Advancing Parkinson's disease: Understanding the disease progression and associated challenges

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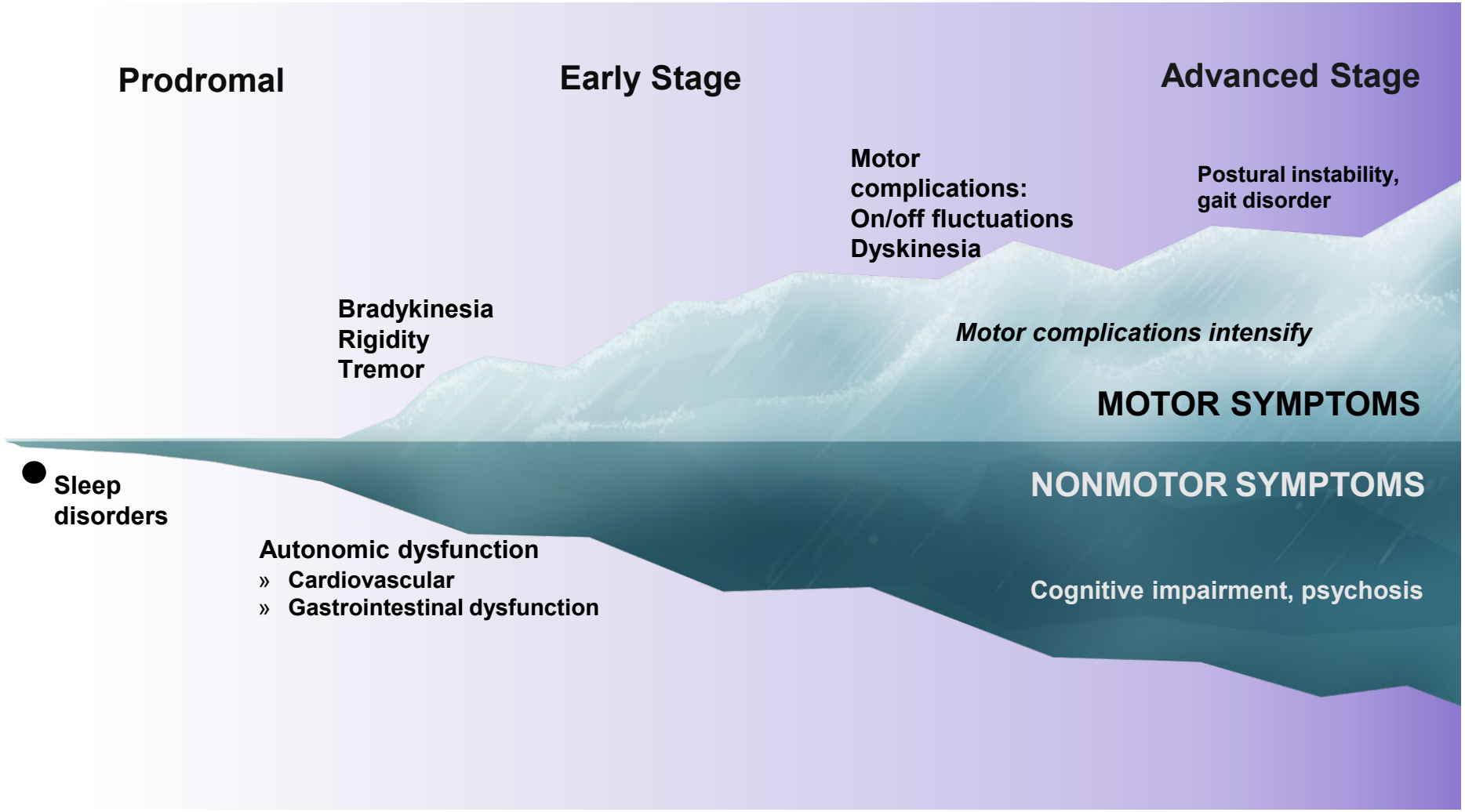
Objectives

