Parkinson Disease

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Presented by: ***Ontario's Geriatric Steering Committee***

Key Learnings

Parkinson Disease (L. Kalia)

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Key Learnings

- Parkinson disease is the most common but not the only cause of parkinsonism
- Parkinson disease is a progressive disorder associated with a wide range of symptoms
- Management of Parkinson disease is not static and is aimed at improving function and quality of life

Common Causes

Parkinson Disease (L. Kalia)

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Overview

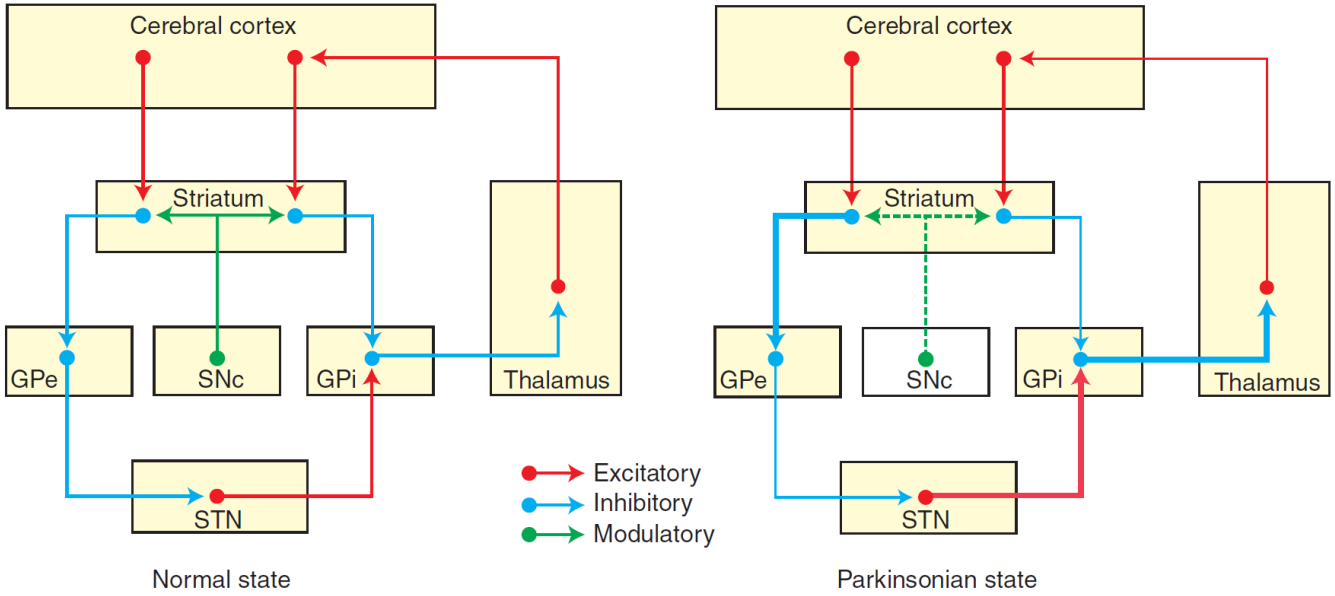
- Definition of parkinsonism
- Differential diagnosis of parkinsonism
- Etiology and risk factors for PD

Parkinsonism – *Definition*

- A clinical syndrome manifested by:
  - Bradykinesia
  - Rest tremor
  - Rigidity
  - Postural disturbances

Parkinsonism – *Cause*

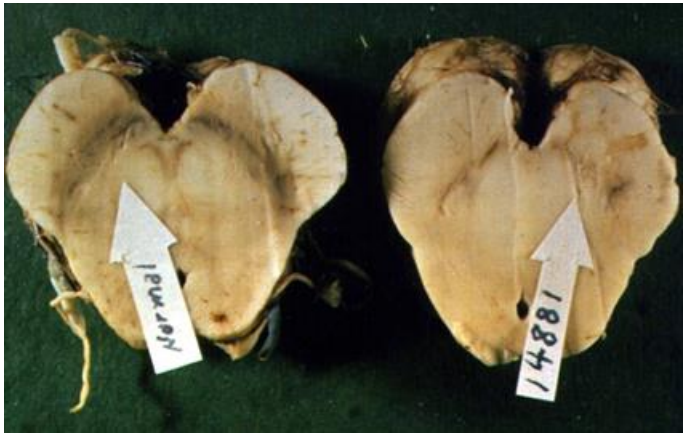
- Impaired dopamine signalling in basal ganglia

