Inhibikase Therapeutics

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The Hows and Whys of Parkinson's Disease and the Challenges for Treatment and Approval

KOL Day, April 20, 2022

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Agenda

- Epidemiology
- Clinical Features
- Timecourse and stages of disease
- Current Approaches to Treatment and the Inhibikase Solution
- Managing PD: Unmet Needs & Challenges
- Extended Q&A

Introduction To The Experts

Werner Poewe, MD
Professor Emeritus and
Past Chair
Dept of Neurology
Medical University Innsbruck
Austria

Robert A Hauser, MD, MBA
Professor of Neurology
Director
Parkinson's Disease and Movement Disorders
Center of Excellence
University Of South Florida

C. Warren Olanow, MD
Interim CMO, Inhibikase Therapeutics, Inc.

CEO Clintrex Research Corporation,

Professor and Chair Emeritus, Department of Neurology and
Professor, Department of Neuroscience
Mount Sinai School of Medicine

Milton H. Werner, PhD
President & CEO
Inhibikase Therapeutics, Inc.

Parkinson‘s Disease Overview

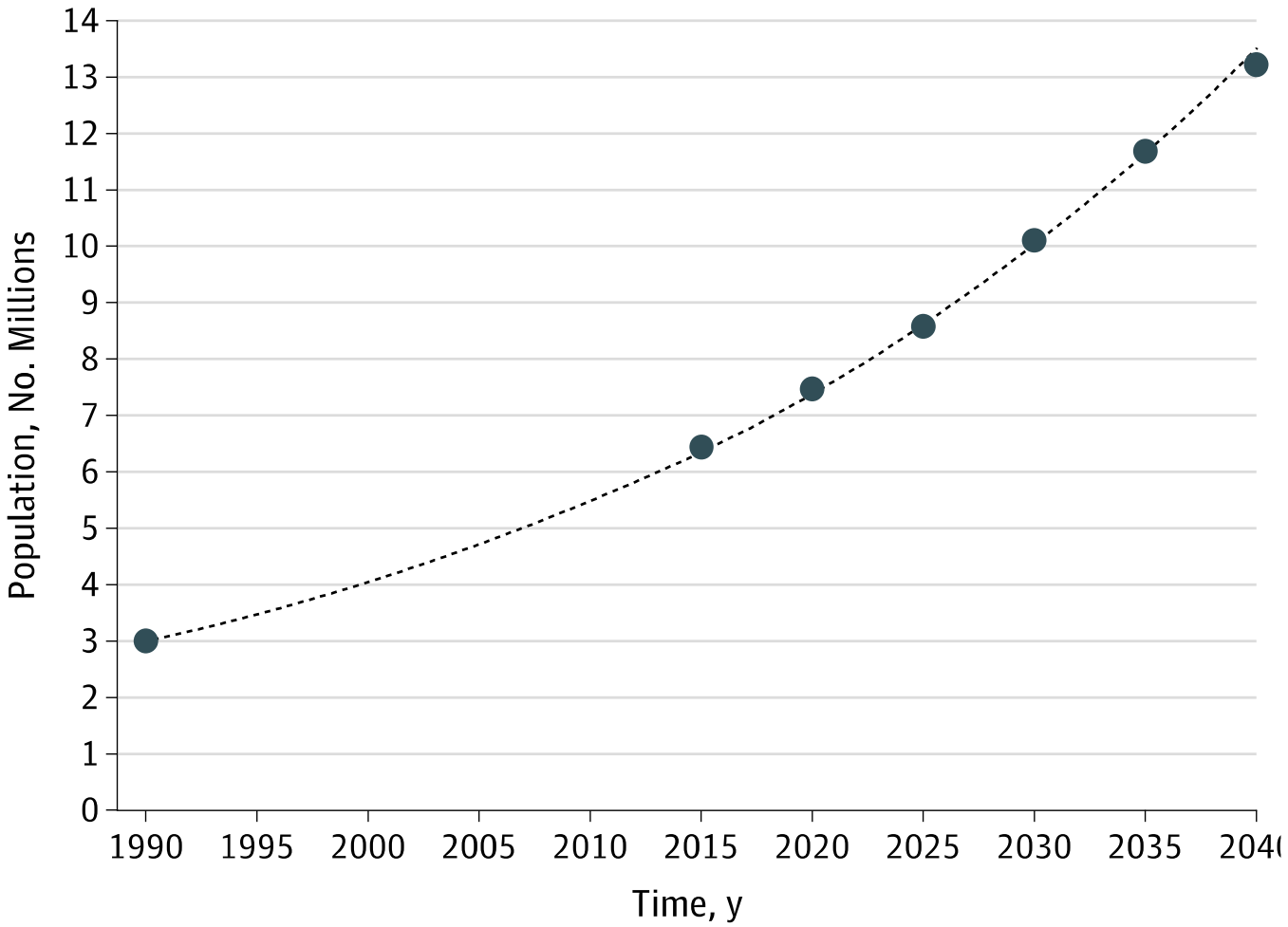
Werner Poewe, MD
Professor Emeritus and
Past Chair
Dept of Neurology
Medical University Innsbruck
Austria

Incidence of PD

VIEWPOINT

The Parkinson Pandemic
A Call to Action

Figure. Estimated and Projected Number of Individuals With Parkinson Disease, 1990-2040



Dorsey & Bloem, JAMA Neurol. 2018;75(1):9-10

Motor Features of PD

Early Disease

- Bradykinesia
  - Hypomimia
  - Loss of dexterity
  - Gait changes
  - Handwriting changes
- Rigidity
  - Feeling of stiffnes
  - Shoulder/arm pain
- Rest Tremor

Advanced Disease

- Gait Difficulites
  - Freezing
  - falls
- Postural deformities
  - Camptocormia
  - Pisa syndrome
  - Contractures hands/feet
- Speech & Swallowing problems
- L-dopa related motor complications
  - Response fluctuations
  - dyskinesias

