Novel approaches to the pharmacological treatment of Parkinson's disease

Peter Jenner
King's College
UK

Disclosures and Disclaimers

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- The content of this presentation is the responsibility of the speaker and does not necessarily reflect the views of the ICPOEP Organising Committee or COLAR Marketing Solution Ltd

Objectives

- To discuss changing concepts on the nature of Parkinson's disease
- To understand how this might impinge on clinical trial design
- To briefly discuss new approaches to treatment – dopaminergic and non-dopaminergic
- The dilemma of treating non-motor symptoms

Current drug treatment of Parkinson's disease

- L-dopa
- Decarboxylase inhibitors – carbidopa, benserazide

- COMT inhibitors – entacapone, tolcapone
- MAO-B inhibitors – selegiline, rasagiline
- Combination forms – Stalevo
- Controlled release – Sinemet CR
- Dispersible – Madopar dispersible
- Liquid formulations – L-dopa methyl ester

- Intraduodenal administration - DuoDopa

- Ropinirole
- Pramipexole

- Pergolide
- Bromocriptine
- Cabergoline

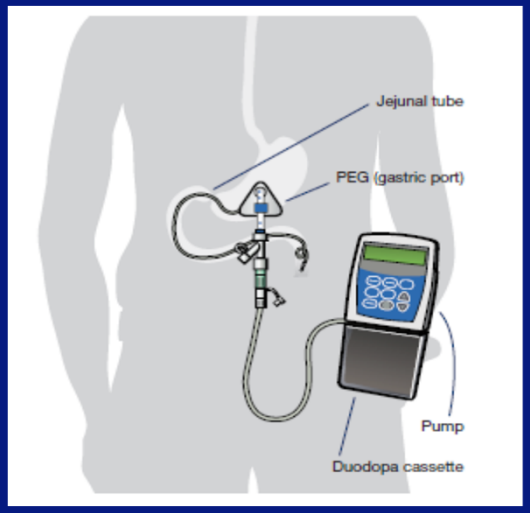
- Extended release – Requip XL
- Transdermal administration – NeuPro
- Rescue therapy – Apokyn

- Subcutaneous infusion - apomorphine

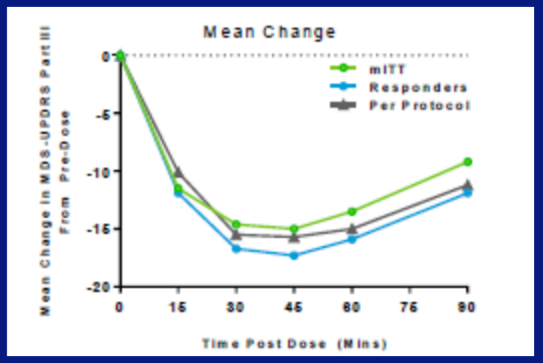
New levodopa formulations – overview

Description	Route	Name	Company
Extended-release CD-LD	Oral	IPX066, Rytary, Numient	Impax
LD prodrug	Oral	XP21279(-CD)	XenoPort
Gastroretentive CD/LD	Oral	DM-1992	DepoMed
Accordion pill CD/LD	Oral	AP-CD/LD	Intec Pharma
Microtablets LD/CD 5/1.25	Oral	LC-5, Flexilev	Sensidose
LD/CD oral device	Oral	DopaFuse	SynAgile
Metal coordinated LD	Oral	MCP-311 bismuth-levodopa	Synthonics
Liquid LD methylester+CD	Oral	Sirio, V1512, melevodopa	Chiesi
Inhaled LD	Pulmonary	CVT-301	Acorda
LD/CD for patch-pump	sc	ND0612L/H	Neuroderm
LD solution	sc/iv	Infudopa	Dizlin
LD/EN/CD intestinal gel	Intestinal	Lecigon	Lobsor

Device orientated drug delivery in Parkinson's disease



APL-130277 – sublingual apomorphine



APL-130277:

- Rapidly converted PD patients' morning OFF to full ON
- Provided statistically significant and clinically meaningful improvement in motor function as assessed by MDS-UPDRS Part III scores

Average duration of benefit was nearly 60 mins, and most patients had a sustained benefit through 90 mins

Phase 3 studies are underway

- APL-130277 is an apomorphine delivery system using a sublingual, thin film strip which rapidly dissolves when placed under the tongue.
- APL-130277 quickly produces blood levels in normal volunteers that in patients with PD are known to restore relatively normal motor function
- Avoids first pass metabolism

Cynapsus Therapeutics

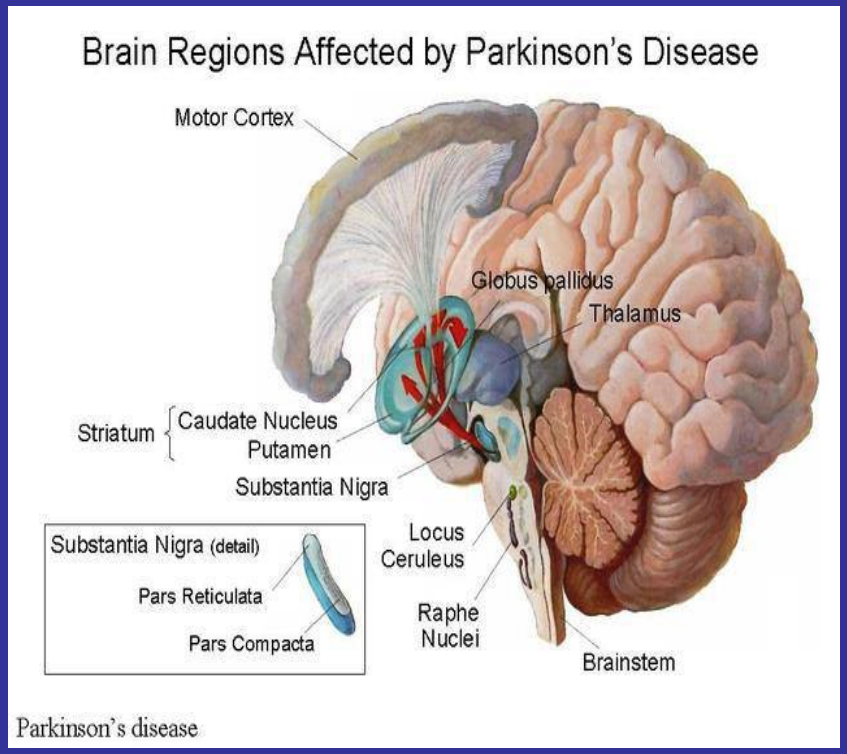
Hauser, R. et al., 2016

Pathology and biochemistry is wide and diverse

REVIEW CME

Neuropathology of Sporadic Parkinson's Disease: Evaluation and Changes of Concepts

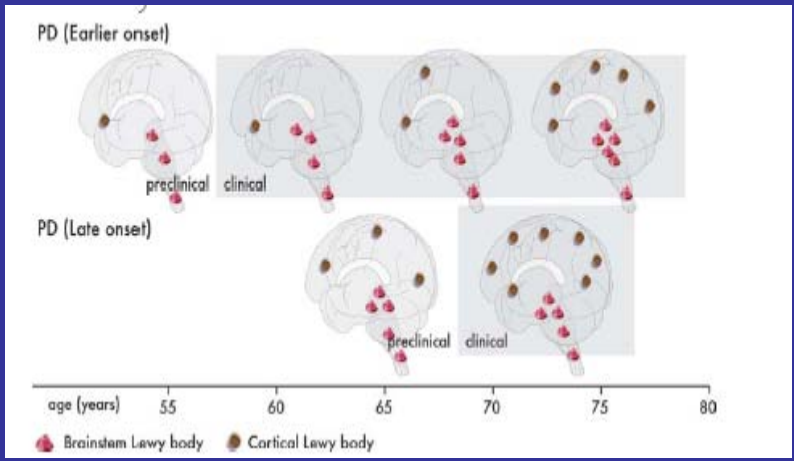
Kurt A. Jellinger, MD*
Institute of Clinical Neurobiology, Vienna, Austria



