Calvary Public Hospital Bruce

Australian National University

THE CANBERRA NEUROLOGY CENTRE

Parkinson's Disease – Diagnosis to Advanced Therapies

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Disclosures

- None

Outline

- Introduction
- Epidemiology
- Clinical features
- Cases
- Prodromal PD
- Diagnosis of PD
- Common errors in PD Diagnosis
- Management
  - Pharmacological
  - Device therapies
- On the horizon

A correct diagnosis of Parkinson’s disease is a prerequisite for patient counselling and therapeutic management.

The diagnosis of PD remains primarily a clinical exercise.

This is despite all the recent advances in imaging and genetics of parkinsonian disorders

However, clinical diagnostic uncertainty is high at initial presentation

Up to 10–30% of patients initially diagnosed as PD are clinically re-classified even in specialized units

Introduction

AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,
Gatteril street,

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.”

An illustration of an individual with Parkinson's Disease from William Gower's work Manual of the Diseases of the Nervous System written in 1886.

Epidemiology of PD

- Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease
- **The main known risk factor is increased age.**
- Median age-standardised annual incidence rates in high-income countries of 14 per 100 000 people in the total population
- 160 per 100 000 people aged 65 years or older
- Lifetime risk
  - Estimated to be 2% for men and 1 · 3% for women for individuals aged 40 years

Ascherio A, Schwarzschild M. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol* 2016; 15: 1257–72

Epidemiology

- Prevalence of PD in industrialized countries is 0.3% in the general population
- 1.0% in people older than 60 years
- 3.0% in those aged 80 years and old
- There are 18 PD-related gene loci that have been identified to date, with at least 7 disease causing genes.

Lee A, Gilbert R. Epidemiology of Parkinson's disease. Neurol Clin 34 (2016) 955–965

- **Risk Factors**
  - Pesticides
  - Dairy
  - Melanoma
  - Traumatic Brain Injury
- **Protective**
  - Smoking
  - Caffeine
  - Physical activity
  - NSAID
  - Calcium channel blockers

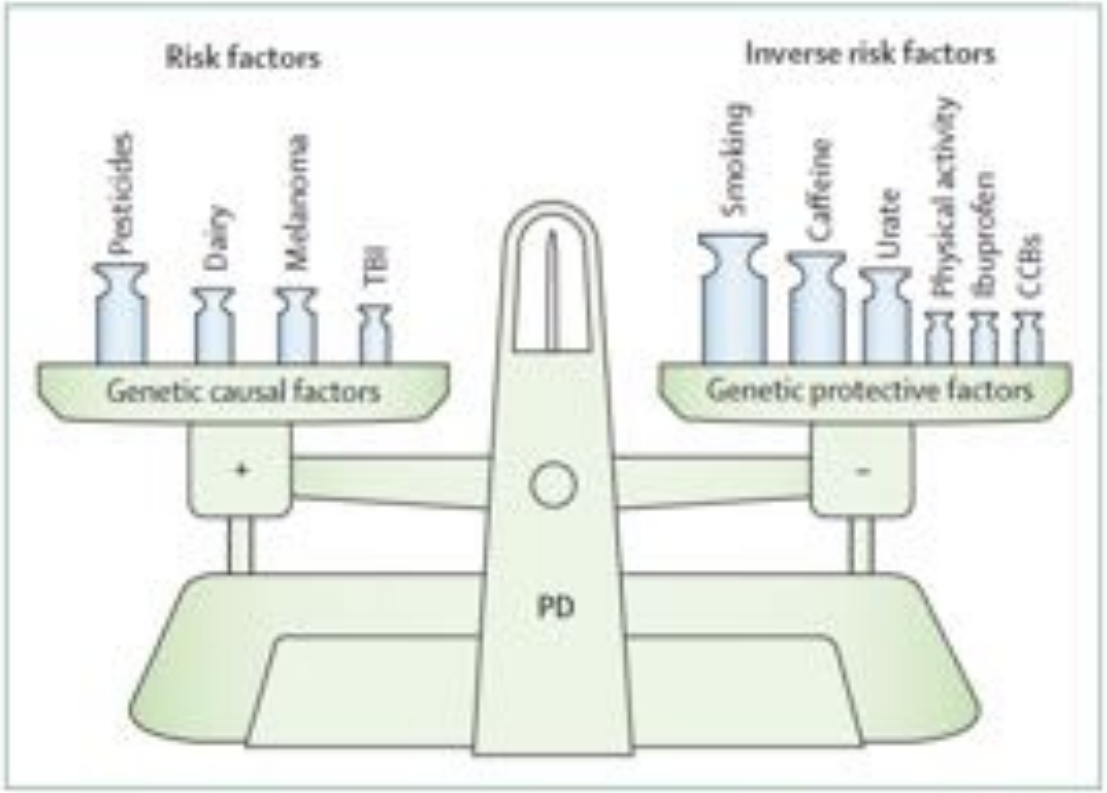


***Figure 4*: The balance of genetic and environmental factors that underlie Parkinson's disease occurrence**

Larger weights have been used for those factors with stronger epidemiological evidence. We have included only factors supported by multiple prospective studies, but the presentation is not exhaustive and it is meant only for illustrative purposes. Factors included might or might not be causal. TBI=traumatic brain injury. PD=Parkinson's disease. CCBs=calcium channel blockers.

Clinical Features

The term *parkinsonism* is used to describe a syndrome manifested by a combination of the following six cardinal features:

(1) Tremor at rest – 4 -6 Hz tremor in fully resting limb, supressed on movement

(2) Bradykinesia – slowness of movement and decrement in amplitude and speed

(3) Rigidity –velocity independent resistance to movement, not solely failure to relax

(4) Loss of postural reflexes,

(5) Flexed posture,

(6) Freezing (motor blocks)

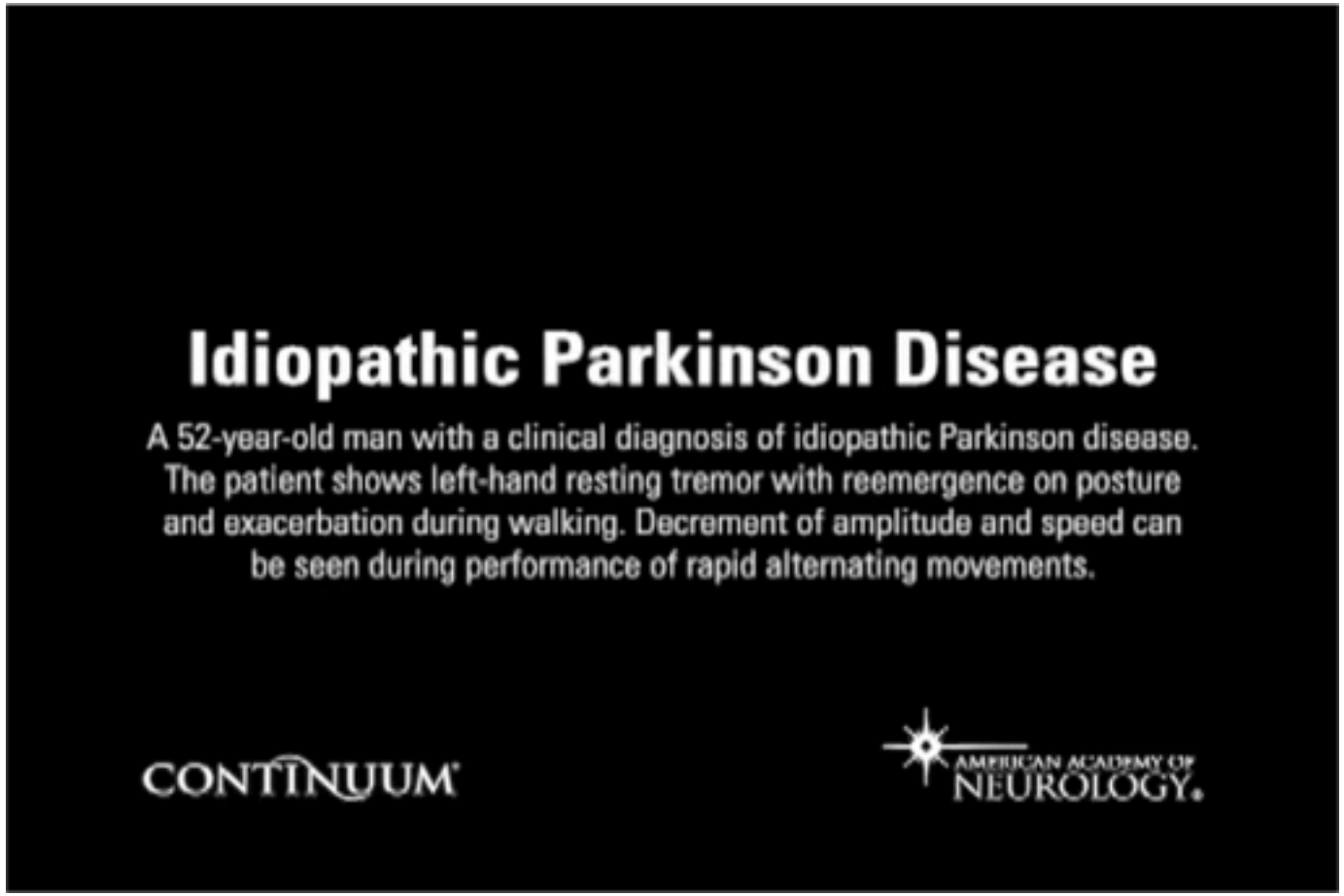
A combination of these signs is the basis to clinically define definite, probable, and possible parkinsonism.

Definite parkinsonism requires that at least two of these features must be present, with one of them being resting tremor or bradykinesia

Probable parkinsonism consists of resting tremor or bradykinesia alone

Possible parkinsonism includes at least two of the remaining four features.