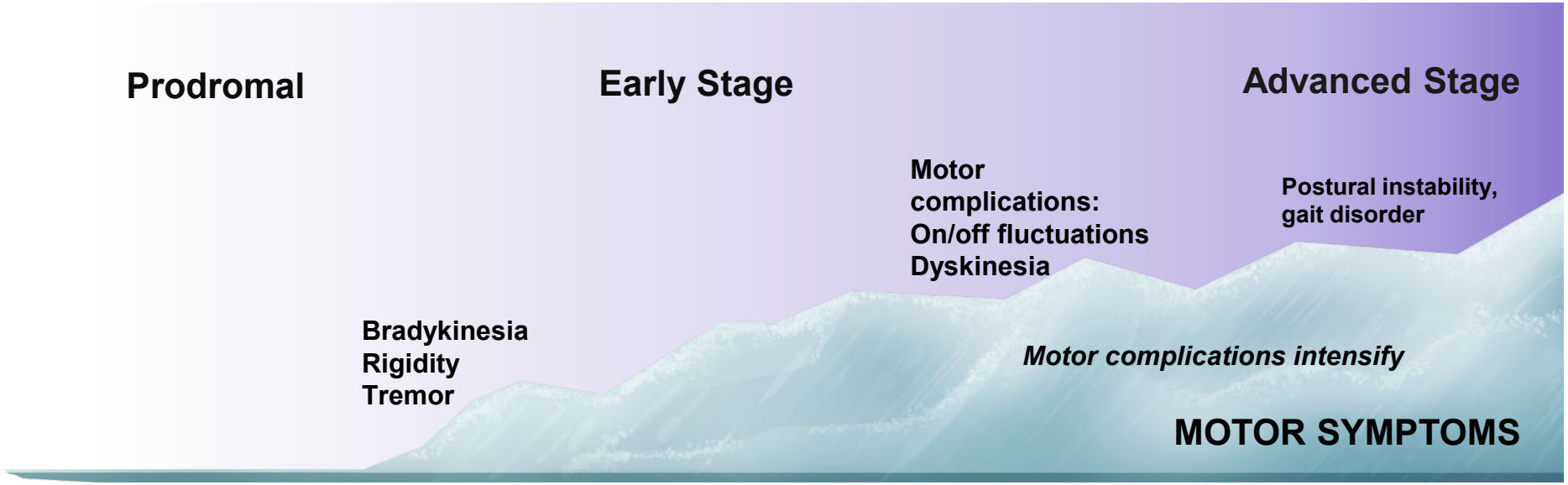
- ❑ Understanding Motor and Non-Motor Symptoms Progression and associated Challenges, such as Dyskinesia, Motor Fluctuations, and Dystonia

- ❑ Learning about Therapeutic Opportunities for Advancing PD

The Frequency and Severity of Symptoms Intensify Throughout the Course of PD



Management Of PD May Vary Of The Course Of Disease



- **Orals**
- **Extended-Release Formulations**
- **Infusion Therapies**
- **Deep Brain Stimulation**