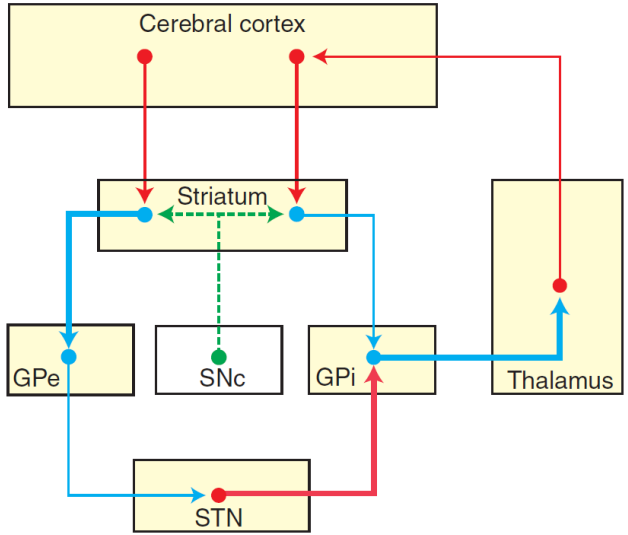


From Lanciego *et al. Cold Spring Harb* 2012

Parkinsonism – *Cause*

- Impaired dopamine signalling in basal ganglia





Parkinsonian state

From www.urmc.rochester.edu

Parkinsonism – *Differential Diagnosis*

Primary Parkinsonism

- Parkinson Disease (Sporadic, Familial)
- Atypical Parkinsonism ("Parkinson Plus" Disorders)
  - Dementia with Lewy Bodies (DLB)
  - Progressive Supranuclear Palsy (PSP)
  - Multiple System Atrophy (MSA)
  - Corticobasal Degeneration (CBD)
- Other Neurodegenerative Disorders (e.g. AD, FTD, CJD)

Parkinsonism – *Differential Diagnosis*

Secondary Parkinsonism

- Drugs/Toxins
- Vascular
- Infectious
- Malignancy
- Other Structural
- Metabolic
- Trauma
- Psychogenic

Parkinsonism – *Differential Diagnosis*

Primary Parkinsonism

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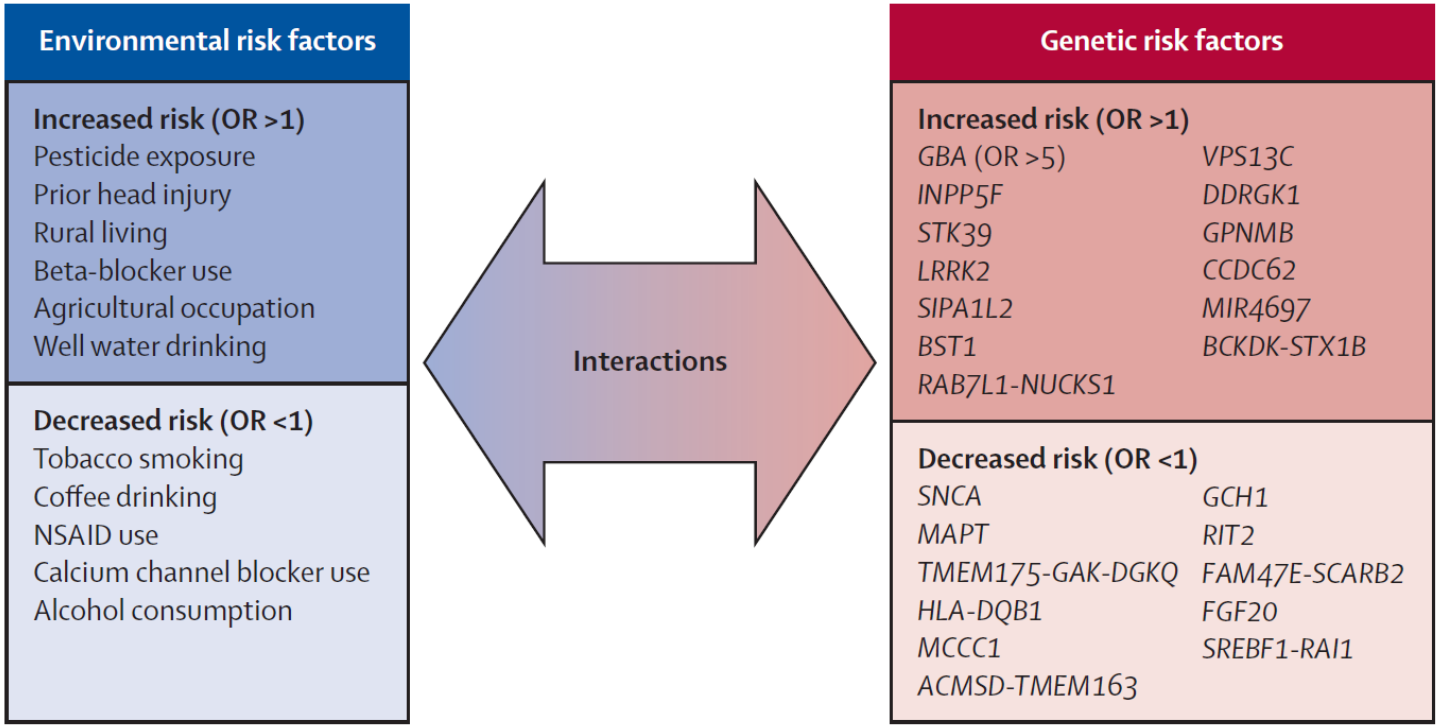
Parkinson Disease – *Genetic Causes*