Videos


Idiopathic Parkinson Disease
A 52-year-old man with a clinical diagnosis of idiopathic Parkinson disease. The patient shows left-hand resting tremor with reemergence on posture and exacerbation during walking. Decrement of amplitude and speed can be seen during performance of rapid alternating movements.
CONTINUUM
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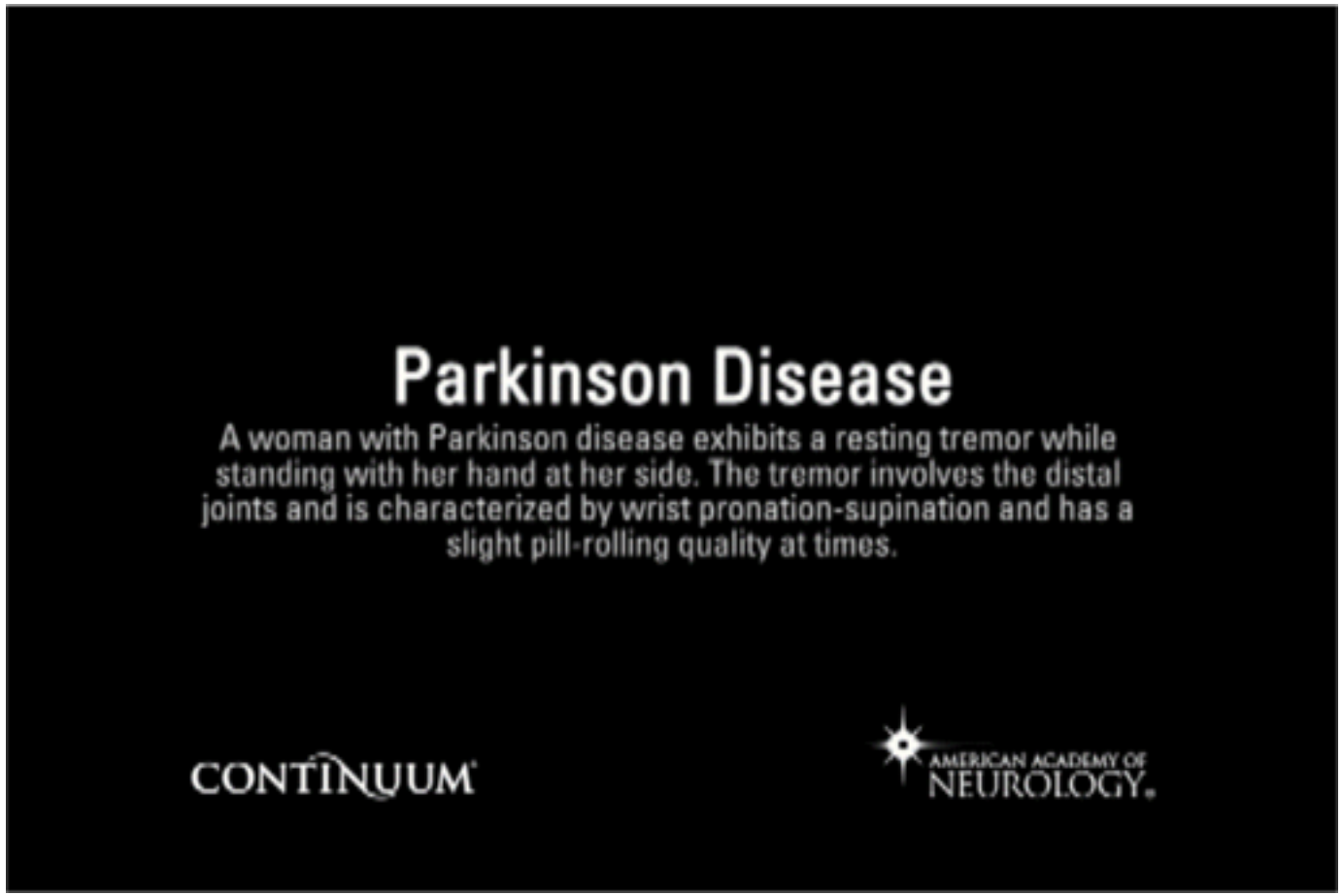
Parkinson Disease
A woman with Parkinson disease exhibits a resting tremor while standing with her hand at her side. The tremor involves the distal joints and is characterized by wrist pronation-supination and has a slight pill-rolling quality at times.
CONTINUUM
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Illustrative cases

- Mr AB
- 48 year old
- Diagnosed in 2011 at the age of 41 in NZ
- Initial symptom – left frozen shoulder
- First met in 2016
- Working full time at ActewAGL
- Main issues – Fatigue, poor sleep, lack of energy
- Madopar 100/25 mg five times daily
- Sinemet CR 200/50 mg five times daily

- November 2018
- No longer working for company
- Self employed
- Freezing in early morning
- Dyskinesias as medications wear off
- Madopar 100/25 mg five times daily
- Comtan 200 mg five times daily
- Sifrol ER 3.75 mg daily
- Sinemet CR 200/50 mg nocte

- Mr CD
- 60 year old male
- Diagnosed in 2013 at 54 years of age by me
- Initial symptoms – no arm swing on left side
- Very fit and active
- Examination – Mild bradykinesia, rigidity
- Commenced on Sifrol

- August 2018
- Still active
- Started Levodopa in 2017
- Reduced fine motor skills in left hand
- Examination – bilateral bradykinesia, rigidity
- Sinemet 250/25 mg QID
- Sinemet CR 200/50 mg night
- Azilect 1 mg daily
- Sifrol ER 15 mg daily

Mr EF

63 year old male

Diagnosed in 2003 at 48 years by Dr Simon Hammond, Orange

Referred in April 2016 for consideration of advanced therapy –Duodopa

Initial symptoms – tremor and reduced arm swing on right

Stopped working in 2011

Fluctuations – freezing, immobile after 6 pm, dyskinesias

Sinemet 100/25 mg two tablets 6 times daily

Sinemet CR 200/50 mg at night

Sifrol ER 1.5 mg daily

Duodopa commenced June 2016

August 2018

Relatively well

Back playing golf, no freezing

Mild dyskinesias

Duodopa – 11 ml morning bolus and 3.5 ml per hour continuous infusion

Sinemet CR 200/50 mg at night

Ms GH

76 year old female, academic at ANU, first met in September 2017

Diagnosed in 2009 at 67 year of age

Initial Symptom – tremor in right foot

Started on Levodopa

Progressed slowly– severe dyskinesia, nausea, intolerance to oral meds

DBS – May 2016

Very Good for 2 years, now difficulty walking, dragging right leg

Started on very low dose Sinemet 100/25 mg half twice daily

June 2018

Still doing well

Returned from overseas trip including travelling Trans Siberian train

DBS

Azilect 1 mg daily

Sinemet 100/25 mg half 4 times daily

- Mrs IJ
- 82 year old lady
- Diagnosed in 2012 at age of 76 by her geriatrician
- Initial symptom – tremor in right hand
- Rapid progression – off periods, dyskinesias, falls
- Sinemet 100/25 mg 6 times daily
- Offered Duodopa - declined

- November 2018
- Nursing home resident
- Poor mobility
- Cognitive impairment
- Continuous dyskinesias
- Sinemet 250/25 mg QID
- Comtan 200 mg QID
- Sinemet CR 200/50 mg night
- Rotigotine patch 4 mg
- Not doing well

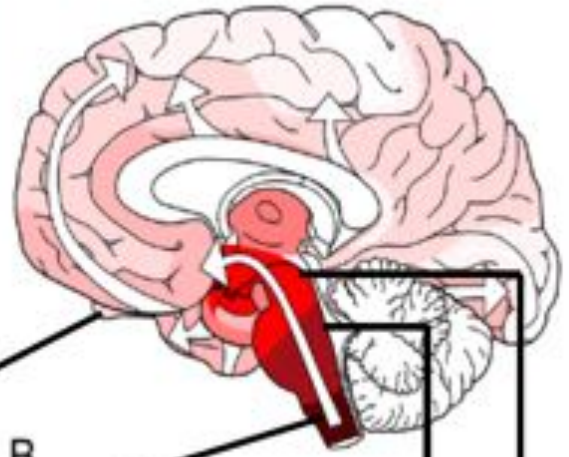
Prodromal PD

- Prodromal disease refers to the stage where early symptoms or signs of PD neurodegeneration are present, but classic clinical diagnosis based on fully evolved motor parkinsonism is not yet possible

PD starts in the Gut!

- ≡ 50% neuron loss in the substantia nigra (SN) at dx
- ≡ 80% striatal dopamine is lost by dx

Synuclein pathology in gut



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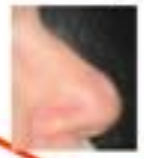

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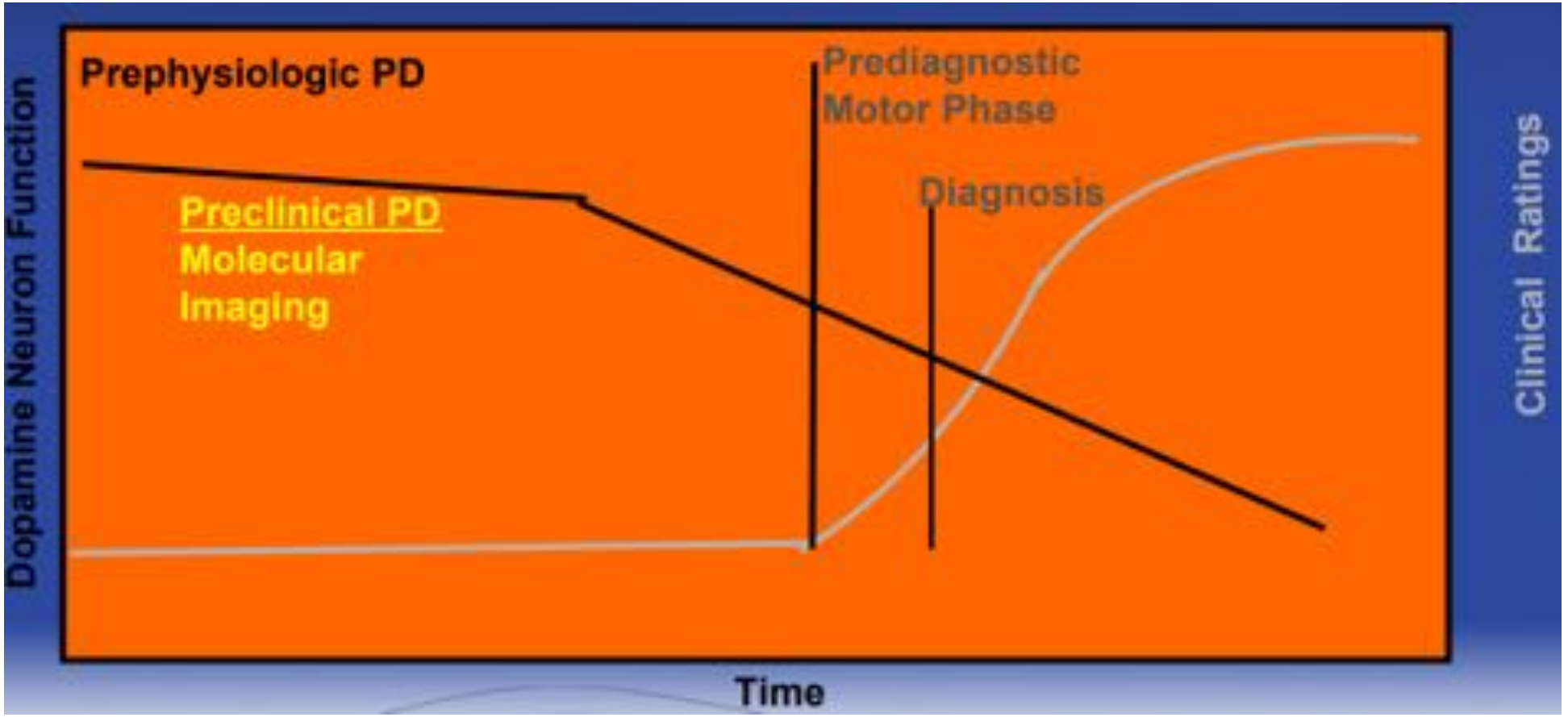
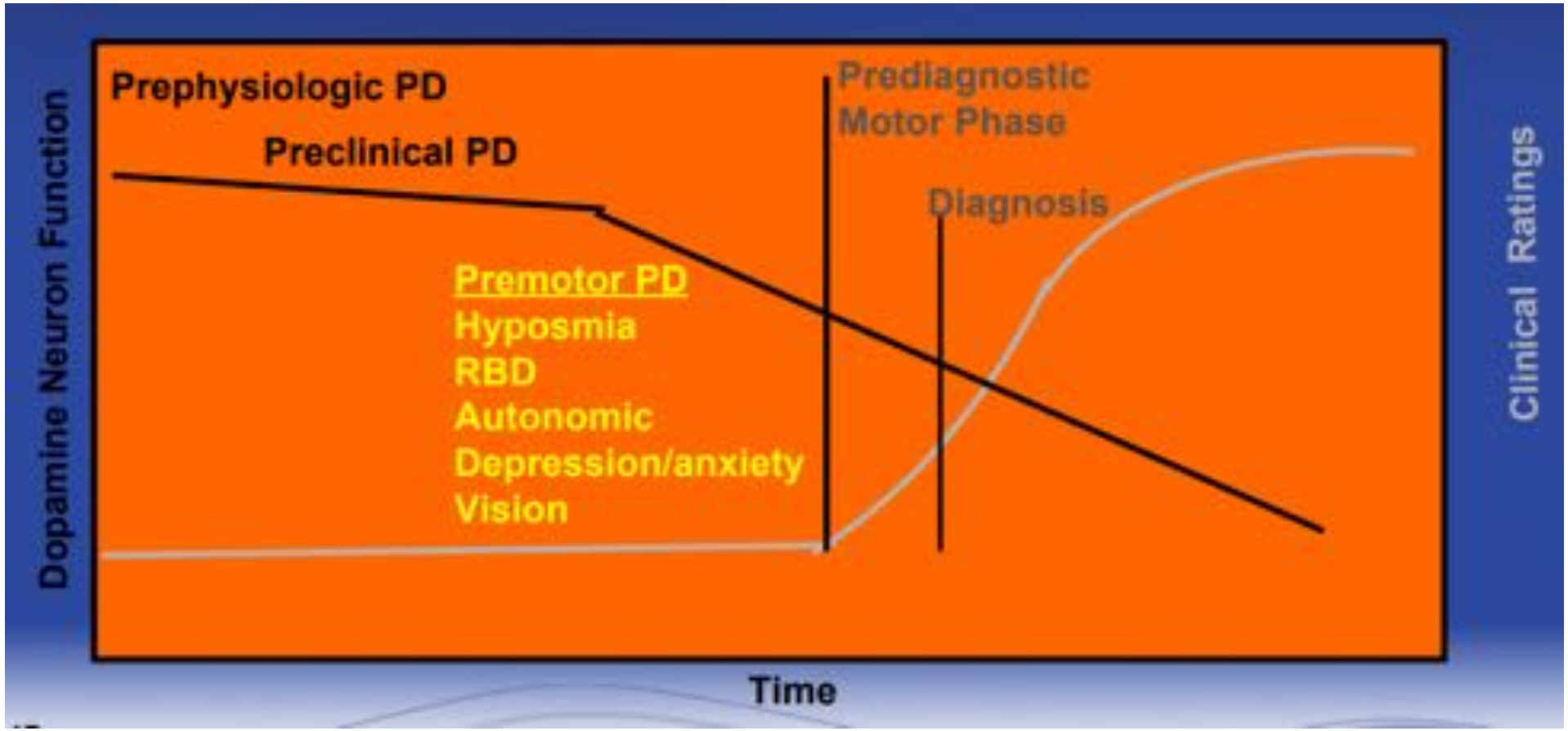
Preclinical PD