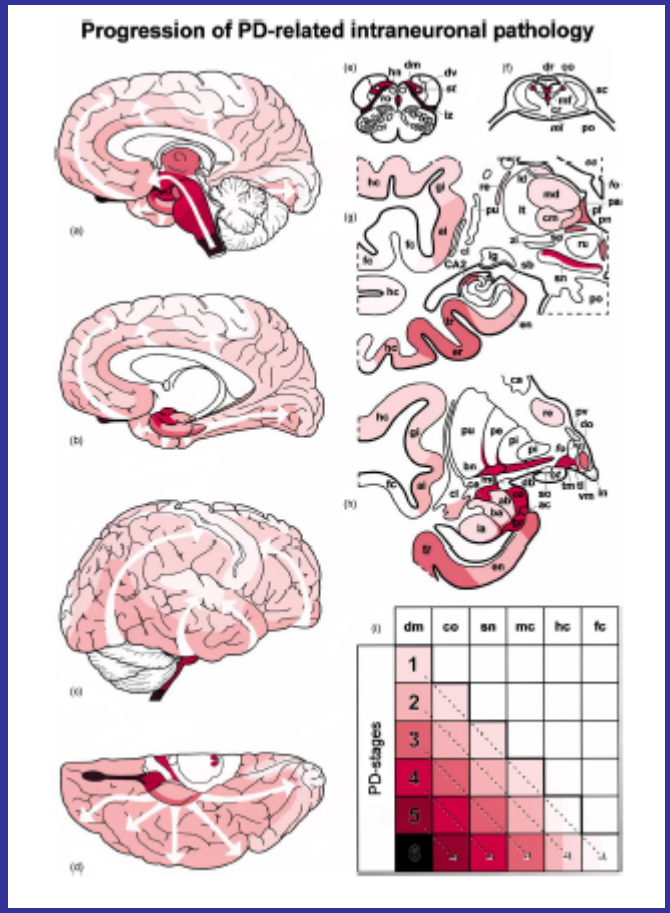
'Parkinson's disease (PD) is no longer considered a complex motor disorder characterized by extrapyramidal symptoms, but a progressive multisystem or — more correctly multi-organ disease with variegated neurological and non-motor deficiencies'

1. Parkinson's is a multi-organ disorder: CNS and extra-CNS
2. Parkinson's is a multi-peptide dysfunction related disorder
3. Non-DA involvement may be greater than DA involvement

Parkinson's disease has a spreading but variable pathology

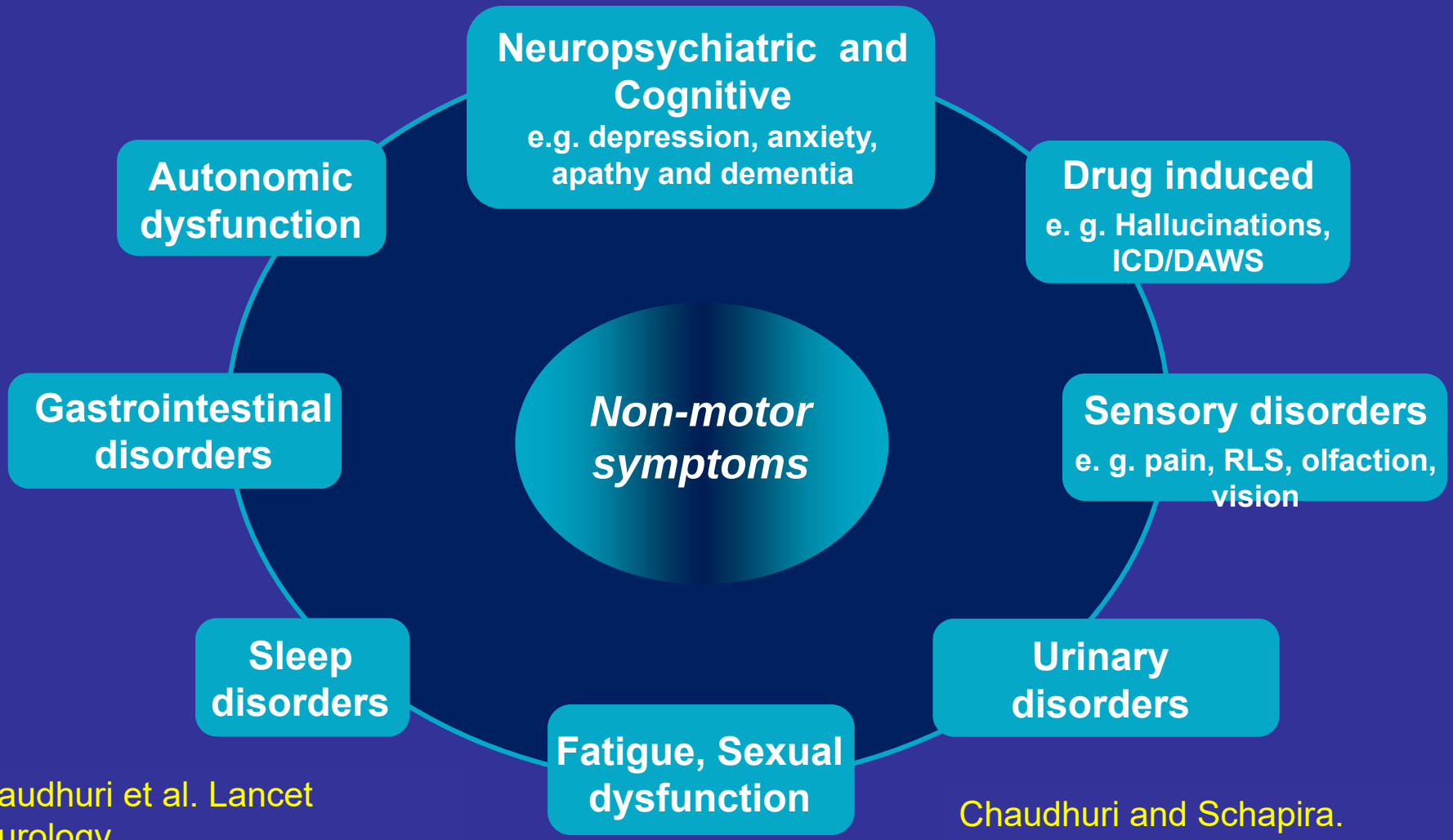


- Pathology sweeps through the brain
- No agreement on the origin or pattern
- Not just a basal ganglia disease



