PARKINSON DISEASE – DIFFERENTIAL DIAGNOSIS TO TREATMENT

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OUR TOPICS FOR TODAY

- What you look for to make a diagnosis
- When it is Parkinson disease
  - Impact of disease
  - Treatments

THE EFFECT OF PARKINSON DISEASE

- At 15 years into diagnosis
  - 62 % patients had died
  - 100% patients had a progressive disease characterized predominantly by non-motor symptoms
  - 90% of patients had disability from non-dopamine responsive symptoms
  - 80% had suffered falls and 25% had had disabling fractures
  - 85 % had cognitive impairment and 50% had frank dementia
  - 50% had required psychiatric management of depression and hallucinations

THE EFFECT OF PARKINSON DISEASE

- At 15 years into diagnosis
  - 50% had experienced significant choking difficulty documented by SLP
  - 35% experienced symptomatic postural hypotension requiring treatment
  - 40% experienced incontinence
  - 50% required substantial care help including nursing home care
  - Finally 90% had fluctuations and dyskinesia
  - All this means 0% were employed

THE EFFECT OF PARKINSON DISEASE

- At 20 years into disease
  - 74% patient had died
  - 70% had disabling urinary incontinence
  - 100% experienced fatigue and pain
  - 50% had significant enough constipation that required medications
  - 80% had speech impairment the most common being hypophonia
    - This was bad enough that the average speech output declined by 75%
    - 10% had tachyphemia and 100% of them had impaired intelligibility

THE EFFECT OF PARKINSON DISEASE

- At 20 years into disease
  - 50% had persistent choking
  - 90% had falls with 35% fracture rate
  - 85% had dementia (which had a median of diagnosis at 10yeras) and the median survival post dementia was 5 years
  - Mortality of was close to 75% (although this was variable)
- Almost 90% of the QoL dysfunction was related to non-motor symptoms and dopamine unresponsive symptoms

AN IMPORTANT PRACTICE SPIN – DO WE OFFER OPTIMAL CARE? CAN WE EVER?

- So we as PD neurologists have to be (and all without any training)
  - Gastroenterologists
  - Urologists
  - Psychiatrists
  - Sleep medicine specialists
  - Autonomic management specialists
  - Rheumatologists or some version of this (pain specialists?)
  - Pharmacologists and physiologists
- Are we actually skilled to do this?

WHAT YOU MUST LOOK FOR IN THE HISTORY

- Onset, progression and duration of symptoms
- Drug history
- Family history
- Occupation (h/o exposure)
- h/o postural dizziness, bladder dysfunction
- h/o dementia/ psychosis (eg, hallucination)
- h/o choking
- h/o RBD

WHAT YOU MUST LOOK FOR IN THE EXAM

- Presence or absence of tremor
- Asymmetry or symmetry of rigidity, bradykinesia
- Site of more rigidity – axial or appendicular
- EOM- gaze restriction, saccade, pursuit
- Postural instability
- Gait- initiation, any FOG, turning
- Presence of postural hypotension
- Presence of myoclonus
- Presence of cortical signs

KEY POINTS FOR THE DIFFERENTIAL DIAGNOSIS

- Major clues as Red flags-

➢ Rapid clinical deterioration

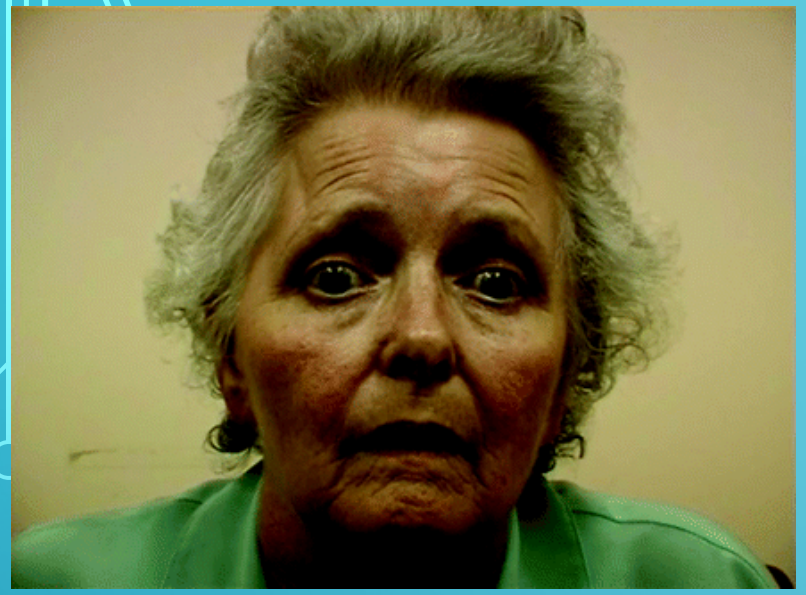
➢ Wheel chair sign (wheel chair dependent within 5 years)

➢ Non responsive to L-dopa

PROGRESSIVE SUPRANUCLEAR PALSY

- Axial rigidity > appendicular rigidity
- Retrocollis
- Round the house sign, Vertical supranuclear gaze palsy (VSGP, predom downgaze restriction)
- Early fall (within 3 years of disease onset)
- Applause sign
- Messy-tie sign
- Apraxia of lid opening (ALO)
- Surprised look, Vertical wrinkling of the forehead (Procerus sign), Reptilian stare
- Apathy, Frontal executive dysfunction
- Motor recklessness, Rocket sign

PSP



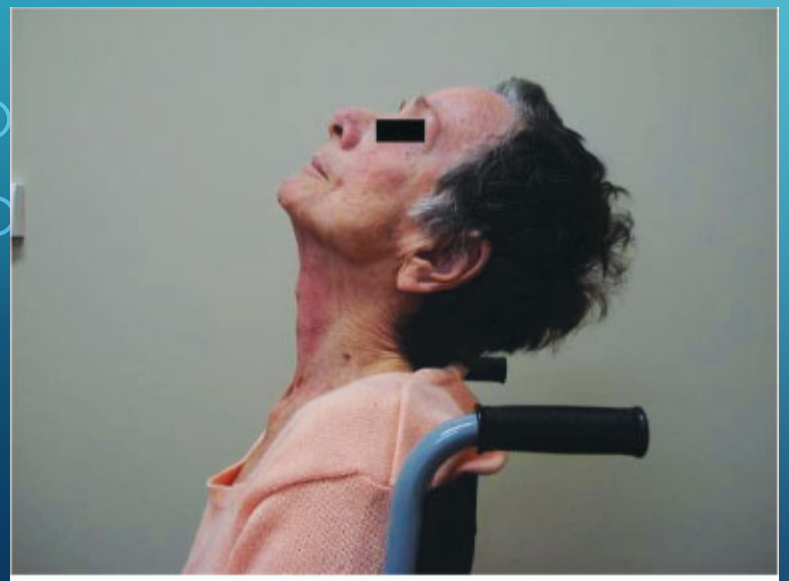
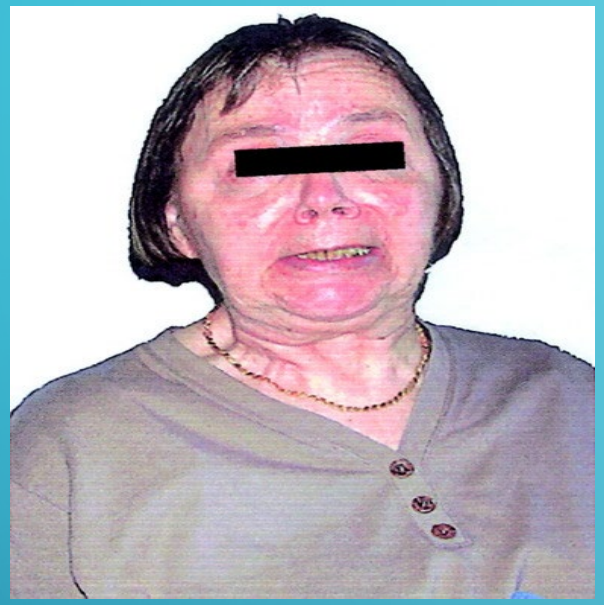