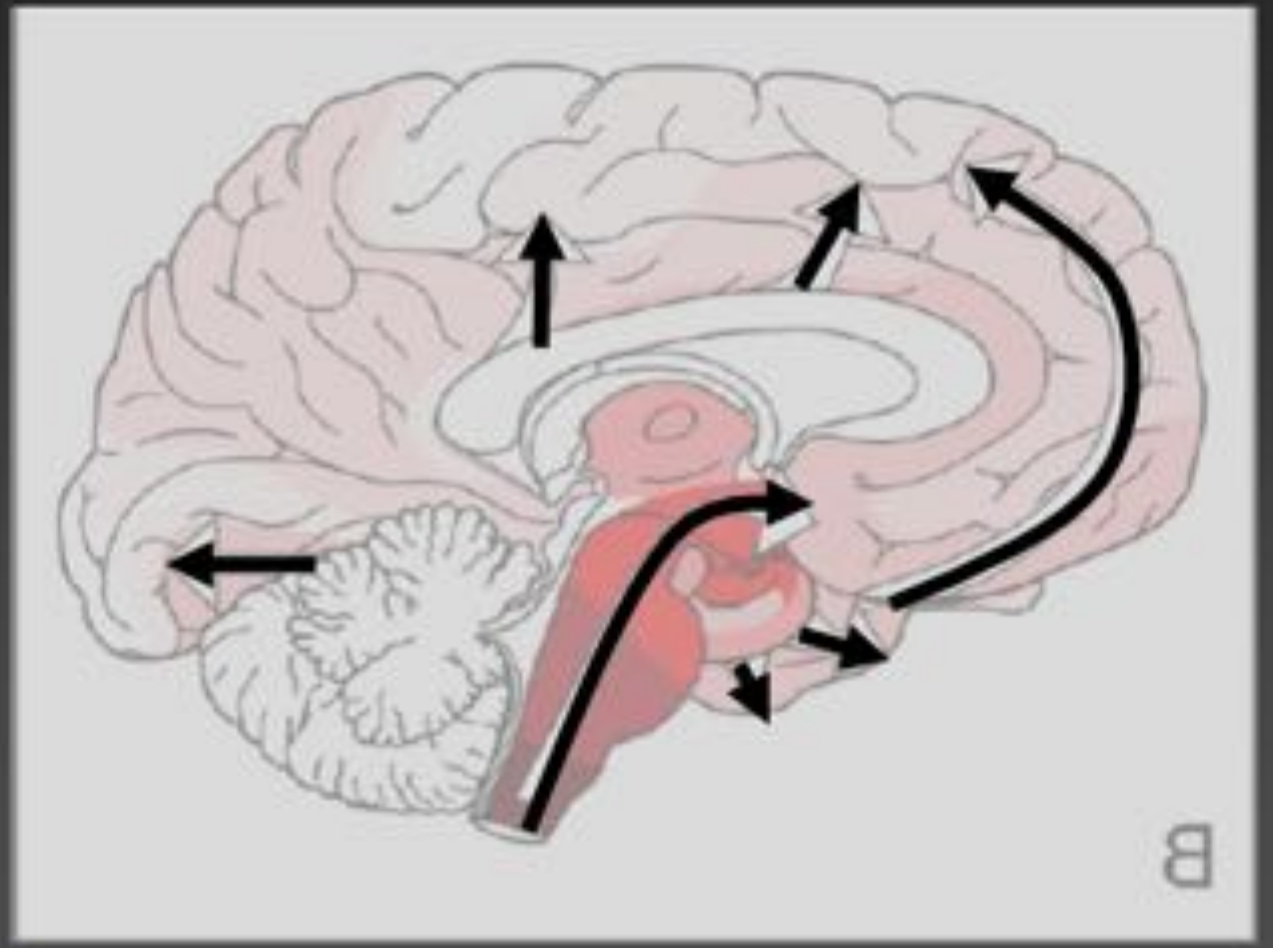


Adapted from Marek and Jennings *Neurol* '09

Premotor PD


Dopamine Neuron Function
Prephysiologic PD
Preclinical PD
Premotor PD
Hyposmia
RBD
Autonomic
Depression/anxiety
Vision
Prediagnostic
Motor Phase
Diagnosis
Clinical Ratings
Time

PD: Diffuse synucleinopathy with the formation of Lewy bodies



Starts in the PNS—lower brainstem—upper brainstem—cerebral cortex
In a topographically predictable sequence!

Pre- Motor PD: non-motor symptoms

RBD – REM Sleep Behaviour Disorder	• 38-91% phenoconvert after 7-14y • 65% idiopathic RBD develop PD or DLB
Hyposmia	• Sensitive not specific for PD
Constipation	
Depression/anxiety	
Heart rate variability	

Diagnosis of Parkinson's Disease

The diagnosis of Parkinson's disease is entirely clinical, as at the present time no imaging, biochemical, or genetic tests definitively diagnose or separate the different diseases

Clinical Diagnosis

- MDS Clinical Diagnostic Criteria – August 2015
- UK Parkinson's Disease Society Brain Bank Clinical Diagnostic 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]

MDS Criteria

- Presence of Parkinsonism
  - Bradykinesia plus either
    - Rest tremor OR
    - Rigidity
    - *Note – 20% will not have tremor
  - Absence of ‘Absolute Exclusionary Criteria’
    - Cerebellar signs
    - Vertical supranuclear opthalmoplegia
    - Cortical sensory loss, apraxia, aphasia, etc
    - Normal functional imaging of presynaptic DA transporter (DaTSCAN)

MDS Criteria

- Supportive Diagnosis
  - Clear/dramatic beneficial response to DA therapy
  - Levodopa-induced dyskinesias
  - Rest tremor
  - Olfactory loss
  - Cardiac sympathetic denervation
  - Unilateral or asymmetric onset
- No Red Flags
  - Rapid progression
  - Early bulbar dysfunction
  - Early falls
  - Early autonomic failure
  - Absence of non-motor features:
    - Autonomic, sleep, neuropsych, hyposmia

- 20 studies (1988 – 2014), 11 with autopsy
- Diagnostic accuracy 80.6%
  - Nonexperts: 73.8%
  - Movement disorder experts: 79.6%
  - Using UKPDS criteria: 82.7%


VIEWS & REVIEWS

Accuracy of clinical diagnosis of Parkinson disease

A systematic review and meta-analysis

Giovanni Rizzo, MD

ABSTRACT

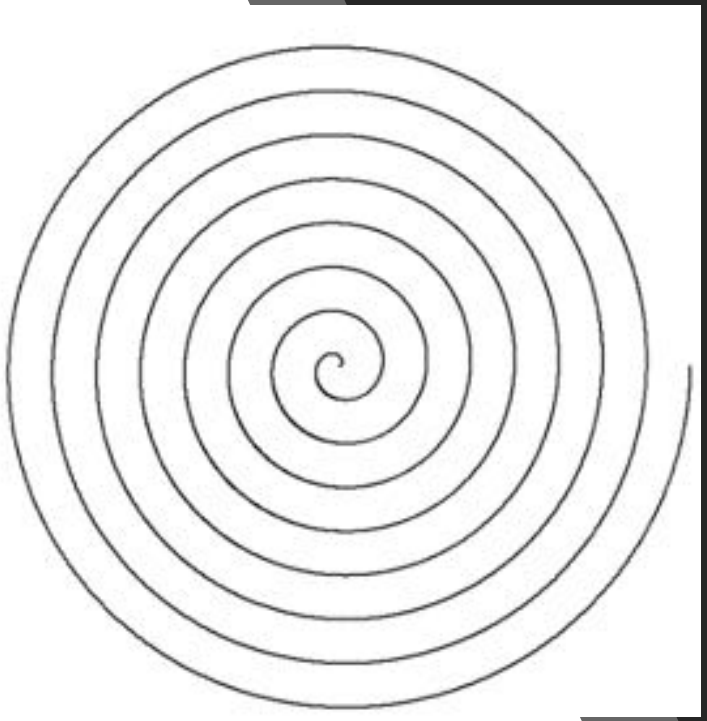
Pitfalls in Diagnosis of PD

- PD vs Essential Tremor
- Atypical Parkinsonian Syndromes

TABLE 1-4 Common Differential Diagnoses of Parkinson Disease

- Atypical parkinsonian syndromes (multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome)
- Dementia with Lewy bodies
- Drug-induced parkinsonism
- Dystonic tremor
- Essential tremor
- Frontotemporal dementias
- Functional or psychogenic parkinsonism
- Normal pressure hydrocephalus
- Vascular parkinsonism