Challenges Associated with Levodopa in the treatment of Parkinson

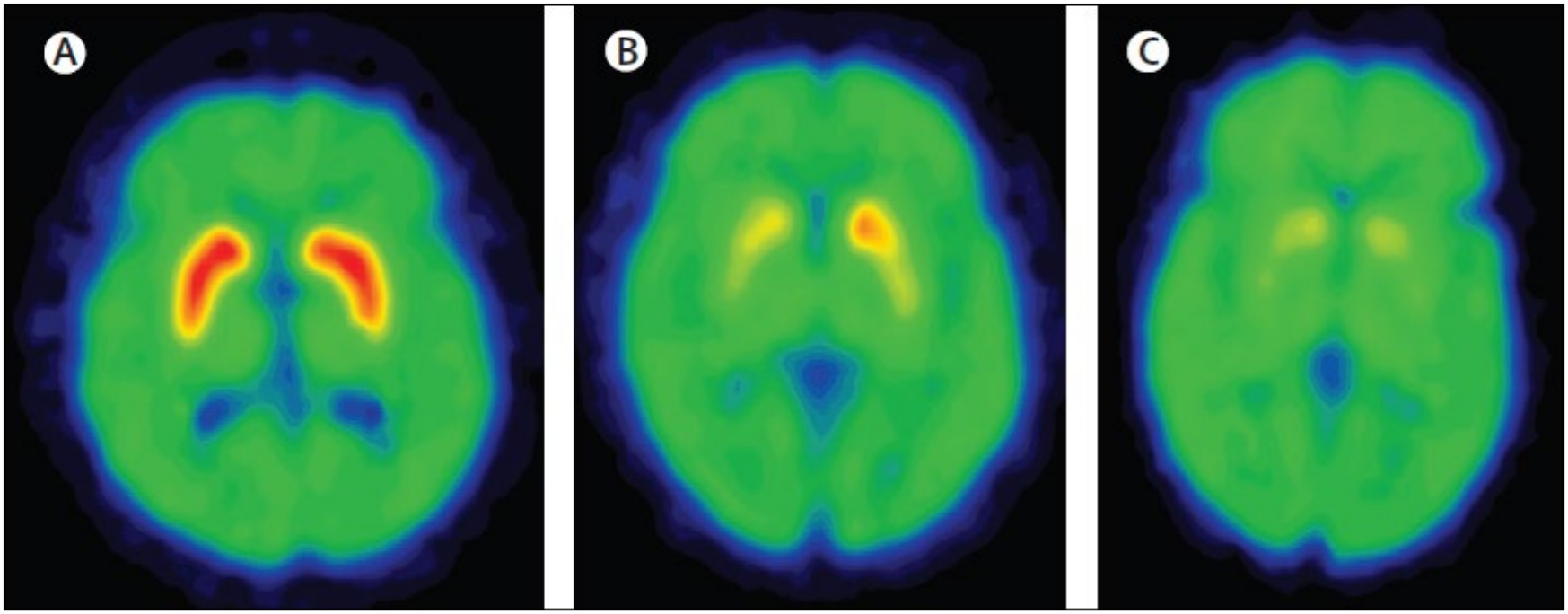


Figure 2: Dopamine transporter binding on PET imaging

Problem: The response to each levodopa dose progressively shortens over time

EUROPEAN JOURNAL of NEUROLOGY 2009, 16: 982-989

Dyskinesia vs. OFF time

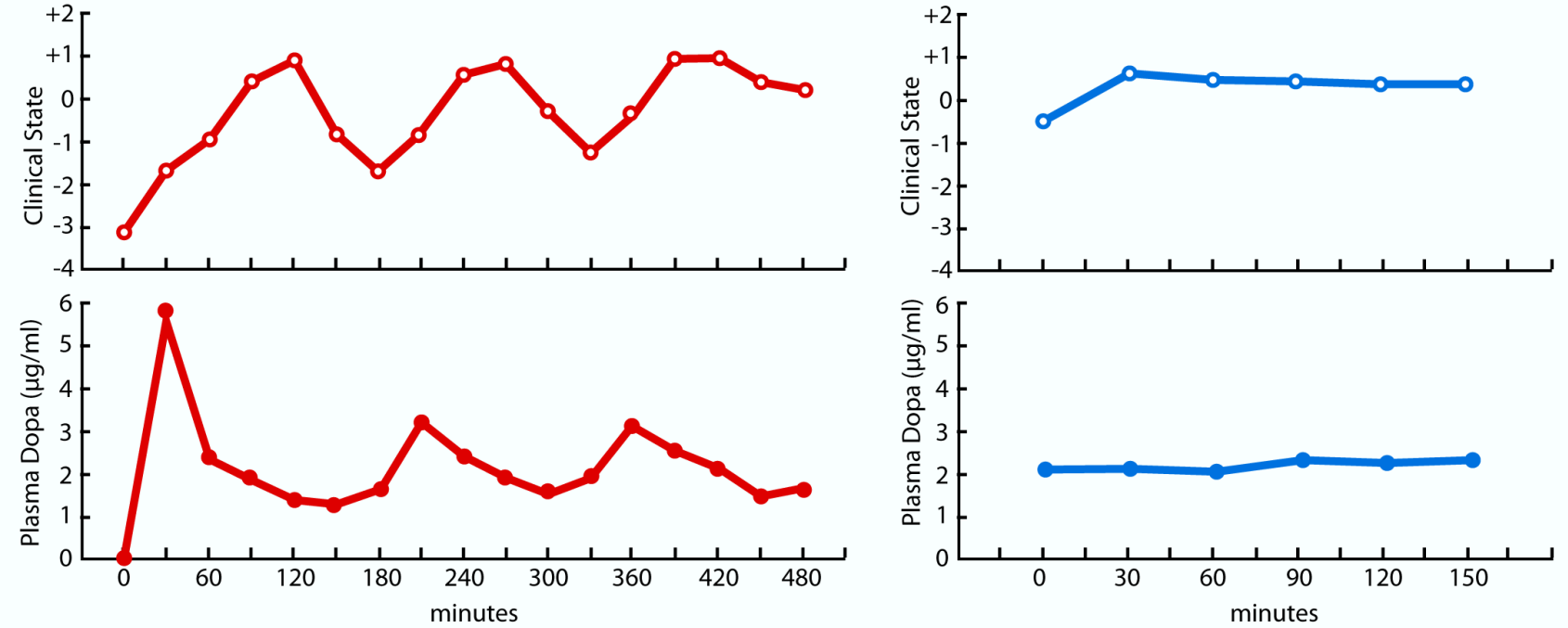
- **Dyskinesias are involuntary, erratic, writhing movements of the face, arms, legs, or trunk.**
  They are often fluid and dance-like, but they may also cause rapid jerking or slow and extended muscle spasms.