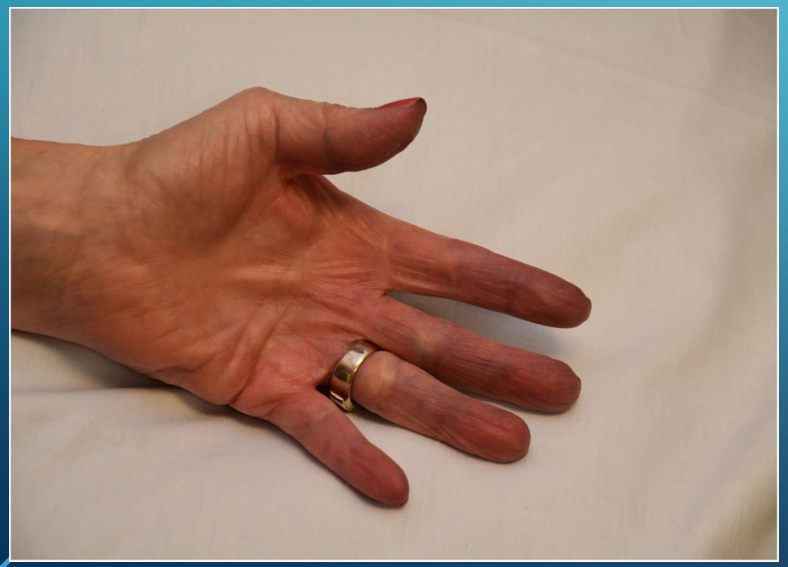
Fig 1. An illustrative image of a patient with progressive supranuclear palsy with 5 years of disease duration and retrocollis. Note that the patient is already in wheelchairs.

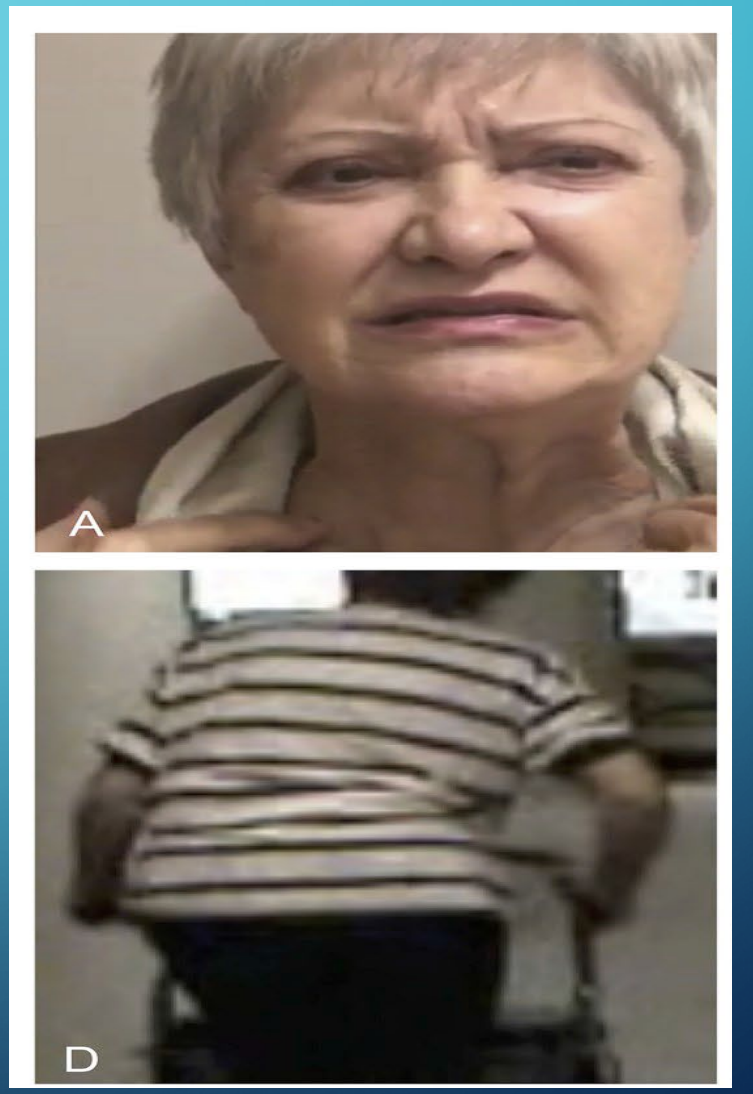
MULTIPLE SYSTEM ATROPHY

- Postural hypotension, supine hypertension
- Bladder dysfunction eg c/o urgency, incontinence, retention
- Erectile dysfunction
- Early fall
- Disproportionate antecollis
- Orofacial dystonia
- Inspiratory sighs, Stridor
- New onset snoring
- Severe dysphonia and dysarthria in short disease duration
- Cold hands and feet
- Polyminimyoclonus on outstretched hands
- Contracture of hands and feet, striatal hand and toe
- Pisa syndrome

MSA







CORTICO-BASAL DEGENERATION

- Apraxia
- Myoclonus
- Alien limb
- Cortical signs
- Asymmetric limb dystonia

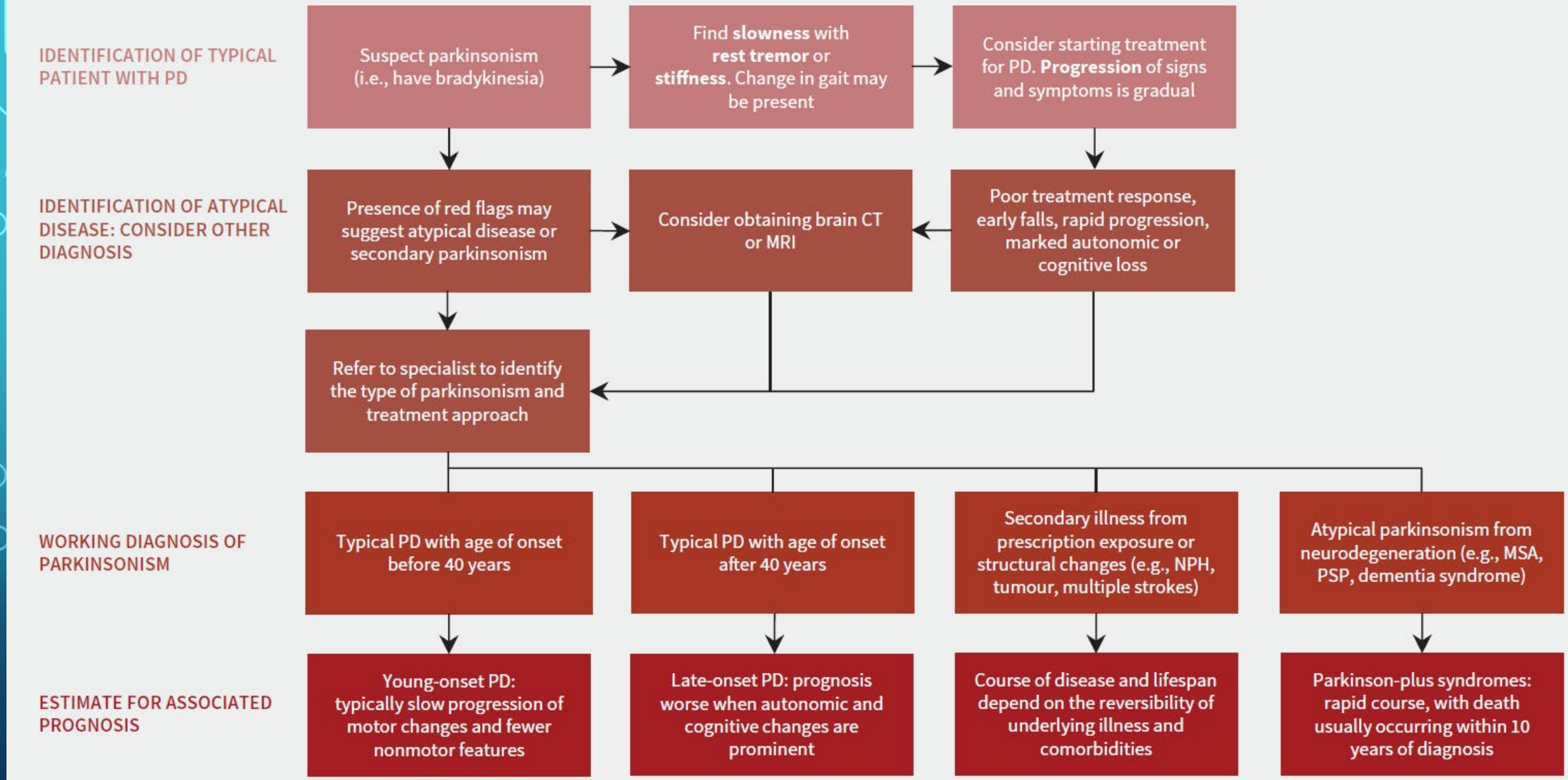
DEMENTIA OF LEWY BODY

- Early dementia, within 1 year of onset of motor signs
- Fluctuating cognition
- Hallucination

OTHER THINGS THAT WE SHOULD CONSIDER

- Drug induced Parkinsonism
- Normal Pressure Hydrocephalus

- Always to ask for h/o exposure to drugs like aripiprazole, haloperidol, lithium, levosulpiride, etc
- Are the symptoms persist even 6 months after stopping the drugs?