Pitfall 1: Parkinson's Disease vs Essential Tremor



- History
  - ET usually present decades, while PD seeks attention 6-12m
- Thirty percent to 50% of ‘‘essential tremor’’ cases are misdiagnosed,
- Many of these patients have PD or dystonia rather than ET.
- Differentiation from PD:
  - Absence of rigidity,
  - Absence of other signs of parkinsonism (eg, hypomimia),
  - Absence of bradykinesia that is in excess of age
  - Absence of bradykinesia accompanied by decrement
- EtOH, FHx, symmetry, while walking
- Body part
  - Head/voice (ET)
  - Jaw/lip/tongue
- Rest, maintenance posture/movement
- Handwriting


Essential Tremor
Kinetic tremor with an intentional component on the finger-nose-finger maneuver. The tremor is slightly asymmetric and worse on the left. A mild head tremor is also present.
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Pitfall #2: Atypical Parkinsonism Syndromes

Multisystem Atrophy

- Autonomic failure: OH, incontinence, ED

Progressive supranuclear Palsy

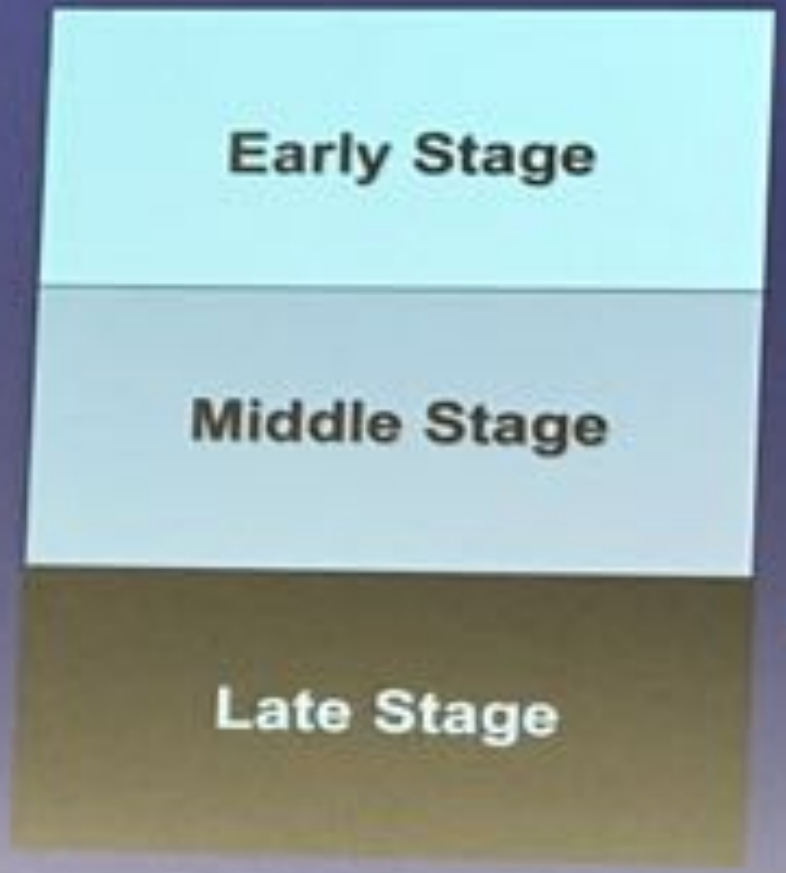
- Axial>appendicular rigidity
- Slowing vertical saccades, purusit retained
- Frontal lobe findings: impulsivity, impaired verbal fluency, eyelid opening apraxia, applause sign

Corticobasal syndrome

- Dystonic, jerky arm with parietal lobe sensory loss

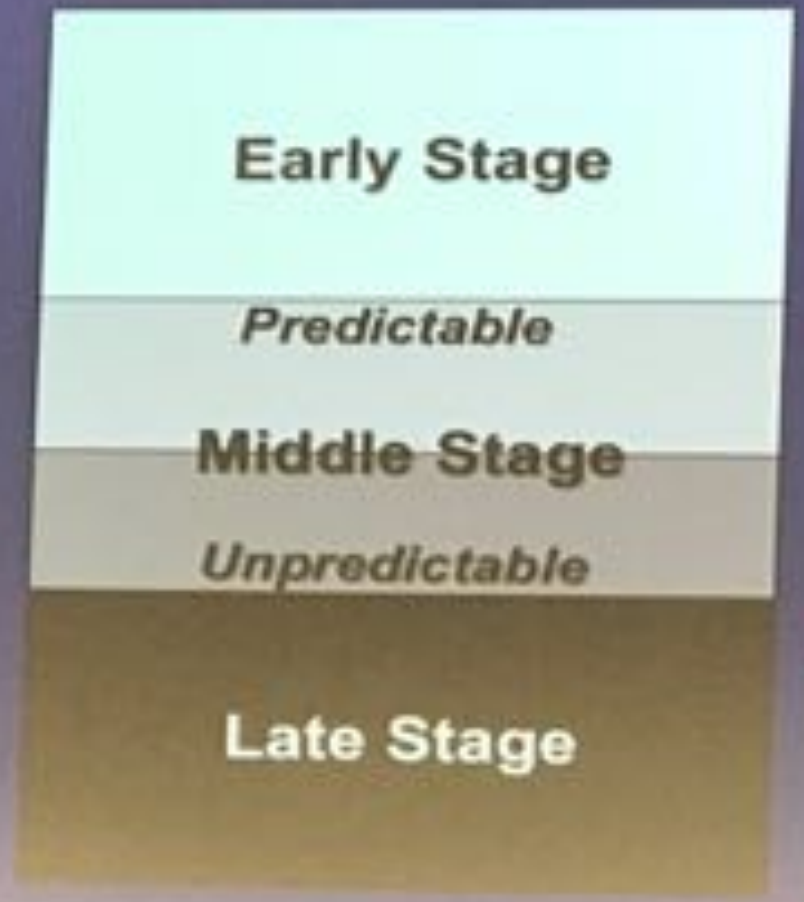
Red Flags” Suggesting a Diagnosis Other than Parkinson Disease
Early or prominent dementia
Symmetrical signs
Bulbar dysfunction
Early gait disorder
Falls within the first year
Wheelchair dependence within 5 years
Early autonomic failure
Sleep apnea
Inspiratory stridor
Apraxia
Alien limb
Cortical sensory loss

Evolution of PD



- Early Stage
  - Stable motor response to medications
- Middle Stage
  - Motor and non-motor fluctuations which are dopamine-responsive
- Late Stage
  - Motor and non-motor symptoms that are non- or poorly- responsive to dopamine

Evolution of PD



- Early Stage
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  - Motor and non-motor fluctuations which are dopamine-responsive
- Late Stage
  - Motor and non-motor symptoms that are non- or poorly- responsive to dopamine

Management

Neuroprotection

Medical Management of Motor Symptoms

- First line
  - DA
  - Levodopa

Management of Non Motor Symptoms

Device therapy


Coordination of Care
Nurses
Neurologists
Physiatrists
Physician Assistants
Physical Therapists
Speech/ Language Pathologists
Primary Care Physicians
Music Therapists
Pharmacist
Occupational Therapists
Dentists
Social workers
Dieticians
Neuro-Psychol-ogist
Psych-ologists

Neuroprotection

PD an ideal candidate for neuroprotective therapeutic strategies

- A preclinical period lasting years
- Slow progression rate
- Increasing understanding of disease etiopathogenesis make

All double-blind placebo-controlled trials designed to explore therapies that may have favorable disease-modifying effects and slow disease progression have been thus far disappointing

Candidate Neuroprotective Approaches in Parkinson Disease

Mechanism	Potential Neuroprotective Approaches
Oxidative stress	Antioxidants (e.g., monoamine oxidase inhibitors, coenzyme Q10)
Mitochondrial dysfunction	Coenzyme Q10, creatine
Excitotoxicity	Glutamate antagonists (e.g., riluzole)
Caspase activation	Caspase inhibitors (e.g., minocycline)
Apoptosis	Antiapoptotic agents (e.g., mixed-lineage kinase inhibitors)
Inflammation	Antiinflammatory drugs
Trophin deficiency	Neurotrophins

Commonly Used Antiparkinsonian Drugs

Drug	Usual Starting Dose	Usual Daily Dose
ANTICHOLINERGICS		
Trihexyphenidyl	1 mg	2-12 mg
Benztropine	0.5 mg	0.5-6 mg
Biperiden	1 mg	2-16 mg
AMANTADINE	100 mg	100-300 mg
LEVODOPA (WITH CARBIDOPA)		
Immediate-release	100 mg	150-800 mg
Controlled-release	100 mg	200-1000 mg
DOPAMINE AGONISTS		
Bromocriptine	1.25 mg	15-40 mg
Pergolide	0.05 mg	2-4 mg
Pramipexole	0.375 mg	1.5-4.5 mg
Ropinirole	0.75 mg	8-24 mg
Rotigotine	2 mg	2- 8 mg
CATECHOL-O-METHYL TRANSFERASE INHIBITORS		
Entacapone	200 mg	200 mg
Tolcapone	300 mg	600 mg

Medications under study / not yet available

Drug	Dose/day	Used for	Ref
Caffeine	400mg	Motor symptoms	Postuma 2013, 2017
Opicapone	25-50mg	COMT inhibitor, once daily	A Lees 2017
Vitamin D_3	1200iu	Slow progression, depending on genotype	M Suzuki 2013
GM1		Motor symptoms, slow progression (?)	J Schneider 2013
H_2 water	1L	Anti-oxidant, motor symptoms	A Yoritaka 2013
L-DOPA	50mg	Inhalor for off periods	M Lipp 2016
Apomorphine	10-30mg	Sublingual for off periods	R Hauser 2016
Exenatide	10µg	Slow progression	I Aviles-Olmos 2013
Safinamide	50-100mg	Motor symptoms	multiple
Droxidopa		Hypotension (NAd precursor)	

Levodopa

- Most potent drug
- Gold standard
- A positive therapeutic response is used to define the disease itself
- Sinemet, Kinson, Madopar
- Levodopa is converted to dopamine via the action of a naturally occurring enzyme - DOPA decarboxylase
- Activation of central dopamine receptors improves the symptoms of Parkinson's disease

- **Adverse Effects**
- Nausea and vomiting
- Orthostatic hypotension
- Sedation
- Confusion
- Sleep disturbance
- Alterations of dream phenomena
- Hallucinations
- **Dyskinesias**

Dopamine Agonists

- Pramipexole – Sifrol
- Rotigotine - Neupro
- Act directly on postsynaptic dopamine receptors
- Removing the need for metabolic conversion, storage, and release

- **Adverse Effects**
- Side effects similar to those of LD
- Orthostatic hypotension, sleepiness, and hallucinations are more common or severe
- **Major concern with DAs are the variety of behavioural problems that include pathological gambling, compulsive shopping and eating, hypersexuality, and other impulse-control disorders**

MAO-B inhibitors

- Selegiline
- Rasagiline – Azilect
- Block MAO-B–dependent dopamine degradation
- Have modest effects in potentiating the action of Levodopa

- **Adverse Effects**
- Dyskinesia
- weight loss
- Postural hypotension
- Vomiting
- Loss of appetite
- Joint pain
- **Abdominal pain**
- Nausea
- Constipation
- Dry mouth

COMT Inhibitors

- Entacapone – Comtan
- Combination with Levodopa, carbidopa – Stalevo
- Block peripheral and central degradation of levodopa increasing central LD and dopamine levels
- Primary role is to prolong the effects of LD
- Useful as adjunctive drugs for patients who experience LD-related motor fluctuations

- **Adverse Effects**
- Increase LD-related dyskinesias
- Nausea
- Postural hypotension
- **Diarrhoea**
- Orange discoloration of urine

Anticholinergics

- Trihexyphenidyl – Artane
- Benztropine – Cogentin
- Antagonize the effects of acetylcholine at muscarinic receptors
- Reduce tremor and rigidity but have no effects on bradykinesia

- **Adverse Effects**
- Confusion
- Hallucinations
- Blurred vision
- Dry mouth,
- Constipation
- urine retention

What to start?

