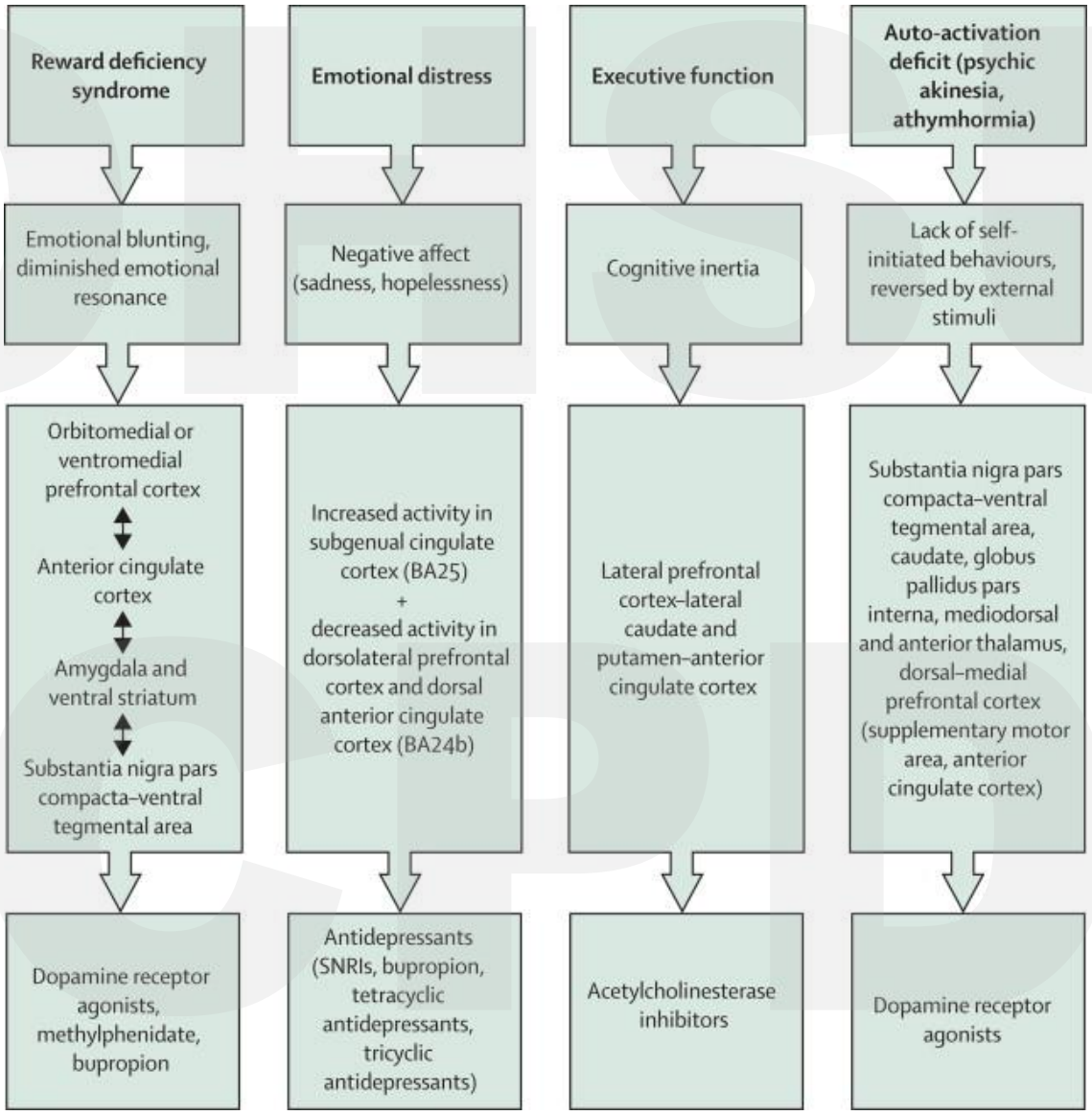
Apathy point prevalence= ~35%



Pagonabarraga, Javier et al. The Lancet Neurology , Volume 14 , Issue 5 , 518 - 531