Braak et al, 2003; Halliday et al, 2011

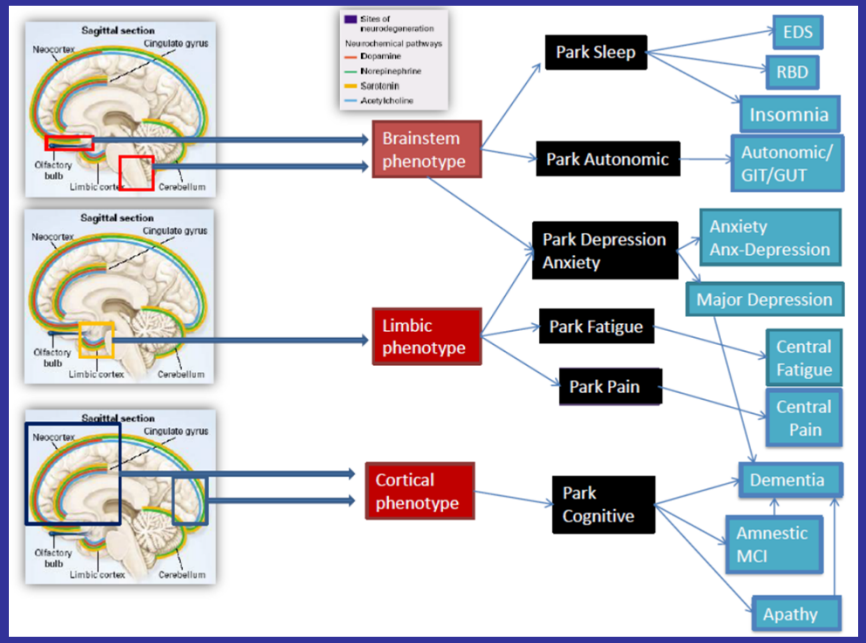
Non-motor symptoms – early and late in the progression of Parkinson's disease



Chaudhuri et al. Lancet Neurology 2006;5:235-245

Chaudhuri and Schapira. Lancet Neurology 2009

Subtype based on phenotype



- PD - sleep
- PD - pain
- PD – depression
- PD-cognitive
- PD – fatigue
- PD - autonomic

- NMS - with ‘OFF’
- NMS – no effect of ‘OFF’

Chaudhuri et al., 2016

Parkinson's disease as a syndrome

Table 1 Parkinson's disease subtypes identified by data driven studies

Author, year	Subtypes identified
Graham 1999[3]	Short duration (mean 5 years): 1. Good motor control without cognitive impairment 2. Good motor control, executive cognitive deficits 3. Older age at onset, poor motor control + complications, mild cognitive impairment Longer duration (mean 14 years): 1. Poor motor control, no cognitive impairment 2. Poor motor control, moderately severe cognitive impairment
Gasparoli 2002[4]	1. Rapid progression 2. Slow progression
Dujardin 2004[5]	1. Mild motor impairment, relatively preserved cognition 2. 'Reduced overall cognitive efficiency', subcorticofrontal syndrome and more severe motor dysfunction
Lewis 2005[6]	1. Young onset 2. Non-tremor dominant, cognitive impairment and depression 3. Rapid progression without cognitive impairment 4. Tremor dominant
Schrag 2006[7]	1. Young onset 2. Older onset, more rapid progression, less dyskinesias and fluctuations
Post 2008[8]	1. Young onset with slow progression 2. Intermediate age onset with anxiety and depression 3. Oldest onset
Reijnders 2009[9]	1. Rapid progression 2. Young onset with motor complications 3. Non-tremor dominant and psychopathology 4. Tremor dominant
Van Rooden 2011[10]	1. Mild all domains, young 2. Severe motor complications, sleep and depressive symptoms, youngest 3. Medium severity, older 4. Most severe, except mild tremor, prominent motor complications, older
Liu 2011[11]	1. Non-tremor dominant 2. Rapid disease progression 3. Young onset 4. Tremor dominant

- Different clinical presentations
- Different genetic backgrounds
- Late versus early onset
- Slow versus rapid progression
- Akinetic-rigid versus tremor dominant
- Different response to drugs

Marras and Lang (2013)

Queen Square Brain Bank Diagnostic Criteria

Step 1 Diagnosis of parkinsonian syndrome
Bradikinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude or repetitive actions)
And at least one of the following:
- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease
- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Oculogyric crises
- Neuroleptic treatment at onset of symptoms
- More than one affected relative
- Sustained remission
- Strictly unilateral features after 3 years
- Supranuclear gaze palsy
- Cerebellar signs
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Babinski signs
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan
- Negative response to large doses of L-dopa (if malabsorption excluded)
- MPTP exposure

Step 3 Supportive prospective positive criteria of Parkinson's disease
Three or more required for diagnosis of definite Parkinson's disease:
- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side onset most
- Excellent response (70–100%) to L-dopa
- Severe L-dopa-induced chorea
- L-dopa response for 5 years or more
- Clinical course of 10 years or more
- Hyposmia
- Visual hallucination

Queen Square brain bank clinical diagnostic criteria

Lancet 2009; 373: 2055–66

- Commonly used to select patients for clinical trial
- Motor signs based diagnosis
- NMS may be an exclusion factor

Staging of Parkinson's disease

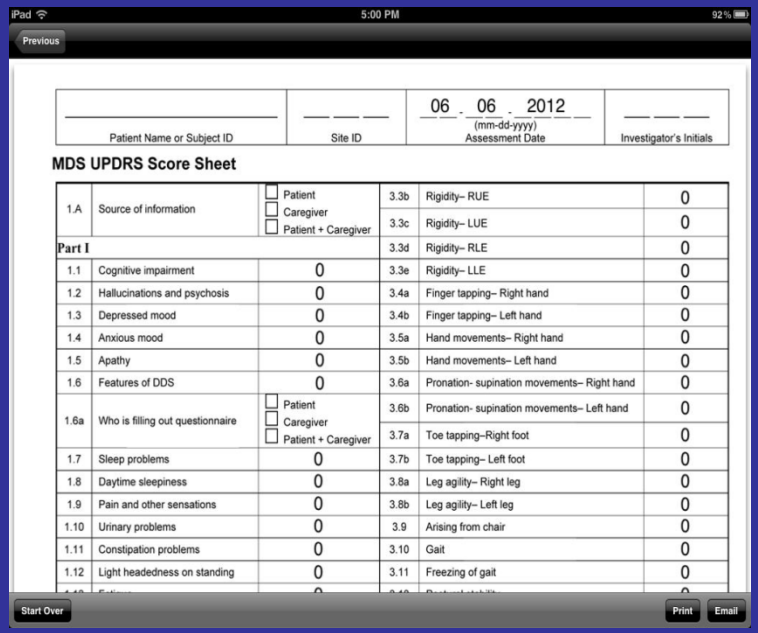
MODIFIED HOEHN AND YAHR STAGING

Stage 0	—No signs of disease.
Stage 1	—Unilateral disease.
Stage 1.5	—Unilateral plus axial involvement.
Stage 2	—Bilateral disease, without impairment of balance.
Stage 2.5	—Mild bilateral disease with recovery on pull test.
Stage 3	—Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4	—Severe disability; still able to walk or stand unassisted.
Stage 5	—Wheelchair bound or bedridden unless aided.

