Psych Congress

TAKING A TEAM APPROACH TO PARKINSON DISEASE PSYCHOSIS:

Evolving Strategies for Patients With or Without Dementia

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Faculty Disclosures

- **Dr. Citrome:** Consultant—AbbVie/Allergan, Acadia, Adamas, Alkermes, Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, INmune Bio, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, Medavante-ProPhase, Marvin, Merck, Mitsubishi-Tanabe Pharma, Neurocrine, Neurelis, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, University of Arizona, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; Speaker's Bureau—AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; Stocks—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer, Reviva [options]; Royalties/Publishing— Taylor & Francis, Wiley, UpToDate, Springer Healthcare, Elsevier

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- **Dr. Kathleen Woschkolup:** Speaker's bureau—Acadia

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

Learning Objectives

- Describe the pathophysiology, burden, risk factors, and clinical presentation of PDP with or without dementia
- Utilize appropriate clinical assessment/evaluation tools for the early identification and care of patients with PDP
- Evaluate the safety/efficacy data and clinical indications for current and emerging therapies for PDP
- Implement collaborative multidisciplinary partnerships (ie, between neurology and psychiatry) to ensure optimal patient care for both PD and PDP.

Overview of Parkinson Disease (PD) and Parkinson Disease Psychosis (PDP)

What is Parkinson Disease?

- Parkinson disease (PD) was first described by Dr. James Parkinson in 1817 as “shaking palsy” with progressive degenerative effects on mobility and muscle control
- Motor symptoms of PD are attributed to the loss of striatal dopaminergic neurons
- Nonmotor symptoms are attributed to neuronal loss in nondopaminergic areas
  - Pathophysiological changes associated with PD may start before the onset of motor features and include nonmotor presentations, such as sleep disorders, depression, and cognitive changes
- Cause of PD remains unknown but certain gene variations can increase risk, as can some environmental triggers
- Risk factors: age, heredity, male sex, ? exposure to toxins

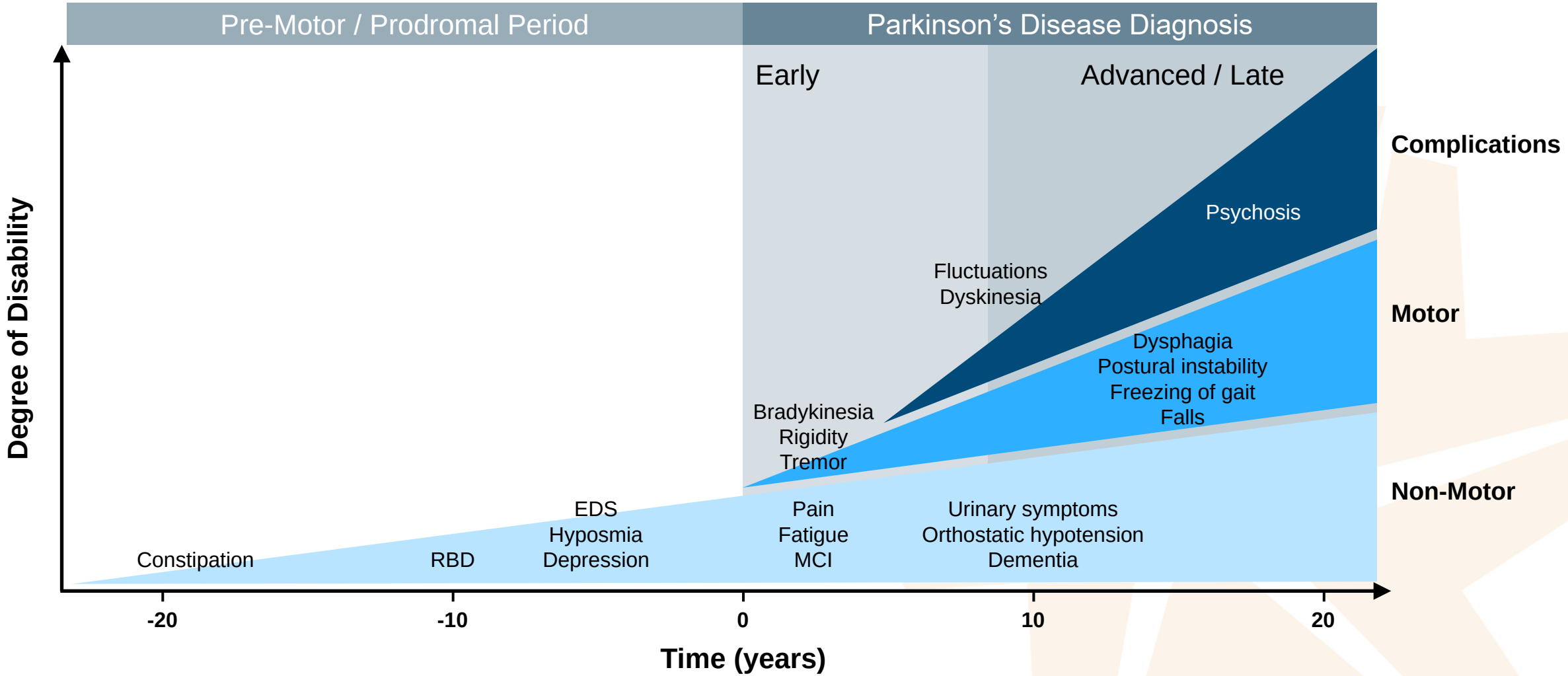
DeMaagd G, Philip A. P&T 2015;40(8):504-510, 532; Bellou V, et al. Parkinsonism Relat Disord. 2016;23:1-9.

How Common is Parkinson Disease?

- One of the most common neurodegenerative disorders with about **1 million Americans** currently having the disease
- Incidence of PD in the U.S. ~20 cases per 100,000 people per year and prevalence **~1% in people 60 years of age and older** and increases to 1% to 3% in the 80-plus age group
- Mean **age of onset ~60 years**, gender (M:F) ratio 3:2
- **Neuropsychiatric complications**, including psychosis, depression, anxiety, and sleep-related disorders, are associated with PD
  - Impulse-control disorders in PD patients usually result from the use of dopamine agonists

DeMaagd G, Philip A. P&T 2015;40(8):504-510, 532.
DeMaagd G, Philip A. P&T 2015;40(12):838-846.

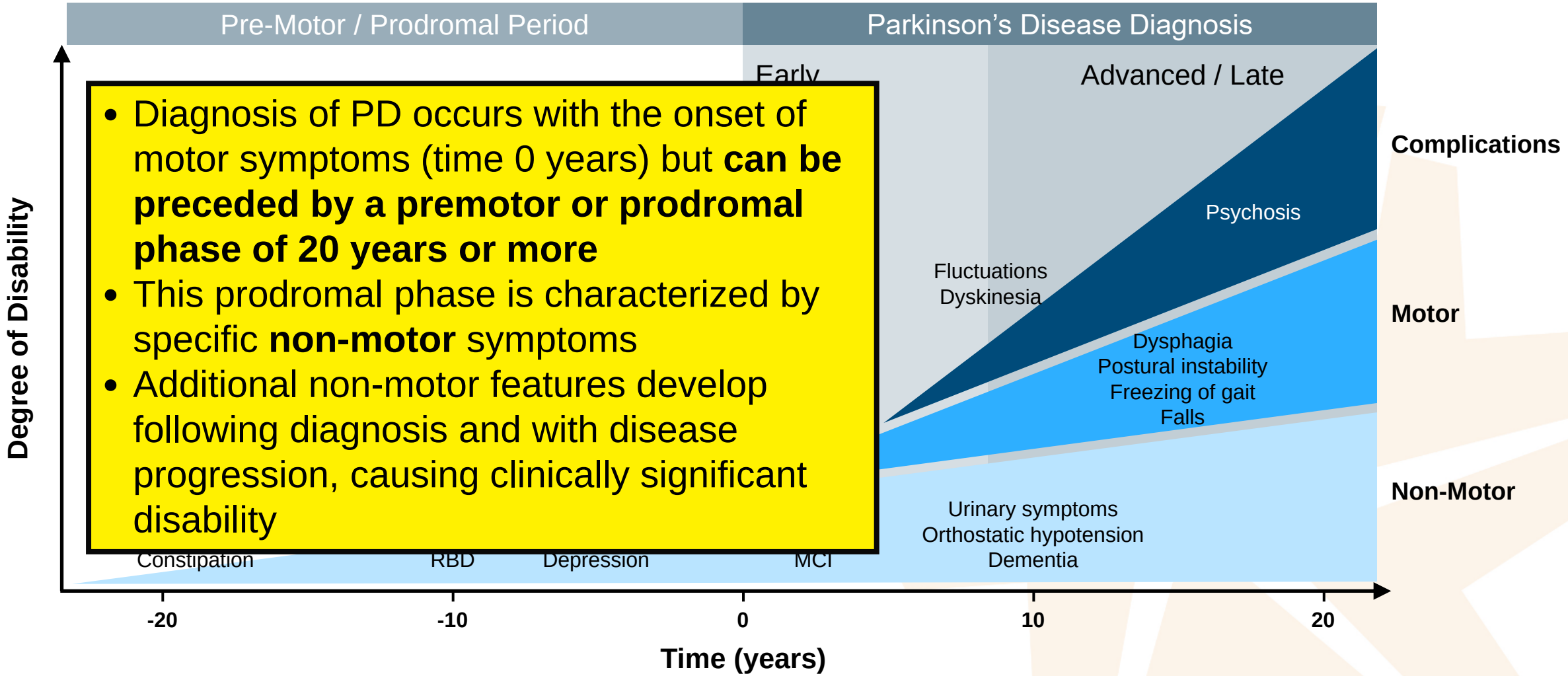
Parkinson Disease:
Clinical Symptoms and Time Course of Disease Progression



EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behavior disorder

Kalia LV, Lang AE. Lancet. 2015; 386: 896-812.

Parkinson Disease:
Clinical Symptoms and Time Course of Disease Progression



- Diagnosis of PD 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 characterized by specific **non-motor** symptoms
- Additional non-motor features develop following diagnosis and with disease progression, causing clinically significant disability

EDS=excessive daytime sleepiness. MCI=mild cognitive impairment. RBD=REM sleep behavior disorder

Kalia LV, Lang AE. Lancet. 2015; 386: 896-812.

Parkinson Disease and Sleep Disorders

- PD patients often experience **sleep problems**, such as rapid eye-movement sleep behavior disorders (RSBDs), vivid dreams, restless legs syndrome, insomnia, and excessive daytime somnolence
- RSBDs involve abnormal behavior or other features that occur during the rapid-eye-movement phase of sleep, such as atonia, twitches, ocular movements, and the acting out of dreams
- Brain pathologies appear to be related to RSBDs, which have been studied as possible early markers of PD
- Excessive daytime sleepiness (EDS) and sudden-onset sleep can occur in PD
- The presence of these disorders is further complicated by “sleep attacks” associated with the use of dopamine agonists

DeMaagd G, Philip A. P&T 2015;40(12):838-846.

Parkinson Disease and Depression

- Up to **90%** of PD patients experience depression, which can occur in both early and advanced disease
- **Dopaminergic losses** may be associated with PD-related depression, based on the observation that depressive features can occur during “off” time, hence the rationale for the dopamine agonist **pramipexole** and pergolide (no longer available)
- Traditional antidepressant agents, including TCAs and SSRIs have also been studied in PD patients with depression
  - SSRIs can contribute to tremor and increase the risk of serotonin syndrome in PD patients receiving MAO-B inhibitors
  - TCAs increase the risk of anticholinergic adverse effects

DeMaagd G, Philip A. P&T 2015;40(12):838-846.

Parkinson Disease and Dementia

- **Up to 75%** of PD patients experience cognitive impairment and dementia
- Pathology involves the degeneration of cortical and subcortical regions, resulting in dopamine and cholinergic dysmodulation along with the formation of Lewy bodies
- Most PD patients with cognitive impairment experience cognitive symptoms during advanced stages of their disease
- Clinical presentations of PD-related dementia include problems with working memory, learning, and planning
- Typically, the onset of dementia in PD patients **occurs after motor symptoms** have been present for at least one year
- **Rivastigmine** (Exelon, Novartis) is approved for use in PD patients with mild-to-moderate dementia

DeMaagd G, Philip A. P&T 2015;40(12):838-846.

Parkinson Disease Psychosis

- **Up to 60%** of patients with PD experience psychotic symptoms for at least one month at some point during the course of their illness
- PDP is characterized by **hallucinations** (often visual), and **delusions** (typically paranoid, such as spousal infidelity), as well as illusions and a false sense of presence
- The **burden** of PDP is substantial for both the patient and the caregiver; PDP is a common reason for hospital admission, nursing home placement, and increased **mortality**
- Often comorbid with **cognitive decline** and **dementia**
- **Pimavanserin** (Nuplazid, Acadia) is approved for use to treat hallucinations and delusions associated with PD psychosis

Citrome L, et al. CNS Spectr. 23(3):228-238.

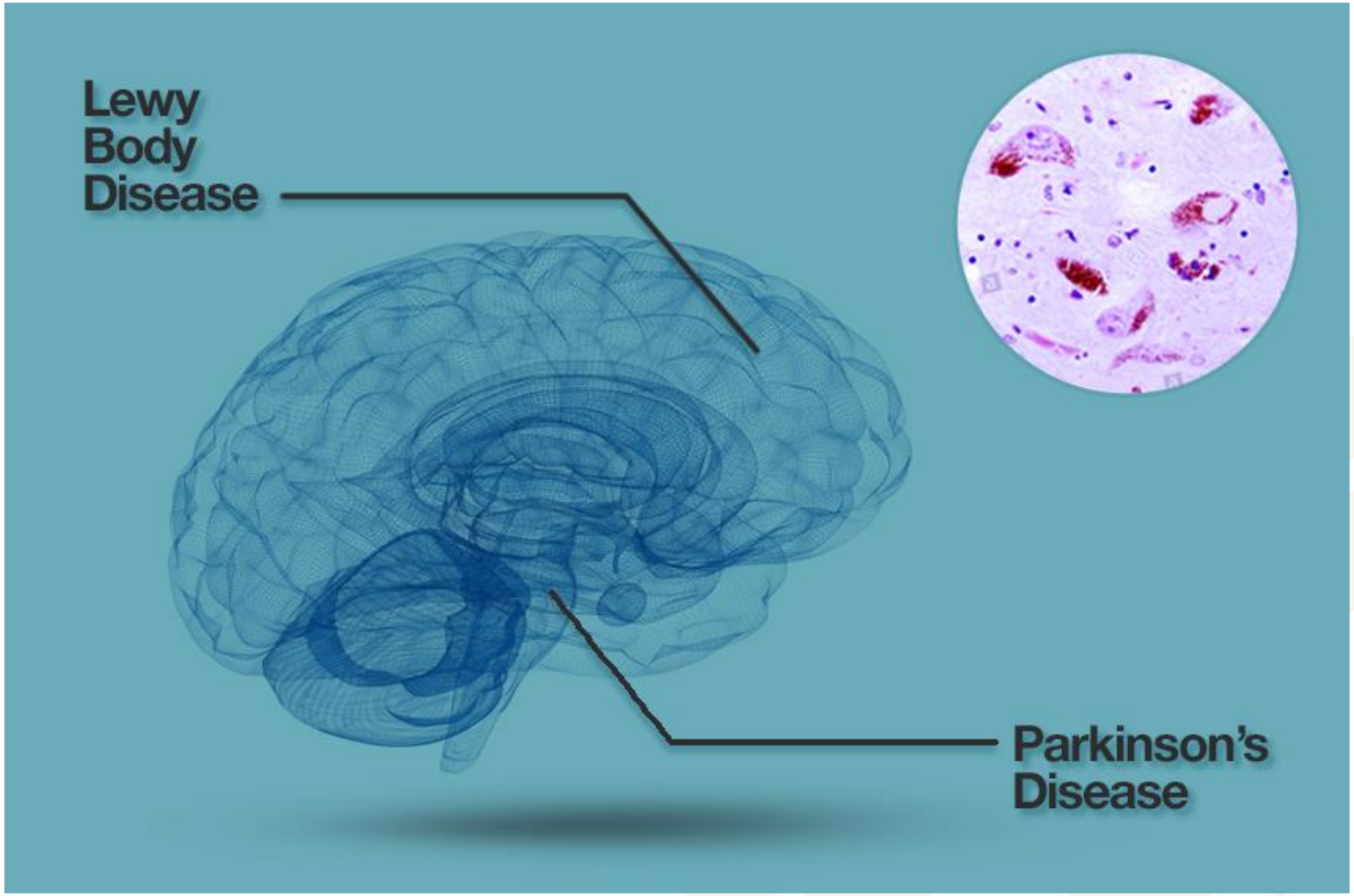
Parkinson Disease Psychosis

The psychotic symptoms associated with PD are not necessarily related to dopaminergic or anticholinergic medications

Fénelon G, et al. Mov Disord. 2010;25(6):763-766; Ravina B, et al. Mov Disord. 2007;22(8):1061–1068.