Non-motor features of PD

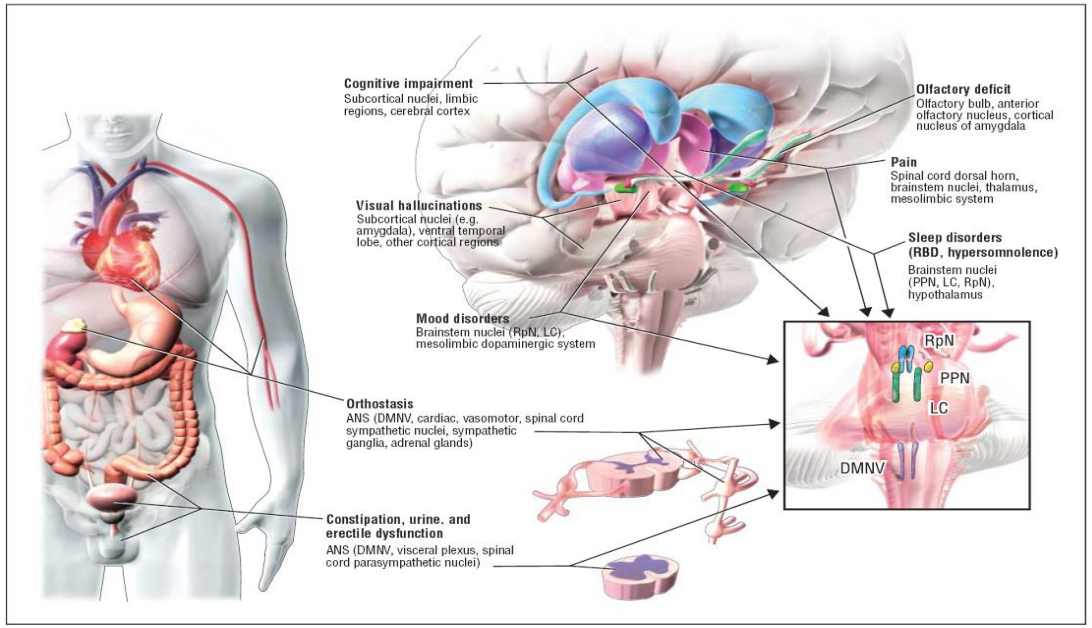


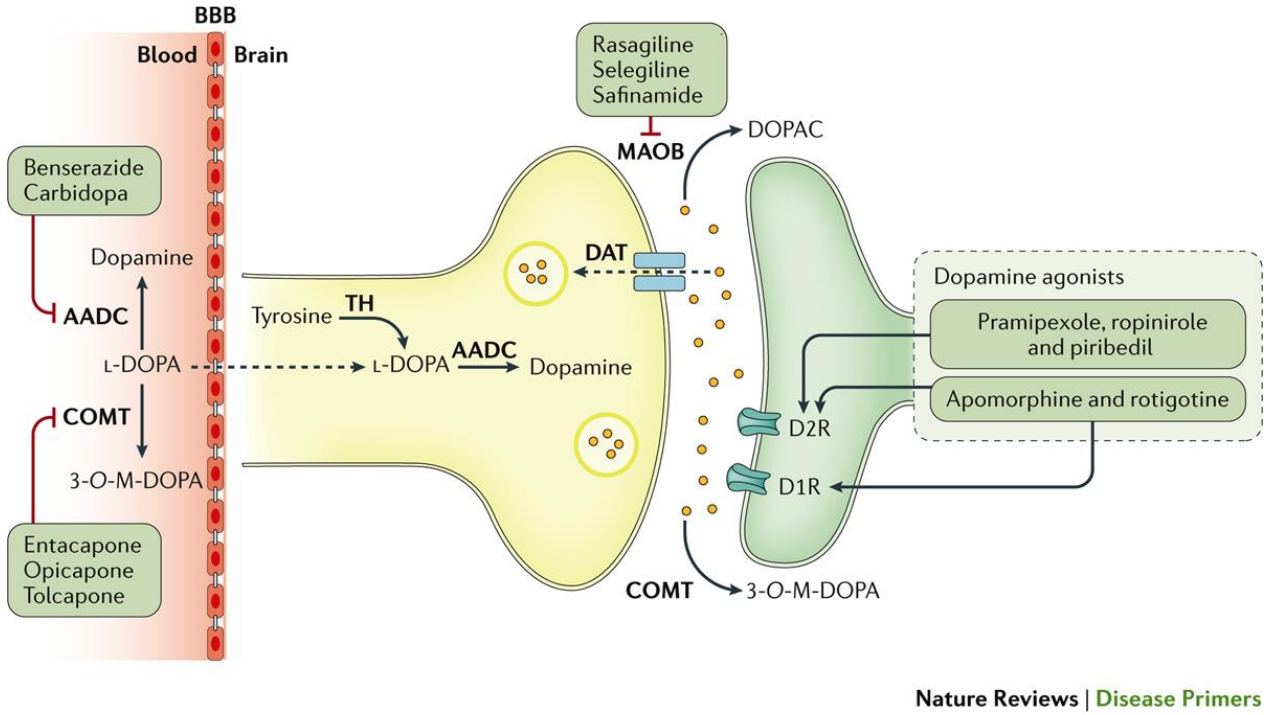
Figure. Putative anatomic substrates for the nonmotor features of Parkinson disease. ANS indicates autonomic nervous system; DMNV, dorsal motor nucleus of the vagal nerve; LC, locus ceruleus; PPN, pedunculopontine nucleus; RBD, rapid eye movement behavior disorder; and RpN, raphe nuclei.

- Neuropsychiatric symptoms
  - Cognitie dysfunction
  - Dementia
  - Hallucinosis
  - Depression
  - Apathy
- Autonomic dysunction
  - Orthostatic hypotension
  - urinary&sexual dysfunction
  - constipation
- Sleep Disorders
  - Insomnia
  - RBD
  - Daytime sleepiness
- Sensory Dysfunction
  - Hyposmia
  - Impaired colour vision
  - diplopia
- Pain

Treating PD – Principles of Management

Drug Treatment

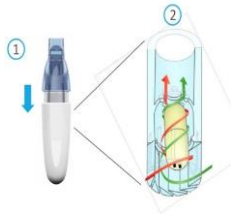
- Dopamine substitution
  - L-Dopa
  - DA-agonists
  - MAO-B inhibitors
  - COMT inhibitors
- Non-dopaminergic drugs
  - Anticholinergics
  - Amantadine
  - A2A antagonists
  - Drugs to treat NMS



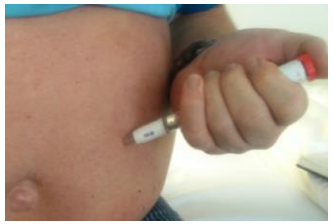
Poewe W, *et al*. (2017) Nat Rev Dis Primers, 3:17013.

‘Device-Aided’ PD-Therapies

On-Demand Therapies

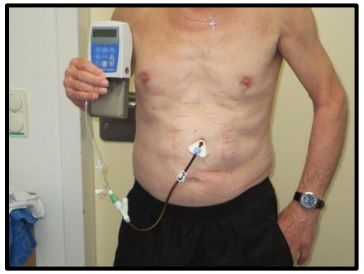


Levodopa Inhaler

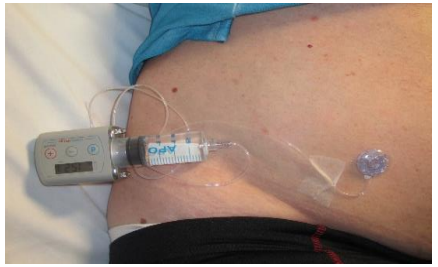


sc apomorphine pen

Infusion Therapies



Le*vodopa intestinal gel*



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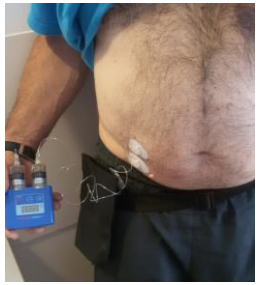

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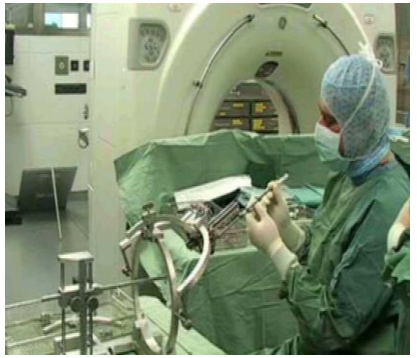
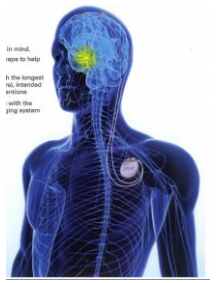
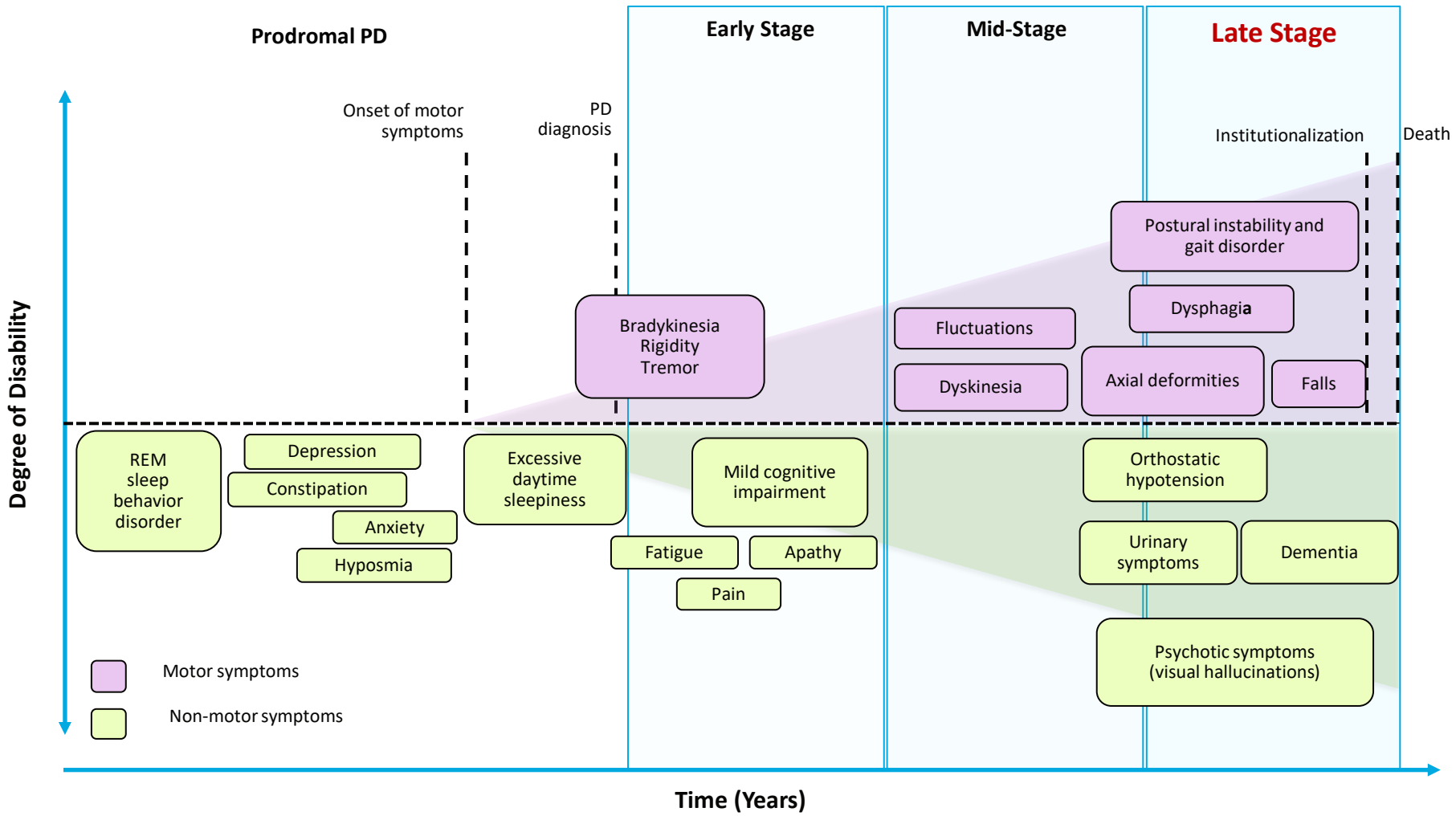
Deep Brain Stimulation