	Protein	Pathogenic mutation(s)
Autosomal dominant		
SNCA	α-synuclein	Missense mutations (Ala18Thr, Ala29Ser, Ala30Pro, Glu46Lys, His50Gln, Gly51Asp, Ala53Glu, Ala53Thr); multiplications (duplications, triplications)
LRRK2	Leucine-rich repeat kinase 2	Missense mutations (Ile1371Val, Asn1437His, Arg1441Cys, Arg1441Gly, Arg1441His, Tyr1699Cys, Gly2019Ser [most common], Ile2020Thr)
VPS35	Vacuolar protein sorting 35	Missense mutation (Asp620Asn)
EIF4G1	Eukaryotic translation initiation factor 4-γ 1	Missense mutations (Arg1205His, Ala502Val)
DNAJC13	Receptor-mediated endocytosis 8 (REM-8)	Missense mutation (Asn855Ser)
CHCHD2	Coiled-coil-helix-coiled-coil-helix domain containing 2	Missense mutations (Thr61Ile, Arg145Gln); splice-site alteration
Autosomal recessive		
Parkin	Parkin	Exon rearrangements, including exon deletions or multiplications (most common); missense mutations, nonsense mutations, small deletions or insertions; splice-site alterations
PINK1	PTEN-induced putative kinase 1	Missense or nonsense mutations (most common); exon rearrangements, including exon deletions or duplications
DJ-1	DJ-1	Missense mutations or exon rearrangements (most common); splice-site alterations

Table 1: **Monogenic forms of Parkinson's disease, by gene**

From Kalia & Lang *Lancet* 2015

Parkinson Disease – *Risk Factors*



From Kalia & Lang *Lancet* 2015

Assessment

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Overview

- Clinical diagnosis of PD
- Motor features
- Non-motor features

Clinical Assessment

- Detailed history and exam aimed at:
  - Confirming features of parkinsonism
  - Identifying any "red flags" for diagnosis of PD
  - Identifying features that support diagnosis of PD
  - Defining symptoms (motor, non-motor) that negatively impact the patient's function or quality of life

Diagnostic Criteria

Panel 1: **UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria[2]**

Step 1: diagnosis of parkinsonian syndrome

Bradykinesia (ie, slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) plus one or more of the following features:

- Muscular rigidity
- 4–6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Modified from Kalia & Lang *Lancet* 2015

Diagnostic Criteria

Step 2: exclusion criteria for Parkinson's disease

One or more of the following features suggest an alternate diagnosis:

- History of repeated strokes with stepwise progression of parkinsonian features
- History of repeated head injury
- History of definite encephalitis
- Neuroleptic treatment at onset of symptoms
- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exposure
- Negative response to large doses of levodopa (if malabsorption excluded)
- More than one affected relative*
- Sustained remission
- Strictly unilateral features after 3 years
- Early severe autonomic involvement
- Early severe dementia with disturbances of memory, language, and praxis
- Oculogyric crises
- Supranuclear gaze palsy
- Babinski sign
- Cerebellar signs
- Presence of a cerebral tumour or communicating hydrocephalus on CT scan or MRI

*This criterion is generally no longer applied.