- PD staging is based on motor signs and disability
- Commonly used to select and balance patient groups in clinical trials

Goetz et al. Mov Disord. 2004;19:1010-8

UPDRS as a clinical tool



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Previous

Patient Name or Subject ID	Site ID	06 - 06 - 2012 (mm-dd-yyyy) Assessment Date	Investigator's Initials

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.3b	Rigidity– RUE	0
			3.3c	Rigidity– LUE	0
Part I			3.3d	Rigidity– RLE	0
1.1	Cognitive impairment	0	3.3e	Rigidity– LLE	0
1.2	Hallucinations and psychosis	0	3.4a	Finger tapping– Right hand	0
1.3	Depressed mood	0	3.4b	Finger tapping– Left hand	0
1.4	Anxious mood	0	3.5a	Hand movements– Right hand	0
1.5	Apathy	0	3.5b	Hand movements– Left hand	0
1.6	Features of DDS	0	3.6a	Pronation- supination movements– Right hand	0
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver	3.6b	Pronation- supination movements– Left hand	0
			3.7a	Toe tapping–Right foot	0
1.7	Sleep problems	0	3.7b	Toe tapping– Left foot	0
1.8	Daytime sleepiness	0	3.8a	Leg agility– Right leg	0
1.9	Pain and other sensations	0	3.8b	Leg agility– Left leg	0
1.10	Urinary problems	0	3.9	Arising from chair	0
1.11	Constipation problems	0	3.10	Gait	0
1.12	Light headedness on standing	0	3.11	Freezing of gait	0

Start Over Print Email

- UPDRS does not reflect the progression or severity of non-motor symptoms
- Individual patients may have a mild or low UPDRS score but high NMSS burden or vice versa

UPDRS is almost universally used to assess drug effect in clinical studies

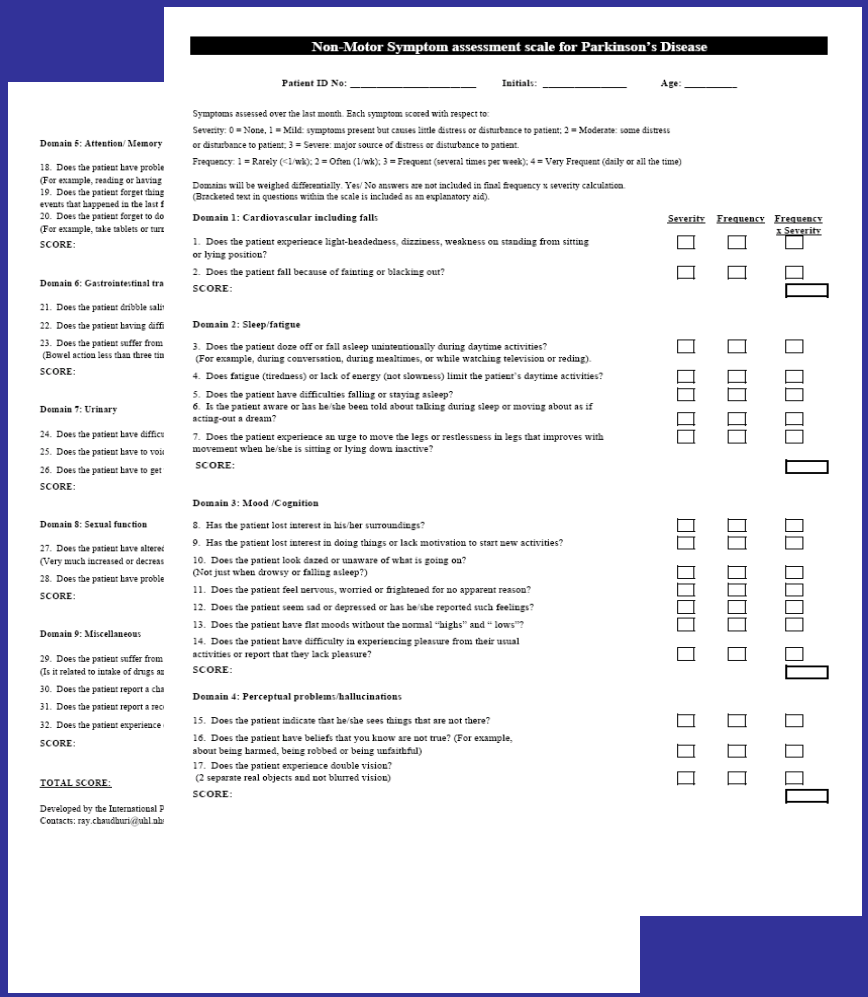
OPEN ACCESS Freely available online PLOS ONE

A Proposal for a Comprehensive Grading of Parkinson's Disease Severity Combining Motor and Non-Motor Assessments: Meeting an Unmet Need

Kallol Ray Chaudhuri[1], Jose Manuel Rojo[2], Anthony H. V. Schapira[3], David J. Brooks[4], Fabrizio Stocchi[5], Per Odin[6], Angelo Antonini[7], Richard J. Brown[8], Pablo Martinez-Martin[9]*

1 National Parkinson Foundation Centre of Excellence, Kings College Hospital and Kings College, and University Hospital Lewisham, London, United Kingdom, 2 Department of Statistics, Centre of Human and Social Sciences, Spanish Council for Scientific Research, Madrid, Spain, 3 Institute of Neurology, University College London, London, United Kingdom, 4 Department of Medicine, Imperial College London, London, United Kingdom, 5 Department of Neurology, IRCCS San Raffaele, Rome, Italy, 6 Department of Neurology, Lund University Hospital, Lund, Sweden, 7 Department for Parkinson's Disease, IRCCS San Camillo, Venice, Italy, 8 Department of Psychology, Institute of Psychiatry, Kings College London, London, United Kingdom, 9 Alzheimer Disease Research Unit and CIBERNED, CIEN Foundation, Carlos III Institute of Health, Alzheimer Centre Reina Sofia Foundation, Madrid, Spain

NMSS: a grade rating scale



Non-Motor Symptom assessment scale for Parkinson's Disease

Patient ID No: _____ Initials: _____ Age: _____

Symptoms assessed over the last month. Each symptom scored with respect to:

Severity: 0 = None, 1 = Mild: symptoms present but causes little distress or disturbance to patient; 2 = Moderate: some distress or disturbance to patient; 3 = Severe: major source of distress or disturbance to patient.

Frequency: 1 = Rarely (<1/wk); 2 = Often (1/wk); 3 = Frequent (several times per week); 4 = Very Frequent (daily or all the time)

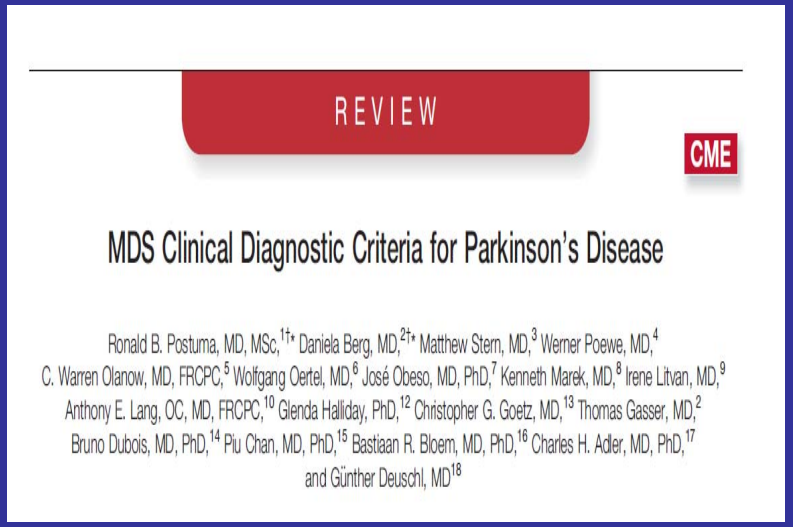
Domains will be weighed differentially. Yes/ No answers are not included in final frequency x severity calculation. (Bracketed text in questions within the scale is included as an explanatory aid).