- Symptomatic pharmacological treatment should begin when the patient is noticing functional, occupational, or social disability related to PD symptoms
- Prospective studies have suggested that approximately 70% of patients with PD will require symptomatic therapy within 2 years of disease onset.
- Less potent therapies such as selegiline, rasagiline, and amantadine may be useful for initial therapy
- LD or DAs are the choices when more potent therapy is indicated

Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

PD MED Collaborative Group*

Lancet 2014; 384: 1196–205

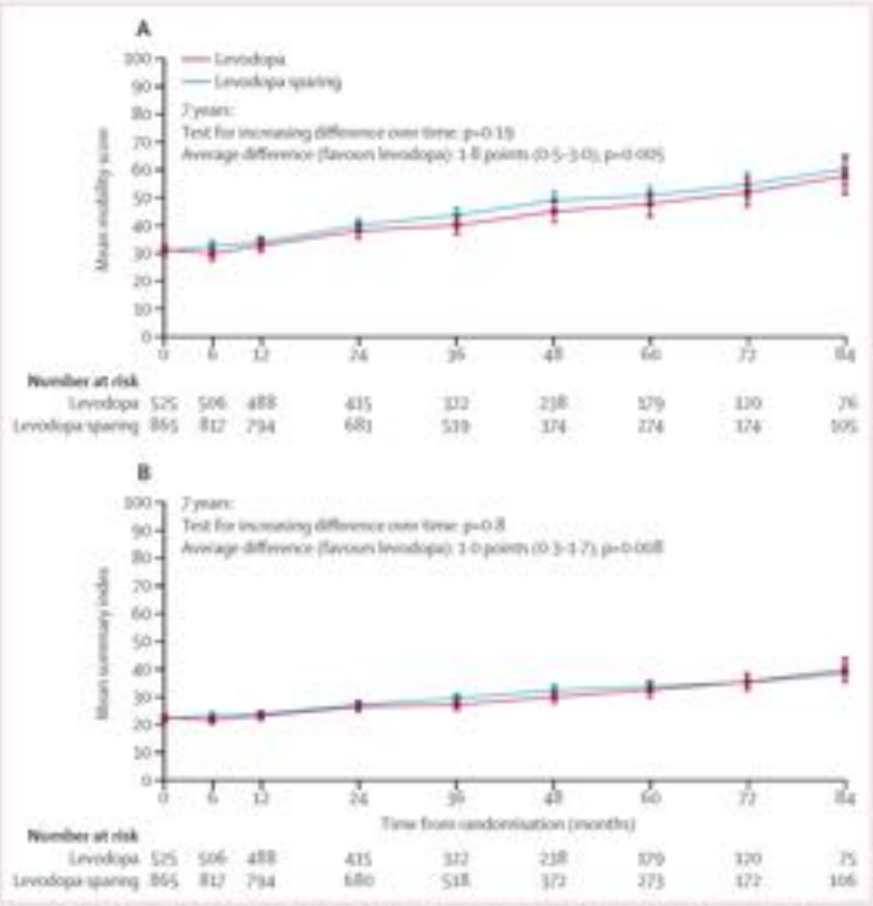


Figure 4: 39-item patient-rated Parkinson's disease questionnaire mobility score (A) and summary index (B) with time in levodopa and levodopa-sparing groups

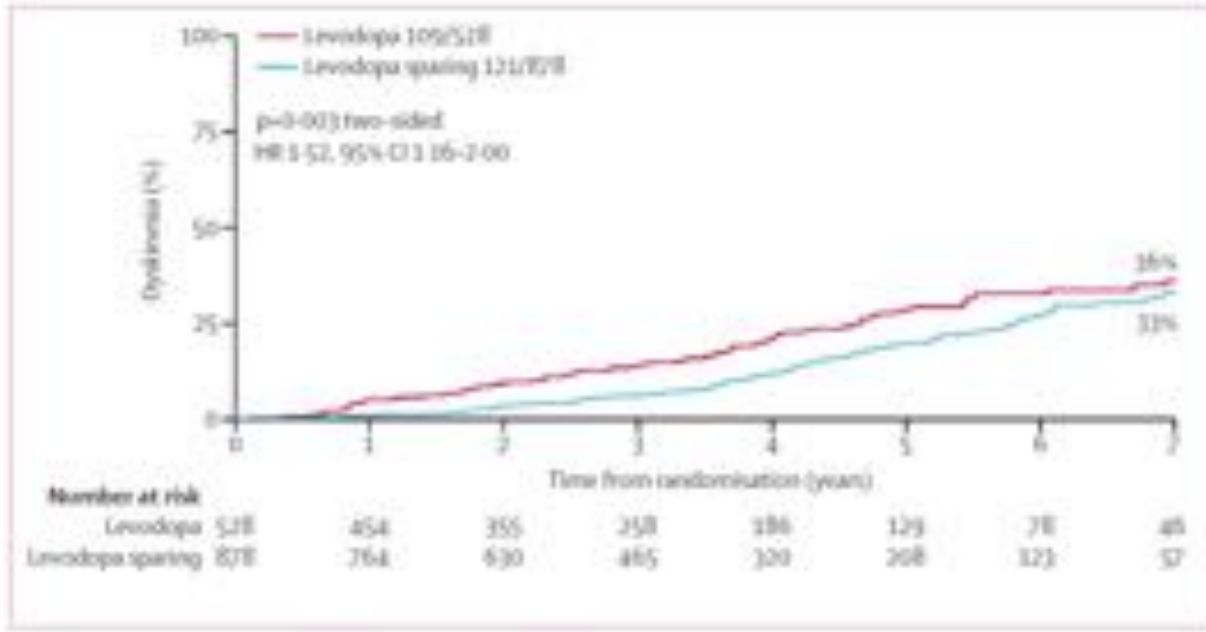


Figure 5: Risk of developing dyskinesia in levodopa and levodopa-sparing groups

Interpretation Very small but persistent benefits are shown for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy. MAOBI as initial levodopa-sparing therapy was at least as effective as dopamine agonists.

- Young patient < 50
- Levodopa
    - Better long-term motor benefit, less physical disability
    - More motor complication risk in the short term
    - Start levodopa if motor disability warrants it
    - Watch and wait strategy out of favour
- Dopamine Agonist
    - Motor benefit
    - Additional antidepressant effect
    - Neuropsychiatric issues -hallucinations, impulse control disorders,and somnolence
- MAOB Inhibitor
    - Rasagiline
    - Well tolerated
    - Mild symptomatic improvement

- Older Patient> 70
- Multiple comorbidites
- Best to use Levodopa as first therapeutic agent
- Avoids neuropsychiatric complications of other drugs

- **Individualize treatment according to the patient, disease burden, co morbidities and patient preference**
- **Levodopa provides the most effective motor benefit for PD,**
- **Should be used in any patient with PD regardless of age or other factors when a patient experiences significant disability due to motor symptoms.**

Nonmotor Symptom Management

Orthostatic Hypotension

- 20/10 within 3min
- Critical times – first thing in AM, postprandial, after prolonged lie, within 30min to 1h after levodopa, after warm baths
- Non-pharmacological
  - Abdominal binders
  - Water bolus (2 x 250ml) cold water raises SBP by 20 mmHg for 1-2h
  - Crossing leg and calf squeezing
- **Pharmacological**
  - Midodrine
  - Fludrocortisone
  - Pyridostigmine

Pain

- ROM exercises
- Topical Rx

Constipation

- Dietary changes, water intake
- Domperidone

Nonmotor Symptoms Managment

- **Aspiration/dysphpagia**
  - Difficult to detect
  - Remove distractions (no TV)
  - No talking while eating
  - Putting fork/spoon down between bites
  - Clearing mouth with small amount of water between mouthfuls
  - Chin/neck in neutral position
  - Swallowing exercises
  - **Enteral feeding did not improve QoL, prolongs life, superior to hand feeding (Cochrane)**

Neuropsychiatric issues

Mood

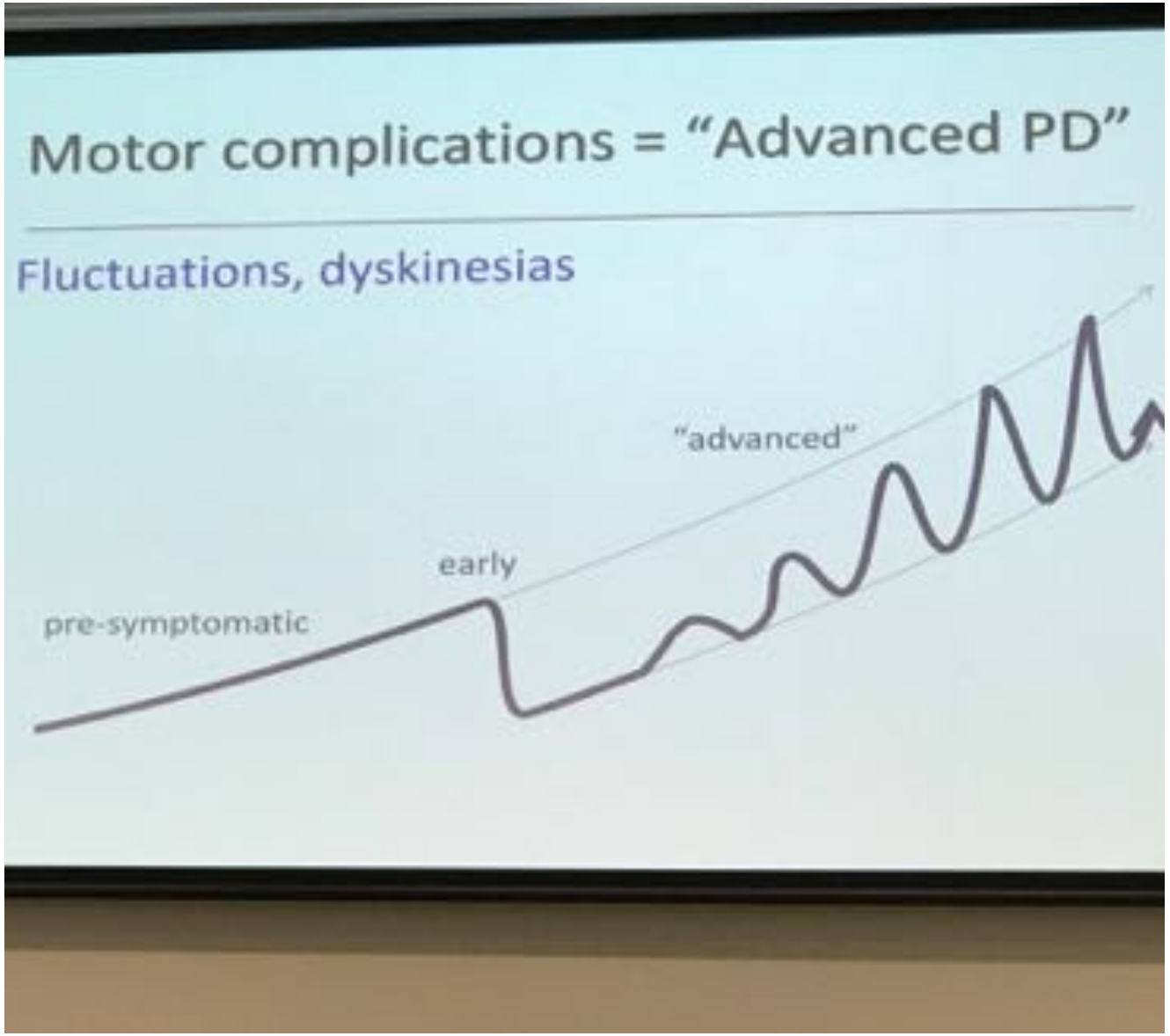
- Biological secondary to mesocortical/mesolimbic degeneration
- Fluctuations with dopaminergic levels
- Depression (40-50%) *(Reijnders 2008)*
  - Nonmotor fluctuation
  - 11% suicidal *(Nazem 2008)*
- Anxiety