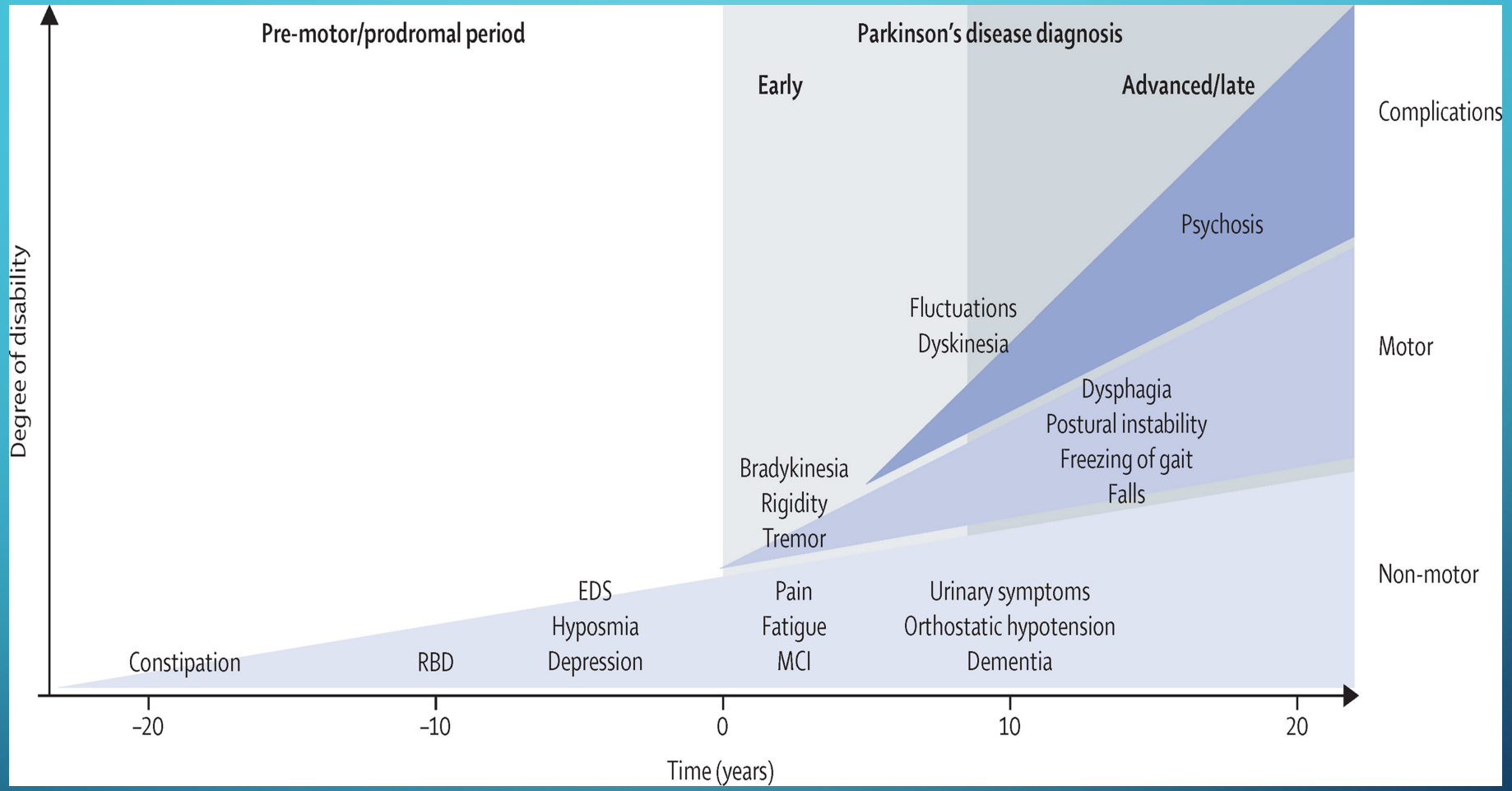

IDENTIFICATION OF TYPICAL PATIENT WITH PD
Suspect parkinsonism (i.e., have bradykinesia)
Find slowness with rest tremor or stiffness. Change in gait may be present
Consider starting treatment for PD. Progression of signs and symptoms is gradual
IDENTIFICATION OF ATYPICAL DISEASE: CONSIDER OTHER DIAGNOSIS
Presence of red flags may suggest atypical disease or secondary parkinsonism
Consider obtaining brain CT or MRI
Poor treatment response, early falls, rapid progression, marked autonomic or cognitive loss
Refer to specialist to identify the type of parkinsonism and treatment approach
WORKING DIAGNOSIS OF PARKINSONISM
Typical PD with age of onset before 40 years
Typical PD with age of onset after 40 years
Secondary illness from prescription exposure or structural changes (e.g., NPH, tumour, multiple strokes)
Atypical parkinsonism from neurodegeneration (e.g., MSA, PSP, dementia syndrome)
ESTIMATE FOR ASSOCIATED PROGNOSIS
Young-onset PD: typically slow progression of motor changes and fewer nonmotor features
Late-onset PD: prognosis worse when autonomic and cognitive changes are prominent
Course of disease and lifespan depend on the reversibility of underlying illness and comorbidities
Parkinson-plus syndromes: rapid course, with death usually occurring within 10 years of diagnosis

DIAGNOSTIC TESTS

- Routine use of functional imaging is not recommended
- Positron emission tomography scanning is not recommended
- Computed tomography or magnetic resonance imaging brain scanning should not be routinely applied
- 123I-ioflupane (123I-FP-CIT) single-photon emission computed tomography (SPECT) scanning should be considered as an aid to clinical diagnosis

EPIDEMIOLOGY OF PD

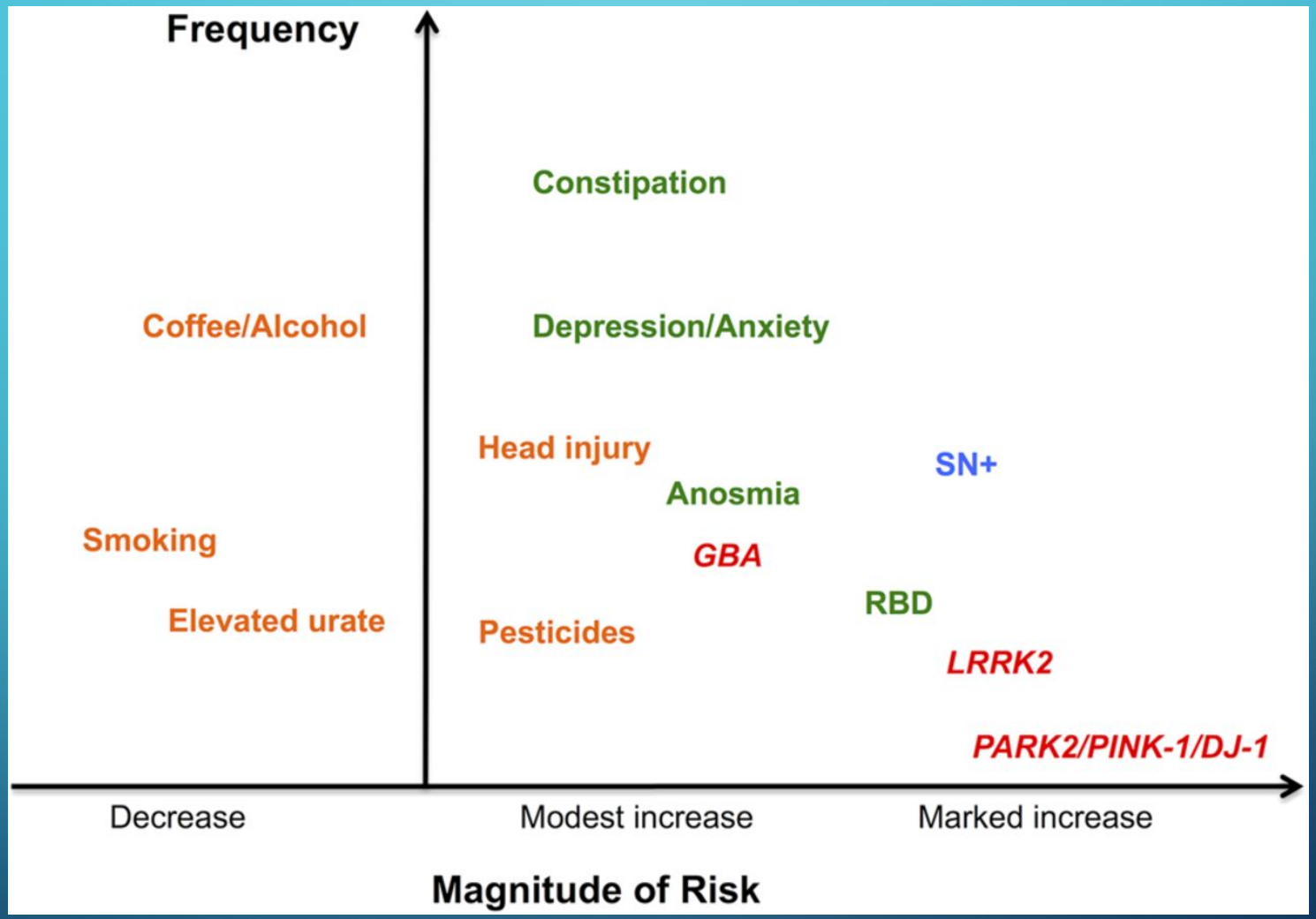
- Parkinson's disease (PD) is a frequent neurodegenerative disease with a premotor phase that lasts several years.