Evolution of PD



Poewe W, *et al*. (2017) Nat Rev Dis Primers, 3:17013.

Managing PD – Unmet needs & Challenges

Levodopa-related motor complications

- response fluctuations
- dyskinesias

Treatment resistant motor symptoms

- Freezing of gait
- Postural instability & falls
- Dysphagia & dysarthria

Non-motor symptoms

- Cognitive dysfunction & dementia
- Autonomic dysfunction
- Sleep disorders

KEY UNMET NEED = DISEASE MODIFICATION

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Parkinson's Disease Strategy & Status

Dr. Milton Werner, President & CEO

Dr. Warren Olanow, Interim CMO, Inhibikase Therapeutics, Inc.
CEO Clintrex Research Corporation,
Professor and Chair Emeritus, Department of Neurology and
Professor, Department of Neuroscience,
Mount Sinai School of Medicine

Stressors Trigger the Production of Misfolded α-Synuclein Which Activates c-Abl to Drive Neurodegeneration[2]

Stressors Trigger the Production of α-Synuclein

Oxidative / nitrosative stress

Point mutation in one or more proteins causing hyper-aggregation

Gene duplication / triplication

Toxin

Inflammation

Stochastic Mechanisms

α-Synuclein Forms Fibrous Aggregates or Plaques

Aggregates or plaques of misfolded α-synuclein are abnormal, but they have not been chemically modified.

CELL ENTRY

c-Abl is a Sentinel which patrols for abnormalities inside an affected neuron

c-Abl acts a sensor for abnormality, such as internalized α-synuclein plaques or aggregates, stimulating a cascade of responses leading to neurodegeneration

The Effects and Results of Activated c-Abl Kinase

Sensing α-synuclein plaques or aggregates, activated c-Abl **chemically modifies** α-synuclein at **Tyr[39]**, converting it into a more highly aggregated form.

C-Abl also chemically modifies Parkin, disrupting survival pathways centered on mitochondrial integrity and protein clearance

NEURODEGENERATION

Cell Death

Movement Disorder

Cognitive Disorder

Immunotherapy acts here[2]

c-Abl inhibition acts here

[1]*Nat Rev Neurosci*. **2**, 492–501 (2001)
[2] Werner and Olanow , Mov Disorders 2021, doi: 10.1002/mds.28858
[3]https://ir.prothena.com/news-releases/news-release-details/update-phase-2-pasadena-study-prasinezumab-prx002rg7935
http://media.biogen.com/node/22876/html

SUMMARY

Key points of Parkinson's Disease Initiation and Progression[1]

- Internalization of misfolded or aggregated α-synuclein and the activation of c-Abl in response is a key event in PD initiation/progression
- The long-sought goal of clearing α-synuclein aggregates for a therapeutic purpose should focus on the aggregates WITHIN the affected neurons
- Reduction and/or clearance of aggregates can be driven by restoring endogenous processes from within the affected neurons
- Recovery of lost functional activity can be achieved

[1]Werner and Olanow, Mov. Disorders 2022 Jan;37(1):6-15; , J Clin Invest. 2016; 126: 2970-2988, Brain 2019; 142:2380-2401, Cell 2011; 144: 689-702, Nat Neurosci. 2013; 16: 1392-1400, Adv Neurobiol. 2017; 15:403-425

Clinical Phase 1 and 1b Programs

Phase 1 Single Ascending Dose Study (SAD)

- Healthy Controls
- 9 dosing cohorts
- Doses – 12.5 – 325 mg per day
- 8 patients per cohort – 6 active and 2 placebo
- 1-day dosing
- Primary endpoints:
  - safety
  - tolerability
  - pharmacokinetics (PK) - plasma

Phase 1/1b Multiple Ascending Dose Study (MAD)

- Healthy Controls/PD Patients
- 2 HC cohorts
  - Doses 12.5 and 25
- 2-3 PD cohorts
  - Doses – 50, 100, 200 mg
- 8 patients per cohort – 6 active and 2 placebo
- 7-day dosing
- Primary endpoints:
  - safety
  - tolerability
  - Steady-state pharmacokinetics (PK) plasma
  - Trough steatdy-state PK spinal fluid and urine
  - Exploratory: UPDRS II+III, II, III, NMSS, PDQ-39, CGI, CSBM, PAGI-SYM

IkT-14809 Phase 1/1b Program Outcomes

Results to date

- Phase 1 Healthy Controls, Age 45-70
  - No deaths
  - No SAEs
  - No clinically significant AEs
  - MTD not defined
  - PK – linearity to 250 mg 1x/day

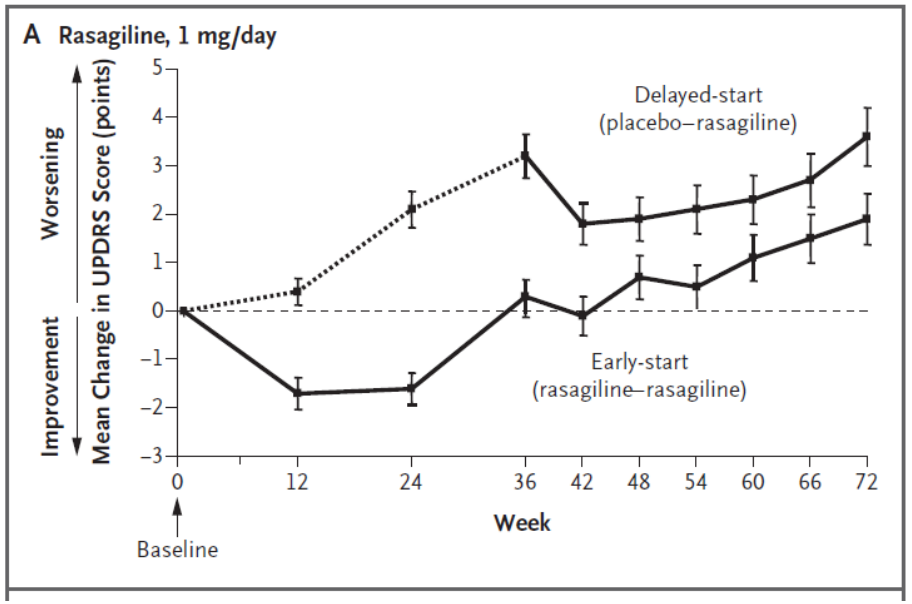
- Phase 1b PD Patients, Hoehn & Yahr < 3.0
  - No deaths
  - No SAEs
  - No clinically significant AEs
  - MTD not defined
  - No evidence of worsening of PD
  - PK – May have reduced exposure relative to healthy controls but similar accumulation

IkT-148009 Development Program Phase 2b/3 Program

- **Phase 2b/3 Double Blind Placebo Controlled Trial**
  - Untreated PD patients
  - 9-month study
  - Likely 2/3 cohorts – 1/2 active doses (chosen from phase 2 study) and Placebo
  - Estimated 150 patients per group
  - Outcome Measures
    - Primary outcome measure – likely UPDRS II + III
    - Measure of Function – CGI-S
    - Non-motor/dopaminergic manifestations – e.g. sleep, cognition, GI function, falling
    - Biomarker – α–synuclein measures in plasma, CSF, skin and others
- **Long-Term Open Label Safety Study**
  - Likely 300 patients treated for 6 months and 100 patients treated for 12 months (50% at highest dose)
  - Patients who participated in previous trials can be enrolled into the long-term safety study