Apathy in PD

Apathy subdomains, neural substrates, and potential treatments



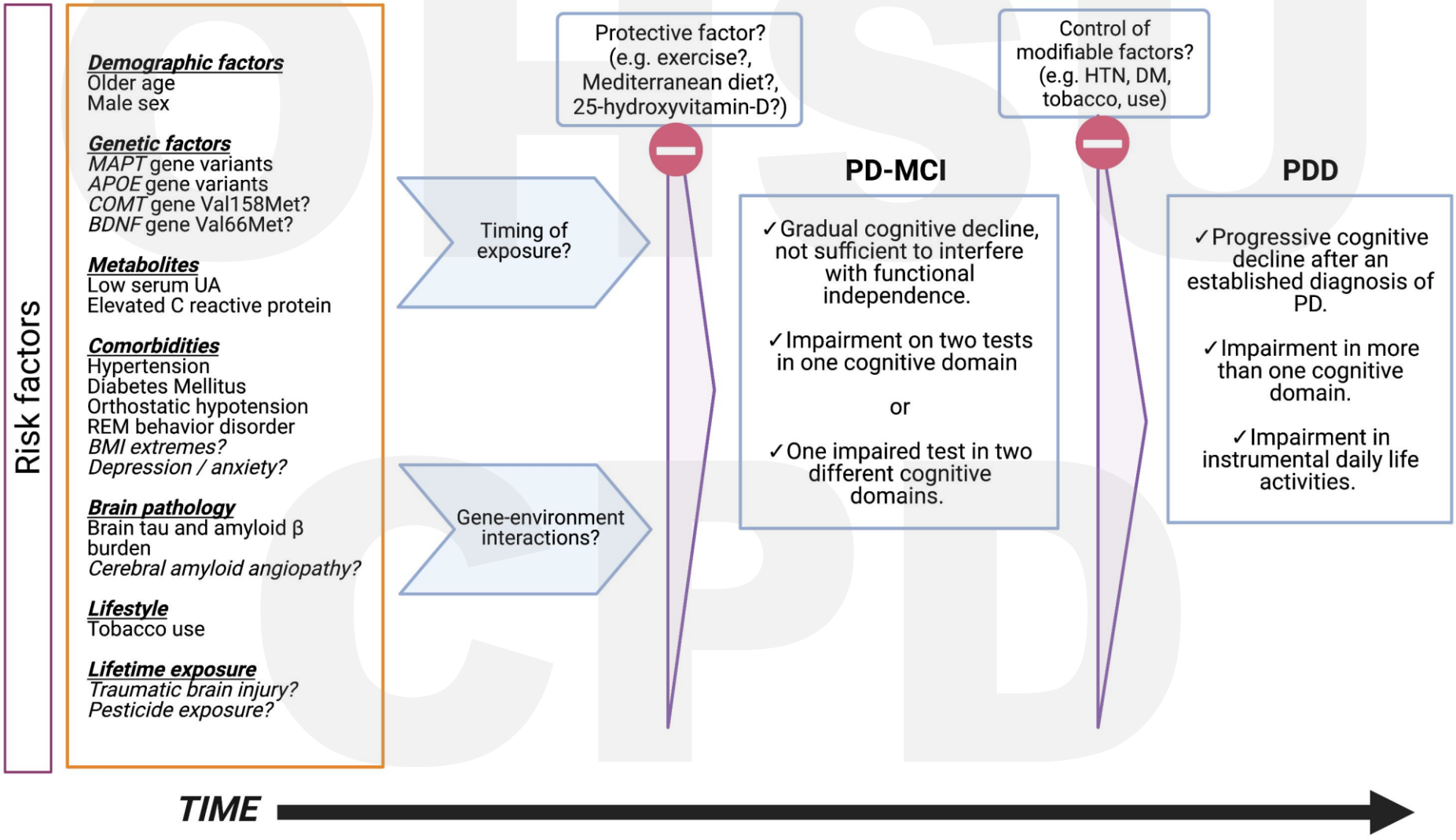
Pagonabarraga et al. *The Lancet Neurology*, 14 (5):518-531

PD Mild Cognitive Impairment

- 25% of non-demented PD patients
- A risk factor for PDD (50%+ conversion at 5 years)

