Redefining Parkinson's disease

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Disclosures for Peter Jenner, BPharm, PhD, DSc, FRPharmS, FBPharmacS, FKC

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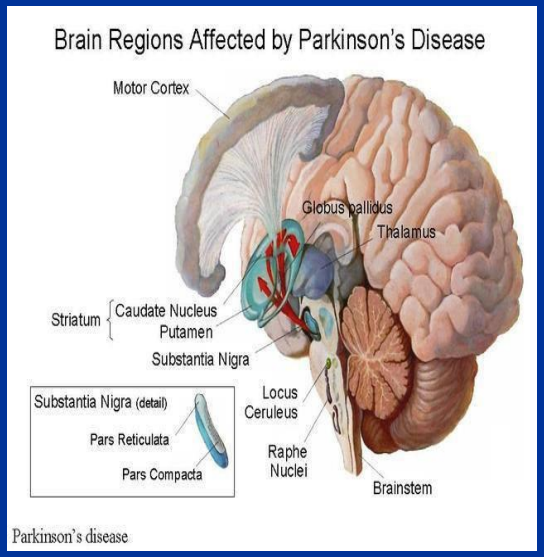
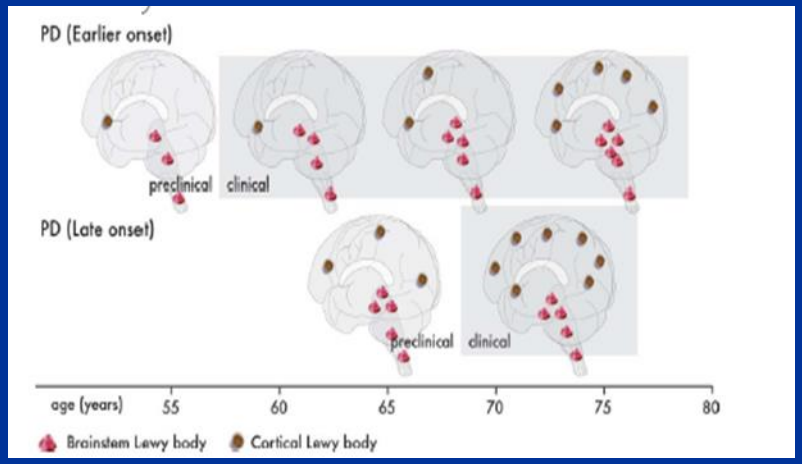
Disclosure of Conflicts of Interest	
Honoraria for Consultancies and Advisory Boards	AbbVie, Adamas, Bial, Britannia Pharmaceuticals, Eisai, FP Pharmaceuticals, Kyowa Hakko, Lundbeck, New β Innovations, Teva, UCB, Worldwide Clinical Trials, Zambon

Objectives

- To explore the evolution taking place in the clinical definition of Parkinson's disease
- To explore the diversity of pathology and pathogenic processes responsible for Parkinson's disease
- To explore whether Parkinson's disease is a single illness or a syndrome
- To explore how the diagnosis, rating and treatment of Parkinson's disease is changing
- To explore why disease modifying treatments are failing

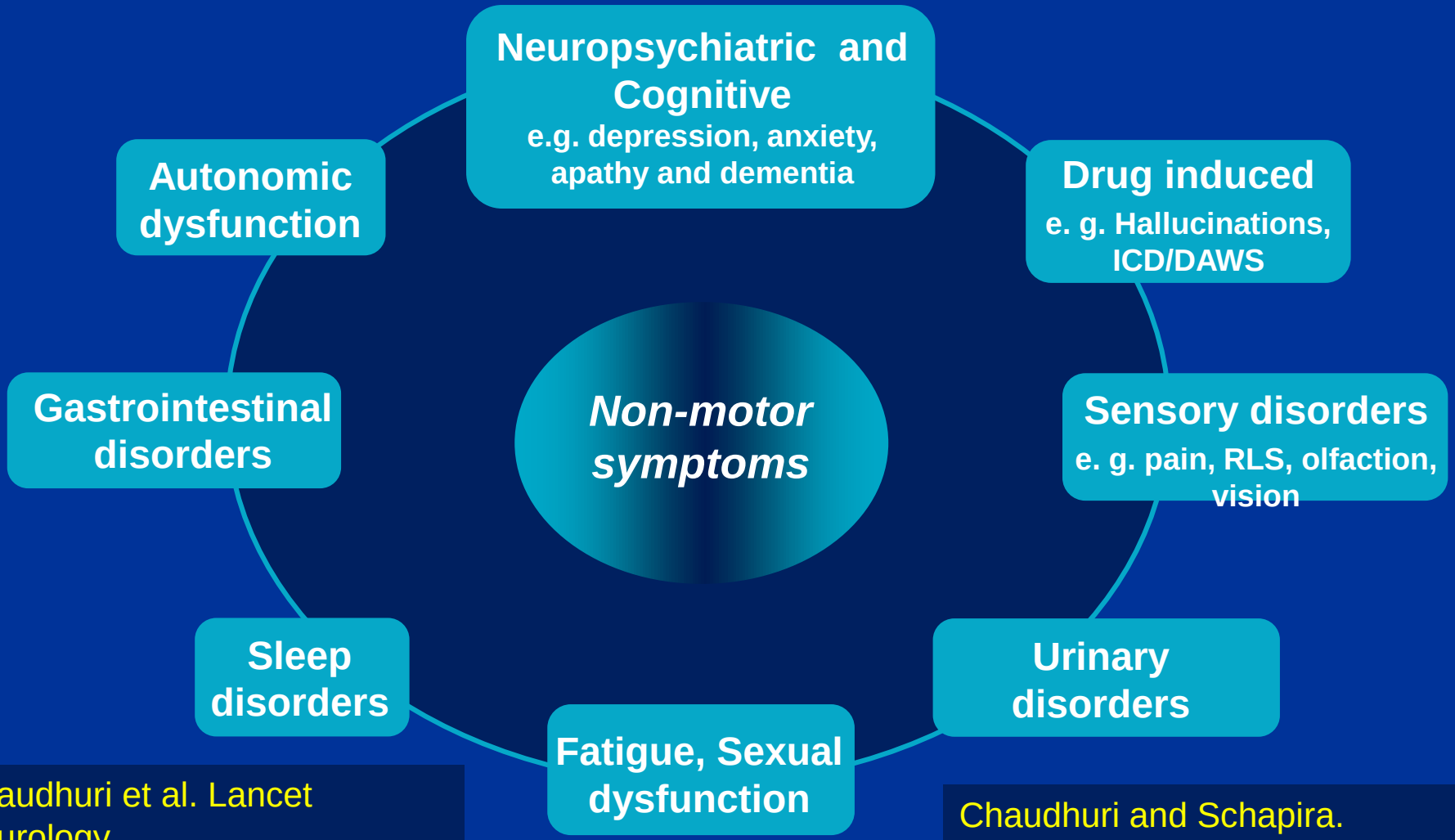
Parkinson's disease is a syndrome





- Parkinson's disease is not just a movement disorder
- Parkinson's disease is not just a basal ganglia disorder
- Parkinson's disease is not just a dopamine disorder
- Parkinson's disease is not just a brain disorder
- Parkinson's disease is not a static disorder
- Parkinson's disease is not a single disease