IkT-148009 Development Program Regulatory Considerations

- **Disease Modification as an indication – no regulatory path to achieve this**
  - No biomarker has been accepted to date for regulatory purposes in PD
  - No agent in the Division of Neurology has been approved with a disease-modifying indication
  - The only design the agency has indicated might be acceptable for this indication is the delayed start study
    - ➢ This is a long and expensive trial with many unresolved issues and no assurance of approval even with positive results (see the ADAGIO study[1])



[1]Olanow et al. N Engl J Med. (2009) 361(13):1268-78

IkT-148009 Development Program Regulatory Considerations

- **Our approach to drug approval**

  - Double Blind, Placebo-Controlled Parallel group design
    - A standard design that has been used for the approval of most drugs in PD
  - Indication would be for treatment of PD
  - Mechanism of Action and demonstration that drug is likely to be disease-modifying can be incorporated into the label
    - Laboratory studies describing relevant basic science could be included in section 12 of the label
    - Clinical results describing features including those that are not affected by currently available therapies could be described in section 14 of the label
    - Information in the label can be communicated for educational and commercial purposes as we've recently published:

    Kieburtz K, Katz R, McGarry A, Olanow CW. A New Approach to the Development of Disease-Modifying Therapies for PD; Treating Another Pandemic. Mov Disord 2021;36:59-63.

Why we need to find a path to slow disease progression

Robert A Hauser, MD, MBA

Professor of Neurology

Director

Parkinson's Disease and Movement Disorders

Center of Excellence

University Of South Florida

“Doctor, how am I going to do?”

https://www.michaeljfox.org/news/get-times-parkinsons-diagnosis-criteria-catches-latest-understanding

Sydney Multicenter Study – 15 years Mortality

- Newly diagnosed patients were recruited and followed
- The standardized mortality ratio was significantly elevated at 1.86
- The median time from onset of disease to death was 12.2 years
- The mean age at death was 75.5 years
- Pneumonia was the most common cause of death (27%) with most of these pts having been bedridden

[1]Hely et al. Mov Disord 2005;20: 190-199

Sydney Multicenter Study – 15 years[1]

- Motor fluctuations = 96%
- Dyskinesia = 94%
  - disabling dyskinesia = 46%

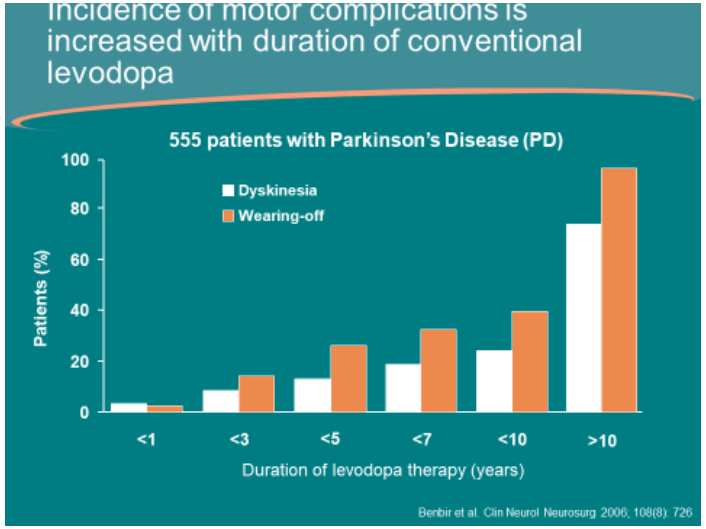
- Cognitive decline = 84%
  - Dementia = 48%
- Falls = 81%

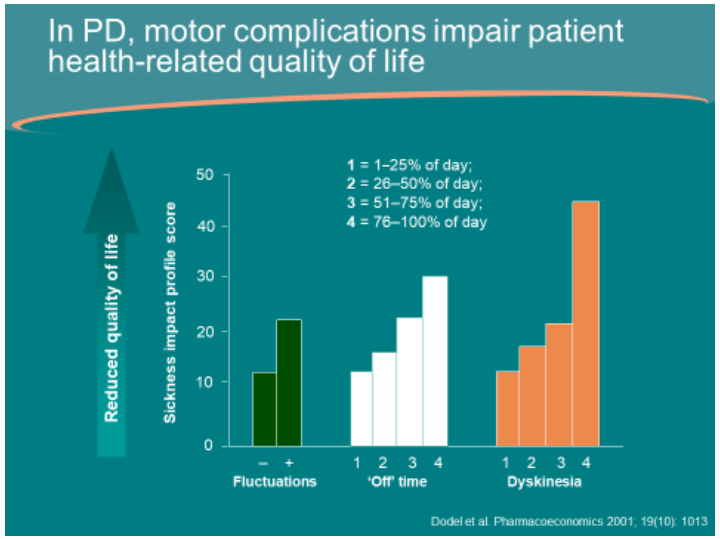
- Hallucinations = 50%
- Depression = 50%
- Choking = 50%
- Urinary incontinence = 41%
- Symptomatic orthostatic hypotension =35%

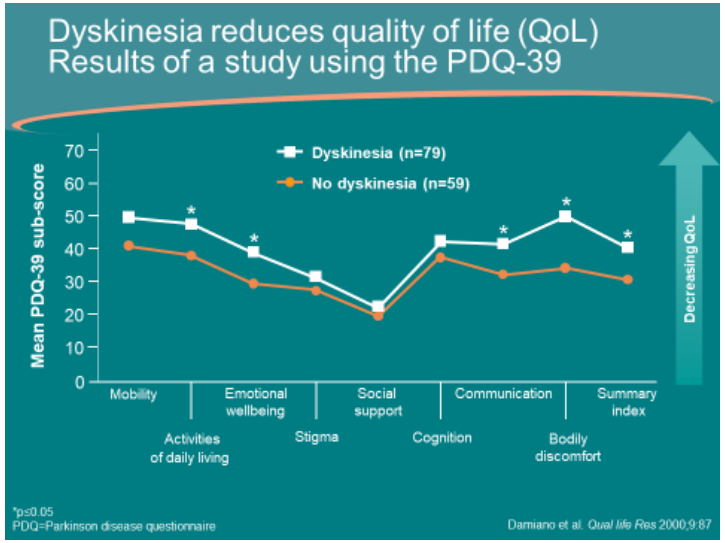
[1]Hely et al. Mov Disord 2005;20: 190-199

Motor Fluctuations and Dyskinesia

- Motor fluctuations and dyskinesia increase over time
- Are associated with decreased QoL
- Despite advances, remain an unmet treatment need