Modified from Kalia & Lang *Lancet* 2015

“Red Flags”

Early postural instability/falls	→	PSP, MSA
Early dementia	→	LBD, PSP, CBD, AD, CJD
Early prominent dysautonomia	→	MSA
Extraocular movement abnormalities	→	PSP, MSA
Apraxia, Cortical sensory abnormalities	→	CBD
Upper motor neuron signs	→	MSA, Vascular, Other
Ataxia	→	MSA
Sudden onset	→	Vascular
Lower body distribution	→	Vascular, NPH
Rapid progression	→	Not PD
Poor response to L-dopa (1000 mg/d)	→	Not PD

Diagnostic Criteria

Step 3: supportive prospective positive criteria for Parkinson's disease

Three or more of the following features are required for diagnosis of definite Parkinson's disease:

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting the side of onset most
- Excellent response (70–100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of 10 years or more

Modified from Kalia & Lang *Lancet* 2015

Motor Features

- Bradykinesia
  - Slowness, fatiguing (*i.e.* reduction in speed and amplitude), or arrests in ongoing movements
  - Slow ADLs, hypomimia, hypophonia, micrographia, reduced hand dexterity, difficulty turning in bed, reduced arm swing, difficulty walking
  - One of the most disabling features of PD

Motor Features

- Rest Tremor
  - Hands > Legs, Face, Other
  - Present or increases with stress or distraction
  - "Re-emergent" with new posture
  - Present or increases with walking
  - Often impacts patient's self perception and social interactions

Motor Features

- Rigidity
  - Involuntary increase in muscle tone to passive movement
  - “Cogwheeling” or “Lead pipe”
  - Mild rigidity can be detected by “activation”
  - Patients may describe muscle stiffness or pain

Motor Features

- Postural disturbances
  - Flexed posture
  - Postural instability
  - Patients report poor balance, unsteadiness, and falls
  - Can be accompanied by gait dysfunction (*e.g.* shuffling, freezing)

Non-Motor Features

- Neuropsychiatric features
  - Apathy
  - Depression
  - Anxiety
  - Dementia
  - Hallucinations, Delusions (usually medication induced)
  - Impulse control disorders (usually medication induced)
- Sleep dysfunction
  - Excessive daytime sleepiness
  - Insomnia
  - RLS/PLMD
  - Sleep apnea
  - REM sleep behaviour disorder
  - Non-REM sleep-related movement disorders

Non-Motor Features

- Dysautonomia
  - Constipation
  - Bladder dysfunction
  - Orthostatic hypotension (exacerbated by meds)
  - Hyperhydrosis
  - Sexual dysfunction
- Sensory
  - Pain
  - Impaired olfaction
  - Visual dysfunction
- Other
  - Fatigue
  - Weight loss

Management

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Overview

- Treatment approach for PD
- Challenges in treatment of PD
- Treatment of motor and non-motor features

Disease-Modifying Therapies

- Current treatments only alleviate symptoms
- No available therapies to stop or slow disease progression
- Ongoing clinical trials to identify disease-modifying therapies

Treatment Approach

- Early PD
  - No treatment
  - Non-pharmacological treatment (*i.e.* exercise)
  - Monotherapy (*e.g.* MAOBi)
- Mild/Moderate PD
  - Monotherapy (*e.g.* L-dopa, Dopamine agonist)
- Advanced PD
  - Polytherapy
  - Surgical treatment

Motor Features

	Treatment of motor symptoms		Treatment of motor complications	
	Monotherapy	Adjunct to levodopa	Fluctuations	Dyskinesia*
Levodopa				
Levodopa-carbidopa	+	..	+	–
Levodopa-benserazide	+	..	+	–
Dopamine agonists (non-ergot)				
Pramipexole	+	+	+	–
Ropinirole	+	+	+	–
Rotigotine	+	+	+	–
Monoamine oxidase type B inhibitors				
Rasagiline	+	+	+	–
Selegiline	+	–§	–§	–
Catechol-O-methyltransferase inhibitors				
Entacapone	..	+	+	–
Tolcapone	..	+	+	–
Others				
Amantadine	+	+	–	+
Anticholinergics†	+‡	+‡	–	–
Clozapine	+‡	+‡	–	+

+ indicates efficacious or likely efficacious. – indicates non-efficacious or insufficient evidence. .. indicates not applicable. *Responses to peak dose dyskinesia (diphasic dyskinesia might respond to drugs used for motor fluctuations, particularly dopamine agonists). †Includes benztropine, ethopropazine, trihexyphenidyl, and others. ‡For treatment of tremor. §There is insufficient evidence but, in practice, selegiline is used and can be effective.