Parkinson Disease: Lewy Bodies in the Substantia Nigra = Motor Symptoms
Lewy Bodies Elsewhere = Other Symptoms!

Lewy bodies are abnormal aggregates of protein (principally **α-synuclein**) that develop inside neurons, contributing to PD and Lewy body disease



Accessed Sept.14, 2022:
https://www.lewybody.org/about-dlb/science/

Assessing PDP in Clinical Practice

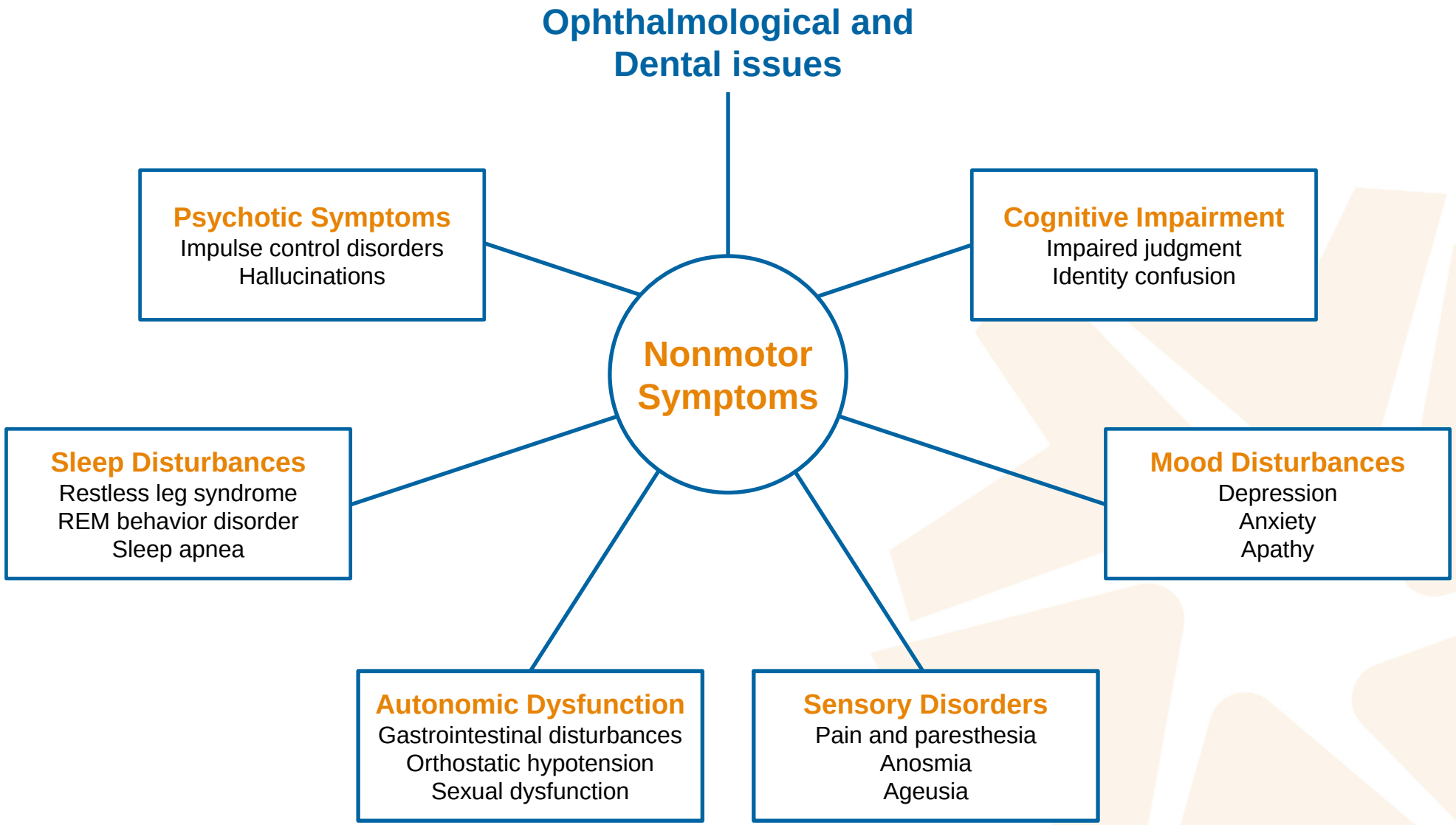
Parkinson's Disease Motor & Non-motor Symptoms

The most recognized symptoms of PD are motor symptoms

- **T**remor
- **R**igidity/stiffness
- **A**kinesia/slowness of movement
- **P**ostural instability/trouble with balance

- Non-motor symptoms
  - Are experienced by the majority of people with PD[2-5]
  - Non-motor symptoms can be more troublesome than motor symptoms in terms of quality of life[3]

1. Olanow C, et al. In: Kasper D et al, eds. ***Harrison's Principles of Internal Medicine.*** 19th ed. New York, NY: McGraw-Hill; 2015. http://accessmedicine.mhmedical.com/content.aspx?bookid=1130&Sectionid=79755616. Accessed February 7, 2017.
2. Martinez-Martin P, et al. *Mov Disord.* 2011;26(3):399-406.
3. Forsaa EB, et al. *Arch Neurol.* 2010;67:996-1001.
4. Chaudhuri KR, et al. *Mov Disord.* 2006;21:916-923.


Ophthalmological and Dental issues
Psychotic Symptoms
Impulse control disorders
Hallucinations
Cognitive Impairment
Impaired judgment
Identity confusion
Nonmotor Symptoms
Sleep Disturbances
Restless leg syndrome
REM behavior disorder
Sleep apnea
Mood Disturbances
Depression
Anxiety
Apathy
Autonomic Dysfunction
Gastrointestinal disturbances
Orthostatic hypotension
Sexual dysfunction
Sensory Disorders
Pain and paresthesia
Anosmia
Ageusia

NIMH Diagnostic Criteria

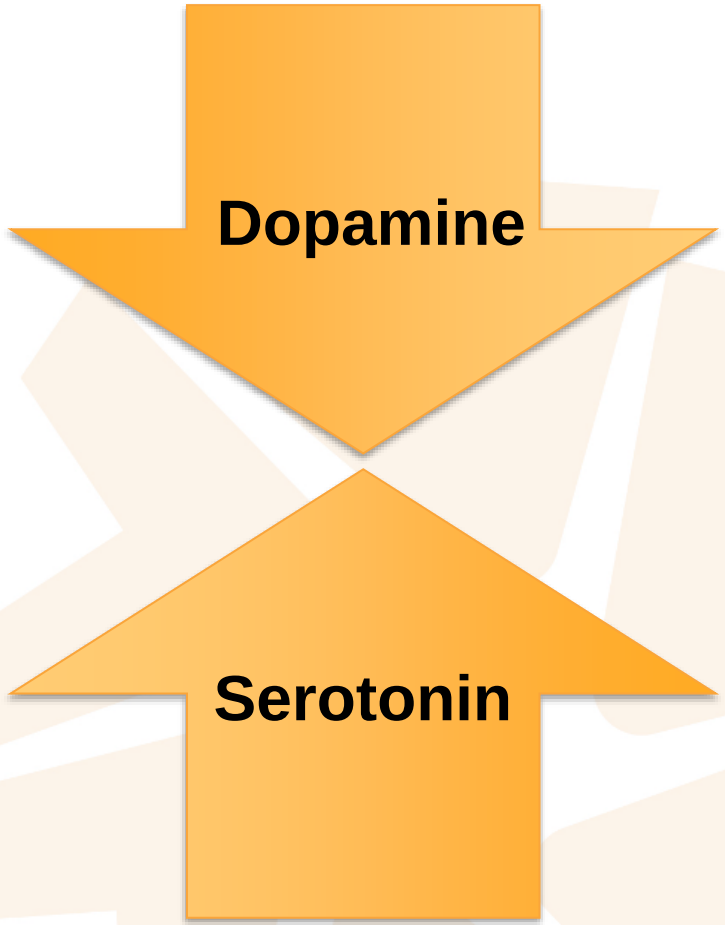
- United Kingdom PD Society Brain Bank Criteria:
  - Bradykinesia
  - Plus one other cardinal feature:
    - Rest tremor
    - Rigidity
    - Postural instability
      - Not visual, vestibular, cerebellar or sensory