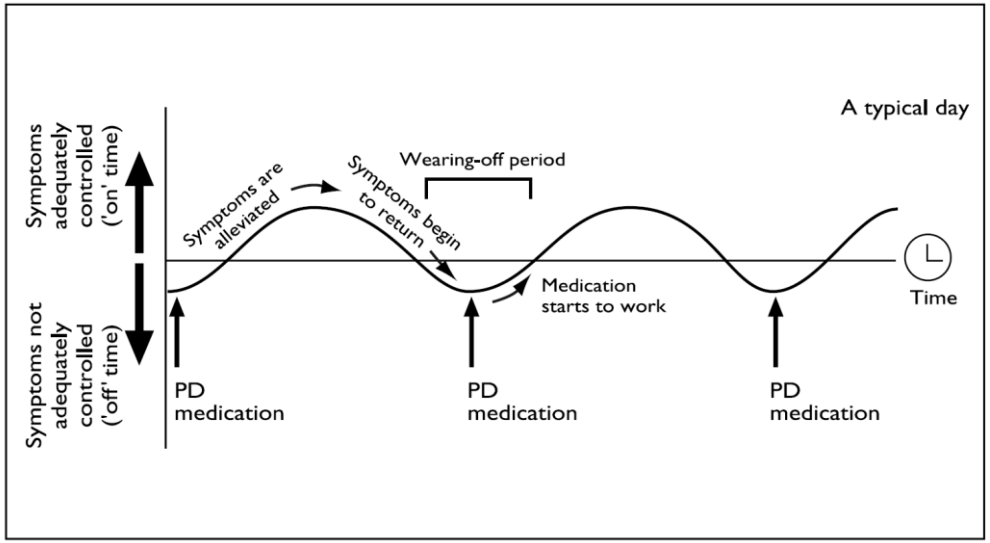






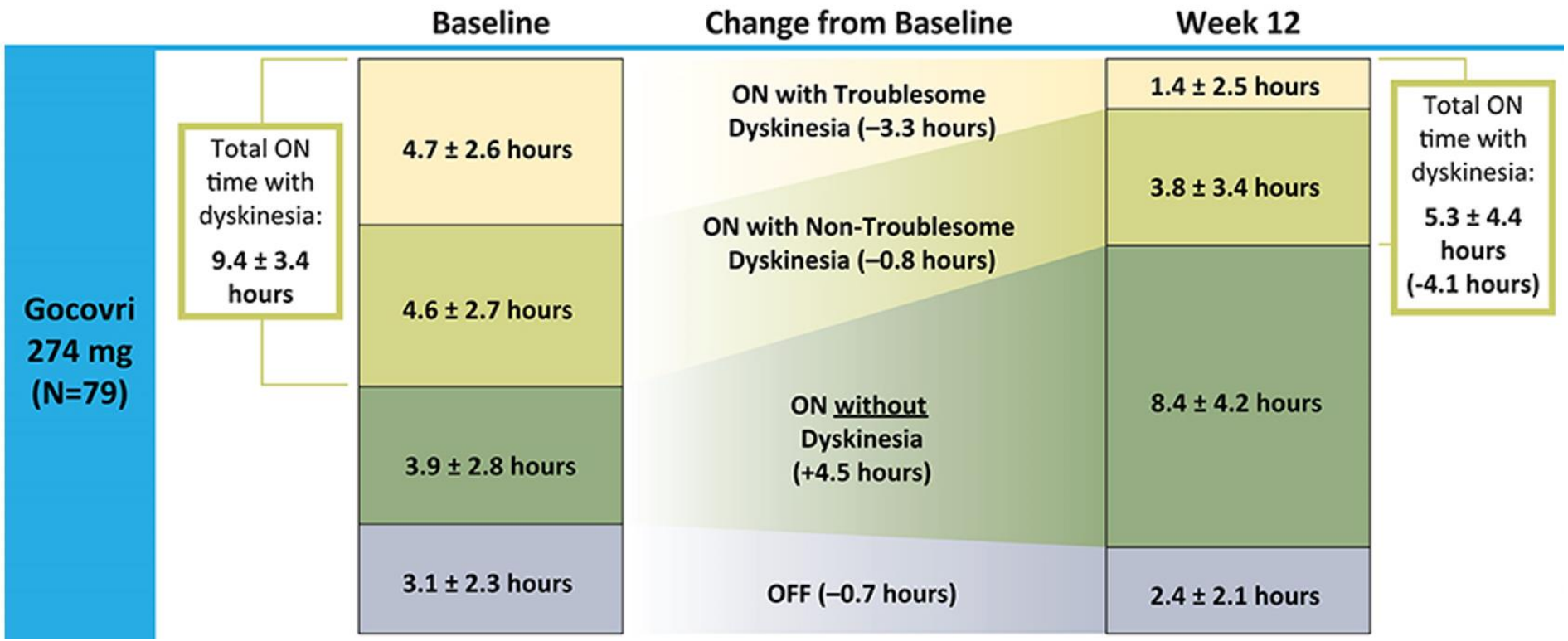
Residual OFF Time

	BL	EOS	Residual OFF time
Rytary	6.1	-2.2	3.9
Duopa	6.3	-4.0	2.3
DBS	5.9	-2.4	3.4



Hauser et al. Lancet Neurol 2013;12:346-56
Olanow et al. Lancet Neurol 2014; 13:141-9
Weaver et al. 2009 JAMA 2009; 301:63-73
Stacy & Hauser. J Neural Transm 2007; 114:211–217

Residual Dyskinesia



Hauser et al. Front. Neurol. 12:645706. doi: 10.3389/fneur.2021.645706

Falls

- Are common in PD
- Are associated with decreased QoL
- Increase in likelihood as PD progresses (up to a point)
- May be due to multiple causes
  - ➢Balance impairment
  - ➢Freezing/festinating
  - ➢Orthostatic hypotension
  - ➢Cognitive/attention deficits

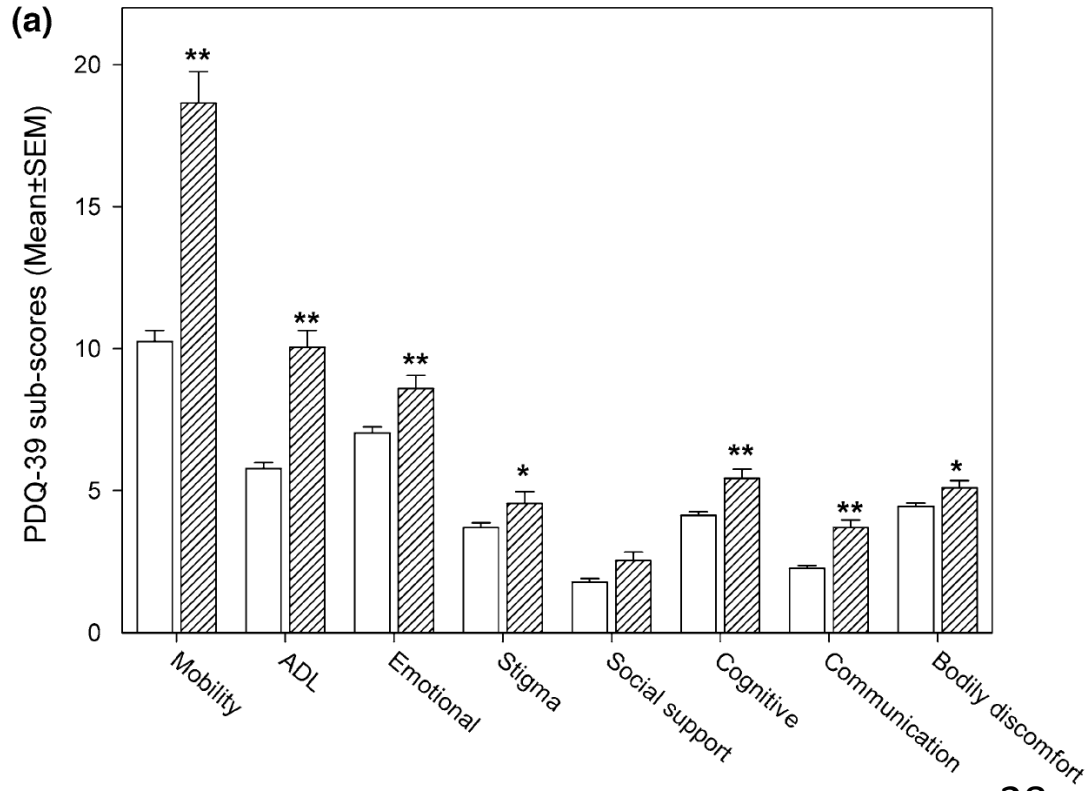


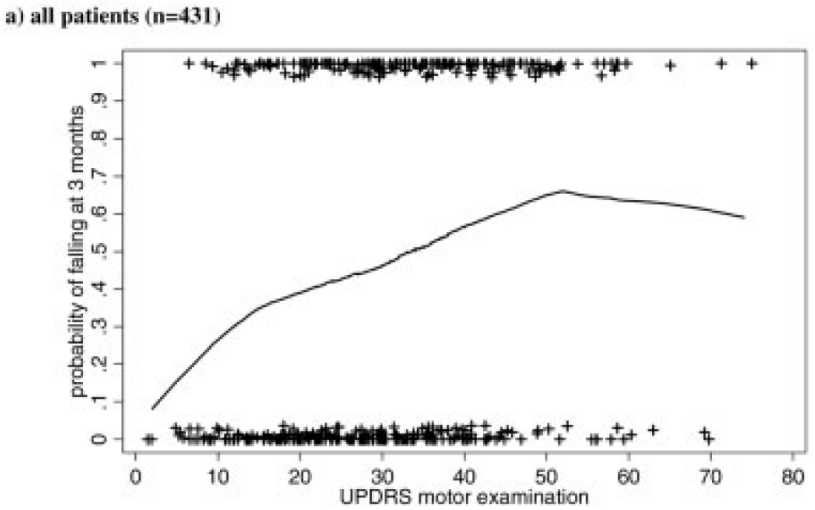
Fig. 1 PDQ-39 scores in patients with or without falls in ON state (in blank or dashed bars, respectively). *p\0.05, **p\0.01 (Student's T test with step-down Holms correction for multiple comparisons).
Higher scores of the PDQ-39 reflect worse Quality of Life.