Modified from Kalia & Lang *Lancet* 2015

Initial Treatment

No functional impairment → Delay therapy, Clinical trial

Mild symptoms → MAOBi

Impact on function/QoL → L-dopa, Dopamine agonist

Discrete symptoms
e.g. Tremor → Anticholinergic
Depression/Anxiety → SSRI

Response to Treatment

- Not all motor features respond uniformly to treatment
  - Bradykinesia and rigidity are most responsive
  - Tremor response is variable
  - Postural disturbances are least responsive

- Treatment of non-motor features often more challenging

Treatment Complications

- Fluctuations (motor, non-motor)
- Dyskinesia
- Psychosis (hallucinations, delusions)
- Impulse control disorders
- Orthostatic hypotension

Motor Complications

	Treatment of motor symptoms		Treatment of motor complications	
	Monotherapy	Adjunct to levodopa	Fluctuations	Dyskinesia*
Levodopa				
Levodopa-carbidopa	+	..	+	–
Levodopa-benserazide	+	..	+	–
Dopamine agonists (non-ergot)				
Pramipexole	+	+	+	–
Ropinirole	+	+	+	–
Rotigotine	+	+	+	–
Monoamine oxidase type B inhibitors				
Rasagiline	+	+	+	–
Selegiline	+	–§	–§	–
Catechol-O-methyltransferase inhibitors				
Entacapone	..	+	+	–
Tolcapone	..	+	+	–
Others				
Amantadine	+	+	–	+
Anticholinergics†	+‡	+‡	–	–
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Non-Motor Features

	Drug class	Drug name
Cognitive impairment		
Dementia	Acetylcholinesterase inhibitor	Rivastigmine
Psychiatric symptoms		
Depression	Dopamine agonist Serotonin reuptake inhibitor Serotonin and norepinephrine reuptake inhibitor Tricyclic antidepressant	Pramipexole Citalopram, escitalopram, fluoxetine, paroxetine, sertraline Venlafaxine extended release Desipramine, nortriptyline
Psychosis	Atypical antipsychotic Acetylcholinesterase inhibitor	Clozapine, quetiapine Rivastigmine
Sleep disorders		
REM sleep behaviour disorder	Benzodiazepine Hormone	Clonazepam Melatonin
Autonomic dysfunction		
Constipation	Osmotic laxative Chloride channel activator	Polyethylene glycol Lubiprostone
Gastrointestinal motility	Peripheral dopamine antagonist	Domperidone
Orthostatic hypotension	Peripheral dopamine antagonist Mineralocorticoid Vasopressor Acetylcholinesterase inhibitor Norepinephrine prodrug	Domperidone Fludrocortisone Midodrine Pyridostigmine Droxidopa
Sialorrhoea	Anticholinergic Neurotoxin	Atropine drops, glycopyrrolate Botulinum toxin A, botulinum toxin B
Other		
Fatigue	Stimulant	Methylphenidate, modafinil

Modified from Kalia & Lang *Lancet* 2015

Surgical Treatments

- Available surgical treatments:
  - Deep brain stimulation (DBS)
  - Ablative surgery (pallidotomy, thalamotomy)
  - Continuous delivery of L-dopa/carbidopa intestinal gel via PEG/J (DUODOPA®)

Surgical Treatments

- When to consider surgical treatments:
  - Best candidates are age ≤70 yrs with minimal or no cognitive dysfunction
  - Good response to L-dopa but complicated by significant fluctuations or troublesome dyskinesia
  - Multiple medication trials
- Refer to specialized centre with multidisciplinary team