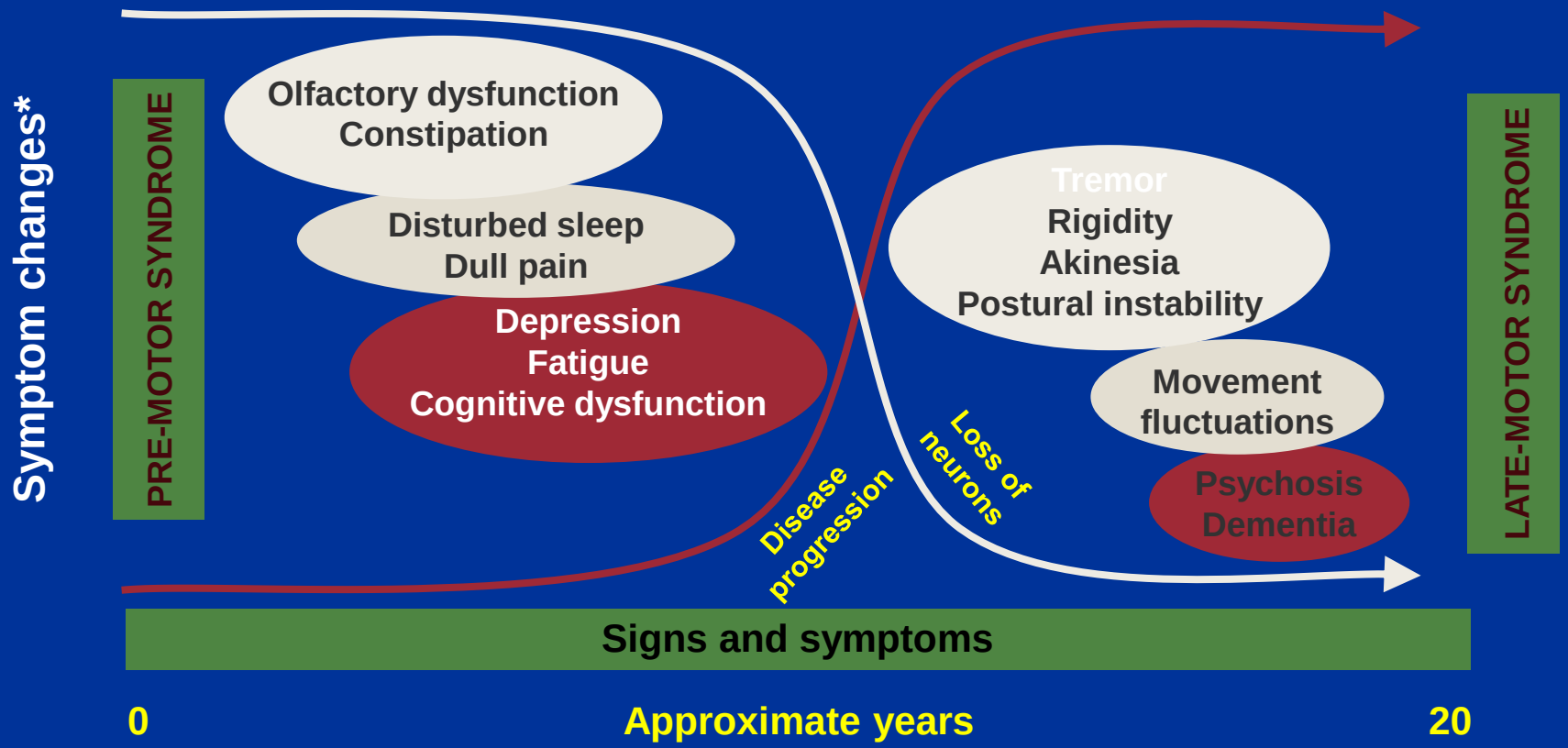
Non-motor symptoms – early and late in the progression of Parkinson's disease



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

Chaudhuri and Schapira. Lancet Neurology 2009

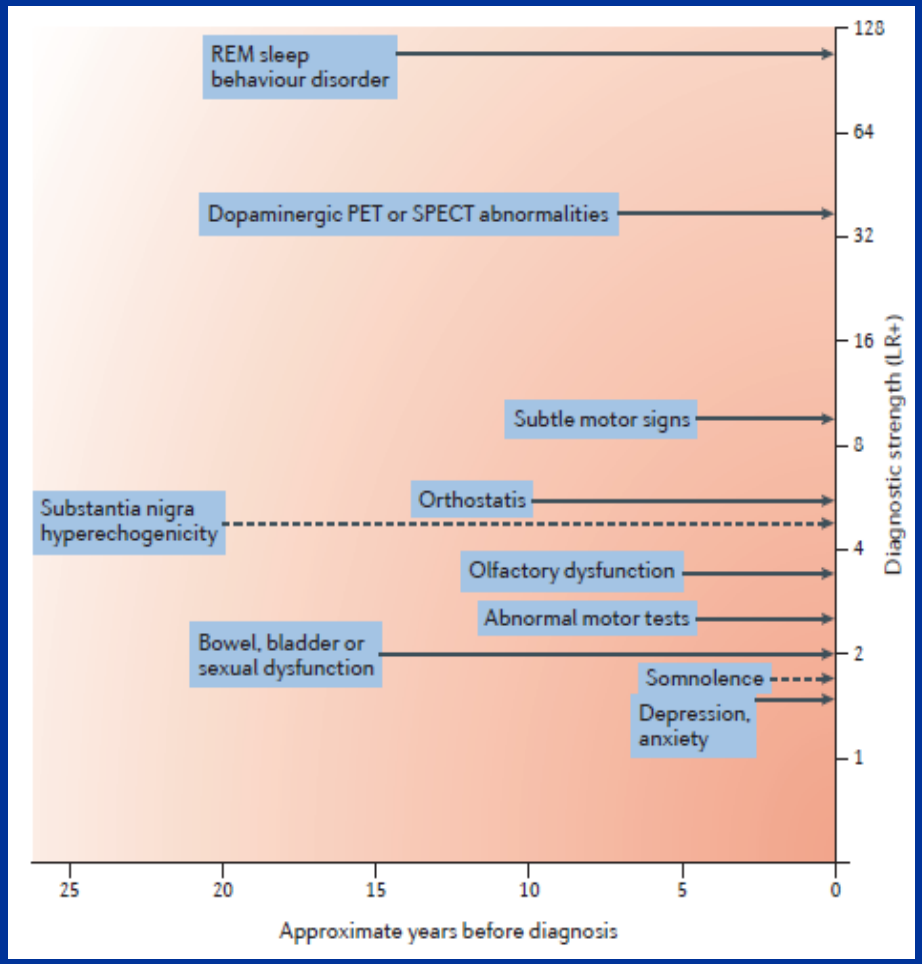
Non-motor symptoms often develop before PD motor symptoms



*Although symptom changes generally occur in the stages shown, the timings are approximate and vary

Przuntek et al. J Neural Transm 2004; 111: 201-216
McNamara and Durso. Behav Neurol 2006; 17: 43-51

Prodromal Parkinson's disease – appears years before diagnosis



Box 2 | Prevalence of prodromal Parkinson disease

- Age 50–54 years: 0.40%
- Age 55–59 years: 0.75%
- Age 60–64 years: 1.25%
- Age 65–69 years: 2.00%
- Age 70–74 years: 2.50%
- Age 75–79 years: 3.50%
- Age ≥80 years: 4.00%

Based on estimates by the International Parkinson and Movement Disorder Society task force[13].

Postuma RM and Berg D, 2016

Markers of premorbid Parkinson's disease

Table 2 Non-motor symptoms in the premotor PD

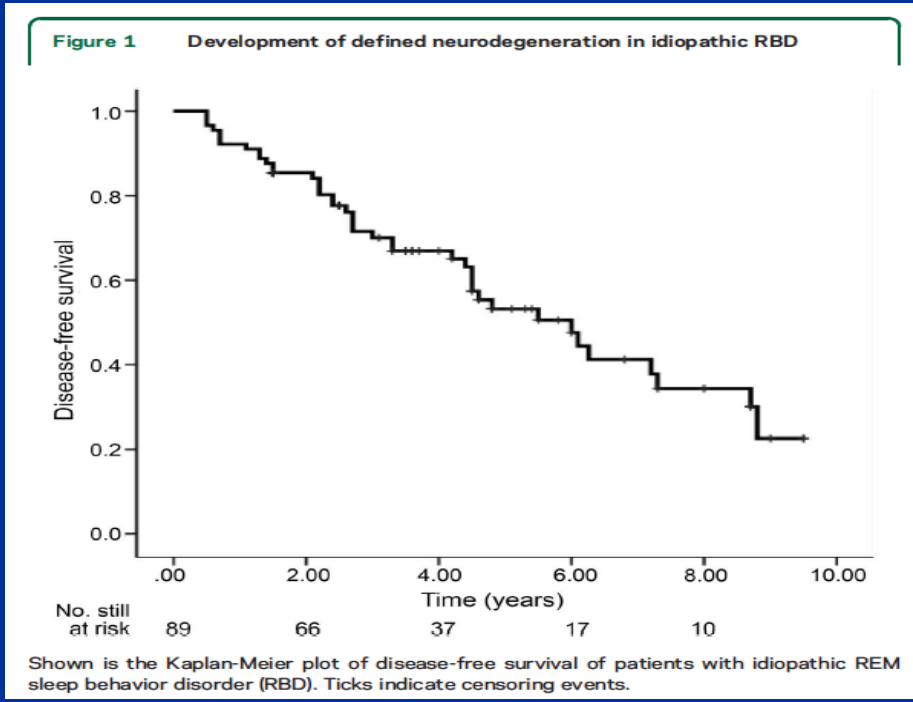
Commonly associated—with reasonable evidence base	
Hyposmia (usually of late onset and idiopathic)	10 times increase in risk of developing PD;+abnormal DATScan—43% develop motor PD in 4 years[29]
Rapid eye sleep movement behaviour disorder	25–40% risk of developing a synucleinopathy at 5 years; 40–65% at 10 years—(50% of rapid eye movement sleep behaviour disorder patients develop PD, 50%—dementia)[30]
Constipation	2.7–4.5 times increased risk of PD[31]
Depression	2.4 times increased risk of developing PD[32]
Described associations	
Excessive daytime sleepiness	3.3 times increased risk of PD[33]
Fatigue (a sense of exhaustion as opposed to sleepiness)	In 45%—a premotor symptom[34]
Pain (often unilateral and in affected limb)	34% increased risk of PD[35]
Erectile dysfunction	3.8 times increased risk of PD[36]

PD, Parkinson's disease.