- Supportive features:
  - Rest tremor
  - Unilateral onset and persistent asymmetry
  - Progressive, disease course > 10 years
  - L-dopa responsiveness, response > 5 years, severe dyskinesia
  - Response to L-dopa, L-dopa induced dyskinesia, >5 year L-dopa response
  - Absence of atypical features

Risk Factors for Psychosis in PD

- Older age
- Greater severity of illness
- Longer duration of illness
- Axial rigidity subtype of PD
- Idiopathic PD
- Underlying dementia, delirium or depression
- Presence of sleep disturbance
- Use of dopaminergic agenda

About 50% of people with PD may develop hallucinations and/or delusions at some point during the course of their disease[1]



1. Forsaa EB, et al. *Arch Neurol.* 2010;67:996-1001.

Risk Factors For PD Psychosis

- Dehydration
- Change in vision/hearing
- Medications
- Infection (ie, urinary tract infection or pneumonia)
- Some PD medications (levodopa or dopamine agonists) or other medications (anticholinergics)
- Alcohol or other recreational drugs
- Dim lighting or time of day
- Poor quality of sleep
- Change in environment

Diagnosing Parkinson Disease Psychosis

TABLE 1. NINDS and NIMH Work Group Diagnostic Criteria for Parkinson Disease Psychosis[11]

1. The presence of at least 1 of the following symptoms of psychosis: illusions, false sense of presence, hallucinations, or delusions
2. A primary diagnosis of Parkinson disease
3. Symptoms of psychosis occur after onset of Parkinson disease
4. The duration of symptoms of psychosis are recurrent or continuous for at least 1 month
5. Symptoms of psychosis are not accounted for by another cause of parkinsonism, including dementia with Lewy bodies, psychiatric disorders (such as schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features), or a general medical condition, such as delirium

NINDS, National Institute of Neurological Disorders and Stroke; **NIMH**, National Institute of Mental Health

Hallucinations

Common Hallucinations in PDP

Infidelity/Jealousy

Impression partner is cheating on you

Persecutory

Impression of someone trying to harm, steal from, or deceive you

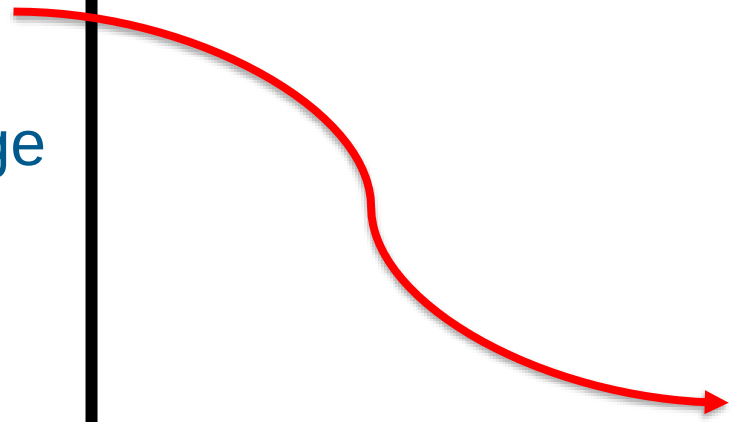
Reference

Believing a song or TV show is speaking to you directly

PDP : Variable and Progressive

Early Symptoms

- Insight is retained
- Illusions
- Feelings of passage or presence
- Hallucinations



Later Symptoms

- Insight is lost
- Complex hallucinations
- Delusions

Importance of Early Recognition/Diagnosis

- Hallucinations and delusions in PD are associated with **increased burden and emotional distress** for caregivers[2,3]

- In one study, motor complications were the primary reason for hospitalizations of people with PD, hallucinations and delusions were responsible for **nearly 25%** of hospitalizations[1]

Klein C, et al. *J Neural Transm.* 2009;116:1509-1512.

Need For Emerging Clinical Diagnostic Tools

2008 Movement Disorders Society (MDS) task force report: Weakness and strengths for several psychosis scales and questionnaires. No one scale is ideal when assessing PDP. Suggesting a need for the creation of a new scale.

NPI (Neuropsychiatric Inventory):

- Easy to administer and capture a wide range of symptoms.
- Separates severity from frequency
- Limited in application in patients with dementia
- Minor phenomena and illusions are excluded from survey but present in PDP

BPRS (Brief Psychiatric Rating Scale):

- 20-30 mins to administer
- Items associated with PDP include hallucinatory behavior, suspiciousness, and unusual thought content
- Most used in studies involving antipsychotics in PDP
- Lacks insight into common hallucinatory phenomena in PDP

SAPS-H+D Scale (Scale Assessment of + Symptoms-Hallucinations and Delusions)

- Length makes it difficult to administer in appts
- Excludes illusions and other common phenomena in PDP
- Does not accurately reflect responses from those with dementia or cognitive impairment

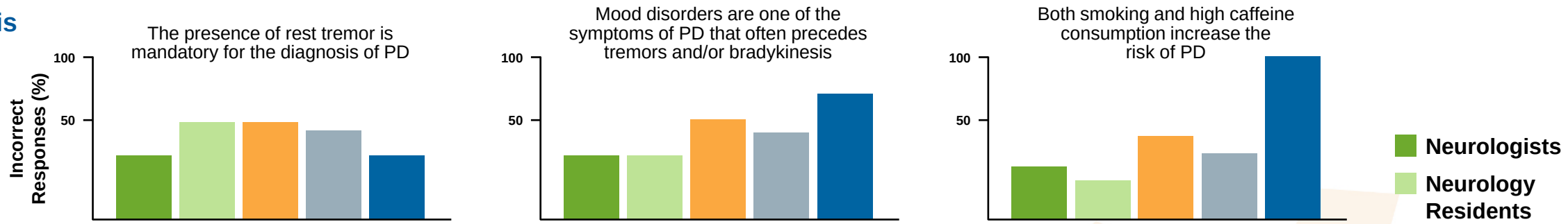
Biomarkers

- Neuropsychiatric symptoms in PD are common but etiology is poorly understood.
- Biomarkers for neurodegeneration: **Plasma Neurofilament A**
- Biomarker for Tau pathology: **p-Tau181**
- Baseline plasma NfL was a significant predictor of psychotic symptoms and shorter time to develop psychosis (after adjusting for other risk factors such as age, disease duration, H&Y stage, baseline cognition).
- Plasma p-Tau 181 was not associated with psychosis

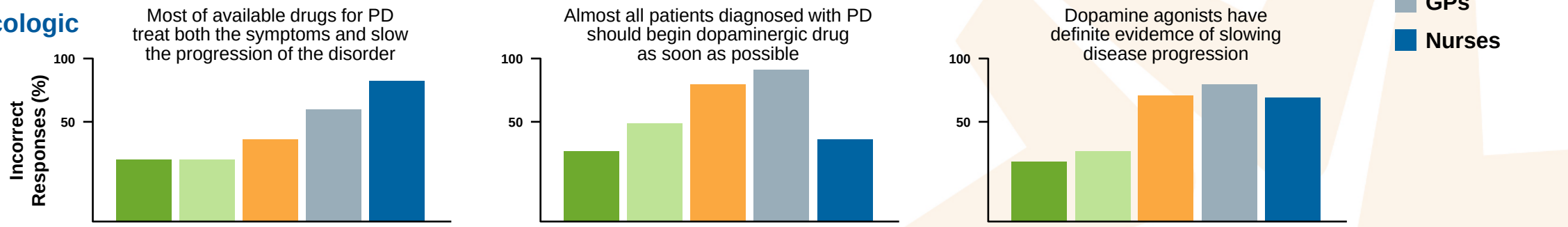
- **Conclusion: Psychotic symptoms in PD are associated with greater neurodegeneration in PD. No association with PDP and Tau.**
- **More research is needed to explore NfL as a biomarker for psychosis**

J.Parkinsons dis. 2022;12(5):1527-1538. doi: 10.3233/JPD-223182.