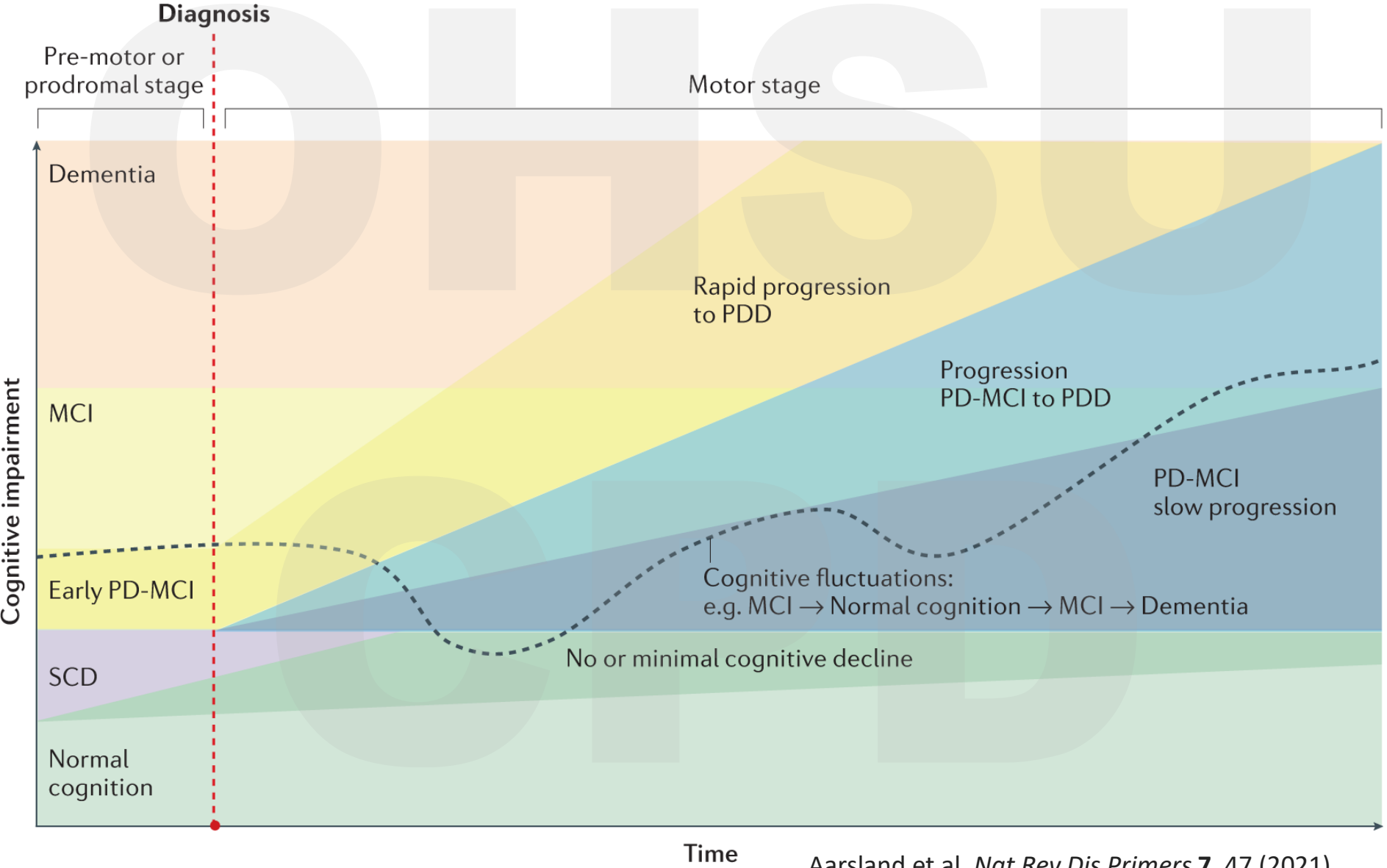
PD Dementia

- Up to 50% at 10 years, 80% over the full course of illness
- Point prevalence: 15-40%



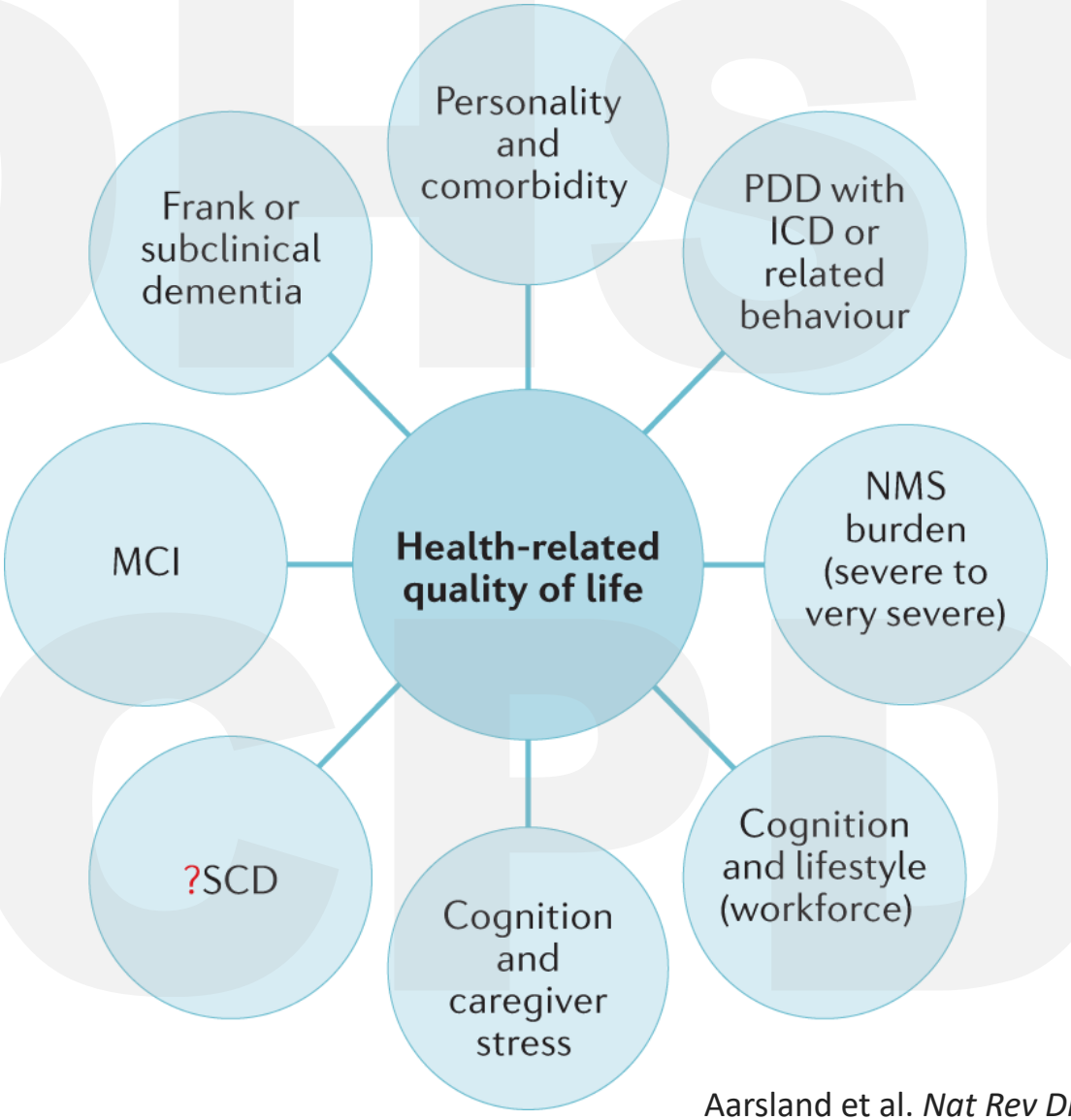
Gonzalez-Latapi et al. *Behav. Sci.* 2021, *11*, 74.