Lorraine V Kalia, MD, Dr Anthony E Lang, MD . Parkinson's disease. *The Lancet* . Volume 386, Issue 9996, Pages 896-912 (August 2015)

The Lancet 2015 386, 896-912DOI: (10.1016/S0140-6736(14)61393-3)

Risk factors and early features of Parkinson's disease associated with increased (or decreased) risk of subsequent diagnosis.



Alastair John Noyce et al. J Neurol Neurosurg Psychiatry 2016;87:871-878

JNNP

EPIDEMIOLOGY OF PD

- Incidence was 37.6 cases per 100,000 person-years in women older than 40 years and 61.2 in men older than 40 years
- The incidence for women and men increased with age.

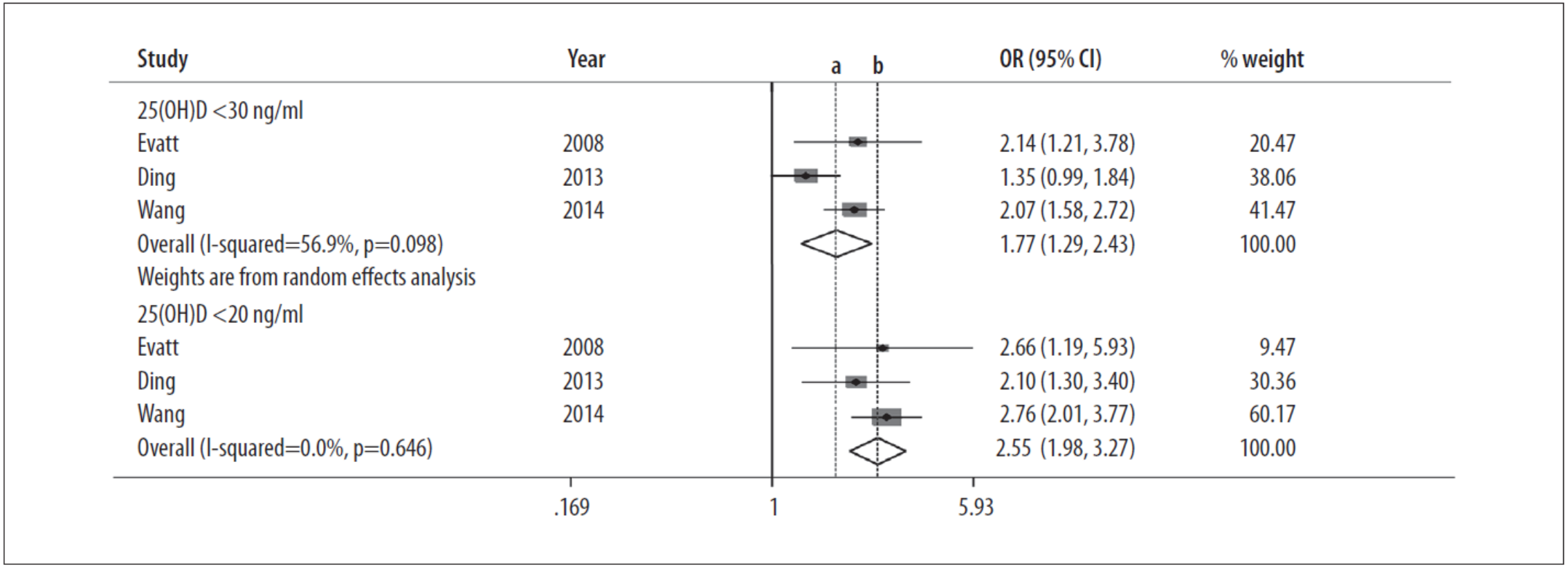
VITAMIN D AND PD

- Vitamin D is suggested to play a neuroprotective and neurotrophic role in the brain
  - Inhibits synthesis of inducible nitric oxide synthase (iNOS), which catalyzes NO, a free radical
  - Stimulates γ-glutamyl trans peptidase activity, which synthesises anti-oxidant glutathione
  - Neurotrophic factor for nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF) and neurotrophin
- A meta analysis of 20 studies showed low serum 25(OH) D levels in PD
- 1 study suggested prevention of worsening on H&Y scale in PD on Vitamin D supplementation

Rimmelzwann et al, 2016

VITAMIN D AND PD

Other studies on association between Vitamin D and PD



VITAMIN D AND PD

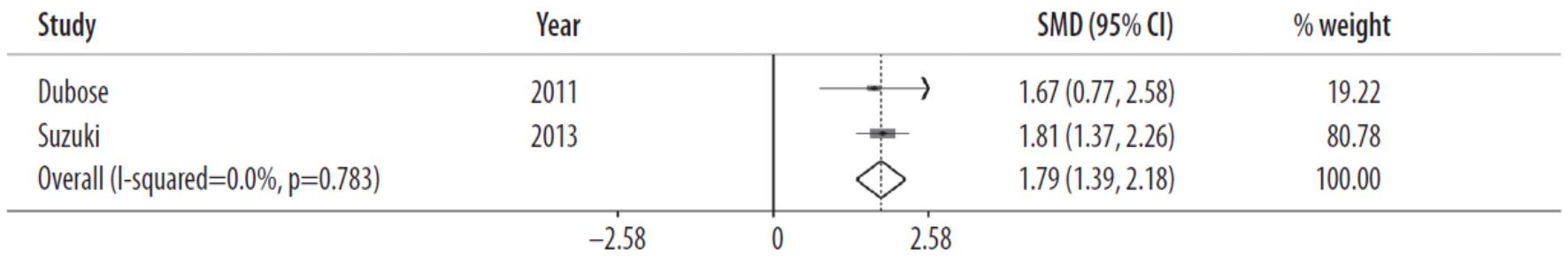


Figure 4. Forest plots of the effects of vitamin D supplementation on vitamin D levels in patients with Parkinson's disease.