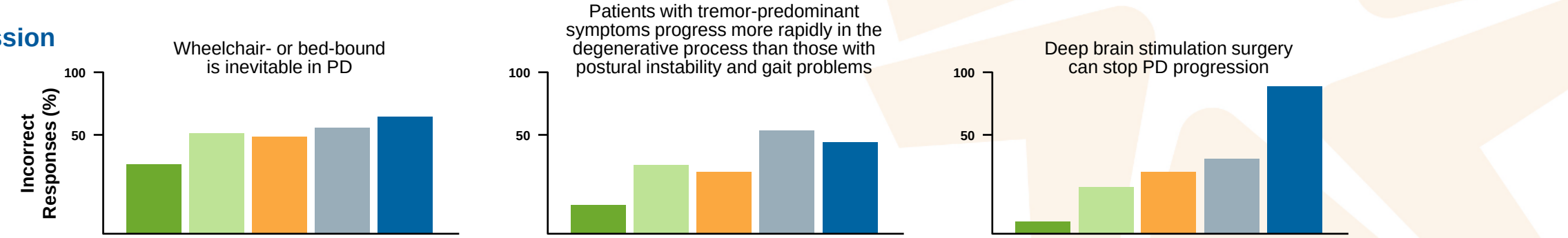
A.
PD Diagnosis



B.
PD Pharmacologic Options



C.
PD Progression



Roongroj B, et al. First published June 16, 2014, DOI: https://doi.org/10.1212/WNL.0000000000000515

Educating Patients and Caregivers

~80% to 90% of people do not voluntarily report their hallucinations and/or delusions to their healthcare provider[1,2]

If you sense or experience something unusual, ask your loved one if they perceived the same thing[3,4]

If your loved one describes or interacts with something that you don't perceive, ask questions to understand what they are experiencing

If you fear or believe that a loved one is deceiving you, speak up[3,4]

If your loved one accuses you of deceiving them, don't stay silent, speak to your healthcare provider[3,4]

1. **Fénelon G, Alves G. *J Neurol.* 2010;289:12-17.**
2. **Fénelon G, et al. *Brain*. 2000;123:733-745.**
3. **Ondo WG, et al. *J Clin Mov Disord.* 2015;2(17):1-7.**
1. **Ravina B, et al. *Mov Disord.* 2007;22:1061-1068.**

Normalize The Topic

- Ask patients about hallucinations and delusions and encourage them to speak up.
- Hallucinations and delusions are NOT dementia or Alzheimer’s and are NOT vivid dreams or problems with sleep
- Patients and caregivers may be confused or unsure how to describe what is happening.
- Seeing ghosts, realistic dreams (to describe hallucinations) or could talk about confusion or dementia (to describe delusions).

Make A Plan With Your Patient

- Ask about how these hallucinations impact their lives.
- Ask caregivers how it impacts life at home.
- It is important to track symptoms over time and discuss your treatment options from day one.
- What to do and to avoid if symptoms progress emergently.

This will not go away.

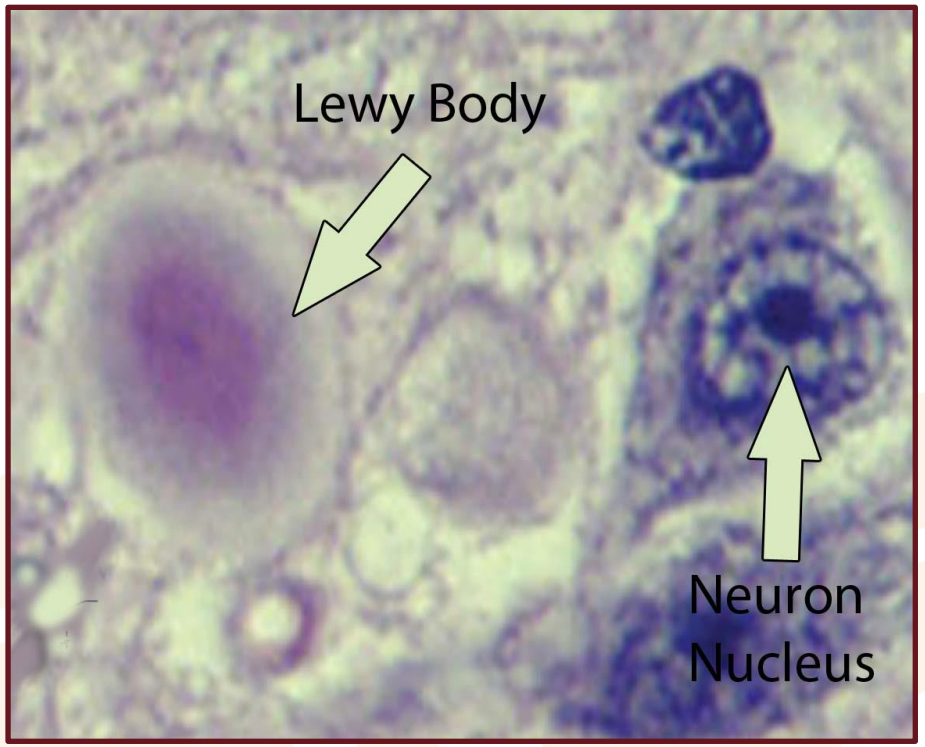
It will continue to progress over time.

Treatment will minimize the symptoms but may not make them disappear.

Current Treatment Options for Parkinson Disease Psychosis

Parkinson Disease Psychosis as a Serotonin-Dopamine Imbalance Syndrome

- PDP may be caused in part by deposition of **Lewy bodies** in the cerebral cortex that hypothetically disrupt both serotonin and dopamine neurotransmission, with **upregulation and overstimulation of cortical 5HT2A receptors** and **excessive release of downstream dopamine in mesolimbic brain circuits**
- **Blocking** hypothetically excessive serotonin neurotransmission at **5HT2A** receptors in patients with PDP theoretically restores the balance between serotonin and dopamine, reducing visual hallucinations and delusions without worsening motor symptoms
- **Blocking dopamine receptors directly can worsen the motor symptoms of PD**



Stahl SM. CNS Spectr. 2016; 21: 355-359; Rietdijk CD, et al. Front Neurol. 2017; 8: 37.

The Double Bind

- Despite the inconsistencies in literature that link PD medications to the symptoms of PDP, minimizing the effects of dopaminergic drugs and other contributing medications remains a central component of the initial PDP assessment and management process
- **However, addressing psychosis symptoms by reducing or eliminating medications that are intended to alleviate motor problems often results in the dilemma of choosing between an improvement in mobility or psychosis**
- Ideally, a management strategy would involve treatments that maintain or prevent worsening of motor issues while reducing hallucinations and delusions
- Unfortunately, the majority of antipsychotic medications worsen motor symptoms of PD

Hermanowicz N, et al. J Manag Care Spec Pharm. 2017;23(6-b Suppl):S2-S8.

When To Treat?

- For patients with PD and new onset PDP or an abrupt worsening of PDP symptoms, review ALL medications (is this an anticholinergic delirium?) and consider other acute or underlying illness (such as infection) as possible provocative factors

- Decision regarding when to initiate treatment requires a discussion between the provider, patient, and patient's spouse/caregiver
  - Thorough history of the occurrence and frequency of hallucinations and delusions and their perceived impact on patient and caregiver quality of life currently and within the near future
  - PDP symptoms that are reported by the patient and caregiver to be infrequent and not disturbing do not necessarily require treatment, **but the natural history of escalation of these symptoms should be given consideration**, and a plan for treatment should be arranged to account for the potential for the PDP symptoms to become problematic before the next scheduled visit

Hermanowicz N, et al. J Manag Care Spec Pharm. 2017;23(6-b Suppl):S2-S8.

Life Before Pimavanserin: Off-Label Antipsychotics for Parkinson's Disease Psychosis
Dopamine Antagonism Can Worsen Movement Disorders

Antipsychotic[1,2]	Efficacy Conclusion[1,2]	Safety Conclusion[1,2]
Clozapine[a]	Efficacious	Acceptable risk with specialized monitoring
Quetiapine[b]	Insufficient Evidence	Acceptable risk without specialized monitoring
Olanzapine[c]	Unlikely efficacious	Unacceptable risk

[a]Efficacy and safety evidence reviewed from 4 randomized controlled trials (n=142 patients).
[b]Efficacy and safety evidence reviewed from 6 randomized controlled trials (n=103 patients).
[c]Efficacy and safety evidence reviewed from 3 randomized controlled trials (n=104 patients).

1.Seppi K, et al. Mov Disord. 2011;26:S42-580.
2.Goldman JG, et al. Expert Opin Pharmacother. 2011;12:2009-2024.