Domain 1: Cardiovascular including falls	Severity	Frequency	Frequency x Severity
1. Does the patient experience light-headedness, dizziness, weakness on standing from sitting or lying position?	☐	☐	☐
2. Does the patient fall because of fainting or blacking out?	☐	☐	☐
SCORE:			☐
Domain 2: Sleep/fatigue			
3. Does the patient doze off or fall asleep unintentionally during daytime activities? (For example, during conversation, during mealtimes, or while watching television or reding).	☐	☐	☐
4. Does fatigue (tiredness) or lack of energy (not slowness) limit the patient's daytime activities?	☐	☐	☐
5. Does the patient have difficulties falling or staying asleep?	☐	☐	☐
6. Is the patient aware or has he/she been told about talking during sleep or moving about as if acting-out a dream?	☐	☐	☐
7. Does the patient experience an urge to move the legs or restlessness in legs that improves with movement when he/she is sitting or lying down inactive?	☐	☐	☐
SCORE:			☐
Domain 3: Mood /Cognition			
8. Has the patient lost interest in his/her surroundings?	☐	☐	☐
9. Has the patient lost interest in doing things or lack motivation to start new activities?	☐	☐	☐
10. Does the patient look dazed or unaware of what is going on? (Not just when drowsy or falling asleep?)	☐	☐	☐
11. Does the patient feel nervous, worried or frightened for no apparent reason?	☐	☐	☐
12. Does the patient seem sad or depressed or has he/she reported such feelings?	☐	☐	☐
13. Does the patient have flat moods without the normal "highs" and " lows"?	☐	☐	☐
14. Does the patient have difficulty in experiencing pleasure from their usual activities or report that they lack pleasure?	☐	☐	☐
SCORE:			☐
Domain 4: Perceptual problems/hallucinations			
15. Does the patient indicate that he/she sees things that are not there?	☐	☐	☐
16. Does the patient have beliefs that you know are not true? (For example, about being harmed, being robbed or being unfaithful)	☐	☐	☐
17. Does the patient experience double vision? (2 separate real objects and not blurred vision)	☐	☐	☐
SCORE:			☐

- The first comprehensive grade rating scale for PD
  - Addresses 9 domains and 30 questions
  - Complementary to NMSQuest
  - To be administered by healthcare professional
  - Good clinimetrics in two international studies and validated in over 600 patients[1,2]
  - Sensitive to change in clinical trials

Chaudhuri KR *et al.*. *Mov Disord* 2007;22:1901–11;
Martinez-Martin P *et al. Neurology* 2009;73:1584–91.

New MDS Criteria



REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,[1†*] Daniela Berg, MD,[2†*] Matthew Stern, MD,[3] Werner Poewe, MD,[4] C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2] Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17] and Günther Deuschl, MD[18]

REVIEW

CME

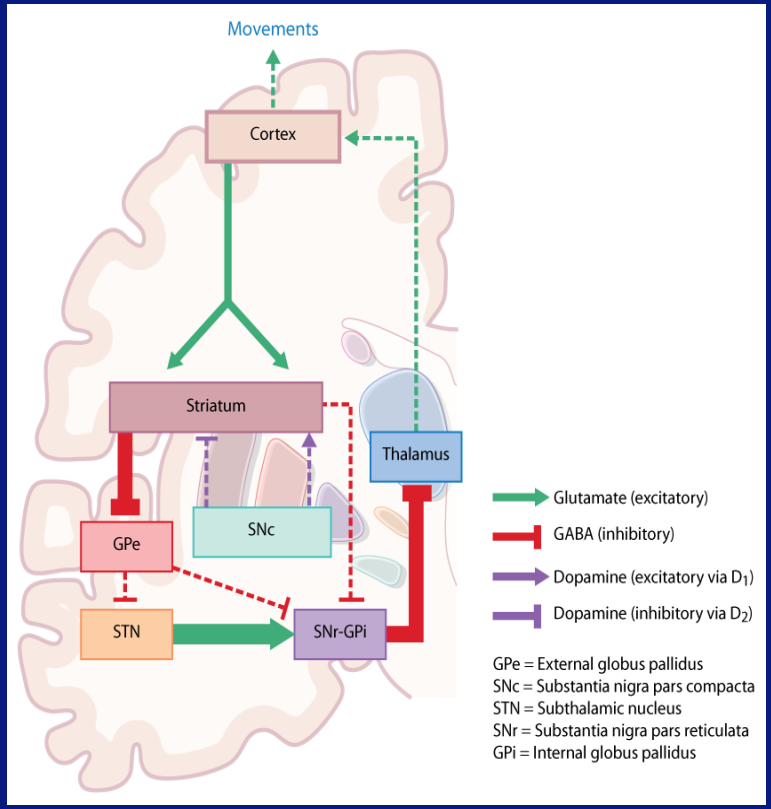
MDS Research Criteria for Prodromal Parkinson's Disease

Daniela Berg, MD,[1*] Ronald B. Postuma, MD, MSc,[2*] Charles H. Adler, MD, PhD,[3] Bastiaan R. Bloem, MD, PhD,[4] Piu Chan, MD, PhD,[5] Bruno Dubois, MD, PhD,[6] Thomas Gasser, MD,[1] Christopher G. Goetz, MD,[7] Glenda Halliday, PhD,[8] Lawrence Joseph, PhD,[9] Anthony E. Lang, OC, MD, FRCPC,[10] Inga Liepelt-Scarfone, PhD,[1] Irene Litvan, MD,[11] Kenneth Marek, MD,[12] José Obeso, MD, PhD,[13] Wolfgang Oertel, MD,[14] C. Warren Olanow, MD, FRCPC,[15] Werner Poewe, MD,[16] Matthew Stern, MD,[17] and Günther Deuschl, MD[18]

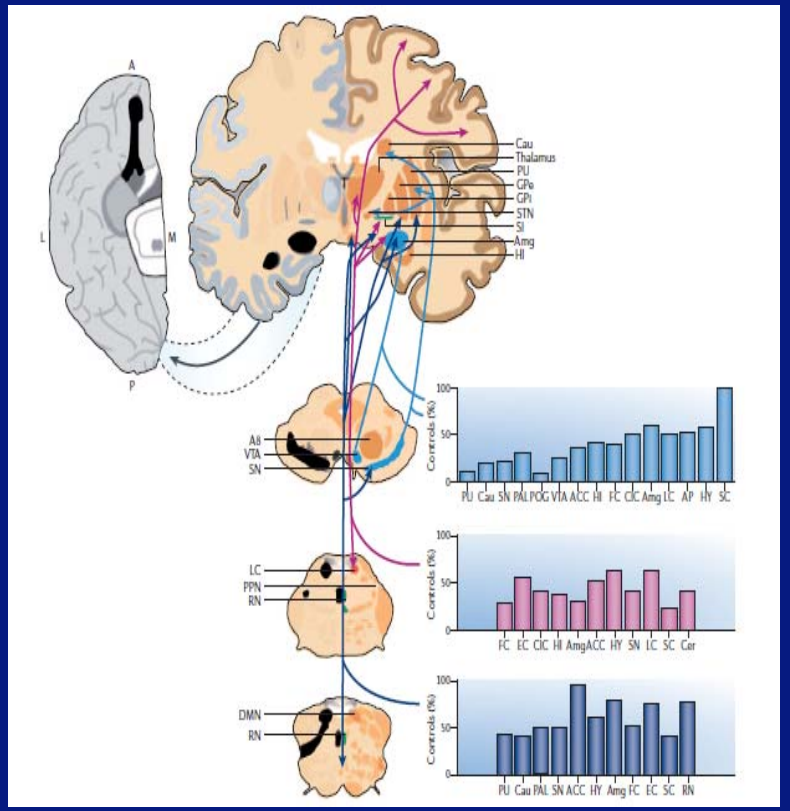
- Motor abnormalities remain central but increasing recognition has been given to non-motor manifestations
- The new criteria represent the first step in the formal delineation of early stages of PD