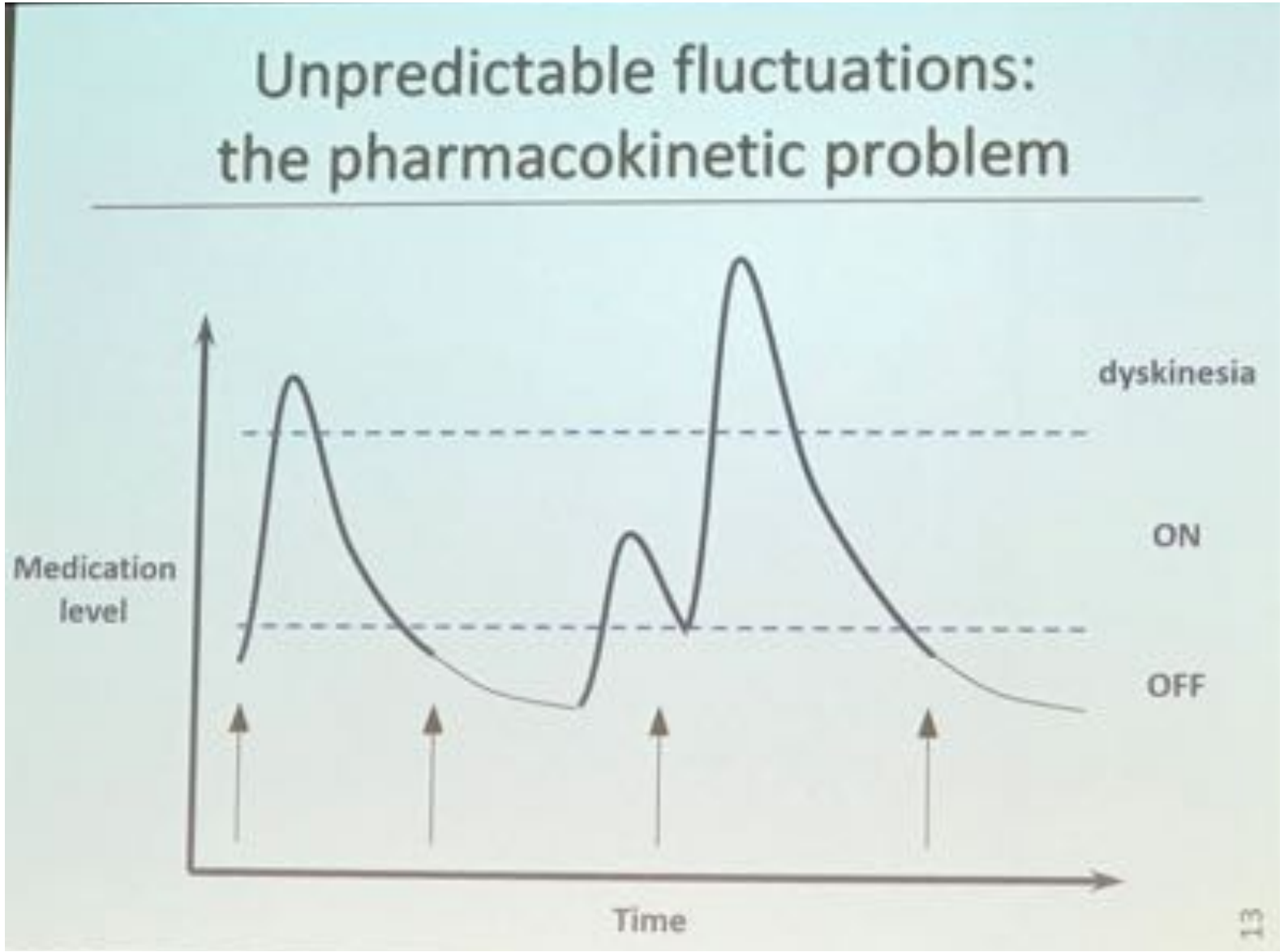
Cognitive

- 19-38% Dementia in PD *(Litvan 2011)*
- 80% PD develop after 8 or more years *(Aarsland 2010)*
- Assessment for acute decline
  - Infections
  - Metabolic
  - Dehydration
  - New neurological disorders (stroke, SDH)
  - Medications (Pain, bladder, sedating meds)
- Rivastigmine only drug approved

Advanced PD – management of motor complications

- Many patients with moderate to advanced disease have a poor quality of life
- Fluctuating medication response
- Troublesome dyskinesia
- Motor Fluctuations
- LD-unresponsive symptoms




Unpredictable fluctuations:
the pharmacokinetic problem
dyskinesia
ON
OFF
Medication level
Time
13

Motor fluctuations

Wearing off - the most common type of motor fluctuation

- Predictable return of parkinsonian symptoms in advance of the next scheduled antiparkinsonian dose.

On/off -unpredictable reappearance of parkinsonism at a time when central levels of antiparkinsonian drugs are expected to be within the target therapeutic range.

Delayed on -prolongation of the time required for the central antiparkinsonian drug effect to appear.

Dose failure - complete failure to develop a favorable response to an incremental dopaminergic dose.

Peak-dose dyskinesias - choreiform or stereotypical movements present at the peak of the therapeutic response

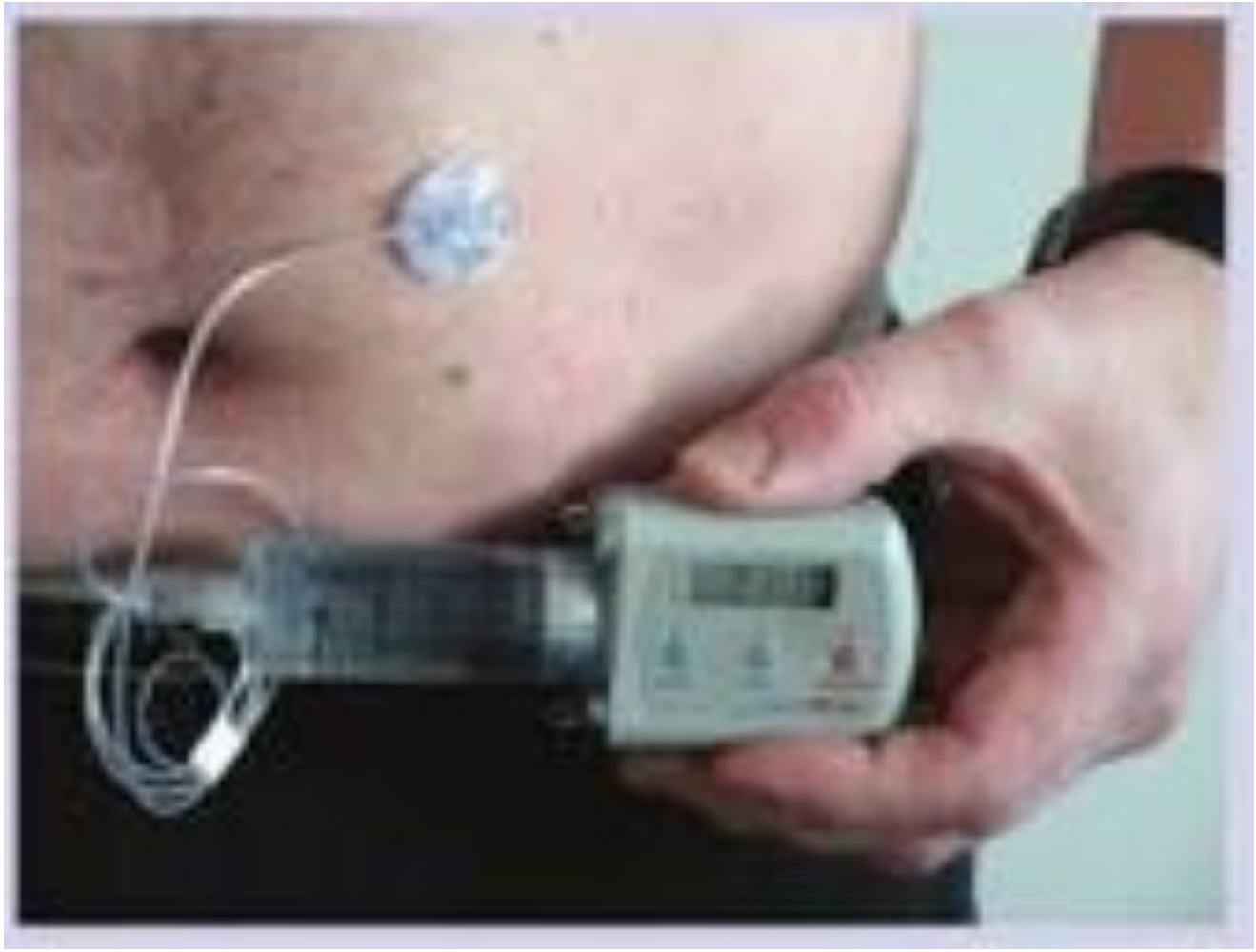
Diphasic dyskinesias -large-amplitude dyskinetic movements of the lower body during the time of increasing and decreasing LD levels.

Advanced PD –treatment options

- Apomorphine
- Duodopa (LCIG)
- DBS

APOMORPHINE

- Apomorphine
  - Dopamine agonist



Apomorphine dosing

- Intermittent rescue injections
  - 3.5 to 5.5mg per dose
  - Aim for benefit in 5-15 min, lasting 60-90 min
  - 1-8 doses/day
  - Continue L-DOPA unchanged
- Continuous apomorphine infusion
  - Approx. 4mg/hr for approx. 16hr/day
  - 24 hour/day: rare
  - Start at 1 to 3.5mg/hr, titrating upwards while titrating L-DOPA down, according to response

Apomorphine subcutaneous infusion in patients with Parkinson's disease with persistent motor fluctuations (TOLEDO): a multicentre, double-blind, randomised, placebo-controlled trial

Regina Katzenschlager, Werner Poewe, Olivier Rascol, Claudia Trenkwalder, Günther Deuschl, K Ray Chaudhuri, Tove Henriksen, Teus van Laar, Kevin Spivey, Senthil Vel, Harry Staines, Andrew Lees