Pimavanserin (PIM): What's Different

- PIM is a **highly selective** *serotonin 5-HT2A receptor inverse agonist/antagonist*
- Approved in the US in April 2016 for the treatment of hallucinations and delusions associated with PDP
- Because PIM has **no measurable activity at dopaminergic**, histaminergic, adrenergic, or muscarinic receptors, this would predict a favorable tolerability profile in that motor symptoms would not be expected to worsen, and urinary retention, constipation, sedation, weight gain, akathisia, and postural hypotension would not be expected obstacles to using PIM
- The recommended dose is 34 mg taken once daily, any time of day, with or without food; titration is not necessary

Citrome L, et al. CNS Spectr. 23(3):228-238.

Pimavanserin Pharmacodynamic Profile

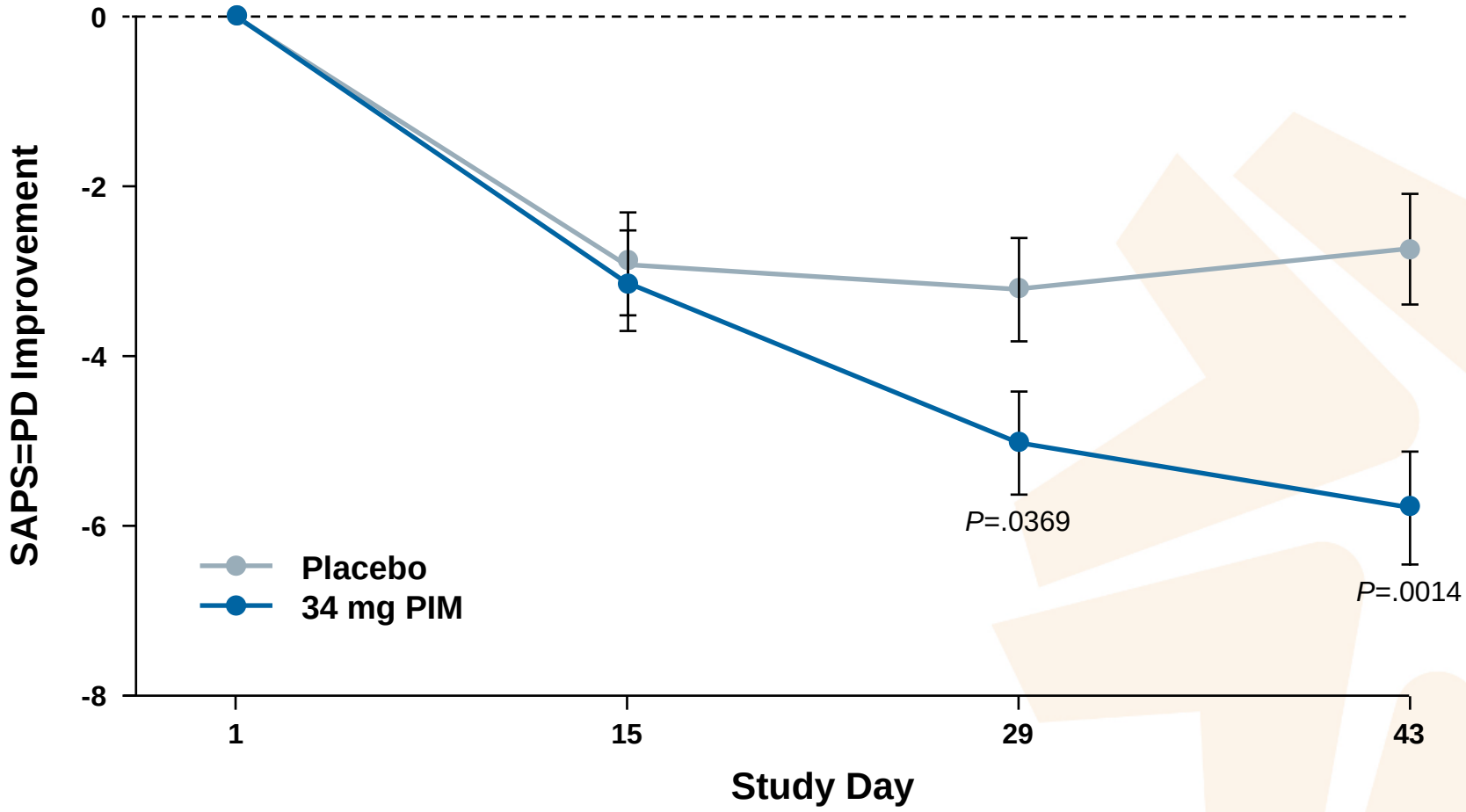
High Selectivity for 5-HT_{2A} Receptor

Receptor	Side Effects	Pimavanserin	Clozapine	Olanzapine	Quetiapine	Risperidone
5-HT_{2A}		0.4	**7**	**2.5**	250	**0.2**
5-HT_{2B}		—	40	80	1100	12
5-HT_{2C}		16	40	80	—	100
5-HT_{1A}		—	—	—	—	—
H1	Sedation	—	**0.5**	**4**	**5**	60
M1	Sialorrhea Urinary Retention	—	16	60	250	—
M2		—	—	150	ND	—
M3		—	**6**	250	200	—
M4		—	—	40	150	—
M5		—	30	60	ND	—
D1		—	250	100	ND	60
D2	EPS+Prolactinemia	—	50	**4**	30	**0.5**
D3		—	200	25	9	13
Alpha 1A	Orthostatic Hypotension	—	**8**	100	ND	**3**
Alpha 1D		—	150	—	—	50
Alpha 2A		—	300	—	—	20
Alpha 2B		—	50	—	—	50
Alpha 2C		—	40	—	—	13

Data are Ki values in nM derived from functional antagonist R-SAT TM assays. "—" denotes no response.

ND = Not Done. Derived from Hacksell et al. 2014; data on file. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM493998.pdf

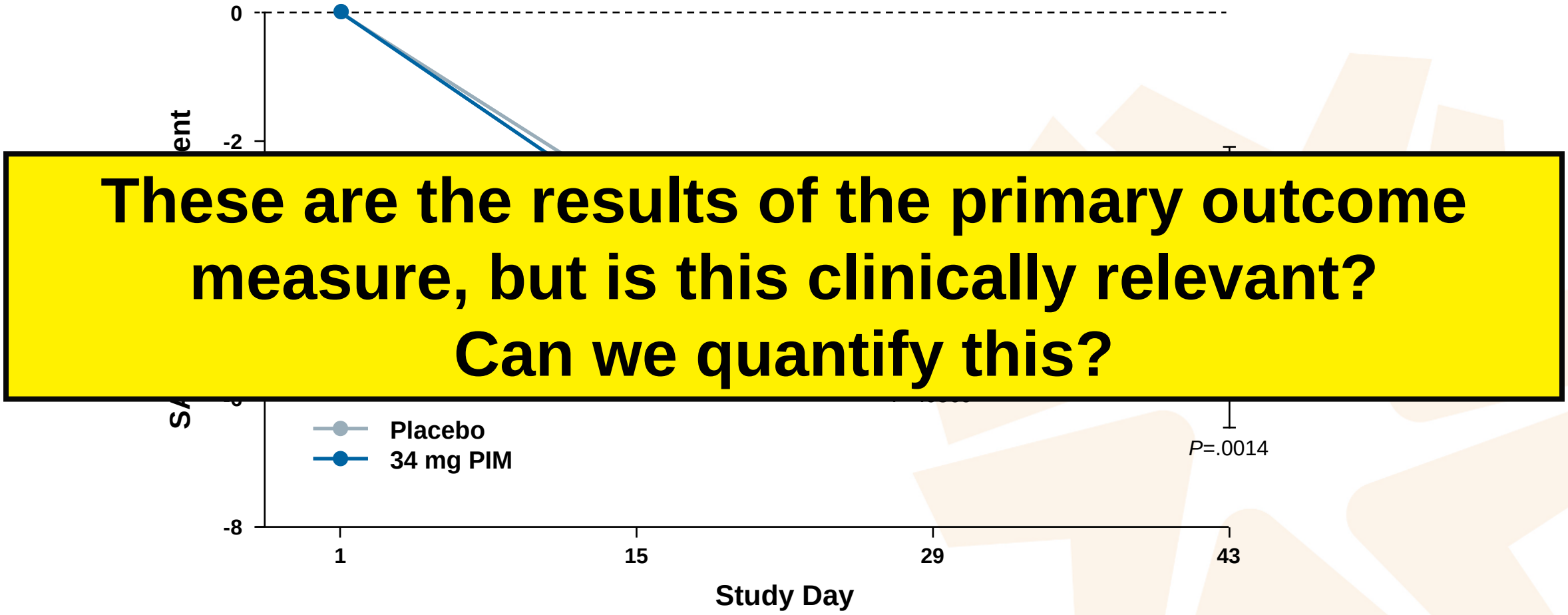
Pimavanserin (PIM) 34 mg versus Placebo (PBO): 6 Week RCT



SAPS = scale for assessment of positive symptoms.