Rascol et al. J Neural Transm 2015;122:1447–1455

A Meta-Analysis of Six Prospective Studies of Falling in Parkinson's Disease

Ruth M. Pickering, RM, BSc, MSc, PhD, CStat,[1] Yvette A.M. Grimbergen, YAM, MD,[2] Una Rigney, BSc, MSc,[1] Ann Ashburn, PhD, MPhil, FCSP,[3] Gordon Mazibrada, MD,[4] Brian Wood, MBChB, MD, FRCP,[5] Peggy Gray, RN, BScN,[6] Graham Kerr, BSC, MPhEd, PhD,[7] and Bastiaan R. Bloem, MD, PhD[2,8]*

- Pooled six prospective studies of falling in PD (n=473)
- The 3-month fall rate was 46% (95% confidence interval: 38 –54%)
- The best predictor of falling was two or more falls in the previous year (sensitivity 68%; specificity 81%).
- Even among subjects without prior falls, this fall rate was 21% (12–35%)
- Injuries were common and occurred in about a quarter of subjects



Mov Disord 2007;22:1892–1900

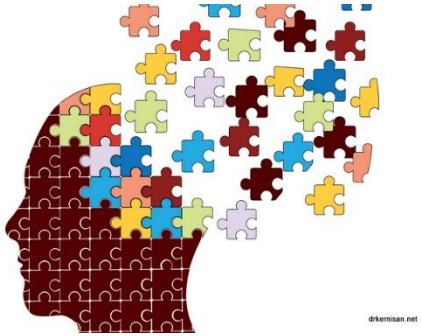
Natural history of falls in a population-based cohort of patients with Parkinson's disease: An 8-year prospective study

Ylva Hivand Hiorth [a, *], Jan Petter Larsen [a], Kirsten Lode [a], Kenn Freddy Pedersen [a, b]

- Among non-fallers at baseline (n=124), the rate of new current fallers was 38% (35 of 92) at 4 years and 68% at 8 years (13 at 4 years and 19 new current fallers)
- Among 64 patients participating in all three study visits, prevalence of falls increased from 27% (n = 17) at baseline to 38% (n = 24) at 4 years and 72% (n = 46) after 8 years.

Parkinsonism and Related Disorders 2014;20:1059-064

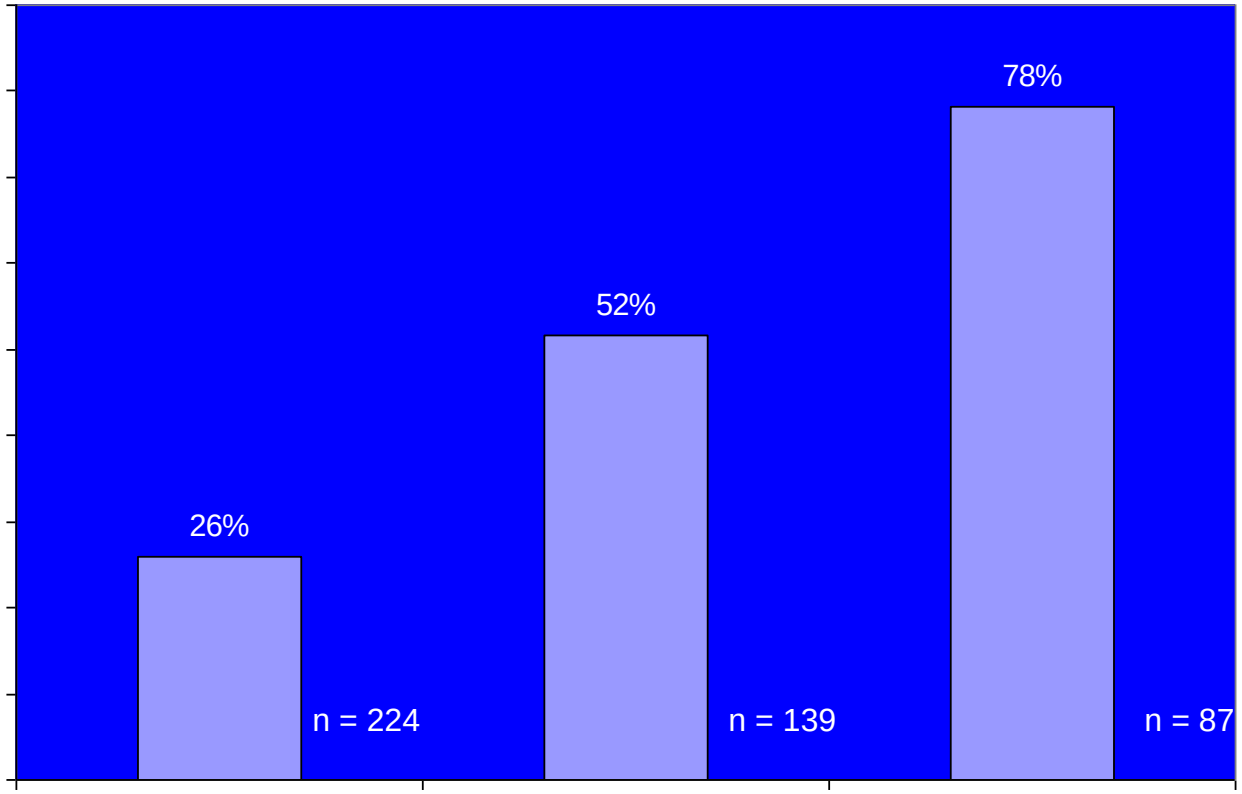
Dementia in PD



- Associated with reduced quality of life[1]
- Shortened survival[2]
- Increased caregiver distress[3]
- Community-based studies have estimated the point prevalence for dementia in PD to be between 28% and 44%[4-7]

1. Schrag A, Jahanshahi M, Quinn N. Mov Disord 2000;15:1112–1118.
2. Nussbaum M, Treves TA, Inzelberg R, Rabey JM, Korczyn AD. Parkinsonism Rel Disord 1998;4:179–181.
3. Aarsland D, Larsen JP, Karlsen K, Lim NG, Tandberg E. Int J Geriatr Psych 1999;14:866–874.
4. Mayeux R, Denaro J, Hemenegildo N, Marder K, Tang MX, Cote LJ, Stern Y. Arch Neurol 1992;49:492–497.
5. Aarsland D, Tandberg E, Larsen JP, Cummings JL. Arch Neurol 1996;53:538–542.
6. Hobson P, Meara J. Mov Disord 2004;19:1043–1049.
7. Marttila RJ, Rinne UK. Dementia in Parkinsons-Disease. Acta Neurol Scand 1976;54:431–441.

Prevalence of Dementia in PD
A Longitudinal Study



Mean disease duration
BL, all pts = 9.2 yrs
At time of PDD = 13.8 yrs

Dementia rates increased by 26% every 4 years when PD patients were followed longitudinally

Aarsland et al. *Arch Neurol*. 2003;60:387-392.

Nonmotor Symptoms in Nursing Home Residents with Parkinson's Disease: Prevalence and Effect on Quality of Life

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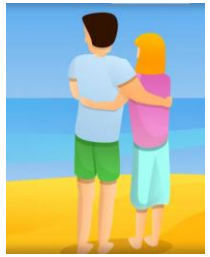
Table 3. Prevalence of Individual Non-Motor Symptoms Scale Items

Item Number and Symptom	n (%)
4. Fatigue	56 (78.9)
22. Urgency[a]	51 (75.0)
17. Forget things or events	49 (69.0)
10. Seem sad	47 (66.2)
8. Lack motivation	45 (63.4)
19. Saliva	45 (63.4)
3. Daytime sleep	43 (60.6)
7. Lost interest surroundings	43 (60.6)
23. Frequency[a]	40 (58.8)
24. Nocturia[a]	39 (57.4)
16. Concentration	40 (56.3)
6. Restless legs	38 (53.5)
9. Feel nervous	38 (53.5)
5. Difficulty falling asleep	37 (52.1)
18. Forget to do things	36 (50.7)
1. Light headedness	34 (47.9)
21. Constipation	34 (47.9)
20. Swallowing	30 (42.3)
12. Difficulty experiencing pleasure	27 (38.0)
11. Flat mood	25 (35.2)
15. Double vision	25 (35.2)
13. Hallucinations	17 (23.9)
27. Pains	17 (23.9)
30. Excessive sweating	15 (21.1)
14. Delusions	14 (19.7)
29. Weight change	13 (18.3)
28. Taste or smell	8 (11.3)
25. Interest in sex	4 (5.7)
26. Problems having sex	4 (5.7)
2. Fainting	4 (5.6)

[a]The urinary domain was incompletely collected in three residents because of an indwelling catheter.