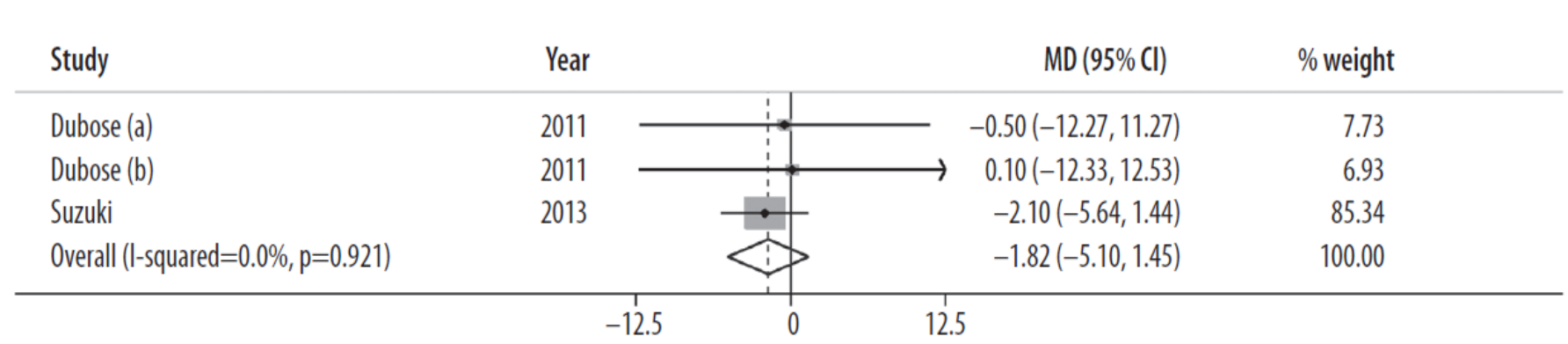


Figure 5. Forest plots of the effects of vitamin D supplementation on motor function in patients with Parkinson's disease.

TREATMENT

ALLIED HEALTH INTERVENTIONS

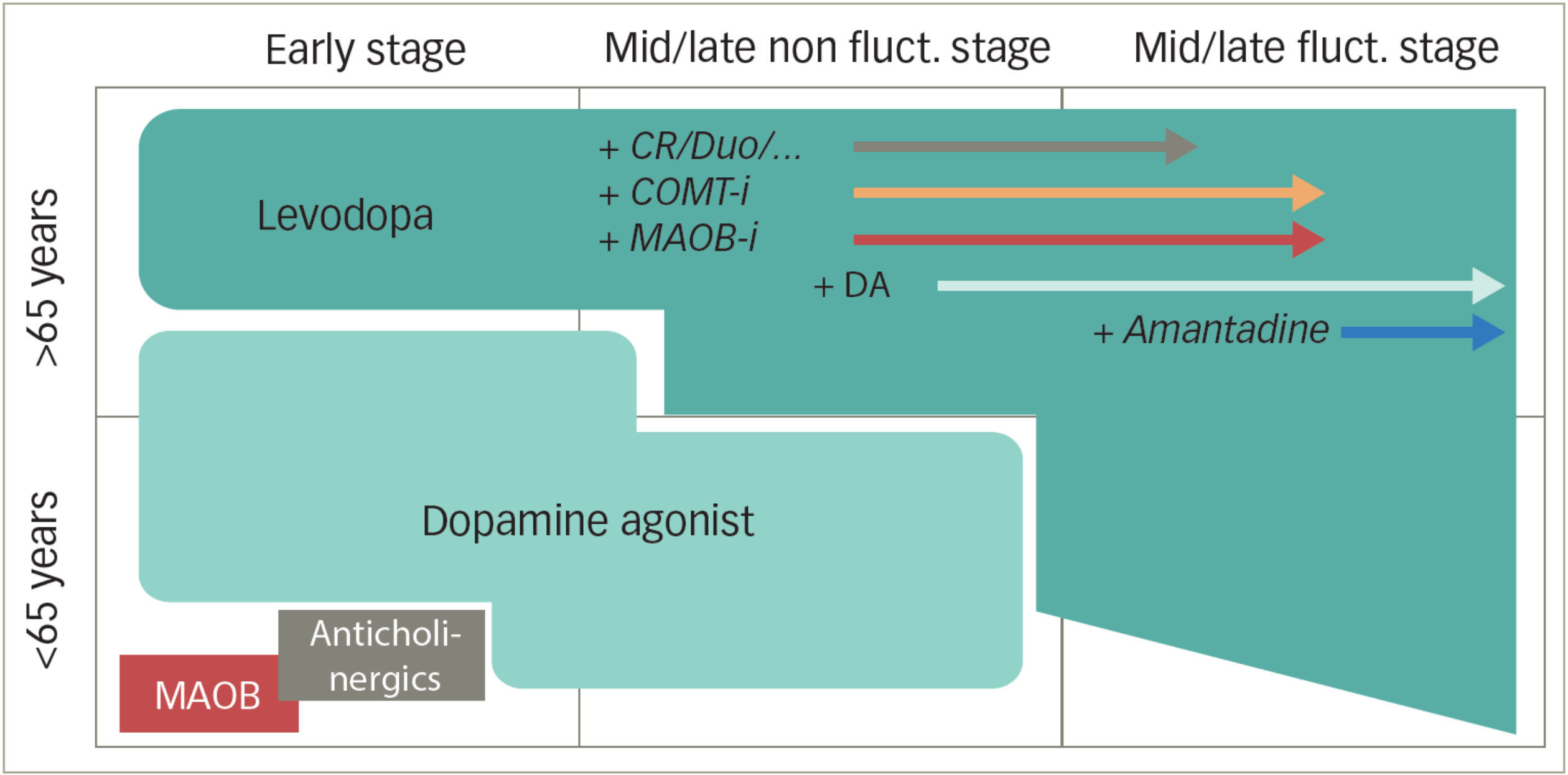
- Consideration to refer early PD patient to physiotherapist with experience of the disease for assessment, education and advice, including information about physical activity
- Physiotherapy specific to PD should be offered to people who are experiencing balance or motor function problems
- Occupational therapist with experience of PD should assess, educate and advice on motor and non-motor symptoms
- Occupational therapy specific to PD should be offered to people who are having difficulties with activities of daily living

ALLIED HEALTH INTERVENTIONS

- Speech and language therapy for PD patients having dysarthria and dysphagia
- Strategies should include
    - Improving safety and efficiency of swallowing
    - Improving speech and communication
- Dietary advice on when to eat/ what to eat especially as these patients are prescribed L-Dopa
- People with PD should be advised to avoid a reduction in their total daily consumption of protein

	Levodopa	Dopamine Agonists	MAO-B Inhibitors
Efficacy	+++	++	+
Acute side effects	++	+	+++
Motor Complications		++	+
Neuroprotection	+/-	+/-	+
Toxicity	+/-		
Convenience	+		+++

			Possible Risk of Side Effects	
Adjuvant Therapy for Later PD	First-choice Option	Symptom Control	Motor Complications	Other Adverse Events
Dopamine Agonists	✓	++	↓	↑
COMT Inhibitors	✓	++	↓	↑
MAO-B inhibitors	✓	++	↓	↑
Amantadine	X	NS	↓	↑
Apomorphine	X	+	↓	↑


Early stage
Mid/late non fluct. stage
Mid/late fluct. stage
>65 years
<65 years
Levodopa
+ CR/Duo/...
+ COMT-i
+ MAOB-i
+ DA
+ Amantadine
Dopamine agonist
Anticholi-
nergics
MAOB

TREATMENT OF THE NEWLY DIAGNOSED PATIENT: GOAL OF THERAPY

- To retain ***functional independence*** for as long as possible
- ***Therapeutic choices*** in early PD are guided by

✓ Effect of symptoms on **function** and quality of life

✓ Consideration of **complications** associated with therapy

✓ Potential for a **neuroprotective** effect

- Before starting treatment the following should be discussed:

  ✓ The individual's lifestyle, preferences, needs and **goals**

  ✓ The individual's clinical comorbidities and risks from **polypharmacy**

  ✓ The potential **benefits and harms** of the different drug classes

Carlos Singer, 2012

INITIAL TREATMENT: WHAT TO START?

- Dopaminergic drugs (**LD, DA**) are the **most effective** symptomatic treatments
- **No evidence to withhold dopaminergic treatment**: start when symptoms bothersome
- Initial treatment options: **LD, DA, MAO-I**
- **MAO-B inhibitors**
  - ✓ Definite small s**ymptomatic** effect
  - ✓ Potential **disease-modifying** effect not entirely excluded
  - ✓ Start treatment with either selegiline10 mg per day or Rasagiline 1 mg per day)
  - ✓ **>75 years: not indicated** as life expectancy shorter and more risk for side effects (Pahwa and Lyons, 2014)

Dietrichs and Odin, 2017; Pahwa and Lyons, 2014

INITIAL TREATMENT: WHAT TO START?

- **Ergot**-derived dopamine agonists should **not be** used as first-line treatment for PD.
- There is **insufficient evidence** for amantadine in the symptomatic treatment
- **Anticholinergic** drugs should **not** be used as **first-line** treatment in patients with PD except in the presence of tremor

INITIAL TREATMENT WITH LD: TO GIVE OR NOT TO GIVE?