Cognitive spectrum and the heterogeneity of progression of cognitive impairment in PD



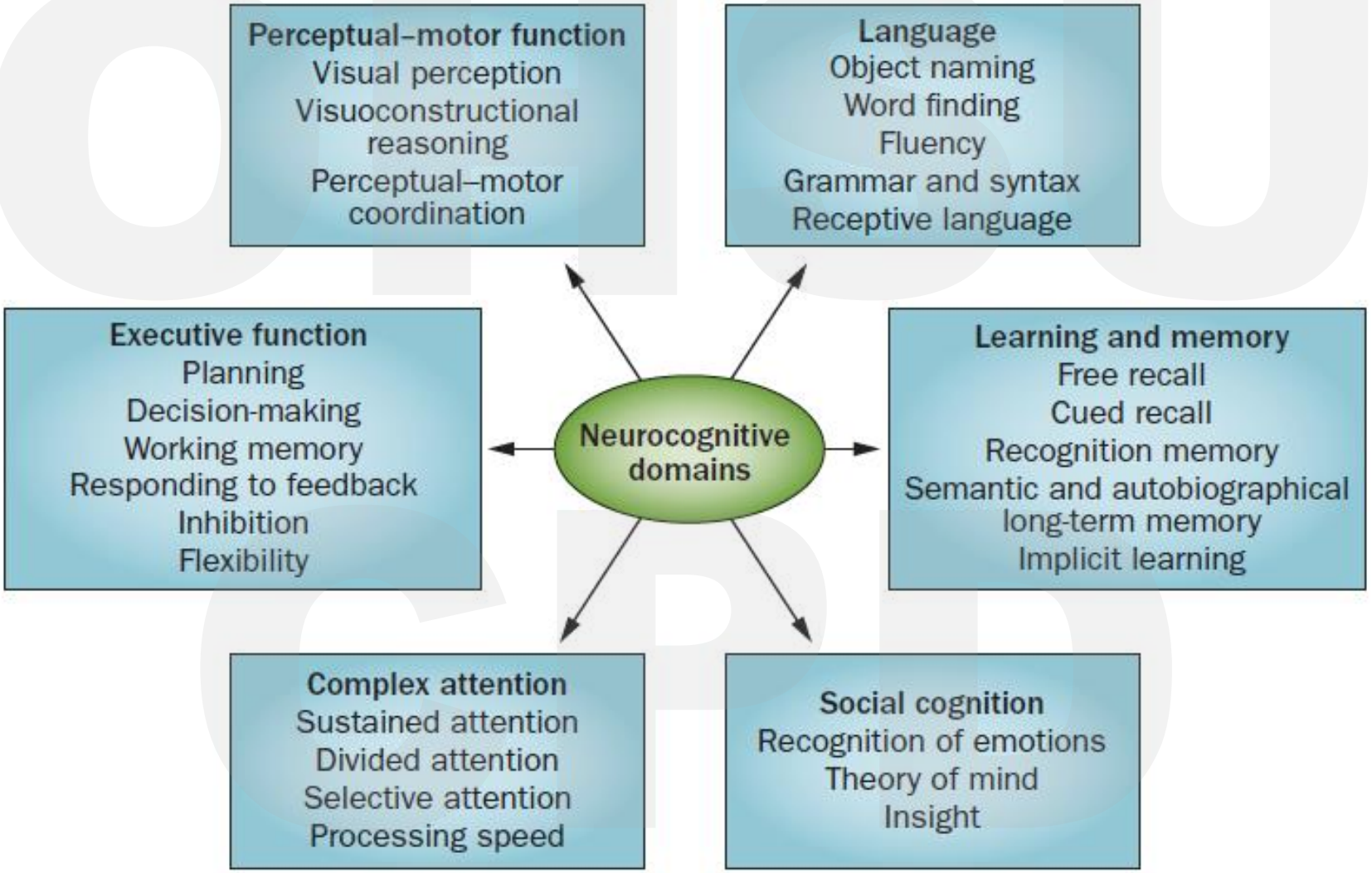
Aarsland et al. *Nat Rev Dis Primers* **7**, 47 (2021).