Cummings J, et al. Lancet. 2014; 383: 533-540.

Pimavanserin (PIM) 34 mg vs Placebo (PBO): 6 Week RCT



These are the results of the primary outcome measure, but is this clinically relevant? Can we quantify this?

SAPS = scale for assessment of positive symptoms.

Cummings J, et al. Lancet. 2014; 383: 533-540.

Concepts Related To Benefit / Risk:
Effect Size - Number Needed To Treat

- NNT is one measure of effect size
- It is independent of p-value and does not say anything about the likelihood of the difference between treatments being due to chance alone
- Helps you judge the clinical significance of a statistically significant result

Citrome L. Acta Psychiatr Scand. 2008;117(6):412-419

Number Needed To Treat

- How many patients would you need to treat with Drug A instead of Drug B before you would encounter one extra outcome of interest, such as response

The smaller the NNT, the larger the differences between the two drugs

Citrome L. Acta Psychiatr Scand. 2008;117(6):412-419

What Is NNH?

- NNH is Number Needed to Harm
- We would use NNH when referring to an outcome we are trying to avoid, such as a side effect

Citrome L. Acta Psychiatr Scand. 2008;117(6):412-419

What Is A Clinically Important NNT?

- A large NNT of 100 or more means that there is little difference between choosing Drug A or Drug B (or placebo) for the outcome measured
- **NNT values vs placebo <10 denote a potentially useful intervention**
- **NNH values vs placebo >10 denote a potentially tolerable intervention**

Citrome L. Acta Psychiatr Scand. 2008;117(6):412-419

PIM 34 mg vs Placebo: Response

- A useful definition of **response** is a **≥3 point decrease** from baseline on SAPS-PD (a 2.33 point change on the SAPS-PD corresponds to a clinically meaningful 1-unit change in the CGI-I scale)

- The **NNT is 4** for a ≥3 point decrease from baseline on SAPS-PD for PIM 34 mg/d vs. placebo

- This is **< 10**, and thus denotes PIM 34 mg as potentially useful

Citrome L, et al. CNS Spectr. 23(3):228-238.

Tolerability Outcomes: Measures

- Spontaneously reported adverse events
- Discontinuation because of an adverse event
- Worsening from baseline on the Unified Parkinson Disease Rating Scale (UPDRS) Parts II and III
- Increase or decrease in weight from baseline ≥7% at early termination/endpoint
- Orthostatic hypotension (defined as the decrease in systolic [≥20 mmHg] or diastolic [≥15 mmHg] blood pressure or an increase in pulse rate of ≥20 bpm from 5 minutes supine to 1-minute standing at the same visit) based on vital sign measurement
- ECG QTcF interval >450 msec, >500 msec, or change in QTcF ≥60 msec over baseline

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Adverse Event Outcomes for PIM 34 mg vs PBO

Outcome	Pimavanserin		Placebo		NNH (95% CI)
	n/N	%	n/N	%	
Adverse Event					
Fall	25/412	6.1	24/262	9.2	**-33 (ns)**
Urinary tract infection	21/412	5.1	16/262	6.1	**-99 (ns)**
Nausea	21/412	5.1	11/262	4.2	**112 (ns)**
Confusional state	21/412	5.1	9/262	3.4	**61 (ns)**
Dizziness	19/412	4.6	14/262	5.3	**-137 (ns)**
Peripheral edema	18/412	4.4	7/262	2.7	**59 (ns)**
Hallucination	16/412	3.9	12/262	4.6	**-144 (ns)**
Constipation	16/412	3.9	7/262	2.7	**83 (ns)**
Somnolence	14/412	3.4	7/262	2.7	**138 (ns)**
Headache	12/412	2.9	15/262	5.7	**-36 (ns)**
Insomnia	11/412	2.7	7/262	2.7	**-53972 (ns)**
Diarrhoea	10/412	2.4	6/262	2.3	**730 (ns)**
Blood creatine phosphokinase increased	10/412	2.4	3/262	1.1	**78 (ns)**

A “negative” NNH results from when the rate of the safety or tolerability outcome is higher for placebo than for pimavanserin

Citrome L, et al. CNS Spectr. 23(3):228-238.

Tolerability Outcomes for PIM 34 mg vs PBO

Outcome	Pimavanserin		Placebo		NNH (95% CI)
	n/N	%	n/N	%	
Discontinuation because of an AE	30/412	7.3	11/262	4.2	**33 (ns)**
Worsening from baseline on the UPDRS (LOCF) Parts II and III (any)	140/399	35.1	100/256	39.1	**-26 (ns)**
Worsening from baseline on the UPDRS (LOCF) Parts II and III (>=5%)	100/399	25.1	69/256	27.0	**-53 (ns)**
Worsening from baseline on the UPDRS (LOCF) Parts II and III (>=10%)	74/399	18.5	53/256	20.7	**-47 (ns)**
Worsening from baseline on the UPDRS (LOCF) Parts II and III (>=20%)	40/399	10.0	21/256	8.2	**55 (ns)**
Increase in weight (LOCF) from baseline ≥7%	4/377	1.1	3/244	1.2	**-594 (ns)**
Decrease in weight (LOCF) from baseline ≥7%	12/377	3.2	2/244	0.8	**43 (23-384)**
Orthostatic hypotension at any post-baseline timepoint	126/403	31.3	103/259	39.8	**-12 (-7 to -99)**
Orthostatic hypotension with no orthostatic hypotension at baseline	66/320	20.6	58/200	29.0	**-12 (-7 to -147)**
ECG QTcF >450 msec at any post-baseline timepoint	42/404	10.4	20/260	7.7	**37 (ns)**
ECG QTcF >450 msec with baseline QTcF ≤450msec	33/392	8.4	11/249	4.4	**25 (13-401)**
ECG QTcF >500 msec at any post-baseline timepoint [b]	1/404	0.2	1/260	0.4	**-730 (ns)**
ECG QTcF change from baseline ≥60 msec at any post-baseline timepoint	13/404	3.2	3/260	1.2	**49 (ns)**

A “negative” NNH results from when the rate of the safety or tolerability outcome is higher for placebo than for pimavanserin

Citrome L, et al. CNS Spectr. 23(3):228-238.

Tolerability Outcomes: Summary

- The tolerability pattern of PIM is different from that of second-generation antipsychotics
- **NNH values regarding tolerability outcomes were consistently >10**, and for the most part not statistically significant, or at times showing an advantage for PIM (such as orthostatic hypotension with a NNH of -12)
- Of note, NNH values for PIM (all doses) vs. placebo for somnolence was 138 and for weight gain ≥7% from baseline, -594
- Akathisia was not observed
- There were no observed deleterious effects on mood

Citrome L, et al. CNS Spectr. 23(3):228-238.

Likelihood to be Helped or Harmed (LHH)

- LHH = NNH/NNT and answers the question of how often would one encounter a benefit vs. a harm
- The **NNT is 4** for a ≥3 point decrease from baseline on SAPS-PD for PIM 34 mg/d vs. placebo and **NNH is 21** for the overall tolerability metric of discontinuation because of adverse event from all pooled data for PIM 34 mg/d vs placebo
- The resulting LHH is 21/4 = 5.25
  - **PIM 34 mg/d is about 5 times more likely to result in response (≥3 point decrease from baseline on SAPS-PD) than discontinuation because of an adverse event**

Citrome L, et al. CNS Spectr. 23(3):228-238.

How Does PIM Perform in Terms of Efficacy Compared to Off-Label Antipsychotics?