- LD is the **most potent** drug
- Higher LD dose (**>600 mg**/day) and **longer disease** duration correlates with motor complications (Cilia et al, 2014)
- **Unwise to withhold the use of levodopa because of the motor complications:** motor fluctuations/dyskinesias **don't** develop as correlates of L-dopa use **duration** but, rather, in **association** with the extent of disease **progression**
- How to solve this conundrum of not giving higher LD doses?
  1. **Combination** of LD (300-400 mg/day) + DA in lower doses: reduces risk of MF and LID (Parkinson Study Group, 2004; Rascol et al, 2000; Watts et al, 2010)
  2. Start with DA/MAOB-I and **add LD** when more potent treatment is needed esp in younger patients (< 70-75 years)

✓No studies done to compare these two scenarios

Dietrichs and Odin, 2017; Pahwa and Lyons, 2014

INITIAL TREATMENT WITH LD: WHEN IS IT YOUR FIRST CHOICE?

- When would you consider LD to be your **first choice?**
  1. **Older** individuals
  2. Patients currently having an **active lifestyle** (e.g. currently employed) and need **maximum control** of symptoms: once LD dose reaches 600 mg/day, add DA/MAOB-I
- **Efficacy** comparison in terms of improvement in **UPDRS III** scores:
  - ✓ **LD** 300-mg/ day: **8.5**
  - ✓ DA: 5–6
  - ✓ MAOB-I: 2–3

Dietrichs and Odin, 2017; Pahwa and Lyons, 2014; Dong et al, 2016; Schapiro et al, 2009

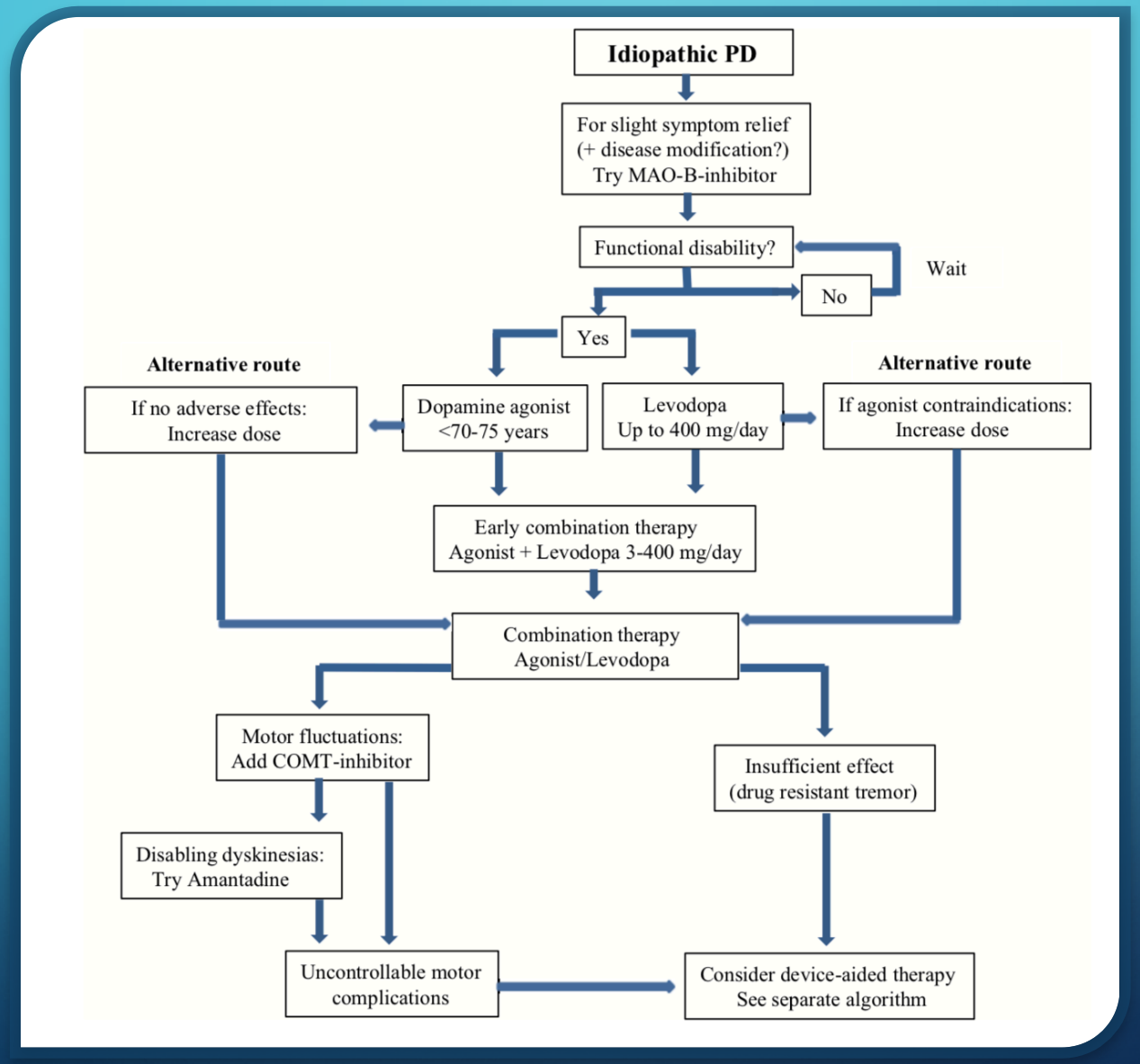
MANAGEMENT OF YOUNG ONSET (20-40 Y) PD AND OLDER ADULT WITH PD

- **All** young-onset patients develop **MF/LID** within **10** years of diagnosis
- **Hesitancy** to start LD on patient's behalf due to complications? **No evidence** to suggest delaying therapy is beneficial
- **DA/ MAOB-I** preferred as first-line therapy

- **Comorbidities** common in older adults
- Falls have serious consequences: screen and **treat osteoporosis**
- **Cognitive** impairment in PD **increases** with age, disease duration and severity
- More likely to develop **hallucinations**: due to disease itself/ drug side effect/ infections/ metabolic derangements

Ryden and Lewis, 2019

ALGORITHM FOR MEDICAL TREATMENT OF PD

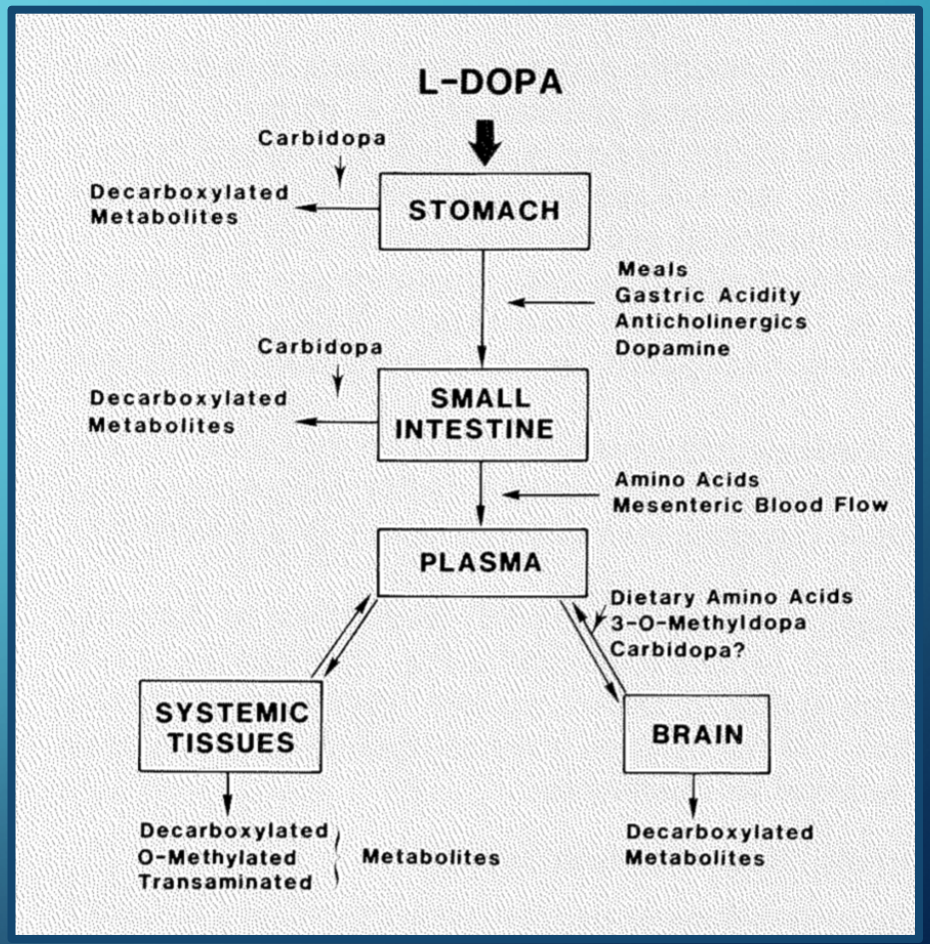


Dietrichs and Odin, 2017

INDIVIDUAL THERAPIES

LEVODOPA PHARMACOKINETICS

- Most important property: plasma half life is approximately **90 min**
- Short plasma half-life of LD and the dependence of striatal dopamine synthesis upon **external LD** has certain implications:
  - ✓ alterations in **absorption, metabolism, and distribution** to brain of L-dopa will immediately translate into clinical effects