Todorova, Jenner and Chaudhuri. 2014

- Hyposmia, REM sleep behavioural disorder, constipation and depression lead to increased risk
- Excessive day time sleepiness, fatigue, pain and erectile dysfunction are associated with premorbid symptoms
- Has lead to cohort studies, such as PARS and PPMI, to develop diagnostic panel

REM sleep behavioural disorder - development of Parkinson's disease

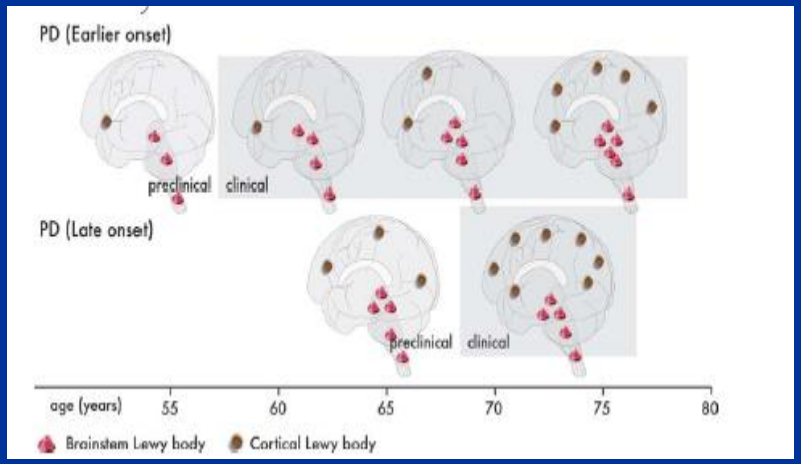


- 10-year prospective cohort, 89 patients with idiopathic RBD
- High conversion rate to Parkinson's disease
- Predictive marker for premotor Parkinson's disease (and other neurodegenerative illnesses)

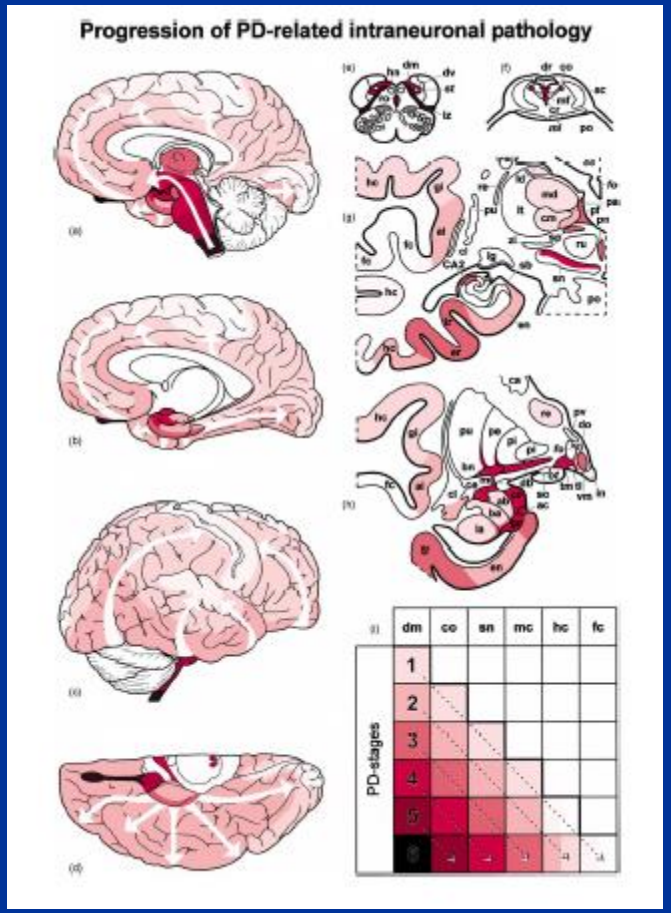
30 % at 3 years
47 % at 5 years
66 % at 7.5 years

Postuma RB et al. Neurology. 2015 84:1104-13.

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

People have Parkinson's disease in many different forms

Clinical Medicine 2016 Vol 16, No 4: 1–6 CME MOVEMENT DISORDERS

New concepts in the pathogenesis and presentation of Parkinson's disease

Authors: Anna Sauerbier, [A] Mubasher Ahmad Qamar, [B] Thadshani Thavayogarajah[B] and K Ray Chaudhuri[C]

Table 2. Proposed phenotypes within Parkinson's disease. Amended from Sauerbier *et al.*[43]

Dominant NMS presentation	Presentation based on proposed phenotypes	Subgroups possible clinical relevance
(Amnestic) Mild cognitive impairment	Park cognitive	High risk of developing dementia
Apathy	Park apathy	Apathy could be treated with dopaminergic drugs
Major depression, anxiety-depression and anxiety	Park depression/anxiety	Often associated with motor fluctuations and treatment with longer acting dopaminergic drugs would be useful
Excessive daytime sleepiness, insomnia, REM behavior disorder, narcoleptic phenotype with or without cataplexy	Park sleep	In the narcoleptic subtype, dopamine agonists (particularly D3 active) should be avoided as the treatment might lead to 'sleep attacks'
Central pain, off related pain	Park pain	Central pain: opioids; off period related pain: long acting dopaminergic drugs
Fatigue	Park fatigue	Emerging evidence of serotonergic origin/involvement? role of serotonergic agents
Gastrointestinal tract dysfunction, genito-urinary disorders, adrenergic (postural hypotension, also includes post prandial and post exercise hypotension)	Park autonomic	Consider noradrenergic therapy and Metaiodobenzylguanidine cardiac imaging