Non-dopaminergic targets in Parkinson's disease

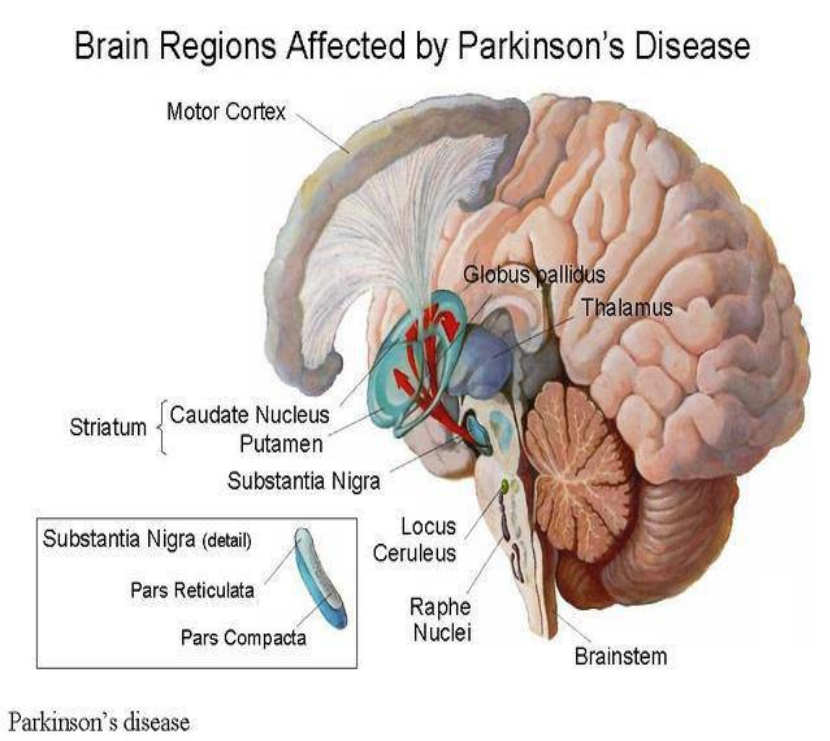
- Alterations in basal ganglia circuitry in non-dopaminergic neurones



- Widespread pathology throughout brain that affects non-dopaminergic neurones

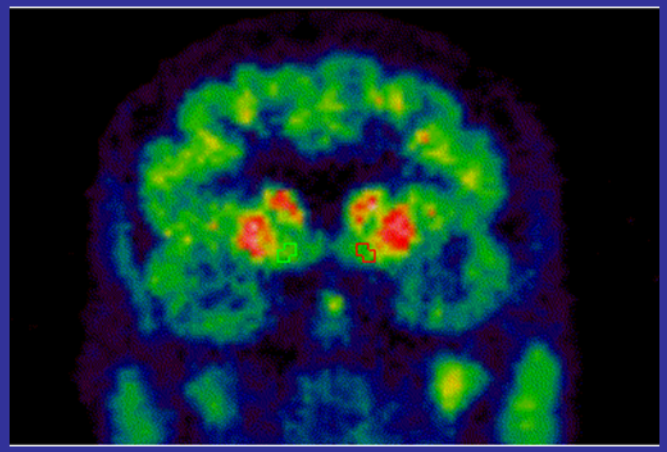


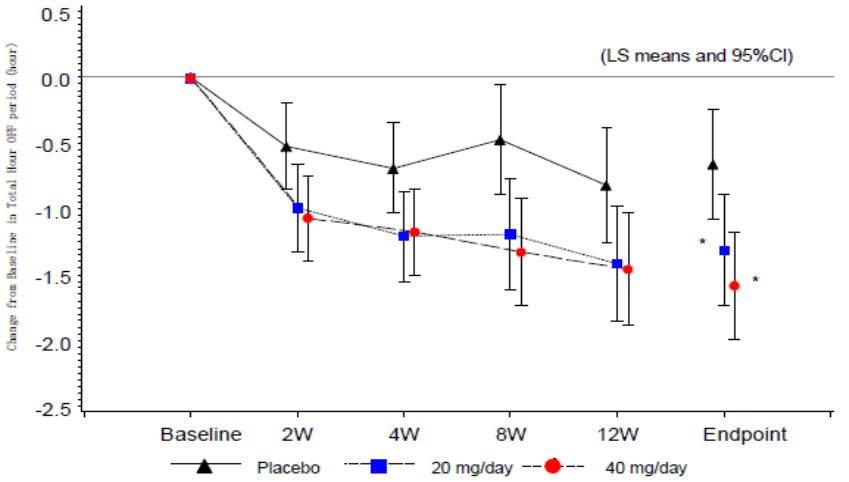
Diverse pathological and biochemical effects offer opportunity



- Non-dopaminergic actions
- Multimodal drugs
- Motor and non-motor symptoms
- Repurposing of existing drugs

Istradefylline – the first in class A2a adenosine antagonist





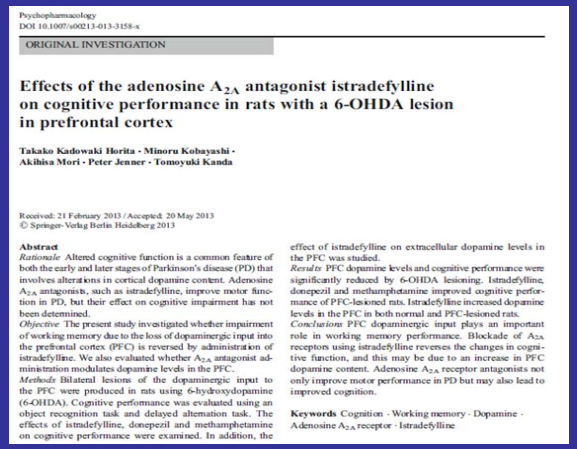
	Placebo (n=118)	20 mg/day (n=115)	40 mg/day (n=124)
Baseline	6.43	6.79	6.55
Change from Baseline at end point	-0.66	-1.31	-1.58
Difference (vs. placebo)	-	-0.65	-0.92
P - value	-	0.013*	<.001*

Williams test *: $P < 0.025$

Nouriast approved in Japan for treatment of Parkinson's disease

Istradefylline and neuropsychiatric disturbance

- Istradefylline active in animal models of depression, anxiety and cognition.
- Potential use in treating motor and non-motor symptoms of PD



Psychopharmacology
DOI 10.1007/s00213-013-3158-x

ORIGINAL INVESTIGATION

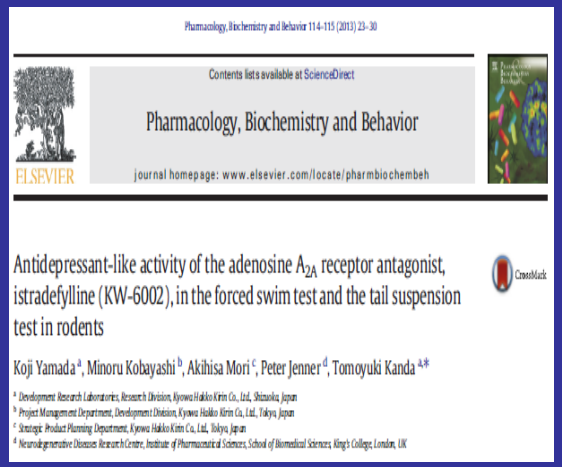
Effects of the adenosine A_{2A} antagonist istradefylline on cognitive performance in rats with a 6-OHDA lesion in prefrontal cortex

Takako Kadowaki Horita · Minoru Kobayashi · Akihisa Mori · Peter Jenner · Tomoyuki Kanda

Received: 21 February 2013 / Accepted: 20 May 2013

Abstract
Rationale Altered cognitive function is a common feature of both the early and later stages of Parkinson's disease (PD) that involves alterations in cortical dopamine content. Adenosine A_{2A} antagonists, such as istradefylline, improve motor function in PD, but their effect on cognitive impairment has not been determined.
Objective The present study investigated whether impairment of working memory due to the loss of dopaminergic input into the prefrontal cortex (PFC) is reversed by administration of istradefylline. We also evaluated whether A_{2A} antagonist administration modulates dopamine levels in the PFC.
Methods Bilateral lesions of the dopaminergic input to the PFC were produced in rats using 6-hydroxydopamine (6-OHDA). Cognitive performance was evaluated using an object recognition task and delayed alternation task. The effects of istradefylline, donepezil and methamphetamine on cognitive performance were examined. In addition, the effect of istradefylline on extracellular dopamine levels in the PFC was studied.
Results PFC dopamine levels and cognitive performance were significantly reduced by 6-OHDA lesioning. Istradefylline, donepezil and methamphetamine improved cognitive performance of PFC-lesioned rats. Istradefylline increased dopamine levels in the PFC in both normal and PFC-lesioned rats.
Conclusions PFC dopaminergic input plays an important role in working memory performance. Blockade of A_{2A} receptors using istradefylline reverses the changes in cognitive function, and this may be due to an increase in PFC dopamine content. Adenosine A_{2A} receptor antagonists not only improve motor performance in PD but may also lead to improved cognition.