Nutt and Fellman, 1984; John Nutt 2008; Nutt et al, 1996; Khor and Hsu, 2007; Peter LeWitt, 2014

LEVODOPA PHARMACOKINETICS

- Absorbed from **duodenum and proximal jejunum**
- Uses sodium-dependent **L-neutral amino acid carrier** system
- **Slow gastric emptying** delays appearance of LD in plasma
  - ✓Drugs (anticholinergics, dopaminergics)
  - ✓Meals
  - ✓High acidity
  - ✓Exercise (also decreases mesenteric blood flow)
- **Oral iron** can chelate iron and interfere with absorption
- 3 O-MD interfere with LD transport into brain ???

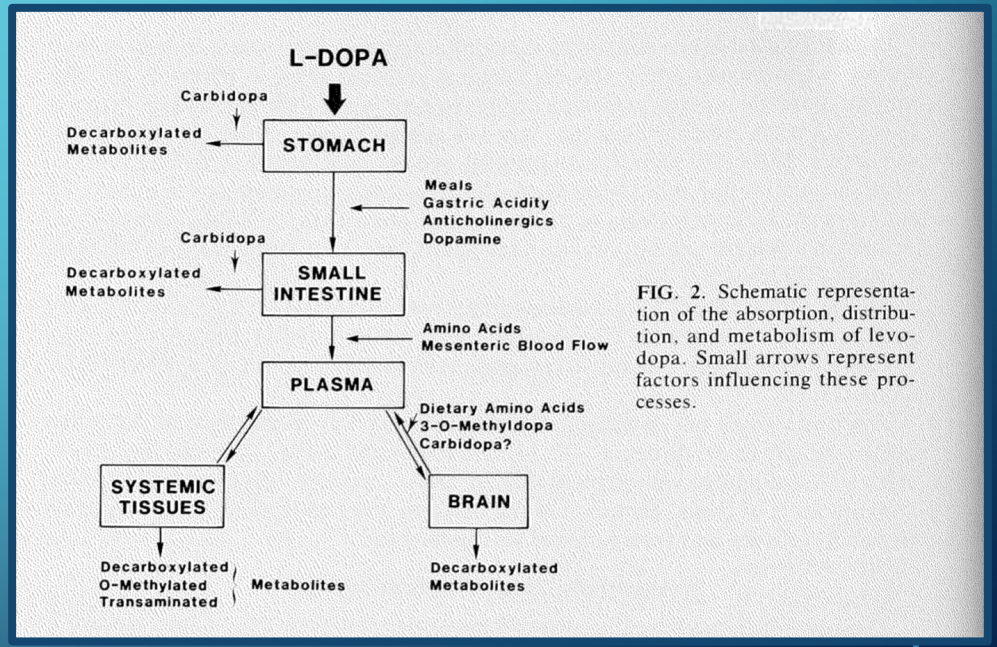


FIG. 2. Schematic representation of the absorption, distribution, and metabolism of levodopa. Small arrows represent factors influencing these processes.

Nutt and Fellman, 1984; John Nutt 2008; Nutt et al, 1996; Khor and Hsu, 2007; Peter LeWitt, 2014; Whitfield et al, 2014; Peter LeWitt, 2014

LEVODOPA PHARMACOKINETICS: EFFECT OF FOOD

- **Fat and L-neutral amino acid** in food: decrease LD bioavailability and **lower Cmax** while **increasing Tmax**
- A **protein**-containing diet **reduces oral** absorption of LD however, decrease in response to LD doesn't correlate with plasma LD concentrations
- Under **fasting** conditions, **60%** of LD is absorbed from an orally administered LD/CD IR formulation
- LD has to be taken **1 hour before or two hours after** a protein meal

Khor and Hsu, 2007

LEVODOPA CONTROLLED RELEASE

- Time of onset of clinical benefit is delayed due to **slower absorption**
- Produces constant elevation of plasma LD levels for **3-4** hours longer than IR LD
- **Not shown to lower the risk** of levodopa-related motor complications
- Clinical benefits: **reduces early morning dystonia, improves nocturnal awakenings and quality and latency of sleep**
- Bioavailability of CR is **~70%** of an IR formulation under fasting conditions
- **Longer Tmax and lower Cmax**

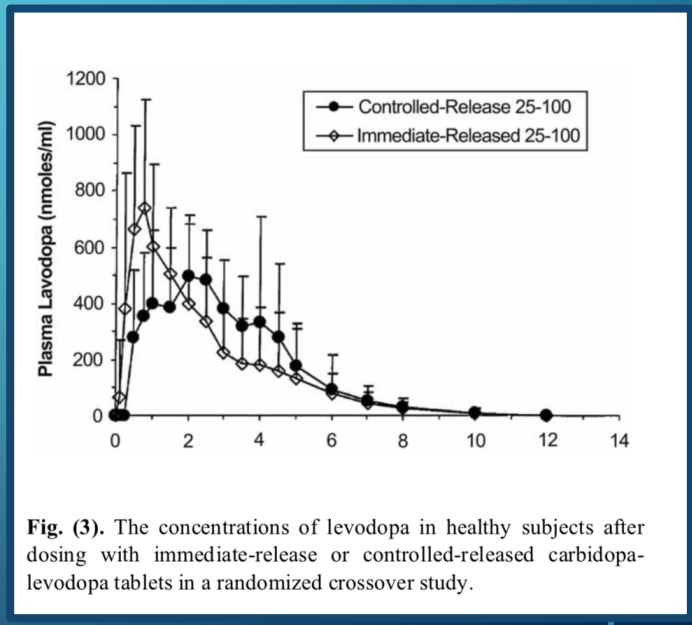


Fig. (3). The concentrations of levodopa in healthy subjects after dosing with immediate-release or controlled-released carbidopa-levodopa tablets in a randomized crossover study.