NMS = non-motor symptoms

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

- NMS - with 'OFF'
- NMS - no effect of 'OFF

Subtypes based on phenotype and neurotransmitter involvement

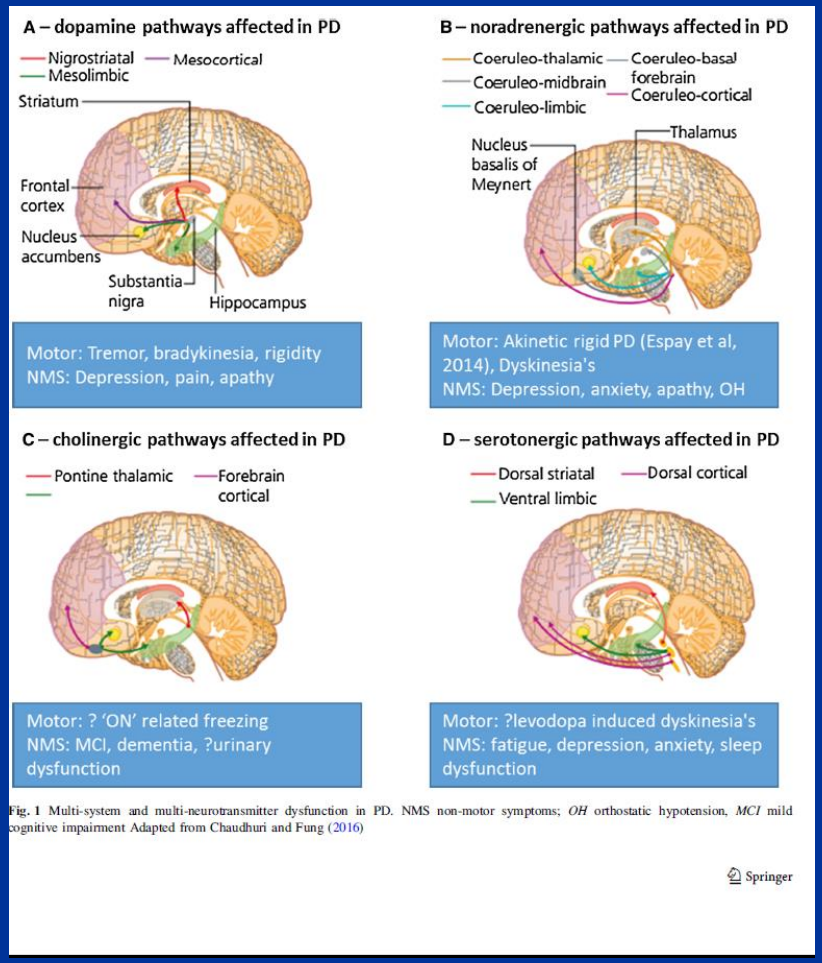


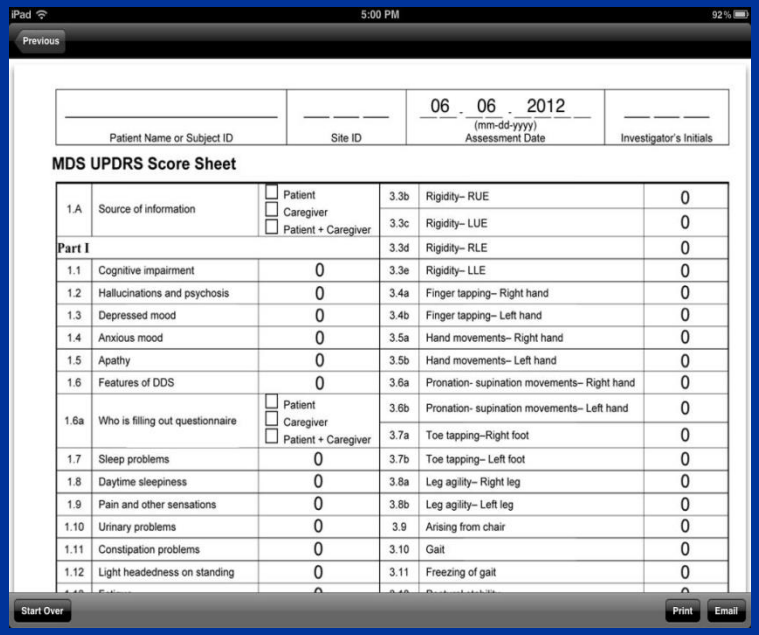
Fig. 1 Multi-system and multi-neurotransmitter dysfunction in PD. NMS non-motor symptoms; *OH* orthostatic hypotension, *MCI* mild cognitive impairment Adapted from Chaudhuri and Fung (2016)

Springer

- Specific non-motor symptoms linked to specific neuronal tracts
- Based on biochemical, pathological and imaging analysis

Titova et al., 2016

UPDRS as a clinical tool



- 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

New MDS criteria for the clinical diagnosis of Parkinson's disease


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]

Motor abnormalities remain central but some recognition has been given to non-motor manifestations

'--- we felt there was still insufficient information to delineate a specific subtype classification' Postuma RB et al., Lancet Neurology 15: 546-8, 2016

- Core features – bradykinesia plus rest tremor or rigidity
- Absolute exclusion criteria – for example, lack of response to levodopa, some other disorders with parkinsonian features, treatment with dopamine antagonists
- Red flags – for example, no progression, gait impairment, bulbar dysfunction, autonomic failure, absence of any of the common non-motor features
- Supportive criteria - for example, response to dopaminergic drugs, levodopa induced dyskinesia, olfactory loss and cardiac sympathetic denervation

New MDS research criteria for prodromal Parkinson's disease

REVIEW

CME

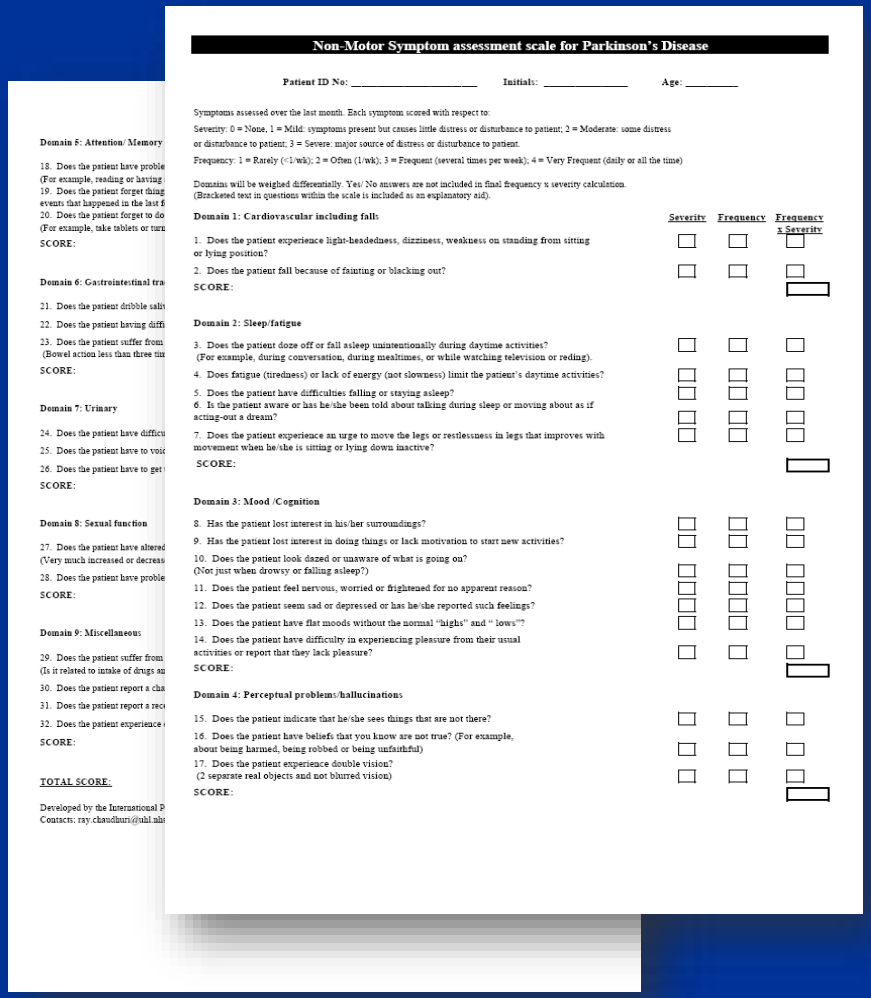
MDS Research Criteria for Prodromal Parkinson's Disease

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]

'The new criteria represent the first step in the formal delineation of early stages of Parkinson's disease and will require constant updating as more information becomes available'

- Clinical non-motor markers – for example, RBD, olfactory dysfunction, constipation, urinary dysfunction
- Clinical motor markers – possible subthreshold parkinsonism
- Neuroimaging or biomarkers – evidence of presynaptic dopamine loss on PET or SPECT
- Risk markers – for example age, sex, genetics, caffeine use, smoking status, solvent or pesticide exposure

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 fall:	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.

Assessing pain in Parkinson's disease

RESEARCH ARTICLE

King's Parkinson's Disease Pain Scale, The First Scale for Pain in PD: An International Validation

K. Ray Chaudhuri, MD, DSc,[1,2,3] A. Rizos, MSc,[1*] C. Trenkwalder, MD, PhD,[4] O. Rascol, MD, PhD,[5] S. Pal, MD,[6] D. Martino, MD,[7] C. Carroll, MD,[8] D. Paviour, MD,[9] C. Falup-Pecurariu, MD,[10] B. Kessel, MD,[11] M. Silverdale, MD,[12] A. Todorova, MD,[1] A. Sauerbier, MD,[1] P. Odin, MD, PhD,[13,14] A. Antonini, MD, PhD,[15] and P. Martinez-Martin, MD, PhD,[16] on behalf of EUROPAR and the IPMDS Non Motor PD Study Group

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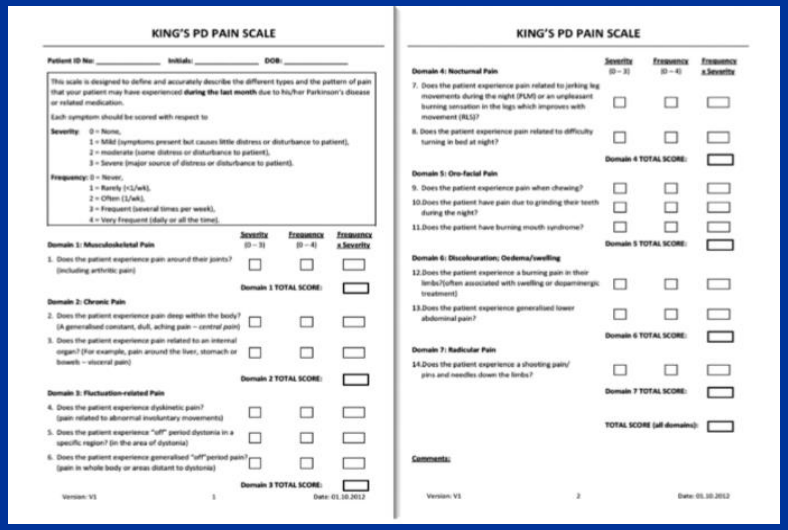

KING'S PD PAIN SCALE

Patient ID No: _____ Initials: _____ DOB: _____

This scale is designed to define and accurately describe the different types and the pattern of pain that your patient may have experienced **during the last month** due to his/her Parkinson's disease or related medication.