- **It's different from OFF time.**
  OFF time is when your PD medication, like levodopa, wears off throughout the day and tremors, slowness, and other Parkinson's disease symptoms return.

- **It can be easy to mistake dyskinesia for other Parkinson's disease symptoms – such as tremors.**
  Dyskinesia is a complication of long-term levodopa use to treat Parkinson's disease.

On-off response: Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients

SHOULSON, MD, GLAUBIGER, MD, PhD, & CHASE MD



"A constant intravenous infusion of levodopa resulted in stable plasma dopa concentrations and virtual disappearance of motor fluctuations."

NEUROLOGY 25: 1144-1148, December 1975

Oral, extended-release forms of levodopa

- Controlled-release carbidopa-levodopa (Sinemet CR®) has unpredictable intestinal absorption and should not be used for daytime use
- Extended-release carbidopa-levodopa (Rytary®) was FDA approved in January 2015

23.75 mg / 95 mg* | 36.25 mg / 145 mg* | 48.75 mg / 195 mg* | 61.25 mg / 245 mg*

Capsules may not be representative of actual size.
**Carbidopa / levodopa.*

Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial

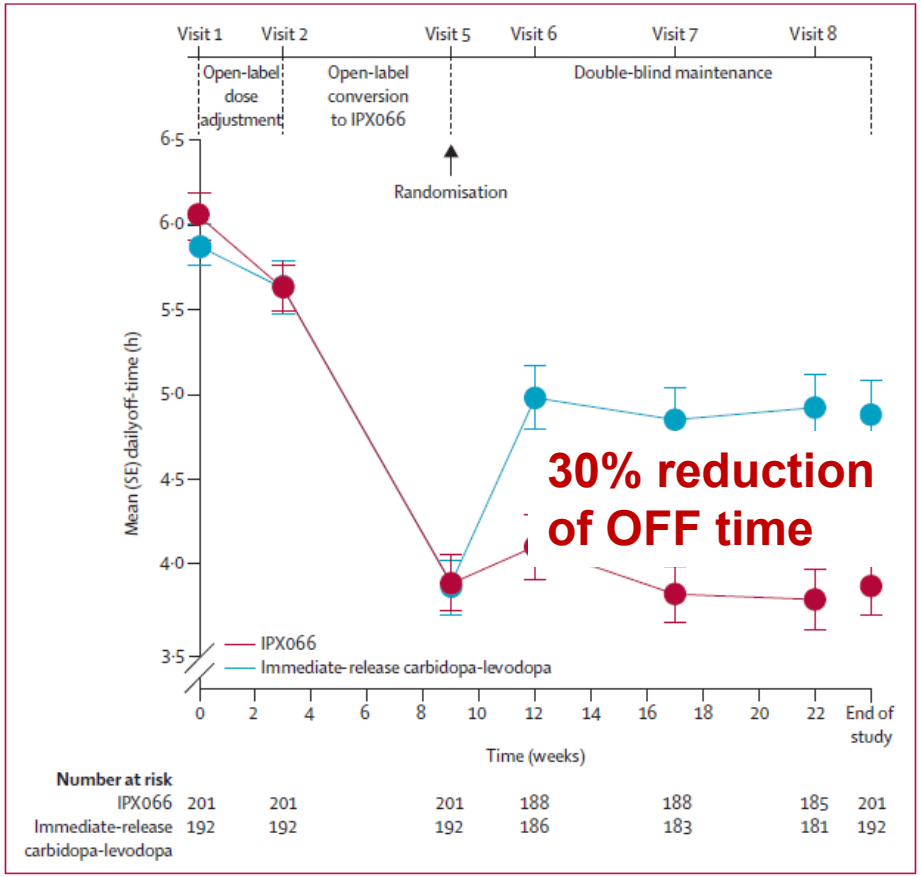


Figure 2: **Mean daily off-time throughout the study**

Hauser et al. Lancet Neurol 2013;12:346

Rescue Therapies

- Apomorphine Injection (Apokyn)
  - Subcutaneous Injection
  - “Rescue Therapy” from OFF-periods

- Apomorphine Sublingual (Kynmobi)
  - Sublingual Film
  - “Rescue Therapy” from OFF-periods

- Levodopa inhalation powder (Inbija)
  - Oral inhaler