Implications for Practice

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Overview

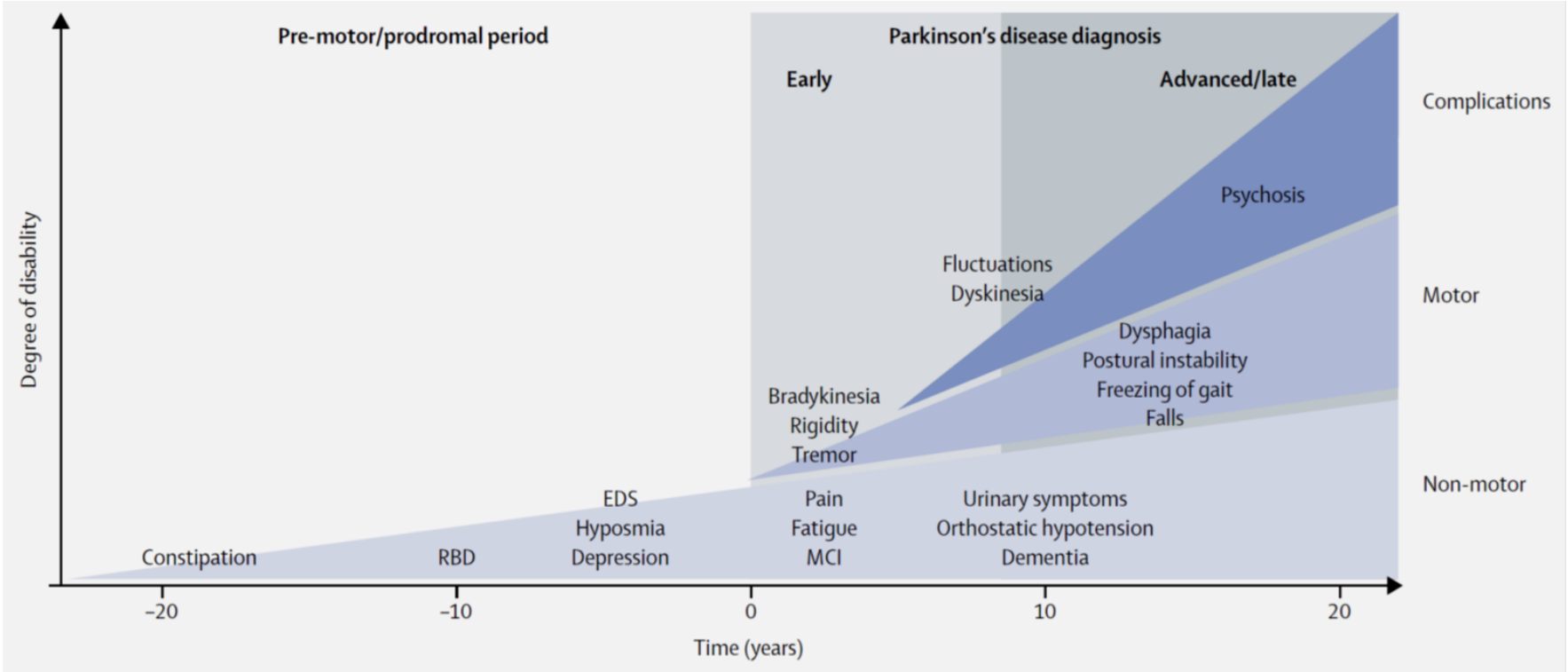
- Diagnostic issues in clinical practice
- Treatment issues in clinical practice
- Safety issues in clinical practice

Diagnostic Issues

- Not all patients with parkinsonism have PD
- Early PD can be difficult to differentiate from other causes
- Neuroimaging (MRI brain) can assist in ruling out other causes
- No definitive diagnostic test for PD (gold standard: pathology)
- Diagnosis has implications for treatment and prognosis
- Accuracy of clinical diagnosis improves with time

∴ Re-assess diagnosis and screen for "red flags" annually (AAN 2009)

Treatment Issues



Kalia & Lang *Lancet* 2015

Treatment Issues

- PD is a progressive disease ∴ treatment is not static
- Goal of treatment is to maximize function and quality of life
- Assess for fluctuations/dyskinesia at all visits (AAN 2009)
- Assess for cognitive dysfunction, psychiatric symptoms, sleep disturbances, and autonomic dysfunction annually (AAN 2009)
- Consider medical/surgical treatment options annually (AAN 2009)
- Consider rehabilitative therapy options (*e.g.* PT, OT, SLP) annually (AAN 2009)

Safety Issues

- Provide counselling on safety issues annually (AAN 2009)
  - Medication management
  - Falls and injury prevention
  - Driving
  - Elder abuse

Thank you!

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