Each symptom should be 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: 0 = Never,
1 = Rarely (<1/wk),
2 = Often (1/wk),
3 = Frequent (several times per week),
4 = Very Frequent (daily or all the time).

	Severity (0 – 3)	Frequency (0 – 4)	Frequency x Severity
Domain 1: Musculoskeletal Pain			
1. Does the patient experience pain around their joints? (including arthritic pain)	☐	☐	☐
Domain 1 TOTAL SCORE:			☐
Domain 2: Chronic Pain			
2. Does the patient experience pain deep within the body? (A generalised constant, dull, aching pain – *central pain*)	☐	☐	☐
3. Does the patient experience pain related to an internal organ? (For example, pain around the liver, stomach or bowels – visceral pain)	☐	☐	☐
Domain 2 TOTAL SCORE:			☐
Domain 3: Fluctuation-related Pain			
4. Does the patient experience dyskinetic pain? (pain related to abnormal involuntary movements)	☐	☐	☐
5. Does the patient experience "off" period dystonia in a specific region? (in the area of dystonia)	☐	☐	☐
6. Does the patient experience generalised "off"period pain? (pain in whole body or areas distant to dystonia)	☐	☐	☐
Domain 3 TOTAL SCORE:			☐

Version: V1 1 Date: 01.10.2012

KING'S PD PAIN SCALE

	Severity (0 – 3)	Frequency (0 – 4)	Frequency x Severity
Domain 4: Nocturnal Pain			
7. Does the patient experience pain related to jerking leg movements during the night (PLM) or an unpleasant burning sensation in the legs which improves with movement (RLS)?	☐	☐	☐
8. Does the patient experience pain related to difficulty turning in bed at night?	☐	☐	☐
Domain 4 TOTAL SCORE:			☐
Domain 5: Oro-facial Pain			
9. Does the patient experience pain when chewing?	☐	☐	☐
10.Does the patient have pain due to grinding their teeth during the night?	☐	☐	☐
11.Does the patient have burning mouth syndrome?	☐	☐	☐
Domain 5 TOTAL SCORE:			☐
Domain 6: Discolouration; Oedema/swelling			
12.Does the patient experience a burning pain in their limbs?(often associated with swelling or dopaminergic treatment)	☐	☐	☐
13.Does the patient experience generalised lower abdominal pain?	☐	☐	☐
Domain 6 TOTAL SCORE:			☐
Domain 7: Radicular Pain			
14.Does the patient experience a shooting pain/ pins and needles down the limbs?	☐	☐	☐
Domain 7 TOTAL SCORE:			☐
TOTAL SCORE (all domains):			☐

Comments:

Version: V1 2 Date: 01.10.2012

- Assessed in 178 PD patients with otherwise unexplained pain
- Rated in 7 domains
- A reliable and valid scale for grade rating of various types of pain in PD

Chaudhuri KR et al., Mov Dis 30: 1623-1631 (2015)

Utilising the King's Pain Rating Scale (KPRS)

Prolonged-release oxycodone–naloxone for treatment of severe pain in patients with Parkinson's disease (PANDA): a double-blind, randomised, placebo-controlled trial

Claudia Trenkwalder, K Ray Chaudhuri, Pablo Martinez-Martin, Olivier Rascol, Reinhard Ehret, Martin Vališ, Maria Sátori, Anna Krygowska-Wajs, Maria J Marti, Karen Reimer, Alexander Oksche, Mark Lomax, Julia DeCesare, Michael Hopp, for the PANDA study group*

Summary

Background Pain is a common non-motor symptom of Parkinson's disease. We investigated the analgesic efficacy of prolonged-release oxycodone–naloxone (OXN PR) in patients with Parkinson's disease and chronic, severe pain.

Methods We did this phase 2 study in 47 secondary care centres in the Czech Republic, Germany, Hungary, Poland, Romania, Spain, and the UK. We enrolled patients with Hoehn and Yahr Stage II–IV Parkinson's disease, at least one type of severe pain, and an average 24-h pain score of at least 6 (assessed on an 11-point rating scale from 0=no pain to 10=pain as bad as you can imagine). Participants were randomly assigned (1:1) with a validated automated system (block size four) to either oral OXN PR or placebo for 16 weeks (starting dose oxycodone 5 mg, naloxone 2·5 mg, twice daily). Patients and investigators were masked to treatment assignment. The primary endpoint was average 24-h pain score at 16 weeks in the full analysis population. This study is registered with EudraCT (2011-002901-31) and ClinicalTrials.gov (NCT01439100).

Findings We enrolled 202 patients; 93 were assigned to OXN PR and 109 to placebo; the full analysis population consisted of 88 patients versus 106 patients. Least squares mean average 24-h pain score at 16 weeks in the full analysis population was 5·0 (95% CI 4·5 to 5·5) in the OXN PR group versus 5·6 (5·1 to 6·0) in the placebo group (difference −0·6, 95% CI −1·3 to 0·0; p=0·058). Similar proportions of patients in each group had adverse events (60/92 [65%] *vs* 76/109 [70%]), treatment-related adverse events (52/92 [57%] *vs* 62/109 [57%]), and serious adverse events (5/92 [5%] *vs* 7/109 [6%]). Treatment-related nausea was more common in the OXN PR group than in the placebo group (16/92 [17%] *vs* 10/109 [9%]), as was treatment-related constipation (16/92 [17%] *vs* 6/109 [6%]).

Interpretation The primary endpoint, based on the full analysis population at week 16, was not significant. Nonetheless, the results of this study highlight the potential efficacy of OXN PR for patients with Parkinson's disease-related pain and might warrant further research on OXN PR in this setting.

Lancet Neurol 2015; 14: 1161–70

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See Comment page 1144

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- Enrolled 202 PD patients at Hoehn and Yahr II-IV with at least one type of severe pain
- In patients with severe musculoskeletal pain, KPRS showed a reduction with treatment
- In patients with severe nocturnal pain, KPRS showed a reduction with treatment

Trenkwalder C et al., Lancet Neurology 14: 1161-1170 (2015)

Treatment of NMS in PD a key unmet need

REVIEW

New Clinical Trials for Nonmotor Manifestations of Parkinson's Disease

Anette Schrag, FRCP, PhD,[1]* Anna Sauerbier, MD,[2] and Kallol Ray Chaudhuri, DSc, FRCP, MD[2]

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Recent trials on
Pain
Sleep
Constipation
PH
Psychosis
ICD

Movement Disorders, Vol. 30, No. 11, 2015

- Specific clinical trials for individual NMS required
- Activity in clinical trials has been limited
- Targeting the individual pathologies responsible for NMS
- Focussed and individual approach to treatment of NMS is the future

Application of personalised medicine in PD

VIEWPOINT

Personalized Medicine in Parkinson's Disease: Time to Be Precise

Natalya Titova, MD, PhD[1] and K. Ray Chaudhuri, MD, FRCP, DSc[2,3,4]