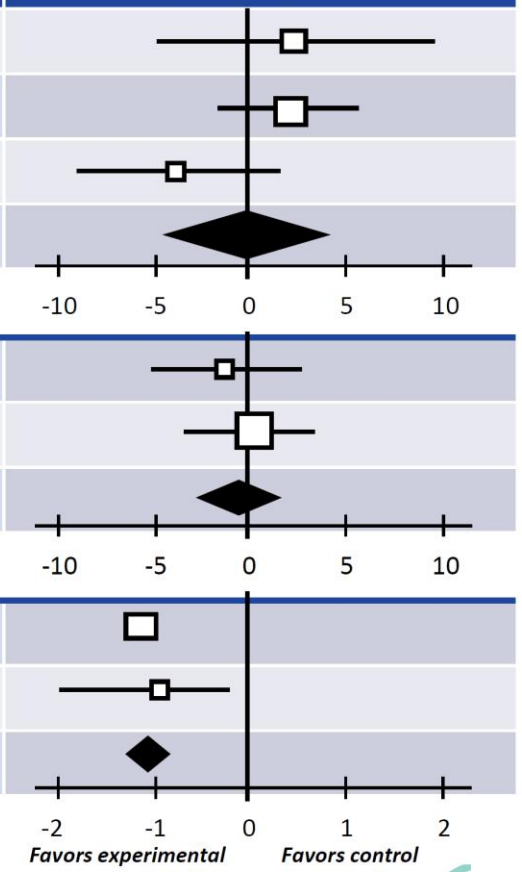
Random effects meta-analysis of the use of quetiapine, olanzapine, and clozapine in the management of PDP

Drug	Study or Subgroup	Experimental			Control			Weight (%)	Mean Difference IV, Random, 95% CI
		Mean	SD	Total	Mean	SD	Total		
Quetiapine	Fernandez	32.2	6.97	8	29.92	7.63	8	22.8	2.28 [-4.88, 9.44]
	Rabey	34	6.7	29	31.9	8.2	27	42.6	2.10 [-1.84, 6.04]
	Shotbolt	35	6.1	11	39	6.4	13	34.6	-4.00 [-9.01, 1.01]
	Total (95% CI)			**48**			**48**	**100.0**	**0.03 [-4.16, 4.23]**
Olanzapine	Breier (Europe)	13.6	8.3	46	15.1	8.3	27	28.9	-1.50 [-5.44, 2.44]
	Breier (USA)	15.4	5.8	41	15.1	5.9	42	71.1	0.30 [-2.22, 2.82]
	Total (95% CI)			**87**			**69**	**100.0**	**-0.22 [-2.34, 1.90]**
Clozapine	Parkinson Study Group	2.8	0.3	**27**	3.9	0.2	27	96.9	-1.10 [-1.24, 0.96]
	Pollack	3.3	1.5	**32**	4.3	1.5	28	3.1	-1.00 [-1.76, -0.24]
	Total (95% CI)			**59**			**55**	**100.0**	**-1.10 [-1.23, -0.96]**

BPRS
Heterogeneity: Tau^2=6.71; χ^2=3.92, df=2 (*P*=0.14); I^2=49%; test for overall effect: Z=0.01 (*P*<0.99).

BPRS
Heterogeneity: Tau^2=0.00; χ^2=0.57, df=1 (*P*=0.45); I^2=0%; test for overall effect: Z=0.20 (*P*<0.84).

CGI
Heterogeneity: Tau^2=0.00; χ^2=0.06, df=1 (*P*=0.80); I^2=0%; test for overall effect: Z=16.06 (*P*<0.00001).



BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; CI, confidence interval; IV, intervention; SD, standard deviation.

Jethwa KD, Onalaja OA. BJPsych Open. 2015;1(1):27-33.

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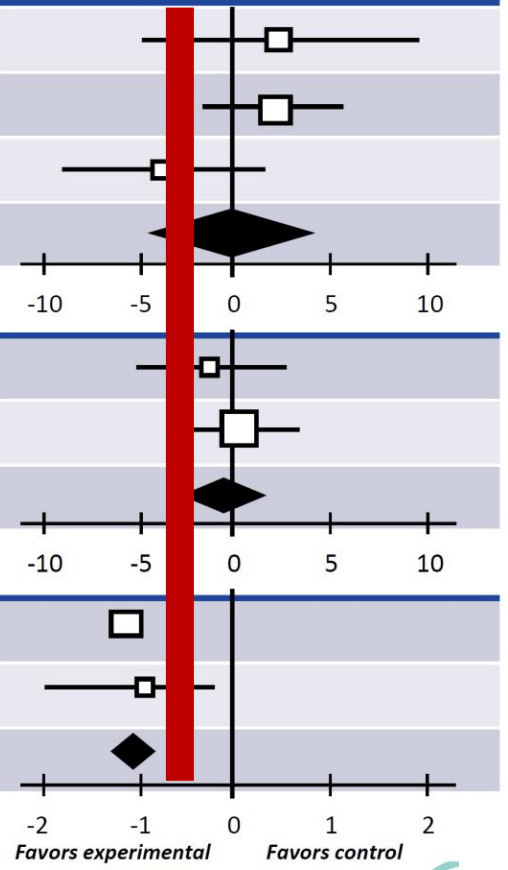
Heterogeneity: Tau^2=0.00; χ^2=0.57, df=1 (*P*=0.45); I^2=0%; test for overall effect: Z=0.20 (*P*<0.84).

CGI
Heterogeneity: Tau^2=0.00; χ^2=0.06, df=1 (*P*=0.80); I^2=0%; test for overall effect: Z=16.06 (*P*<0.00001).

BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; CI, confidence interval; IV, intervention; SD, standard deviation.



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BPRS									
Hete									
Ola									
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CGI
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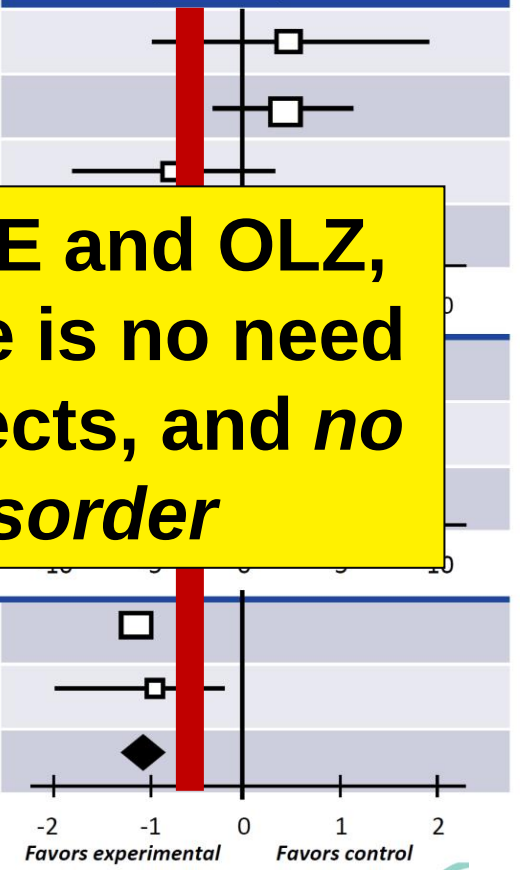
BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression Scale; CI, confidence interval; IV, intervention; SD, standard deviation.



Effect size in reducing symptoms for PIM > QUE and OLZ, but not as robust as for CLO, but with PIM there is no need for blood monitoring, no metabolic adverse effects, and *no worsening of the underlying movement disorder*

Citrome L, et al. CNS Spectr. 23(3):228-238. ; Jethwa KD, Onalaja OA. BJPsych Open. 2015;1(1):27-33.

Switching?

- Expert panel came to a consensus that patients could be switched safely from atypical antipsychotics to PIM
- It was recommended that PIM 34 mg be added for 2–6 weeks before tapering and the discontinuing quetiapine or clozapine over days to weeks
  - Need to avoid avoiding rebound effects when discontinuing agents with anticholinergic and antihistaminergic actions (such as clozapine and quetiapine)
  - If the older medicine is stopped abruptly, withdrawal symptoms and rebound phenomena can emerge, and the prescriber (and patient) will likely blame the new agent for these problems and summarily declare PIM ineffective

Black KJ, et al. CNS Spectr. 2018;23(6):402–413; Citrome L. CNS Spectr. 2018;23(6):355-357.

Integrating a Collaborative Approach to Care

Multi-Disciplinary Care Teams

Integrating A Collaborative Approach

Management of psychiatric disorders in neurological disease can be very complex and nuanced and can’t be addressed by neurology or psychiatry alone.

We are the two faces of the same coin. Brain and mind

Recommendations on how to coordinate care is very sparse.

How do we efficiently integrate psychiatric care and neurological care in patient management of PDP?

Inpatient

- Delineate a specific question
- Establish roles
- Implement the recommendations of the consulting team
- Establish clear communications (oral communication preferred)
- Be organized and specific in your recommendations
- Give doses, duration of treatment and generic names or alternative options
- Anticipate potential problems and develop contingency plans
- Be clear when you are signing off

Outpatient

- Ensure that team members have access to clinic notes and be clear on what questions we need answered from a referral consultation.

Questions?