  - “Rescue Therapy” from OFF-periods

Add-ON Medications

- Safinamide (Xadago)
  - IMAO-B
  - Improves OFF time without troublesome dyskinesia

The recommended starting dose is **50 mg once daily**

- Istradefylline (Nourianz)
  - Adenosine receptor antagonist – Add on therapy to levodopa
  - Reduction of OFF time

NOURIANZ®
(istradefylline) tablets
20 mg | 40 mg

Treatment of PD-associated symptoms

- Gocovri (Amantadine Extended Release)
  - Improves troublesome dyskinesia
  - Once a day administration with fewer side effects than regular amantadine

- Pimavanser (Nuplazid)
  - Once a day capsule
  - Treatment of PD-associated hallucinations

Neuropsychiatric symptoms associated with PD

- Depression
- Anxiety
- Psychosis
- Dementia
- Impulsivity

A Systematic Review of Prevalence Studies of Depression in Parkinson's Disease

Jennifer S.A.M. Reijnders, MA,[1] Uwe Ehrt, MD,[2] Wim E.J. Weber, MD, PhD,[3]
Dag Aarsland, MD, PhD,[2,4] and Albert F.G. Leentjens, MD, PhD[1]*

In this review we aimed to determine the prevalence of depression in patients with PD across the range of clinical settings and diagnostic approaches. The average prevalence of major depressive disorder in PD is 17%, the prevalence of dysthymia is 13%, while minor depression occurs more frequently in 22% of PD patients. Although these prevalences are lower than previously reported, this systematic review nevertheless confirms that depression is a common complication in patients with PD.

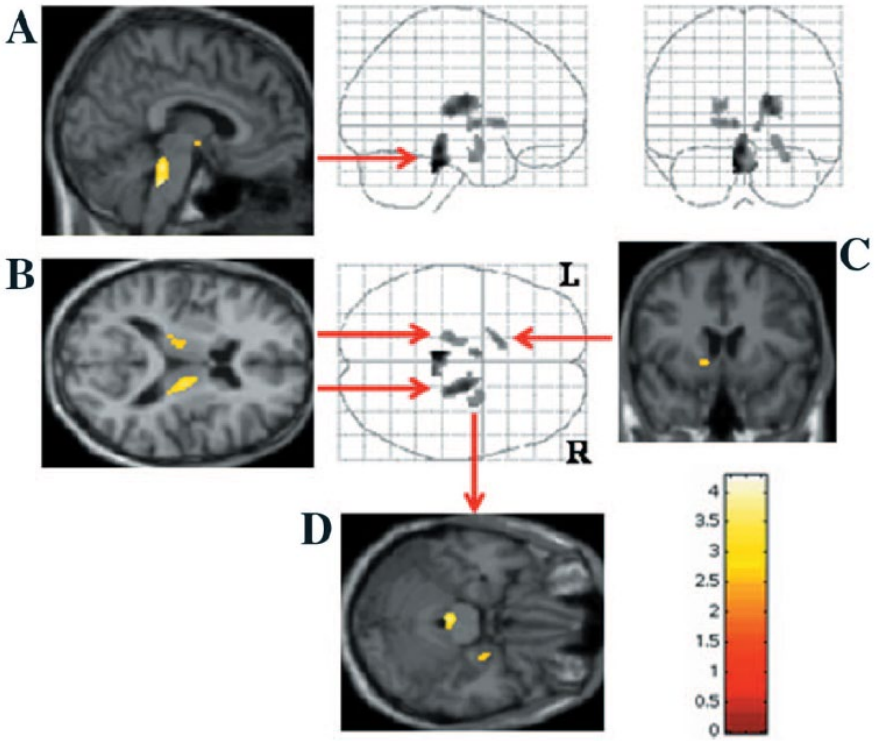
Movement Disorders
Vol. 23, No. 2, 2008, pp. 183–189