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[2]National Parkinson Foundation International Centre of Excellence, King's College London and King's College Hospital, London, UK
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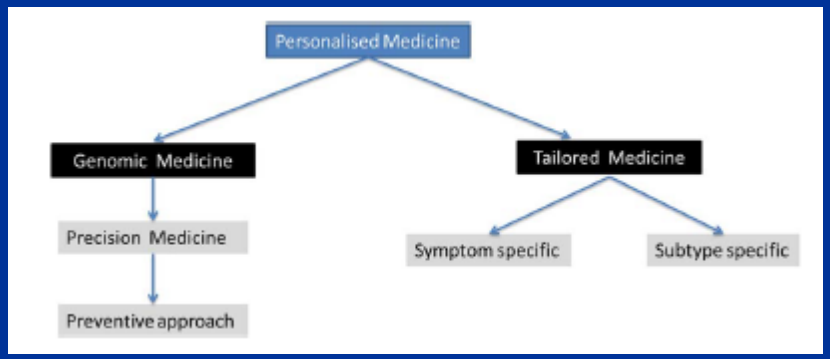
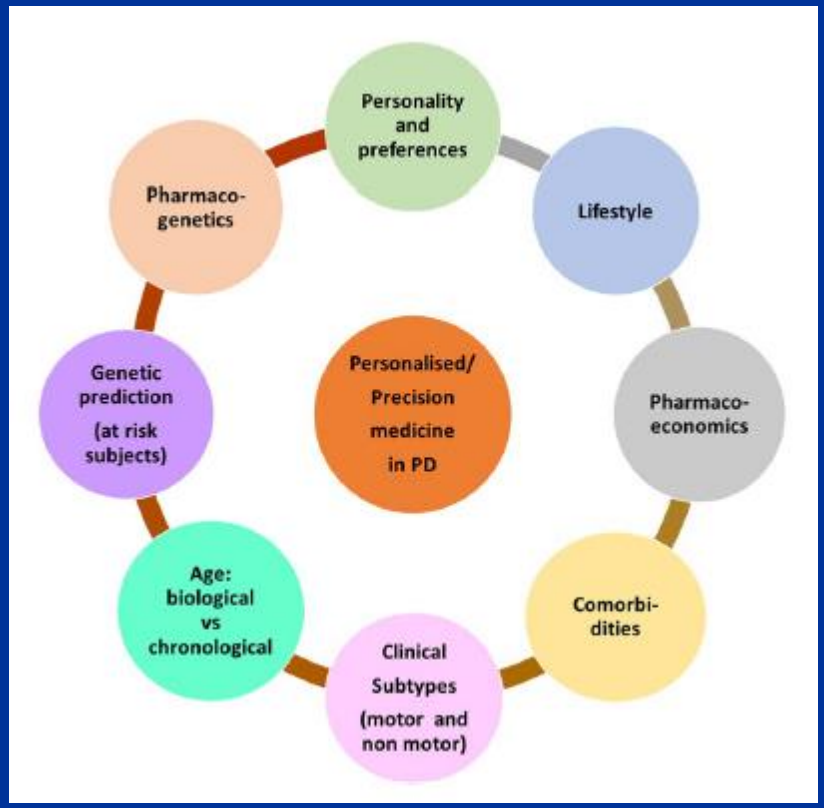
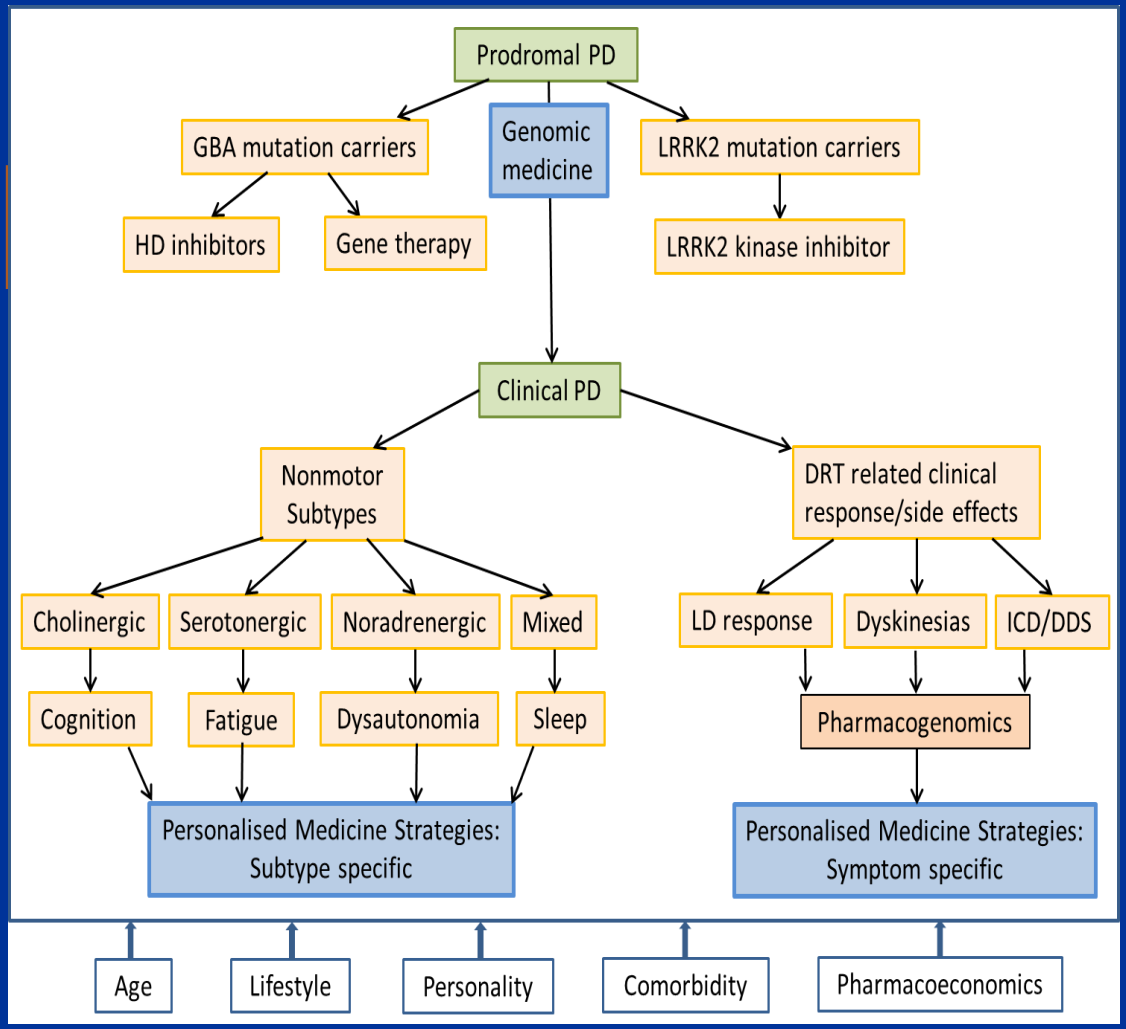
[4]National Institute for Health Research South London and Maudsley NHS Foundation Trust and King's College London, London, UK



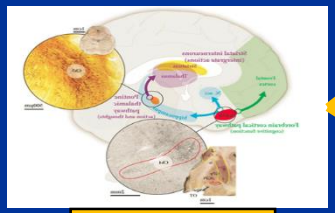


Personalised medicine in the 21st Century



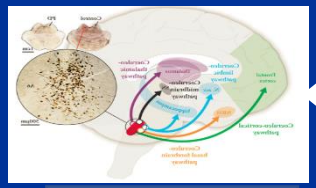
Titova and Chaudhuri. Movement Disorders 2017; Titova et al. JNT. 2017 .

Applying personalised medicine to non-motor symptoms of PD



Cholinergic

- Counselling regarding cognitive decline
- Forward planning
- Consider DRT + AchE ↓ drugs + Gait training
- Cognitive training/CBT



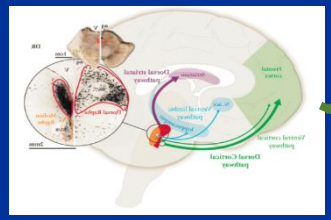
Noradrenergic

- Non-oral therapies for GI phenotype
- Nutritional /Dietetic advice, Probiotics
- Management of OH
- Non-motor fall prevention (focus on osteporotic cases)

CHAPTER FORTY-FIVE

Personalized Medicine and Nonmotor Symptoms in Parkinson's Disease

Nataliya Titova*, K Ray Chaudhuri†,1



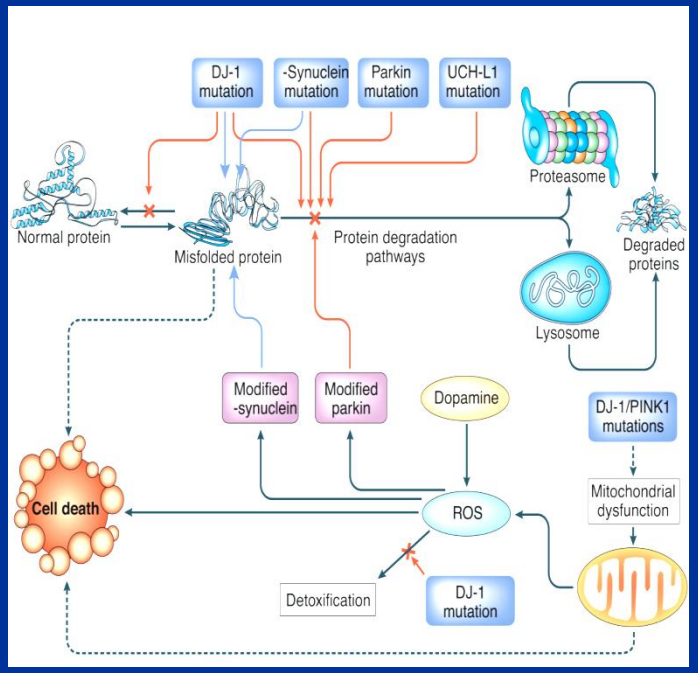
Serotonergic and mixed

- Avoid D3 agonists/ Consider alerting agents
- Consider fatigue management ? Serotonergic
- Lifestyle advise/driving/machinery