QoL in PD Cognitive Impairment



Aarsland et al. *Nat Rev Dis Primers* **7**, 47 (2021).

Neurocognitive Domains



Sachdev, P. S. *et al. Nat. Rev. Neurol*. 10, 634–642 (2014)

PD Dementia: Duration of illness

Supplementary Table 2. Estimated probability of dementia and cumulative number of diagnoses by PD duration in Penn cohort

PD Duration	Dementia Diagnosis Probability 95% CL	Cumulative Dementia Diagnoses
Year 5	11.82% (8.8%, 15.77%)	27
Year 10	26.5% (22.15%, 31.51%)	74
Year 15	49.66% (44.42%, 55.15%)	133
Year 20	74.39% (69.76%, 78.8%)	167
Year 25	90.23% (86.57%, 93.25%)	178
Year 30	90.23% (86.57%, 93.25%)	183
Year 35* (24.756 - 34.693 years) (35.622 - 38.052 years)	 90.23% (86.57%, 93.25%) 95.12% (92.47%, 97.05%)	183

Unpublished data from Penn U19 Cohort, N=389

What to do?

Recommendations for early to mid-stage PD:

1. Exercise (American Heart Association guidelines)
2. Stay active socially; join a support group
3. Engage in cognitive training exercises
4. Learn coping strategies such as with an occupational therapist
5. Nutrition affects cognition; try a Mediterranean diet
6. Take your time when doing tasks; do not multitask
7. Communicate with family/friends if you are struggling

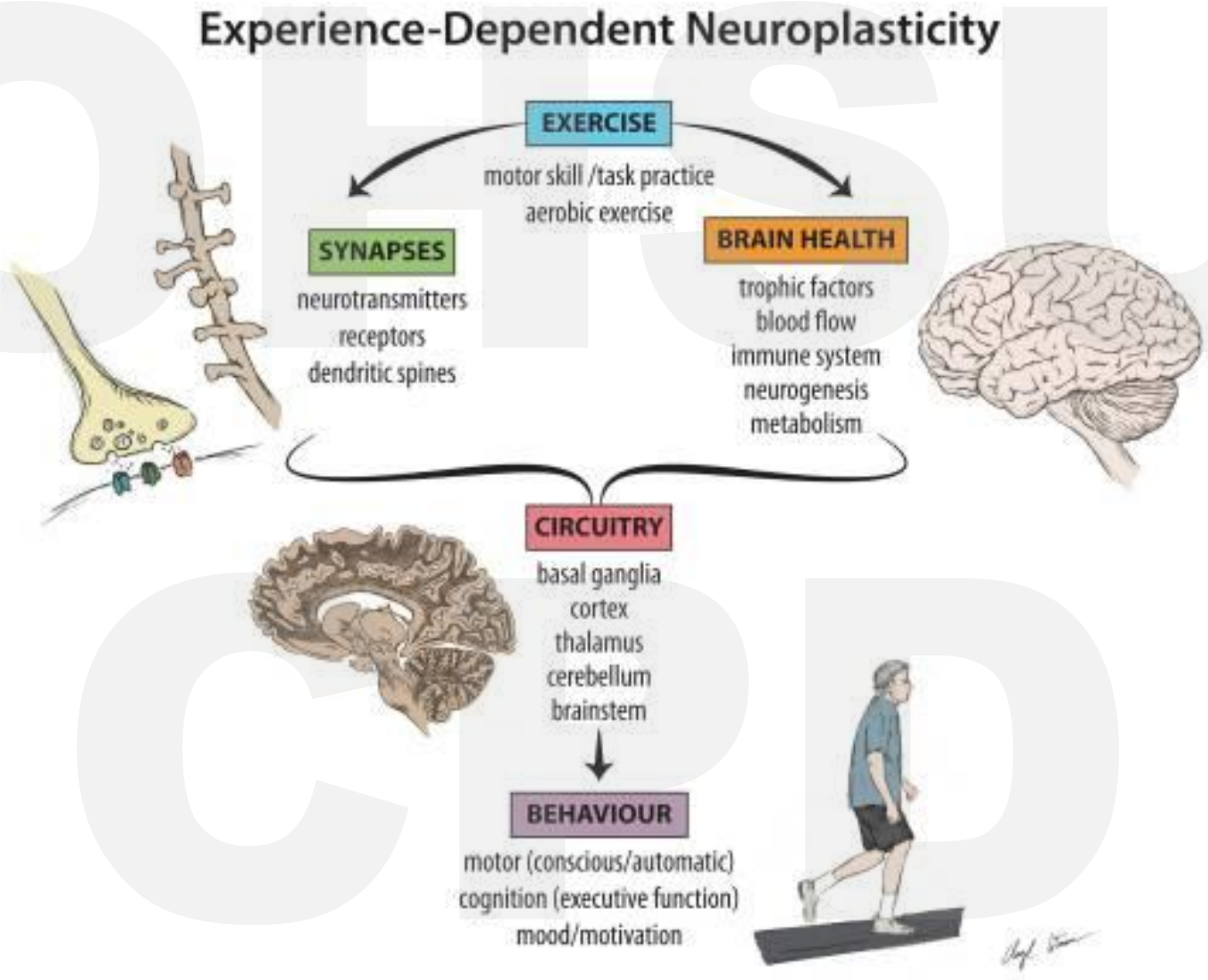
Recommendations for advanced PD:

Continue above recommendations, PLUS:

1. Develop a highly structured daily routine that you follow
2. Consider the use of medication for cognitive impairment
3. Have an advanced directive in place (living will, treatments)
4. *Care partners*- take care of your own health as well
5. *Care partners*-- seek support such as counseling

Cognitive Problems in Parkinson's Disease—Beth Vernaleo, PhD at www.movementdisorders.org (March 2017).

Exercise Enhances Neuroplasticity in PD



Petzinger et al. Lancet Neurol. 2013 Jul; 12(7): 716–726.

Offending Medications

Table 3. Common medications associated with adverse cognitive effects.

Drug Class	Examples
Anticholinergics	
Tricyclic antidepressants	Amitriptyline, nortriptyline
First generation antihistamines	Diphenhydramine, hydroxyzine
Bladder antimuscarinics	Oxybutynin, trospium
Antipsychotics	Fluphenazine
Antimuscarinic spasmolytic	Atropine, hyoscyamine
Antiemetics	Meclizine
Muscle relaxants	Tizanidine
Anti-Parkinson	Benztropine, trihexyphenidyl
Benzodiazepines	Alprazolam, clonazepam, diazepam, lorazepam
Opioids	Codeine, hydrocodone, morphine, oxycodone, tramadol, methadone, fentanyl

This table is non-exhaustive.

Sun C, Armstrong MJ. *Behav Sci (Basel)*. 2021;11(4):54.

PD Dementia: Medications

PD Dementia Medications				
Drug class	Drug/Typical dose	Efficacy	Common Adverse Effects	Practice implications
Dementia				
Acetylcholinesterase inhibitors	**Donepezil** 5-10 mg/day	Insufficient evidence	Nausea, diarrhea, vomiting, cramping, weight loss Severe: Cardiac/GI complications	*Possibly useful*
	Rivastigmine Capsule: 3-12 mg/day Patch: 4.6-13.3 mg/day	Efficacious	Capsules: Nausea, Vomiting, weight loss Patch: nausea, vomiting, falls Severe: Cardiac/GI complications	Clinically useful
	Galantamine 8-24mg/day	Insufficient evidence	Nausea, vomiting, diarrhea Severe: SJS, seizure, GI	*Possibly useful*
N-methyl-D-aspartate (NMDA) antagonists	**Memantine** 10 mg twice daily ER: 28 mg/day	Insufficient evidence	Dizziness, HA, Diarrhea, constipation, confusion Severe: stroke, seizure, renal failure	Investigational

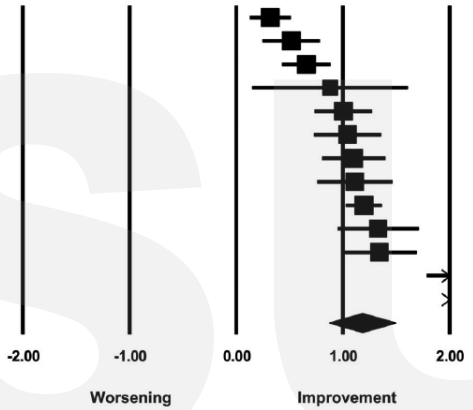
Others are investigational: rasagiline and atomoxetine; cognitive rehabilitation; brain stimulation

Adopted in part from:
Seppi K, Ray Chaudhuri K, Coelho M, et al. *Mov Disord*. 2019;34(2):180–198.