- Frequently underdiagnosed
- Can precede motor symptoms
- Different from a «normal» depression:
  - More anxiety components
  - Less introspection

doi:10.1093/brain/awh445 *Brain* (2005), **128**, 1314–1322

Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system

Philippe Remy,[1,2] Miroslava Doder,[2] Andrew Lees,[3] Nora Turjanski[2] and David Brooks[2]



- Reduction in serotonin and noradrenaline in:
  - Locus coeruleus
  - Thalamus
  - Amigdala

Anxiety Disorders in Parkinson's Disease: Prevalence and Risk Factors

Nadeeka N.W. Dissanayaka, PhD,[1,2,3]* Anna Sellbach, FRACP,[3] Sally Matheson, FRANZCP,[3,4]
John D. O'Sullivan, MD, FRACP,[1,3] Peter A. Silburn, PhD, FRACP,[1,2,3,5]
Gerard J. Byrne, PhD, FRANZCP,[3,4] Rodney Marsh, FRANZCP,[1,3]
and George D. Mellick, PhD[1,2,6]*

PD-associated anxiety main features:

- Panic attacks
- Associated with motor fluctuations
- Social phobia
- More frequent in young onset PD

TABLE 4. *Influence of the examined factors to anxiety in Parkinson's disease*

Variable[a]	Odds ratio (95% CI)	*P*
Age of <62 yr[b,c]	4.20 (1.34–13.21)	0.01
Higher UPDRS-II-ADL score[c]	1.19 (1.07–1.32)	0.001
Higher UPDRS-III-Motor score[c]	1.07 (1.01–1.13)	0.02
Moderate Hoehn and Yahr staging[c]	6.09 (1.40–26.48)	0.02
Severe Hoehn and Yahr staging[c]	10.75 (1.36–85.08)	0.02
Higher swab and England score[c]	0.95 (0.92–0.99)	0.02
Experiencing dyskinesias or motor fluctuations[c]	4.92 (1.38–17.57)	0.01
Higher levodopa dose	1.00 (1.00–1.00)	0.23
PD onset age of <61yr[c]	4.31 (0.99–18.79)	0.05
Longer duration of PD	0.98 (0.90–1.08)	0.73
Right sided symptom onset of PD	0.41 (0.12–1.46)	0.17
Left sided symptom onset of PD	1.42 (0.44–4.54)	0.56
Tremor dominant PD	0.61 (0.14–2.63)	0.50
PIGD[d] PD	3.13 (0.92–10.66)	0.07
Have had functional neurosurgery for PD	1.15 (0.29–4.63)	0.84
Higher PDQ8 score[c]	1.57 (1.21–2.03)	0.001
Cigarette smoking (pack years)	1.00 (0.97–1.03)	0.95

Movement Disorders
Vol. 25, No. 7, 2010, pp. 838–845

Hallucinations in Parkinson disease

Nico J. Diederich, Gilles Fénelon, Glenn Stebbins and Christopher G. Goetz

Diederich, N. J. *et al. Nat. Rev. Neurol.* **5**, 331–342 (2009); doi:10.1038/nrneurol.2009.62

Key points

- According to cross-sectional studies, one-third of individuals with Parkinson disease (PD) experience visual hallucinations; however, up to 75% of patients will develop such phenomona over a 20-year period
- Hallucinations have substantial psychosocial effects and are a prominent factor influencing the placement of patients with PD in nursing homes
- Hallucinations usually occur in the context of dopaminergic or anticholinergic drug therapy for PD
- Multifaceted visual deficits, sleep–wake cycle dysregulation and cognitive dysfunction are increasingly recognized as contributory factors to hallucinations in PD
- Treatments for hallucinations include atypical neuroleptics and, possibly, cholinesterase inhibitors
- In the future, a more discriminative phenomenological exploration could delineate distinct types of hallucinations with differing pathophysiological mechanisms, treatment strategies, and prognoses

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Figure 1 | Subject of visual illusions in PD. Illusions in PD often involve inanimate objects viewed as living beings or parts of living beings. The flowers were repeatedly perceived as staring faces by a 74-year-old patient with PD and mild dementia. Abbreviation: PD, Parkinson disease.