Lancet Neurol 2018; 17: 749-59

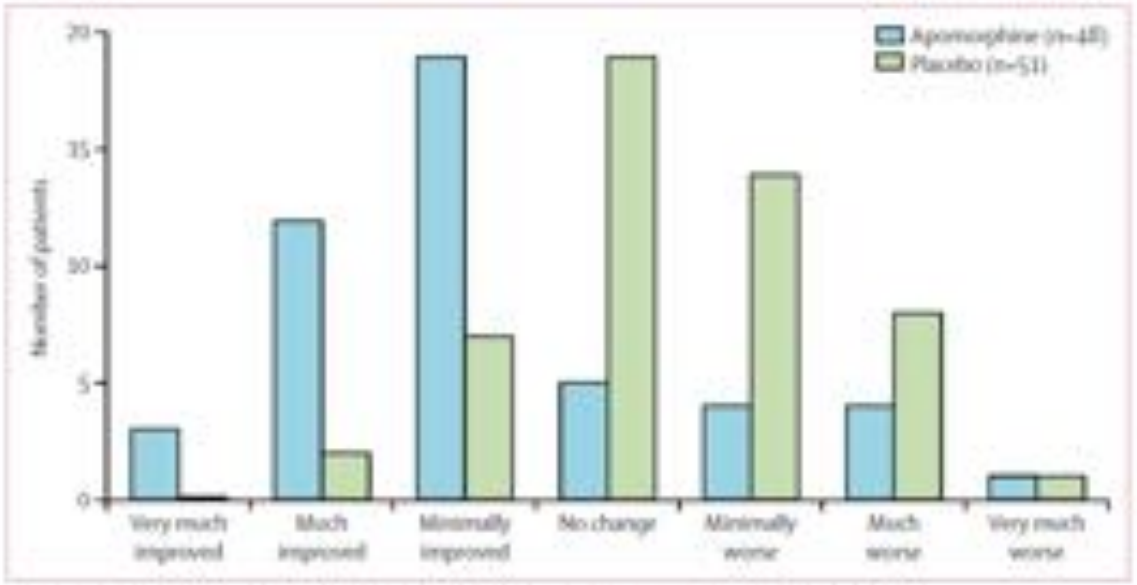
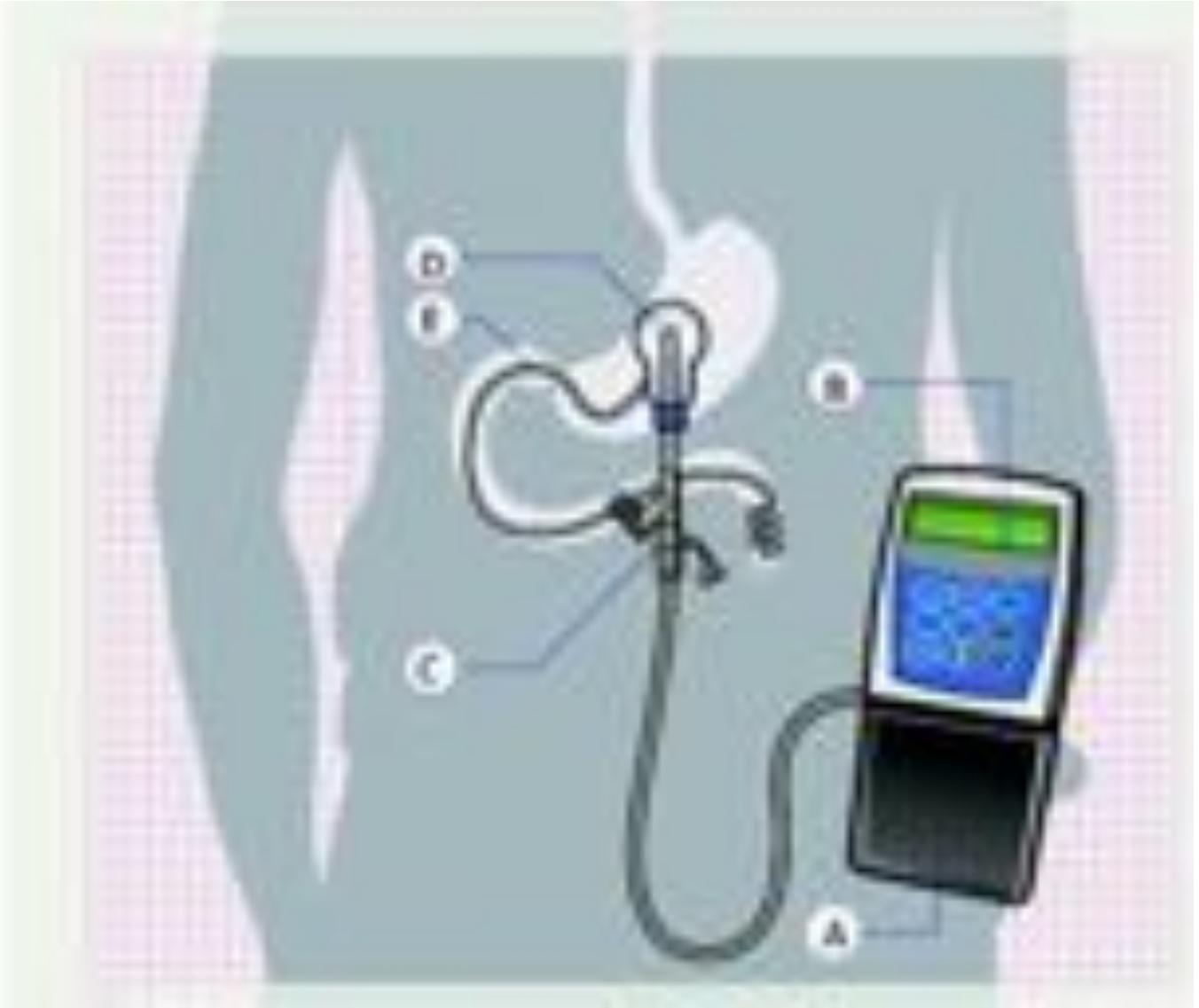


Figure 4: Patient Global Impression of Change from baseline to week 12 (full analysis set)

- N=106 advanced PD
- Continuous apomorphine vs placebo
- At 12w, reduction in 'off': 2.5 vs 0.6h

- Complications
  - Skin site reactions (70%)
  - Somnolence, nausea, confusion, VH, orthostatic hypotension, yawning, rhinorrhea, sleep attacks

Levodopa Carbidopa Intestinal Gel (LCIG)



LCIG

- "Levodopa-Carbidopa Intestinal Gel"
  - Overcomes pharmacokinetic problems with gastric emptying interfering with L-DOPA absorption
- Similar principles to apomorphine infusion
  - Daytime monotherapy
  - Generally initiated as an inpatient
- Growing evidence base

Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study

C Warren Olanow, Karl Kieburtz, Per Odin, Alberto J Espay, David G Standaert, Hubert H Fernandez, Anaydas Vanagunas, Ahmed A Othman, Katherine L Widnell, Weining Z Robieson, Yili Pritchett, Krai Chatamra, Janet Benesh, Robert A Lenz, Angelo Antonini, for the LCIG Horizon Study Group

Lancet Neurol 2014; 13: 141–49

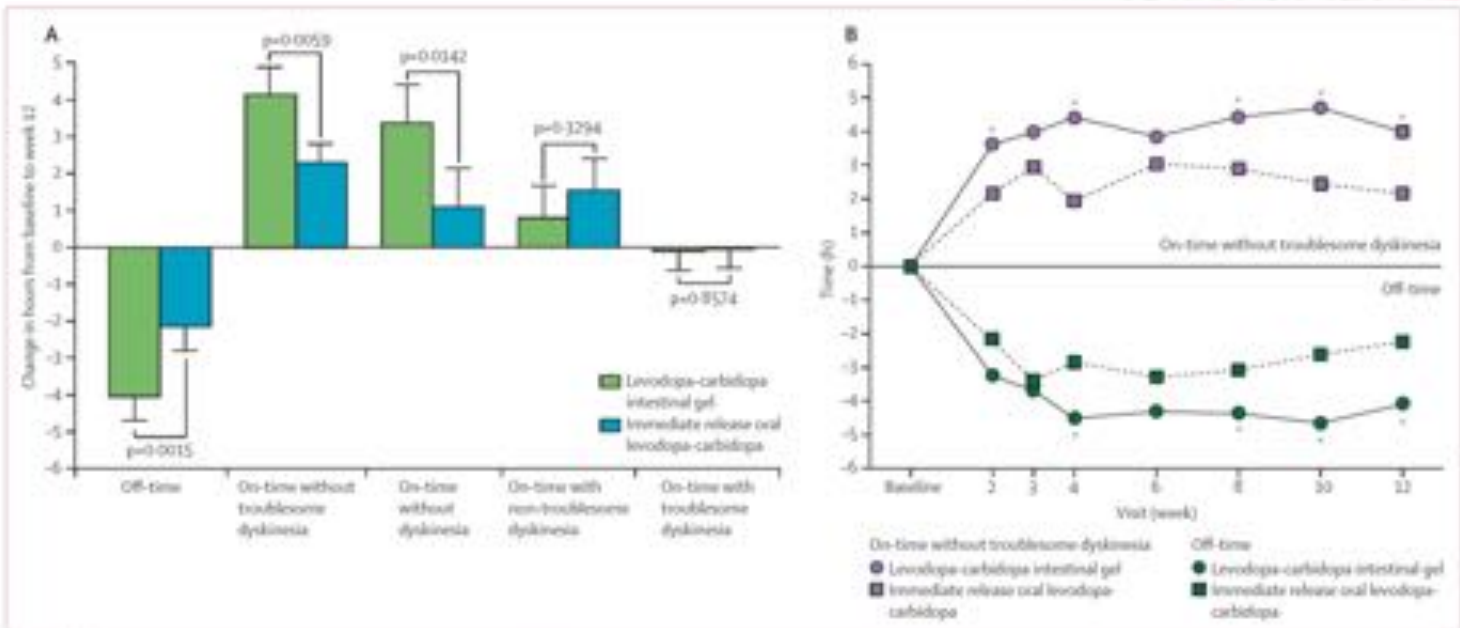
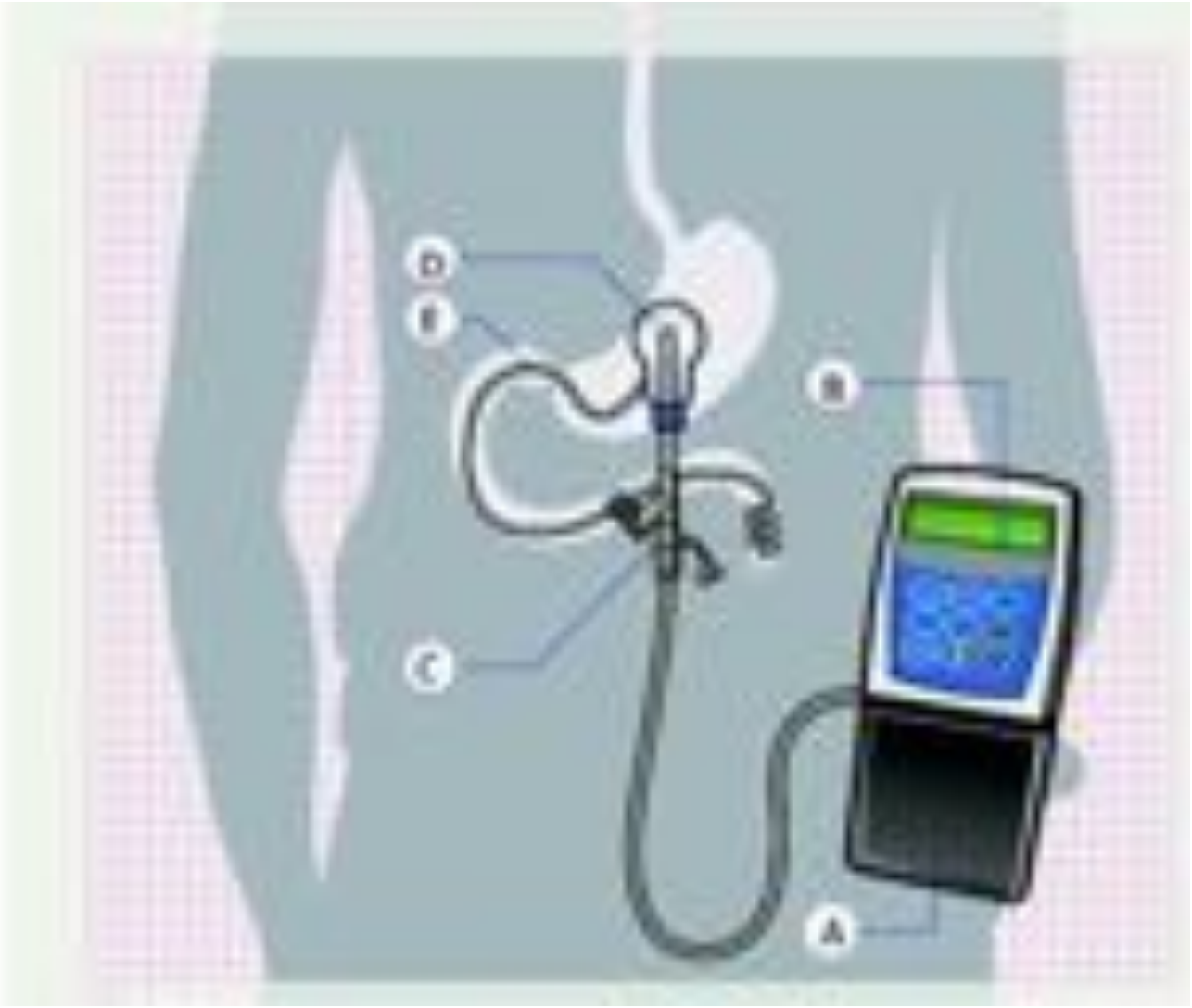