ECT in PD

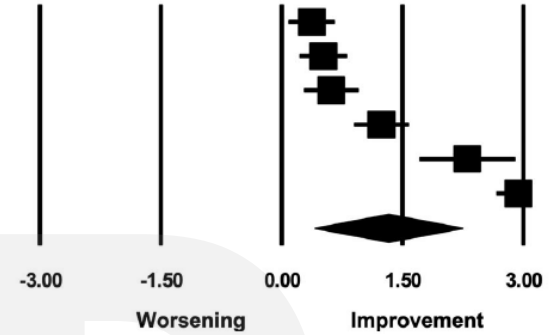
Motor

	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Anderson et al. (1987)	0.318	0.098	0.127	0.510	3.256	0.001
Fall et al. (2000)	0.515	0.137	0.246	0.785	3.751	0.000
Pintor et al. (2012)	0.657	0.116	0.429	0.884	5.650	0.000
Pridmore et al. (1995)	0.880	0.372	0.150	1.610	2.363	0.018
Usui et al. (2011)	1.004	0.137	0.735	1.273	7.323	0.000
Grover et al. (2018)	1.044	0.160	0.730	1.359	6.507	0.000
Douyon et al. (1989)	1.100	0.151	0.803	1.397	7.264	0.000
Ueda et al. (2010)	1.111	0.180	0.759	1.464	6.178	0.000
Calderón-Fajardo et al. (2015)	1.197	0.086	1.028	1.366	13.856	0.000
Birkett. (1991)	1.331	0.184	0.950	1.711	6.852	0.000
Williams et al. (2017)	1.342	0.178	0.993	1.691	7.541	0.000
Fall et al. (1995)	2.059	0.140	1.785	2.332	14.745	0.000
Nishioka et al. (2014)	3.647	0.437	2.790	4.504	8.339	0.000
	1.181	0.157	0.873	1.489	7.509	0.000



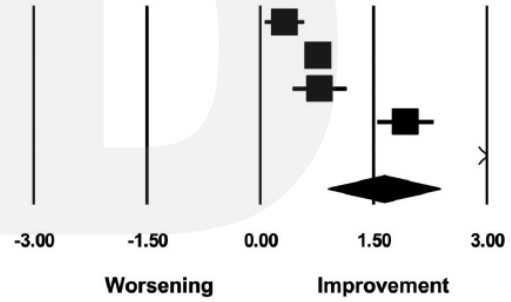
Depression

	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Birkett. (1991)	0.375	0.146	0.088	0.662	2.563	0.010
Ueda et al. (2010)	0.518	0.151	0.223	0.814	3.442	0.001
Nishioka et al. (2014)	0.615	0.172	0.277	0.953	3.565	0.000
Williams et al. (2016)	1.239	0.172	0.902	1.575	7.218	0.000
Grover et al. (2018)	2.305	0.302	1.712	2.897	7.623	0.000
Calderón-Fajardo et al. (2015)	2.940	0.140	2.665	3.215	20.941	0.000
	1.325	0.464	0.415	2.235	2.852	0.004



Psychosis

	in means	error	limit	limit	Z-Value	p-Value
Williams et al. (2017)	0.318	0.132	0.059	0.578	2.406	0.016
Calderón-Fajardo et al. (2015)	0.763	0.069	0.627	0.898	11.031	0.000
Nishioka et al. (2014)	0.785	0.181	0.430	1.139	4.340	0.000
Usui et al. (2011)	1.921	0.189	1.551	2.290	10.186	0.000
Ueda et al. (2010)	5.846	0.601	4.667	7.025	9.720	0.000
	1.637	0.378	0.897	2.377	4.335	0.000



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Resources

- Parkinson's Foundation MIND guide: Cognition

Cognition: A Mind Guide to Parkinson's Disease | Parkinson's Foundation

- Parkinson's Resources of Oregon

Numerous resources for wellness, support groups, exercise, mindfulness, etc

- Davis Phinney Foundation: https://davisphinneyfoundation.org/resources/

- Brian Grant Foundation:
  - Journaling Together - A stand alone class offered monthly.
  - MBSR Course - Next 8-week session starts Oct '24.
  - Breath by Breath - A weekly meditation class every Tuesday at 12pm PT.

- UCSD Center for Mindfulness (guided mindfulness meditations):

https://medschool.ucsd.edu/som/fmph/research/mindfulness/programs/mindfulness-programs/MBSR-programs/Pages/audio.aspx

- "Living with Parkinson's Disease: A Complete Guide for Patients and Caregivers" by Michael Okun

- Rock Steady Boxing: Home - Rock Steady Boxing

- Tai Chi classes in Oregon: Oregon Health Authority : Tai Chi: Moving for Better Balance : Falls Prevention for Older Adults : State of Oregon

NTMHC Parkinson's Neuropsychiatry Consultation

The Parkinson's Disease Neuropsychiatry Telehealth Program within the National TeleMental Health Center (NTMHC) has expert clinicians have availability to see any of your Veterans with psychiatric and cognitive complications of Parkinson's disease.