Keywords Cognition · Working memory · Dopamine · Adenosine A_{2A} receptor · Istradefylline



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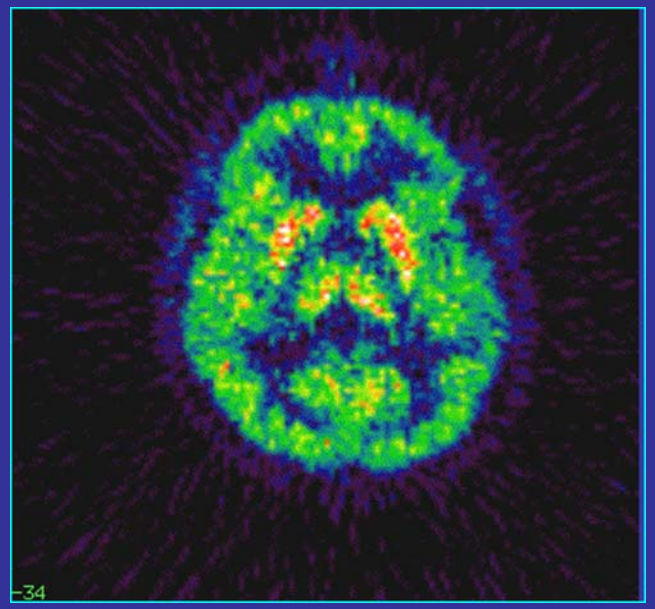
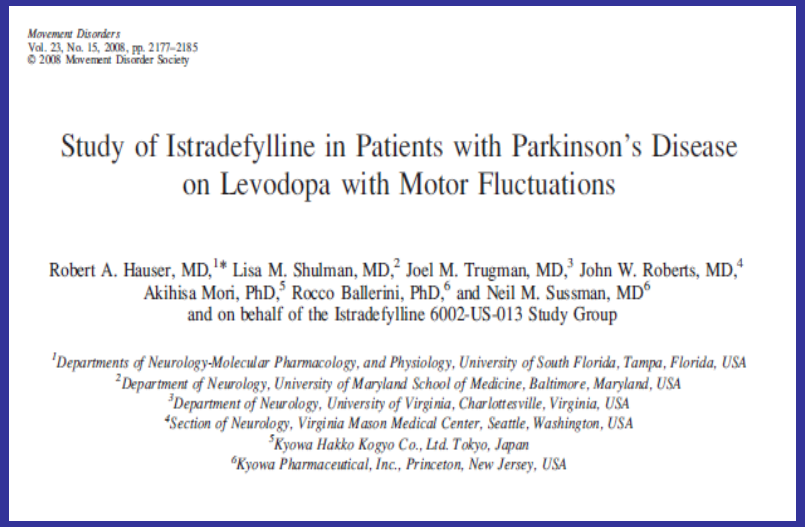
Antidepressant-like activity of the adenosine A_{2A} receptor antagonist, istradefylline (KW-6002), in the forced swim test and the tail suspension test in rodents

Koji Yamada [a], Minoru Kobayashi [b], Akihisa Mori [c], Peter Jenner [d], Tomoyuki Kanda [a,*]

[a] Development Research Laboratories, Research Division, Kyowa Hakko Kirin Co., Ltd., Shizuoka, Japan
[b] Project Management Department, Development Division, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan
[c] Strategic Product Planning Department, Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan
[d] Neurodegenerative Diseases Research Centre, Institute of Pharmaceutical Sciences, School of Biomedical Sciences, King's College, London, UK



Clinical trials should reflect preclinical science



Movement Disorders
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Study of Istradefylline in Patients with Parkinson's Disease on Levodopa with Motor Fluctuations

Robert A. Hauser, MD,[1]* Lisa M. Shulman, MD,[2] Joel M. Trugman, MD,[3] John W. Roberts, MD,[4] Akihisa Mori, PhD,[5] Rocco Ballerini, PhD,[6] and Neil M. Sussman, MD[6]
and on behalf of the Istradefylline 6002-US-013 Study Group

[1]*Departments of Neurology-Molecular Pharmacology, and Physiology, University of South Florida, Tampa, Florida, USA*
[2]*Department of Neurology, University of Maryland School of Medicine, Baltimore, Maryland, USA*
[3]*Department of Neurology, University of Virginia, Charlottesville, Virginia, USA*
[4]*Section of Neurology, Virginia Mason Medical Center, Seattle, Washington, USA*
[5]*Kyowa Hakko Kogyo Co., Ltd. Tokyo, Japan*
[6]*Kyowa Pharmaceutical, Inc., Princeton, New Jersey, USA*

- Trials consistent with FDA Guidelines
- Effect in addition to optimised dopaminergic therapy
- Synergistic effect with low doses of L-dopa
- No additive effect with high doses of L-dopa
- Clinical trial design important

Zonisamide – a multifunctional drug for PD

RESEARCH ARTICLE

Zonisamide Improves Wearing-Off in Parkinson's Disease: A Randomized, Double-Blind Study

Miho Murata, MD, PhD,[1]* Kazuko Hasegawa, MD, PhD,[2] Ichiro Kanazawa, MD, PhD,[3] Junichi Fukasaka,[4] Kenji Kochi,[4] Rieko Shimazu,[4] and The Japan Zonisamide on PD Study Group

[1]*Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan*
[2]*Department of Neurology, Sagamihara National Hospital, Kanagawa, Japan*
[3]*International University of Health and Welfare Graduate School, Tokyo, Japan*
[4]*Sumitomo Dainippon Pharma Co., Ltd., Tokyo, Japan*

- Adjunct to levodopa treatment with low incidence of dyskinesia and psychosis
- Inhibition of striatal GABAergic transmission
- Inhibition of sodium and calcium channels
- Inhibition of MAO-B
- Activation of dopamine synthesis and release

Non-dopaminergic nature of non-motor symptoms

Review

D-08-00834R2

S1474-4422(09)70068-7

Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment

K Ray Chaudhuri, Anthony HV Schapira

Several studies, including work from the Parkinson's disease (PD) non-motor group and others, have established that the non-motor symptoms of PD are common, occur across all stages of PD, are under-reported, and are a key determinant of quality of life. Research suggests that the non-motor symptoms of the disease are frequently unrecognised by clinicians and remain untreated. Even when identified, there is a common perception that many of these symptoms are untreatable. The role of dopaminergic drugs in treating the various non-motor problems of PD, although clinically recognised, has received little attention. In this Review, we investigate the dopaminergic basis of the range of non-motor symptoms that occur in PD such as depression, apathy, sleep disorders (including rapid-eye movement behaviour disorder), and erectile dysfunction. We discuss the evidence that these symptoms are treatable, at least in part, with various dopaminergic strategies and, where relevant, we also refer to the use of deep-brain stimulation of appropriate targets in the brain. This Review provides a comprehensive overview of the management of this challenging aspect of PD.