- Quality of life was poor, and was largely determined according to the presence and severity of NMS.
- Each resident endorsed a mean of 12.9 items on the NMSS.
- Autonomic problems were highly prevalent - urinary urgency (75%), nocturia (57%), and constipation (48%).
- Depression was present in 45.1%.
- Sleep-related complaints were common.
- The percentage of residents fulfilling criteria for PDD was 56.9% on the MMSE and 77.1% on the SCOPA-Cog

J Am Geriatr Soc 61:1714–1721, 2013.



The non-motor side of the honeymoon period of Parkinson's disease and its relationship with quality of life: a 4-year longitudinal study

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Table 1 Evolution of non-motor symptoms and domains over 4 years from diagnosis

	Baseline	2-year evaluation	4-year evaluation	Percentage change (4 years vs. 2 years)
Gastrointestinal domain	47.2[a]	65.3[b,d]	89.2[c,d]	
Dribbling	19.4[c]	15.3[d]	33.8[c,d]	+120.9%
Taste/smell	25.0[c]	19.4[d]	44.6[c,d]	+129.9%
Swallowing difficulty	11.1[c]	5.6[d]	22.9[c,d]	+308.9%
Nausea/vomiting	1.4[c]	2.6[d]	14.8[c,d]	+469.2%
Constipation	11.1[a]	23.6[a,d]	48.6[a,d]	+105.9%
Bowel incontinence	–	–	–	–
Incomplete emptying	12.5	10.9	13.5	+23.8%
Urinary domain	29.2[c]	25.0[d]	51.3[c,d]	
Urgency	18.1[c]	19.4[d]	35.1[c,d]	+80.9%
Nocturia	13.8[c]	8.3[d]	29.7[c,d]	+257.83%
Attention/memory domain	44.4	40.3[d]	56.7[d]	
Memory	19.4[c]	25.0[d]	36.5[c,d]	+46%
Loss of interest	30.5[c]	20.8[d]	40.5[c,d]	+94.7%
Concentration	18.0	16.7	29.7	+77.8%
Hallucinations domain	1.4	5.6	13.5	
Hallucinations	1.4[c]	2.8[d]	12.2[c,d]	+355.7%
Delusion	–	2.8	2.7	−3.5%
Mood domain	65.3[b]	48.6[b,d]	67.6[d]	
Sad, blue	43.1[b]	25.3[b,d]	52.7[d]	+108.3%
Anxiety	59.7[b]	40.3[b]	48.6	+20.6%
Sexual domain	11.1[a]	26.4[b]	28.3[a]	
Sex drive	–	4.1[d]	18.9[d]	+360.9%
Sex difficulties	11.1[b]	23.6[b]	22.9	−2.9%
Cardiovascular domain	16.6[c]	8.3[d]	33.8[c,d]	
Dizziness	16.6[c]	8.3[d]	27.0[c,d]	+225.3%
Falls	–	–	12.1[c,d]	NA
Sleep domain	50.0[c]	54.2	68.9[c]	
Daytime sleepiness	2.8[c]	8.3[d]	32.4[c,d]	+290.3%
Insomnia	20.8	22.9	25.7	+12.2%
Vivid dreams	11.1[c]	13.9[d]	29.7[c,d]	+113.6%
Acting out	37.5	33.8	33.8	–
Restless legs	4.6	6.5	16.3[c,d]	+150.7%
Miscellaneous domain	26.4[a]	51.4[a,d]	72.9[a,d]	
Pain	9.7[c]	20.8[d]	35.1[c,d]	+68.7%
Weight change	5.5[a]	23.6[b]	21.6[c]	−8.5%
Swelling	6.9	8.3	13.5	+62.6%
Sweating	5.5	8.3	10.8	+30.1%
Double vision	5.5	12.5	22.9	+83.2%

[a]Baseline vs. all, $P < 0.01$. [b]Baseline vs. 2 years, $P < 0.01$. [c]Baseline vs. 4 years, $P < 0.01$. [d]2 years vs. 4 years, $P < 0.01$.

91 Consecutive de-novo (disease duration < 2 years), untreated patients with PD were enrolled in this observational study

- The large majority of NMSs significantly increased in prevalence at 4 years.
- NMSs showing the highest percentage change (> 150%) between 2 and 4 years were: swallowing difficulties, nausea/vomiting, nocturia, hallucinations, sex drive, dizziness, daytime sleepiness and restless leg syndrome
- There were no associations with medications (i.e. L-dopa, DA, etc.) or total LEDD for any of these NMSs except for daytime sleepiness

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The bodily discomfort dimension of the PDQ-39 significantly worsened from year 2 to year 4

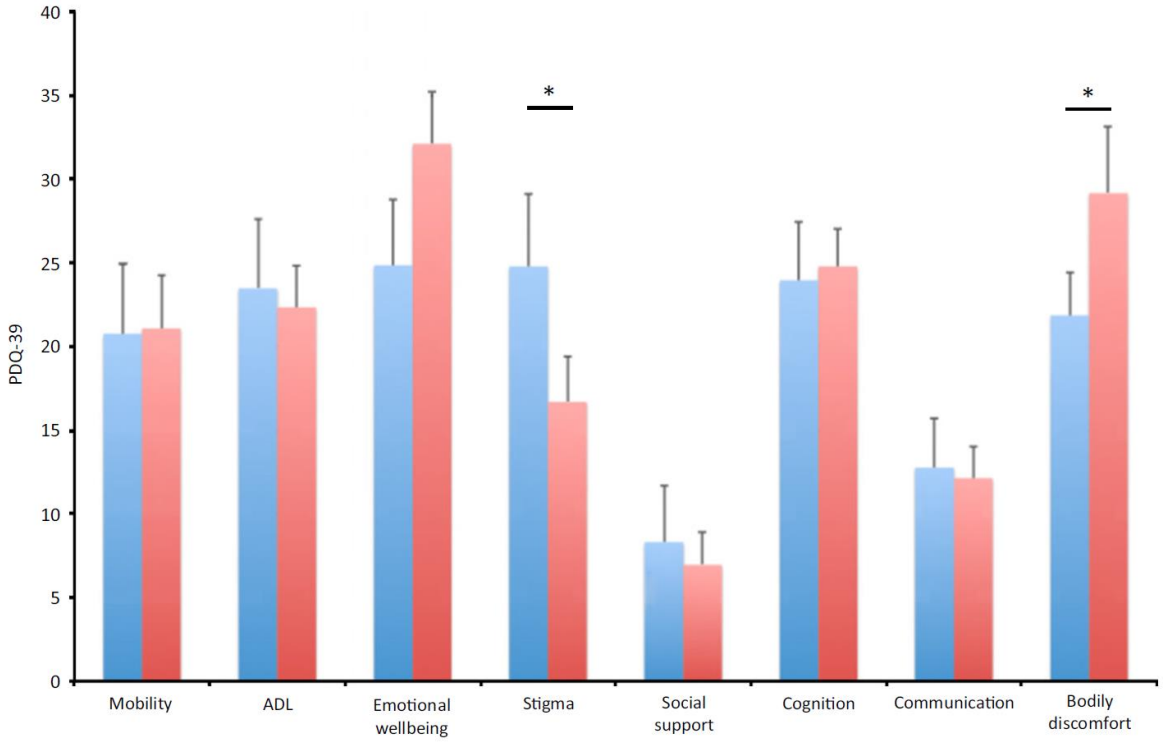

Figure 1 Dimensions of the Parkinson's Disease Questionnaire-39 (PDQ-39) at 2 years (left blue columns) and 4 years (right red columns). Error bars represent SDs. ADL, activities of daily living. *$P < 0.01$.

There was a significant difference in the motor burden among PDQ-39 quartiles (Kruskal–Wallis v2 = 7.9; P < 0.05). There was a significant difference among the subgroups for the nonmotor burden (Kruskal–Wallis v2 = 14.4; P < 0.01).