- Dr. Dan Weintraub (VA Philadelphia) & Dr. Joel Mack (VA Portland)

- The NTMHC Parkinson's Disease Neuropsychiatry Telehealth Program has the ability to:

1. Conduct telehealth video-consultations with Veterans either in clinic or via VVC into the home
2. Provide e-consultations to providers who work across inpatient or outpatient settings
3. Answer any questions via the 'Ask The Expert' emails: AskTheExpert-ParkinsonsDiseaseNeuropsychiatry@va.gov

Parkinson's Disease
Research, Education & Clinical Center
Northwest VA PADRECC

Thank You

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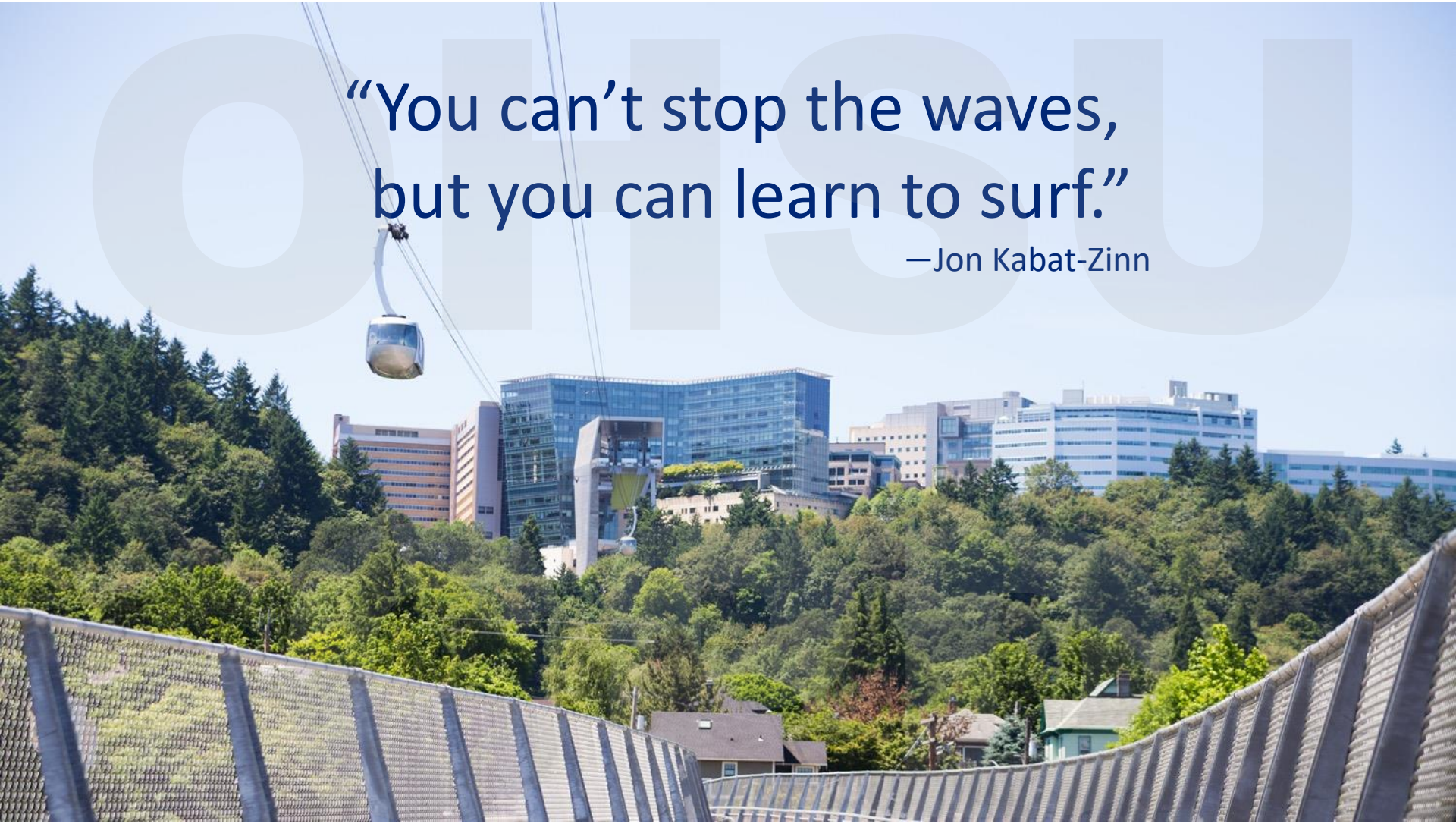
“You can’t stop the waves,
but you can learn to surf.”
—Jon Kabat-Zinn