Figure 2: Diary measures

(A) Home diary results: change between baseline and week 12 in various Parkinson's disease motor states. (B) Home diary results: Parkinson's disease motor states at each visit. *p<0·05. For each variable, data shown are the least squares means (error bars) from the symptom diary for the 3 consecutive days before the clinic visit, normalised to a 16 h waking day. On-time without troublesome dyskinesia equals on-time without dyskinesia plus on-time with non-troublesome dyskinesia. Data for 35 patients in the levodopa-carbidopa intestinal gel group and 31 patients in the immediate-release oral levodopa-carbidopa group.

- **Duodopa**
  - Up to 16h/d via PEJ
  - Improvement
    - ‘off’ time (4.0 vs 2.1h) *(Wirdefeldt 2016)*
    - ‘off time’ reduction 40-80%) *(Timpka 2017)*
    - Dyskinesia (4.1h vs 2.2)
  - **Complications**
    - Neuropathy – need to check micronutrients
    - Device/surgery related



Currently 7 active patients on Duodopa

1 patient discharged this week

Varying degrees of improvement

Failed in 1 patient, unable to cope with complexity of treatment and withdrawn

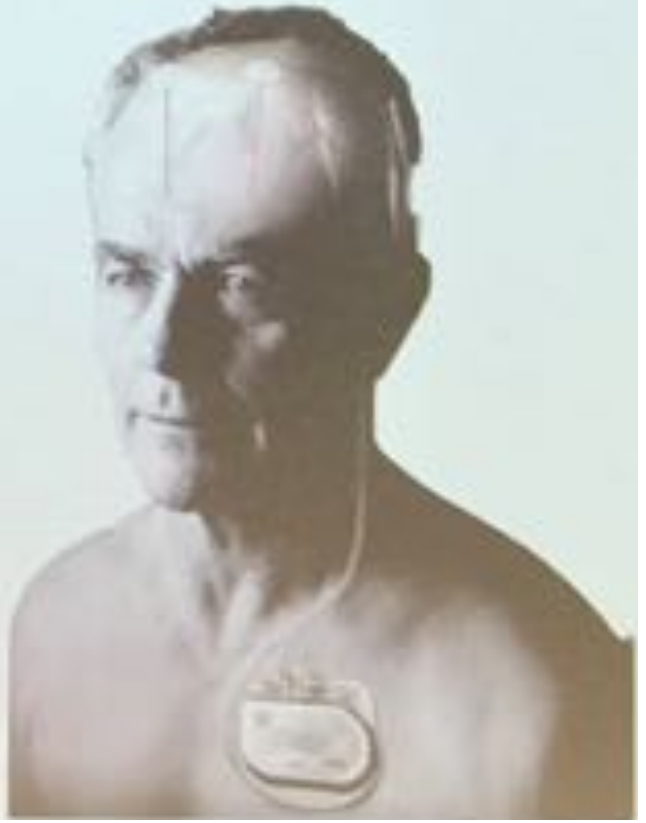
Deep Brain Stimulation - DBS

What is DBS?

- Electrical stimuli delivered to precise target within the brain
  - STN
  - GPi
  - (Vim / cZI / PSA for PD tremor)

What is DBS?

- Implanted electrode
- Extension lead
- Implanted pulse generator



DBS

DBS (STN or GPi)

- More effective in improving motor function and QoL than best medical therapy (at least short term)
- Reduced 4.6h/d of dyskinesia
- Meaningful motor improvement (71 vs 32%) and QoL

Complications

- Surgically related
- Diminished cognition function on (memory, processing speed, verbal fluency, delayed recall)

What DBS does for PD

YES	NO
•Fluctuations	•Cure PD
•Dyskinesia	•Alter progression
•Disability	•Better than L-dopa
•Medications	•Non-dopa responsive features
•Quality of life	
•Risks of treatment	

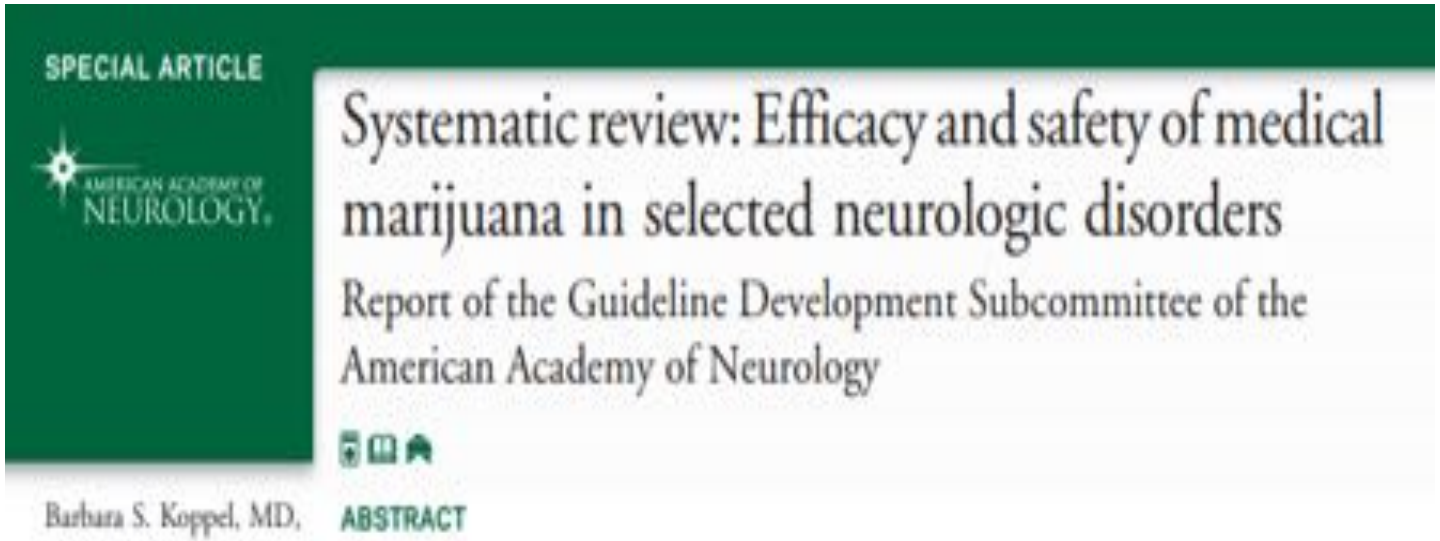
Which Advanced Therapy?

	Good	Not so good
Apo	Effective, minimally invasive	Skin nodules, carer, need to wear pump / frequent needles, night-time symptoms, expense Need expert nurses
Duodopa	Very effective, few centres	PEG-J insertion, hospital time, limited availability, need to wear pump, expense Need expert nurses & gastro
DBS	Very effective, Least expensive	Most invasive, still costly Neurosurgery, voice, balance, apathy, ... Need expert team

Controversial

- **Cannabis**

  - No evidence as of 2018



Controversial

- Nilotinib
  - Approved for Chronic Myeloid Leukemia, inhibits c-Abl
  - Phase 2 trial
  - No evidence, high risk

Breaking News –trials from MDS 2018 Hong Kong

Non invasive Brain stimulation

- Repeated Transcranial magnetic stimulation with transcranial direct current stimulation may slow PD progression with no side effects.
- 30 patients

Zonisamide improves parkinsonism in DLB patients: A randomized phase 3 trial

- 351 patients randomized

Low fat Versus Ketogenic Diet In Parkinson's Disease: A Pilot Randomized Controlled Trial

- 47 patients
- Ketogenic diet improved motor function

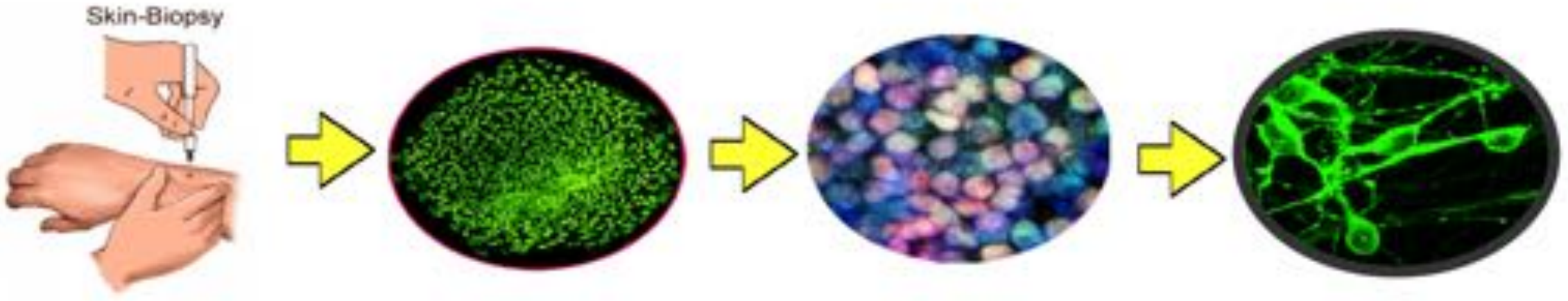
Light Therapy

- Double-blind controlled trial of Spectramax™ light therapy for the treatment of Parkinson's disease patients on stable dopaminergic therapy.
  - First long term phototherapy trial – 6 months
  - 94 patients
  - Improvement in motor and non motor performance in subjects vs controls

Future

- Stem cells
  - Somatic stem cells → can only make same type of tissue
  - Hematopoietic stem cells → 15 blood cell types in body
  - Pluripotent stem cells → 210 cell types in body

FROM SKIN (OR BLOOD) TO DOPAMINERGIC NEURONS



Skin cells (fibroblasts)

Induced pluripotent stem (iPS) cells

Neural stem cells

Dopaminergic neurons

Summary

Complex neurodegenerative disorder

Prodromal stage

Potential targets for therapeutic intervention

Diagnostic challenges

Management – motor/nonmotor

Still lacking disease modifying treatment

Thank You