National Parkinson Foundation Centre of Excellence, King's College Hospital and University Hospital Lewisham, London, UK (K R Chaudhuri FRCP, MD, DSc); King's College and Institute of Psychiatry, London, UK (K R Chaudhuri); University Department of Clinical Neurosciences, Institute of Neurology, Queen Square, University College London, London, UK (A HV Schapira FRCP, MD, DSc,

for the treatment of depression in PD. These studies

	Responsive to dopaminergic treatment
Neuropsychiatric symptoms	
Depression, apathy, anxiety	Yes
Anhedonia	Yes
Cognitive dysfunction	–
Attention deficit	–
Hallucinations, illusions, delusions	–
Dementia	–
Confusion	–
Panic attacks	Yes (when related to "off" period)
Sleep disorders	
Restless legs and periodic limb movements	Yes
REM behaviour disorder	Yes?
REM loss of atonia	–
Non-REM sleep-related movement disorders	–
Excessive daytime somnolence	–
Vivid dreaming	–
Insomnia	–
Sleep-disordered breathing	–
Autonomic symptoms	
Bladder disturbances	–
Urgency	Yes (detrusor overactivity)
Nocturia	Yes
Frequency	–
Sweating	–
Orthostatic hypotension	–
Erectile impotence	Yes

(Continued in next column)

	Responsive to dopaminergic treatment
(Continued from previous column)	
Gastrointestinal symptoms	
Dribbling of saliva	Yes?
Ageusia	–
Dysphagia, choking	–
Reflux, vomiting	–
Nausea	–
Constipation	Yes
Unsatisfactory voiding of bowel	Yes
Faecal incontinence	
Sensory symptoms	
Pain	–
Primary pain related to Parkinson's disease (central pain)	Yes
Secondary pain	–
Fluctuation-related pain (wearing off, dyskinesias)	Yes
Paraesthesia	–
Olfactory disturbance	–
Visual dysfunction (contrast sensitivity, colour vision)	–
Other symptoms	
Non-motor fluctuations	Yes
Autonomic symptoms	–
Cognitive or psychiatric symptoms	–
Sensory symptoms including pain	–
Fatigue	Yes

Yes?=some anecdotal reports of response to dopaminergic treatment. Some unmarked symptoms might also respond to treatment.

Table 1: The non-motor symptom complex of Parkinson's disease

- Some non-motor symptoms show some improvement to dopaminergic medication
- Related to motor state
- But clearly dopaminergic treatment is not the whole answer to non-motor symptoms

Non-dopaminergic drugs used to treat non-motor symptoms of PD

Table 4 Examples of existing drugs used to treat non-motor symptoms of PD

Non-motor symptom	Example	Status
Bladder dysfunction	Anticholinergics - oxybutinin	Marketed
Depression/anxiety	SSRI - paroxetine	Marketed
	SNRI - venlafaxine	Marketed
	Tricyclic antidepressants – nortryptyline, desipamine	Marketed
	Dopamine agonist - pramipexole	Marketed
Psychosis	Atypical antipsychotics – quetiapine	Marketed
	5-HT antagonist - primavanserin	Approved in USA
Dementia	Cholinesterase inhibitors - rivastigmine	Marketed
Sleep disturbance - insomnia	Hypnotic - zolpidem	Marketed
Excessive daytime somnolence	Modafinil	Marketed

Jenner P, Trans Neurodegen, 4, 1-9, 2015

- Treat on a symptomatic basis using drugs already available for other indications eg. cholinesterase inhibitors, atypical antipsychotics, antidepressants
- Examine non-dopaminergic agents used in PD for effects on non-motor symptoms eg. adenosine A2a antagonists
- Test using classical models of other disease states eg. depression, anxiety, cognition

Differences between NMS in animal models and clinical PD

- Phenomenology not established
- Rating scales not established
- Relationship to progression of pathology not established
- Relationship to motor fluctuations not established
- Response to current dopaminergic treatment not established

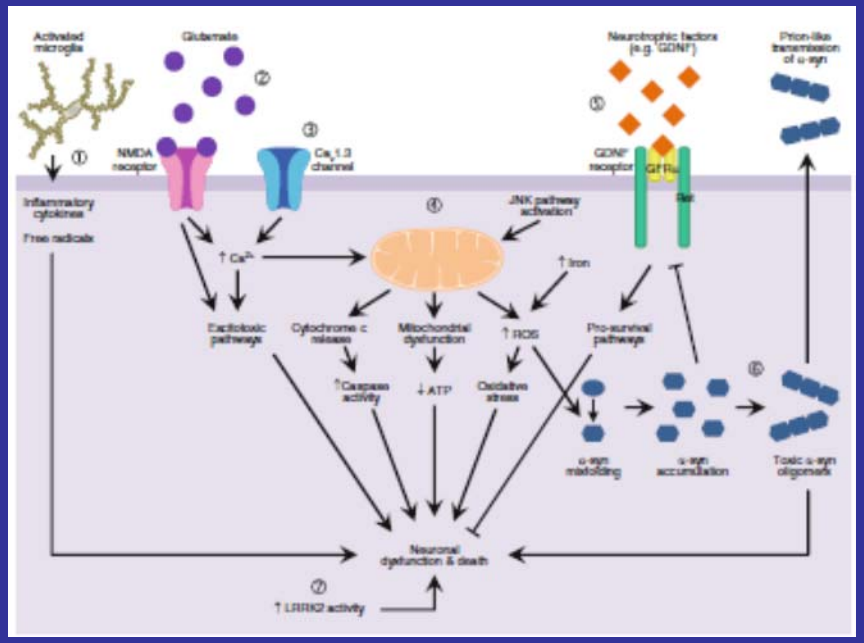
- Relationship to pattern of pathological change and progression – limited by models used

Neuroprotection or disease modification is difficult

Pathogenesis-Targeted, Disease-Modifying Therapies in Parkinson Disease

Amaal AlDakheel · Lorraine V. Kalia · Anthony E. Lang

Published online: 2 October 2013



- 38 clinical trials reviewed

- Dopamine agonists and L-dopa
- Glutamate antagonists
- Trophic factors
- Antioxidants
- Mitochondrial enhancers
- Anti-apoptotic agents

- Nothing proven to be effective

Al Dakheel et al., 2014

Not a single approach to disease modification

- Parkinson's disease is a syndrome
- Differing patterns of pathology and biochemical change
- Different subtypes of PD

- No single cause or pathogenic mechanism

- Classical clinical trial design ignore subtypes
- Unlikely to find that 'one size' drug fits all

Repositioning existing drugs from other therapeutic areas

- Development of neuroprotective drugs is a high risk strategy
- Long development time – 15 years from molecule to medicine
- Clinical trials complex and expensive
- Reposition drugs already used in man for other indications that may also be effective in PD – shorter time, less risk, less cost, side-effects known, rapidly explored hypothesis – eg. anti-diabetics, anti-hypertensives, anti-cancer drugs

Conclusions

- Dopaminergic therapies remain the mainstay of the treatment of Parkinson's disease
- New approaches are focused on delivery and devices

- The definition of Parkinson's disease is under review
- This reflects on the assessment of Parkinson's disease and the design of clinical trials

- New approaches to therapy are focussed on non-dopaminergic drugs and the treatment of non-motor symptoms

- Designing clinical trials for neuroprotective/disease modifying therapies may require sub-type selection of patients