Halliday 2014; Espay et al 2016; Williams Grey et al 2010; Maselis et al 2016; Titova et al 2017

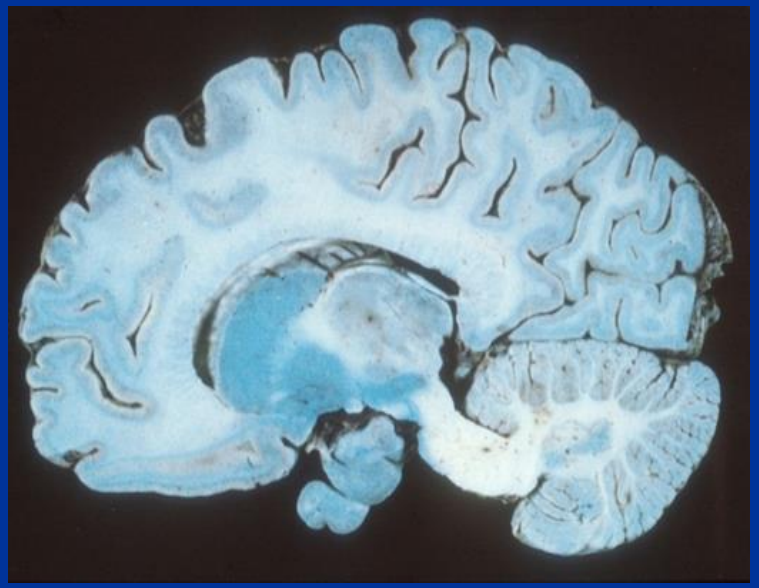
Titova and Chaudhuri. Int Rev Neurobiol 2017

What causes Parkinson's disease?



- Many different mechanisms proposed
- Genes – inherited disease
- Environment – toxin based disease
- Interaction
- Remainder of currently unknown aetiology – sporadic disease

Looking for core mechanisms



Preclinical studies *in vitro* and *in vivo* using toxins to look at susceptibility of dopaminergic neurones through different mechanisms – eg. MPTP, 6-OHDA

Post-mortem analysis of brain material to look for biochemical markers of neuronal cell death in Parkinson's disease

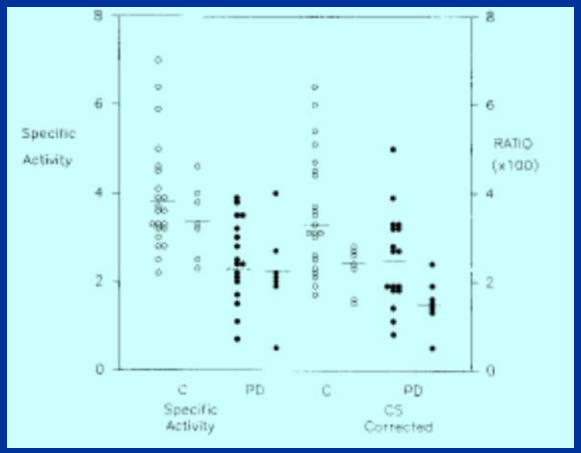
Not everybody shows the same changes

Complex I, Iron, and Ferritin in Parkinson's Disease Substantia Nigra

V. M. Mann, PhD,* J. M. Cooper, PhD,* S. E. Daniel, FRCPath,‡ K. Srai, PhD,† P. Jenner, DSc,† C. D. Marsden, FRS,§ and A. H. V. Schapira, MD*§

Elevated iron levels, enhanced oxidative damage, and complex I deficiency have been identified in the substantia nigra of Parkinson's disease patients. To understand the interrelationship of these abnormalities, we analyzed iron levels, ferritin levels, and complex I activity in the substantia nigra of patients with Parkinson's disease. Total iron levels were increased significantly, ferritin levels were unchanged, and complex I activities were decreased significantly in the substantia nigra samples. The failure of ferritin levels to increase with elevated iron concentrations suggests that the amount of reactive iron may increase in the substantia nigra of Parkinson's disease patients. There was no correlation between the iron levels and complex I activity or the iron-ferritin ratio and complex I activity in the substantia nigra samples.

Mann VM, Cooper JM, Daniel SE, Srai K, Jenner P, Marsden CD, Schapira AHV. Complex I, iron, and ferritin in Parkinson's disease substantia nigra. Ann Neurol 1994;36:876–881



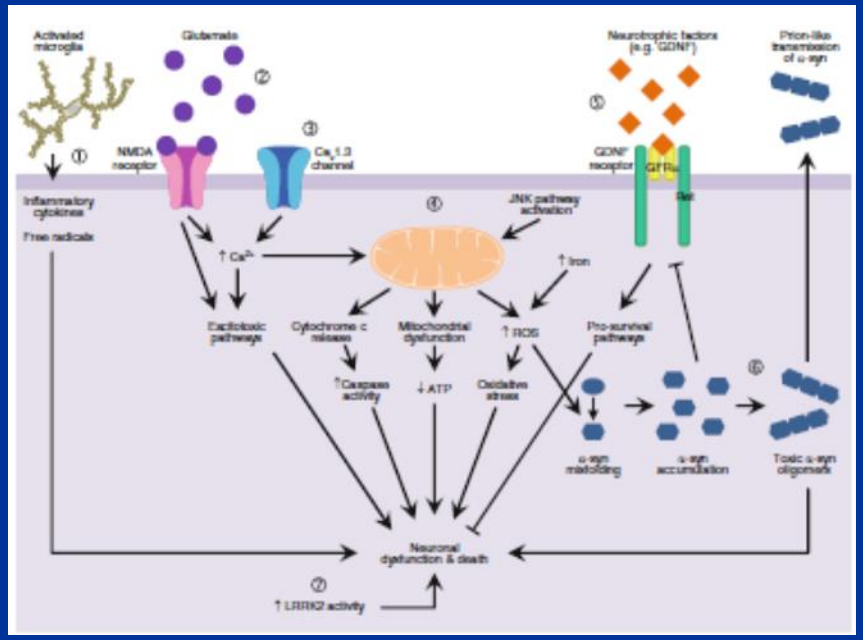
- Mitochondrial Complex I defect in PD
- Overall Complex I activity is decreased
- However, only 30% of PD patients have Complex I levels outside the normal range