Robert Hauser 2009; Tolosa et al, 1998; Yébenes et al, 1997; Khor and Hsu, 2007

LEVODOPA FORMULATIONS

- **Sinemet (carbidopa/levodopa):**

✓ 25 mg/100 mg

✓ 10 mg/100 mg

✓ 25 mg/250 mg

- **Sinemet CR (carbidopa/levodopa):**

✓ 25 mg/100 mg

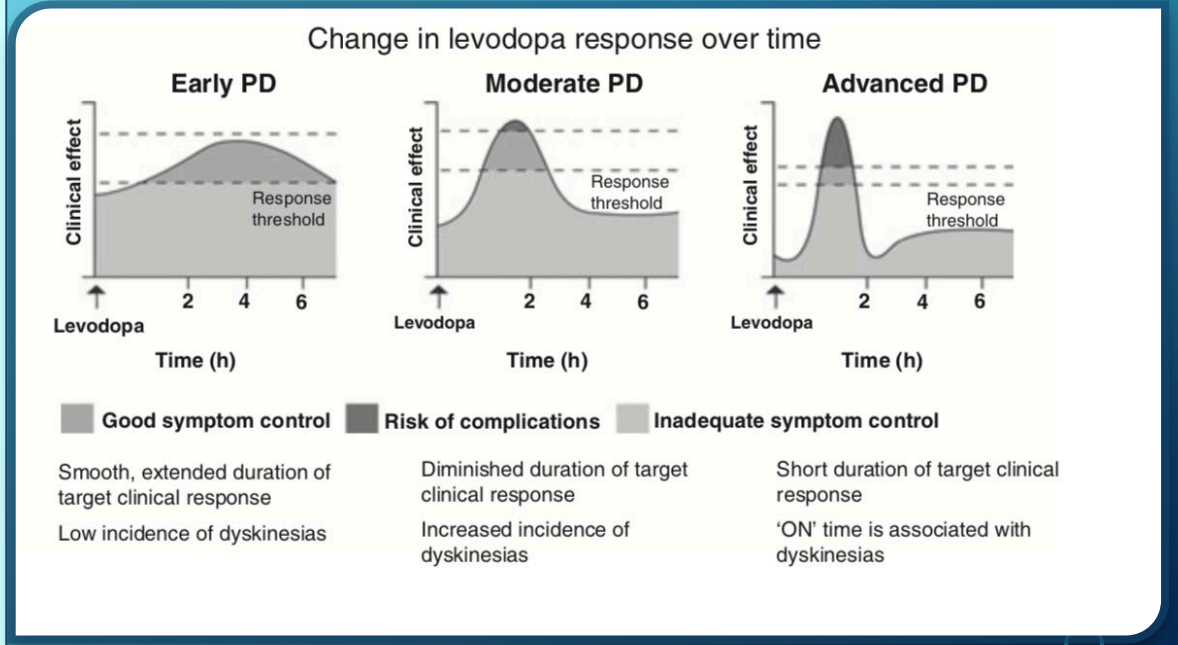
✓ 50 mg/200 mg

- **Stalevo (carbidopa/levodopa/entacapone):**
- 12.5 mg/50 mg/200 mg
- 18.75 mg/75 mg/200 mg
- 25 mg/100 mg/200 mg
- 31.25 mg/125 mg/200 mg
- 37.5 mg/150 mg/200 mg
- 50 mg/200 mg/200 mg.

Schapira et al, 2009

CHANGE IN RESPONSE TO LD OVER TIME

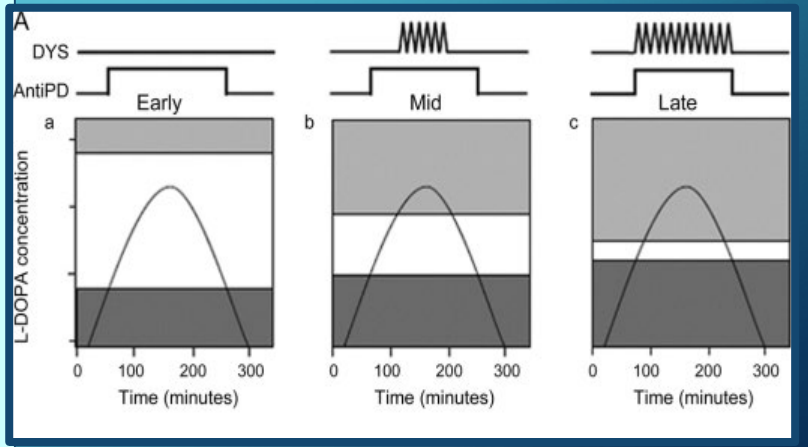
- **LDR** in early disease: LD **TID/QID** is sufficient
  - ✓Ability of nigrostriatal system to convert LD to dopamine, store it in pre-synaptic vesicles and release it in response to physiological stimuli
- Disease progresses→ this ability is lost: **'Wearing off'**
  - ✓Conversion of LD to dopamine is limited, stored in non-neuronal cells and is no longer released in response to physiological stimuli
- **70%** of patients with PD develop motor complications within **6 years** of initiation of LD



Schapiro et al, 2009; *Robert Hauser 2009*

COMPLICATIONS OF LONG TERM LEVODOPA USE

- **Motor fluctuations:**
  - ✓ Start to emerge in **40%** patients by **4-6 years**
  - ✓ Repeated emergence of "off" states
  - ✓ Can occupy up to **1/3rd** of a typical waking day
- **How to treat?**
  - **Smaller,** more frequent dosing
  - **CR + IR LD**: faster onset, sustained duration of response, reduced LID and end of dose wearing off
  - Inhibit peripheral metabolism with **AADC/COMT inhibitors**
  - Augment central effects by adding **DA/MAOB-I**
  - **Device** therapies



John Nutt 1994; Peter LeWitt, 2014; Pahwa and Lyons, 2014; Yébenes et al, 1997; Khor and Hsu, 2007

COMPLICATIONS OF LONG TERM LEVODOPA USE

- **Levodopa induced dyskinesias (LID)**
  - ✓ Seen in **1/3rd** of patients after **2 years** and **80%** after treatment for **10 years**
  - ✓ Marker of good response to LD
  - ✓ **Larger doses** of LD accelerate the appearance of LID
- **Risk factors** for development (STRIDE-PD)
  - ✓ **Young** age at onset
  - ✓ **Higher** levodopa dose
  - ✓ Low body weight
  - ✓ North American geographic region
  - ✓ **Women**
  - ✓ **More severe** UPDRS ADL scores

- Treatment
  - ✓ Peak dose LID: **dose reduction**
  - ✓ Add **amantadine (200-400 mg/day)**

John Nutt 2008; Whitfield et al, 2014; Pahwa and Lyons, 2014; Dietrichs and Odin, 2017

MANAGEMENT OF MOTOR AND NON- MOTOR SYMPTOMS

Tremor	• Dopaminergic therapy • Beta blockers PRN • Anticholinergic therapy • Deep Brain Stimulation
Freezing and Falls	• Dopaminergic therapy • Physiotherapy • Gait aids • Cognitive enhancement therapy
Fluctuations and Dyskinesia	• Fragmented doses of dopaminergic therapy • Amantadine • Advanced Therapies - deep brain stimulation, carbidopa / levodopa gel via PEJ, apomorphine SC
Speech	• Speech pathology and training • Mobile phone applications and devices for severe hypophonia
Dystonia	• Stretching and physiotherapy • Dopaminergic therapy • Botulinum toxin

Bladder Function	• Physiotherapy • Pharmacology - mirabegron, anticholinergics • Urology referral - botulinum toxin
Bowel Function	• Increased water intake • Aperients
Sialorrhoea	• Gum and lollies to promote swallowing • Pharmacological treatment - anticholinergic inhaler • Botulinum toxin
Dysphagia and Aspiration Risk	• Speech pathology review • Modified diets
Hallucinations	• Medication review • Counselling • Pharmacological - clozapine, quetiapine
Mood and Anxiety	• Counselling, psychotherapy and mindfulness training • Psychiatry review • Pharmacological treatment - antidepressants
Cognition	• Promote lifestyle intervention, exercise and social engagement • Brain training - online applications, puzzles, reading • Consider pharmacology e.g. rivastigmine
Sleep and REM Sleep Behaviour Disorder	• Ensure safe sleeping environment • Rule out sleep disordered breathing, PSG and sleep physician referral • Pharmacology (REM Sleep Behaviour) - melatonin, clonazepam
Orthostatic Symptoms	• Physiotherapy, hydration, high salt intake, compression stockings • Pharmacological therapy - fludrocortisone, midodrine, pyridostigmine • Cardiology review if indicated
Sexual Dysfunction	• Counselling • Pharmacology - sildanefil • Referral for surgical intervention
Pain	• Simple analgesia • Physiotherapy • Dopaminergic therapy

Ryden and Lewis, 2019; Dong et al, 2016

LET'S SEE SOME CASE EXAMPLES

CASE SCENARIO 1

- 58 year old female
- 3 years of disease
- Has been on levodopa for 2 years
- Can only tolerate ½ tablet 6 times a day
- Any higher and she is dyskinetic
- Any lower and she is off for too long
- Has tried dopamine agonist but produced hallucinations
- Is this advanced disease?
- What are your strategies here?

CASE SCENARIO 2

- 67 year old male
- 16 years history of PD
- Doing well until 1 year ago on 800 mg of levocarb and pramipexole
- Past 1 year rapid onset of fluctuations and dyskinesia
- These have become disabling

- What are your next steps?
- Would this be advanced PD?

CASE SCENARIO 3

- 73 year old male
- 14 years of disease
- Having fluctuations that are now becoming somewhat troublesome but not disabling
- Cognitively perfect in clinic
- Drugs already optimized by MDS

CASE SCENARIO 4

- 84 year old female
- 18 years of disease
- Cognitively intact
- Able to do all ADLs by herself
- Has had fluctuations and dyskinesias for 4 to 5 years
- Now on levodopa every 2 to 3 hours with unpredictability

- What are our options?

THANK YOU