Hallucinations in Parkinson disease

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Pathogenesis: an unfinished puzzle

Levodopa psychosis—still a valid hypothesis?

- Dopaminergic stimulation is a co-factor
- Possible role for cholinergic deficiency
- retinal alterations might worsen/cause disperception
- Alterations in the sleeping rythm might worsen hallucinations

MANAGEMENT:

1) Rule out infections

2) Simplify the pharmachological therapy as per the following order

- Anticholinergics
- Selegiline
- Amantadine
- Dopamine-agonisti
- COMT-I

3) Start a medication for hallucinations:

- Nuplazid
- Seroquel
- Zyprexa

Movement Disorders
Volume 23 Issue 11, Page 1541-1545
Published Online: 19 June 2008

Antipsychotic medication treatment for mild hallucinations in Parkinson's disease: Positive impact on long-term worsening

Christopher G. Goetz, MD*, Wenqing Fan, MS, Sue Leurgans, PhD
Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois, USA

We found that early treatment of hallucinations at the point when they occurred with retained insight not only acutely resolved hallucinations in nearly half the treated patients but more importantly positively influenced long-term progression of hallucinations into hallucinations with loss of insight and delusional psychosis. The same rate of acute

Targeting Non-Motor Symptoms: The other face of Parkinson's disease

The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

Multicenter International Study (13 Centers)

242 PD patients were asked to fill in the NMSQ

After completion they were asked if they had discussed the positive symptoms with any Health Care Professional before

Movement Disorders
Vol. 25, No. 6, 2010, pp. 704–709

Targeting Non-Motor Symptoms: The other face of Parkinson's disease

The Nondeclaration of Nonmotor Symptoms of Parkinson's Disease to Health Care Professionals: An International Study Using the Nonmotor Symptoms Questionnaire

Symptom	Positive	Non-declared
Dribbling	41.7%	45.5%
Constipation	47.5%	46.1%
Urinary Urgency	59.9%	42.1%
Dizziness	38.8%	50.0%
Sweating	30.6%	33.8%

Movement Disorders
Vol. 25, No. 6, 2010, pp. 704–709

Non-Motor Symptoms are a Primary Cause of HealthCare Utilization in PD

Average 5-year cumulative healthcare utilization per person among 611 veterans with medically-managed APD

Often overlooked symptoms of APD, such as orthostatic hypotension, **significantly increase** annual healthcare utilization

1. Stroupe KT, et al. *Movement Disorders Clin Prac*. 2019;6:369–378.
2. Merola A, et al. *Parkinsonism Relat Disord.* 2018;47:45–49.

Orthostatic hypotension in Parkinson disease: Impact on health care utilization

Aristide Merola [a,*], Russell P. Sawyer [a], Carlo Alberto Artusi [b], Ritika Suri [a], Zoe Berndt [a], Jose' Ricardo Lopez-Castellanos [a], Jennifer Vaughan [a], Joaquin A. Vizcarra [a], Alberto Romagnolo [b], Alberto J. Espay [a]

Healthcare utilization cost in United States Dollars per patient per year.

	PD-OH+ (n = 93)	PD-OH− (n = 224)	P-value
Hospitalizations	$22,813 ± $6280	$7995 ± $4001	**0.038**
ER visits	$1425 ± $426	$911 ± $302	**0.044**
Outpatients visits	$863 ± $61	$852 ± $47	0.854
Telephone calls/e-mails	$62 ± $7	$39 ± $5	**0.006**
TOTAL	$25,205 ± $6546	$9831 ± $4167	**0.037**

Parkinsonism and Related Disorders 47 (2018) 45–49

Droxidopa and Reduced Falls in a Trial of Parkinson Disease Patients With Neurogenic Orthostatic Hypotension

Clinical Neuropharmacology • Volume 39, Number 5, September/October 2016

Phase 3, randomized, placebo controlled, double-blind study
225 PD, non-demented patients with OH