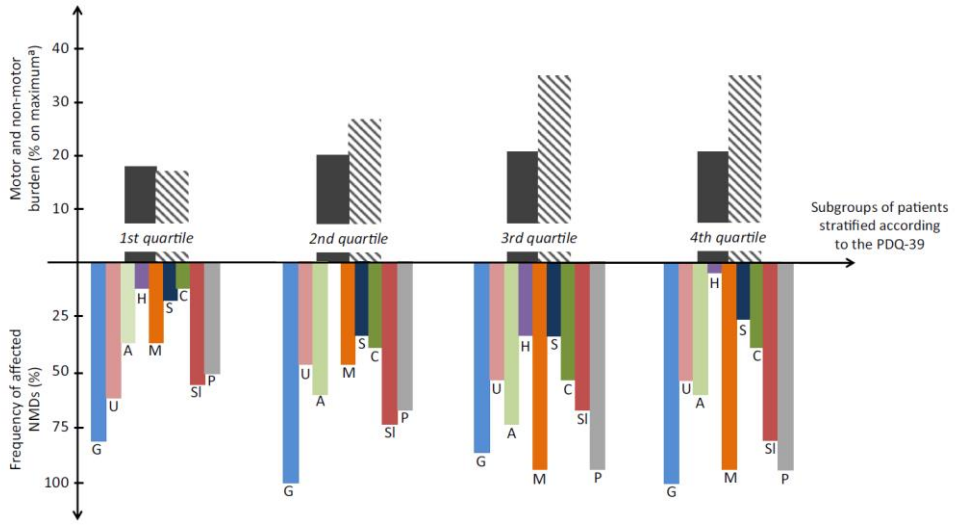

Figure 2 Upper panel: motor (plain columns) and non-motor (striped columns) burden across Parkinson's Disease Questionnaire-39 (PDQ-39) quartiles. Lower panel: prevalence of non-motor domains (NMDs). [a]These are calculated as a percentage of the highest Unified Parkinson's Disease Rating Scale, part-3 and Non-Motor Symptoms Questionnaire score, respectively (see text for details). G, gastrointestinal domain; U, urinary domain; A, attention/memory domain; H, hallucinations domain; M, mood domain; S, sexual domain; C, cardiovascular domain; Sl, sleep domain; P, miscellaneous domain.

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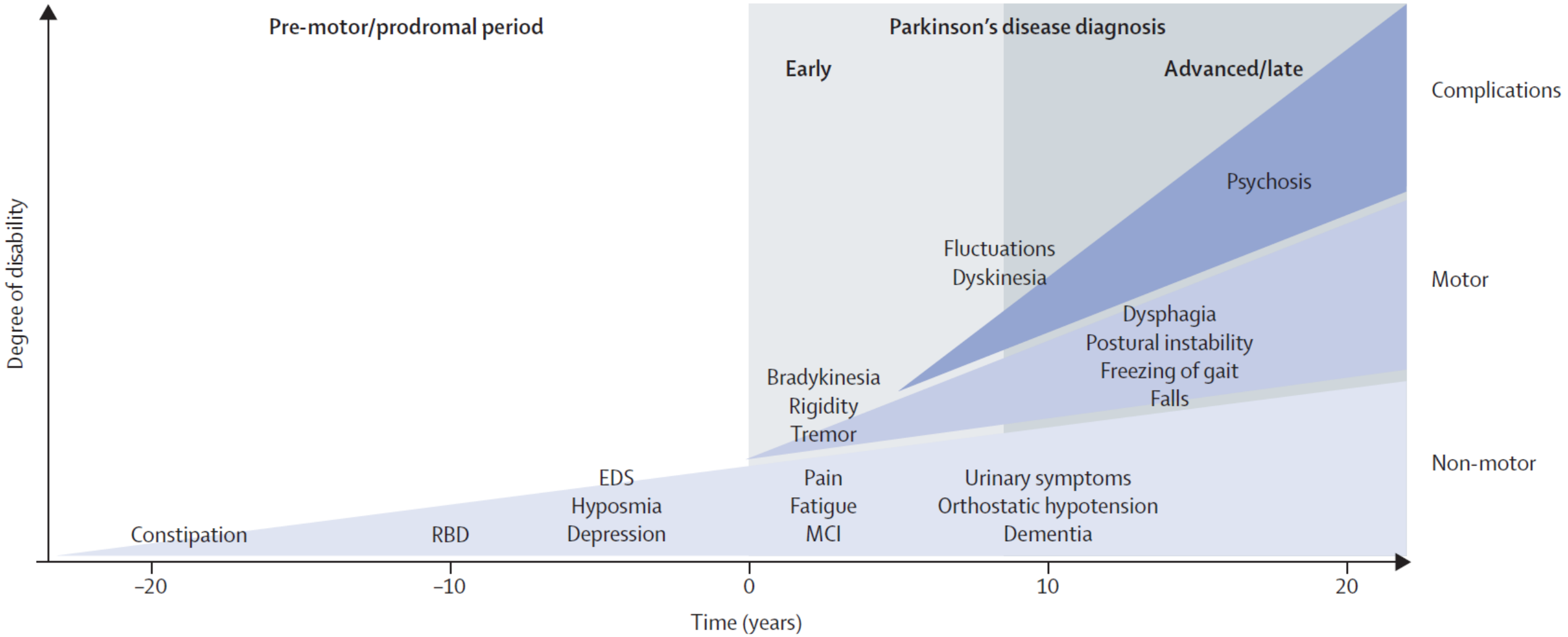

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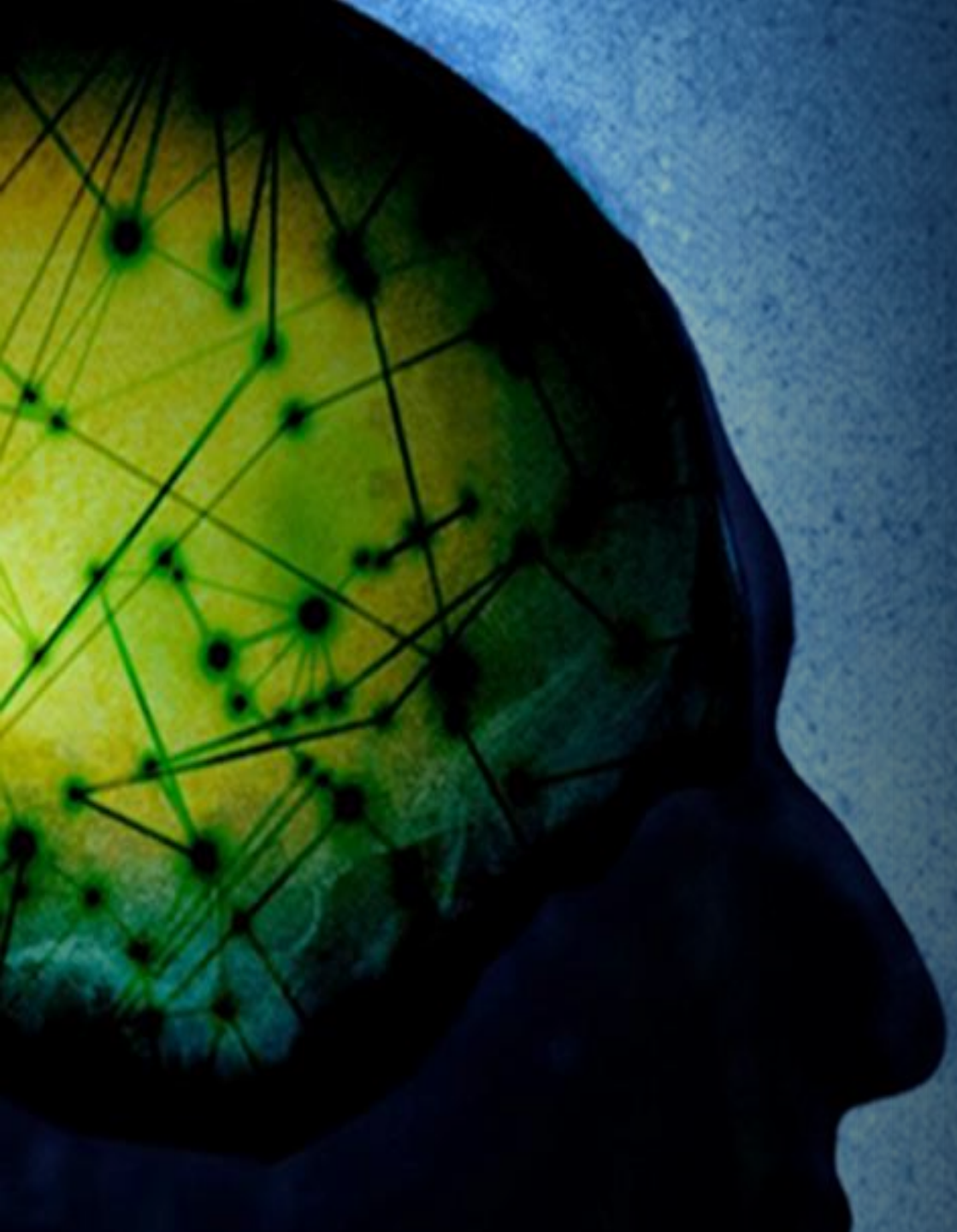

Q&A

Targeting c-Abl we believe is transformational to treatment of Parkinson's disease