Neuroprotection or disease modification is proving difficult

Pathogenesis-Targeted, Disease-Modifying Therapies in Parkinson Disease

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

Published online: 2 October 2013



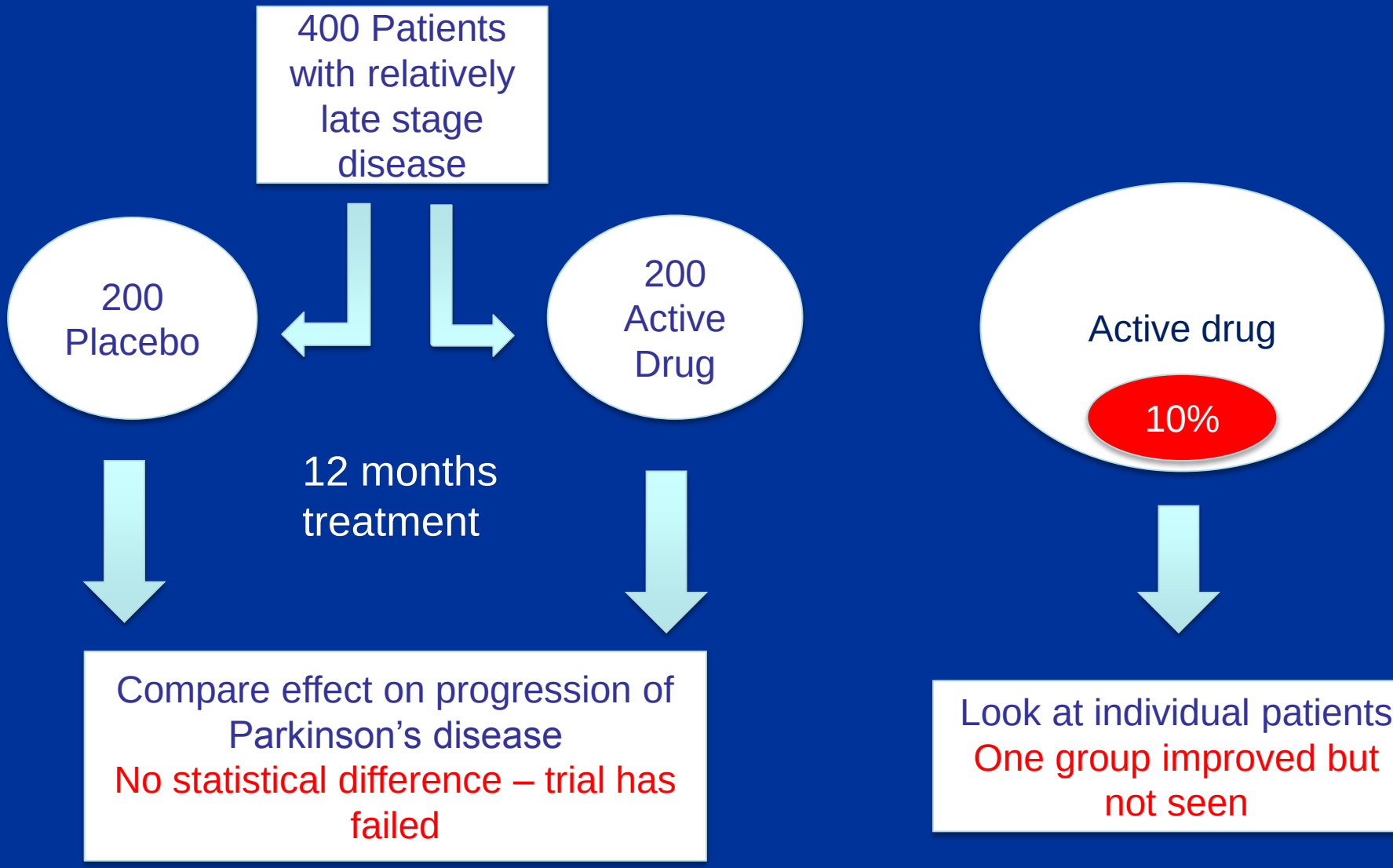
- 38 clinical trials reviewed

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

- Nothing so far proved to be effective – but watch this space

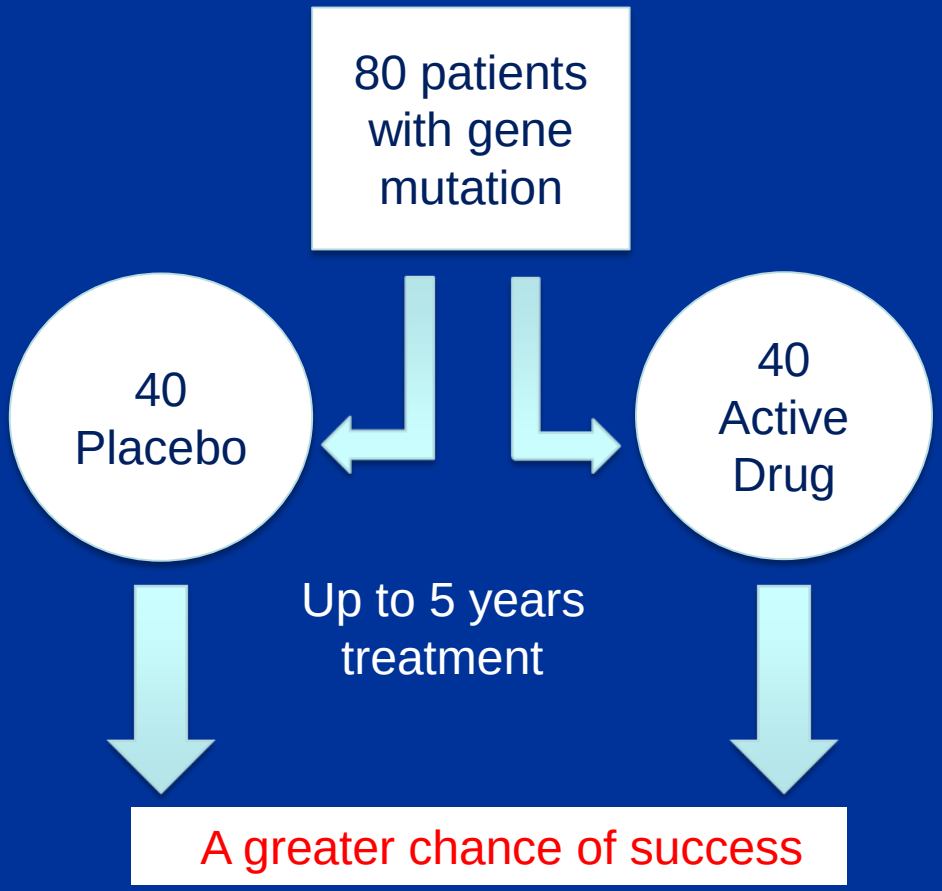
Al Dakheel et al., 2014

How do we do the clinical trials?

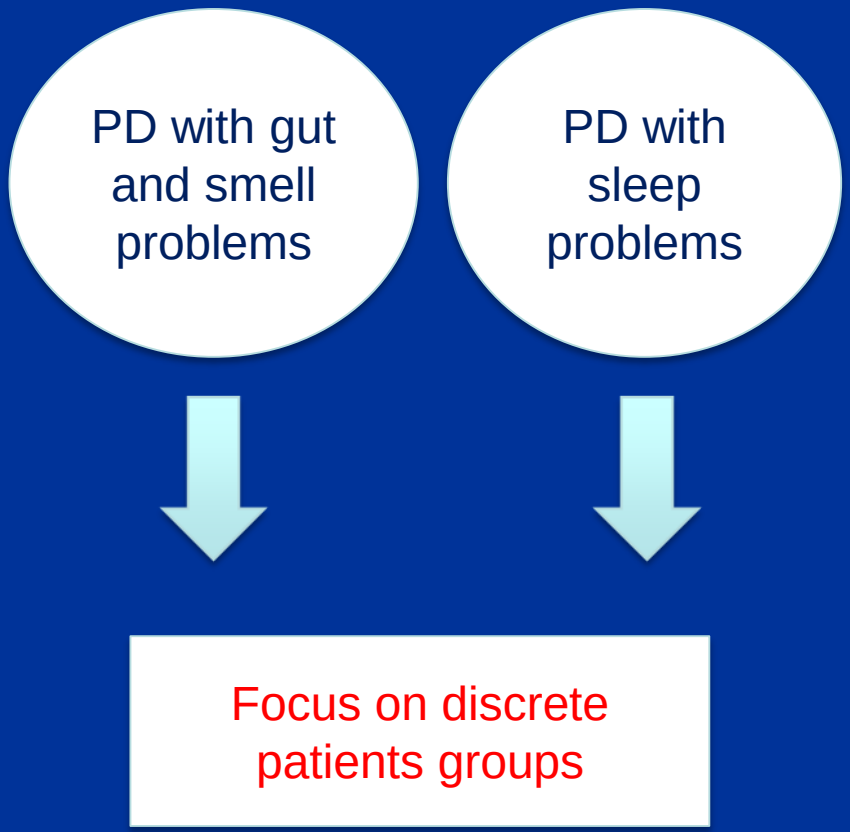


How to do the clinical trials?

- Early stage patients with a well defined cause of Parkinson's disease



- Early stage patients with well defined subtype of Parkinson's disease



Lessons from Alzheimer's disease

Review

Biological Psychiatry

Anti-Amyloid-β Monoclonal Antibodies for Alzheimer's Disease: Pitfalls and Promise

Christopher H. van Dyck

'We should expect to see additional studies of presymptomatic Alzheimer's disease to join the ongoing prevention trials for which mAbs continue to serve as the mainstay'

Antibody	Manufacturer
Bapineuzumab	Pfizer Inc./Janssen Pharmaceuticals, Inc.
Solanezumab	Eli Lilly and Company
Gantenerumab	Hoffman-La Roche
Crenezumab	Genentech, Inc.
Ponezumab	Pfizer Inc.
BAN2401	BioArctic Neuroscience, AB/Eisai Co., Ltd.
Aducanumab	Biogen, Inc.

van Dyck CH. Biol Psychiat 83: 311-319 (2018)

- Limited efficacy to date in later disease
- Higher dose required
- Earlier disease stage
- Presymptomatic disease needs to be studied
- Amyloid hypothesis wrong

Don’t expect a single treatment to work in everybody

- 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 trials design ignores subtypes

- Unlikely to find that ‘one size’ drug fits all

Conclusions

- Not only a movement disorder
- Not only a basal ganglia disorder
- Not only a dopaminergic disorder
- Not only a central nervous system disorder
- Not a single disorder
- Perhaps a systemic disorder

Conclusions

- In the future, the clinical rating of Parkinson's disease will reflect the complexity of the illness
- Personalised approaches to treatment will emerge from the complexity as sub-group recognition becomes accepted