Is Delaying Levodopa a Disservice to Patients?

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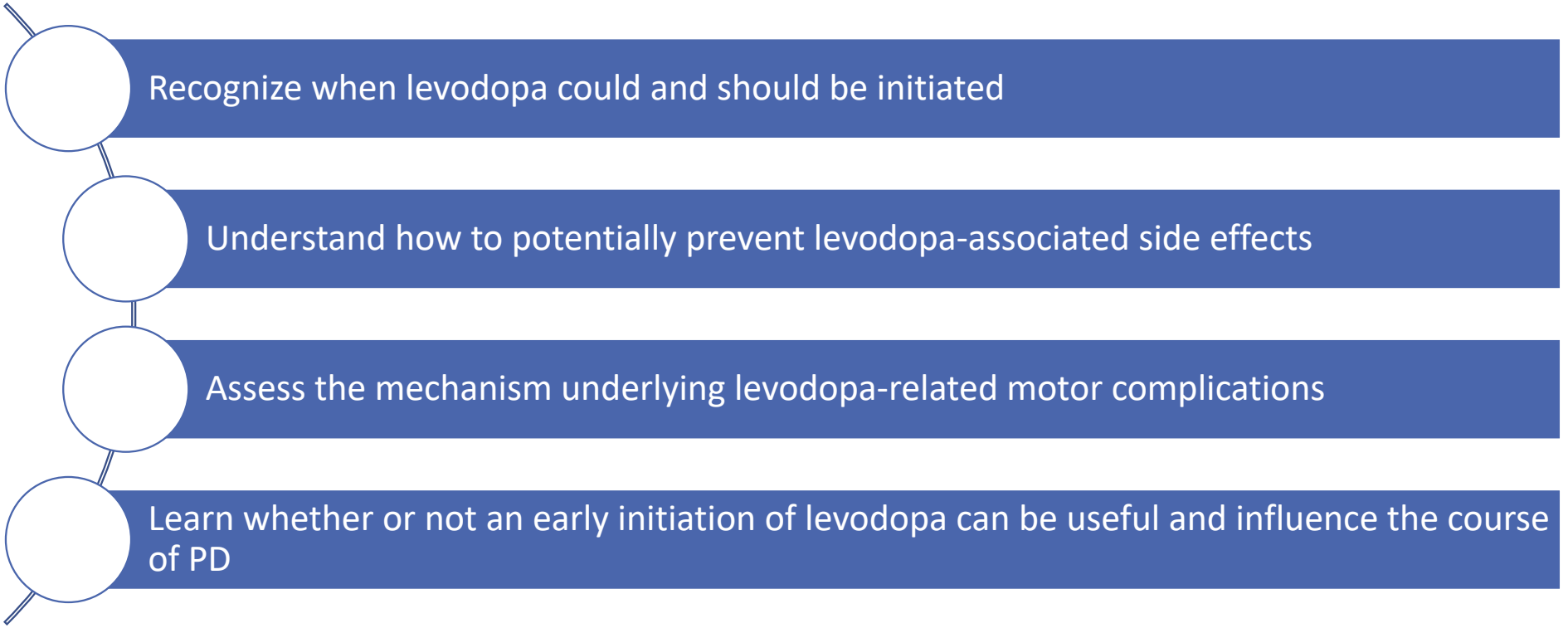
Learning Objectives



Overview of Parkinson Disease

Progressive neurodegenerative movement disorder

- Mean age of onset: 65 years
- Affects men to women on ratio of 1.5:1

Classic motor features: bradykinesia, rigidity, rest tremor

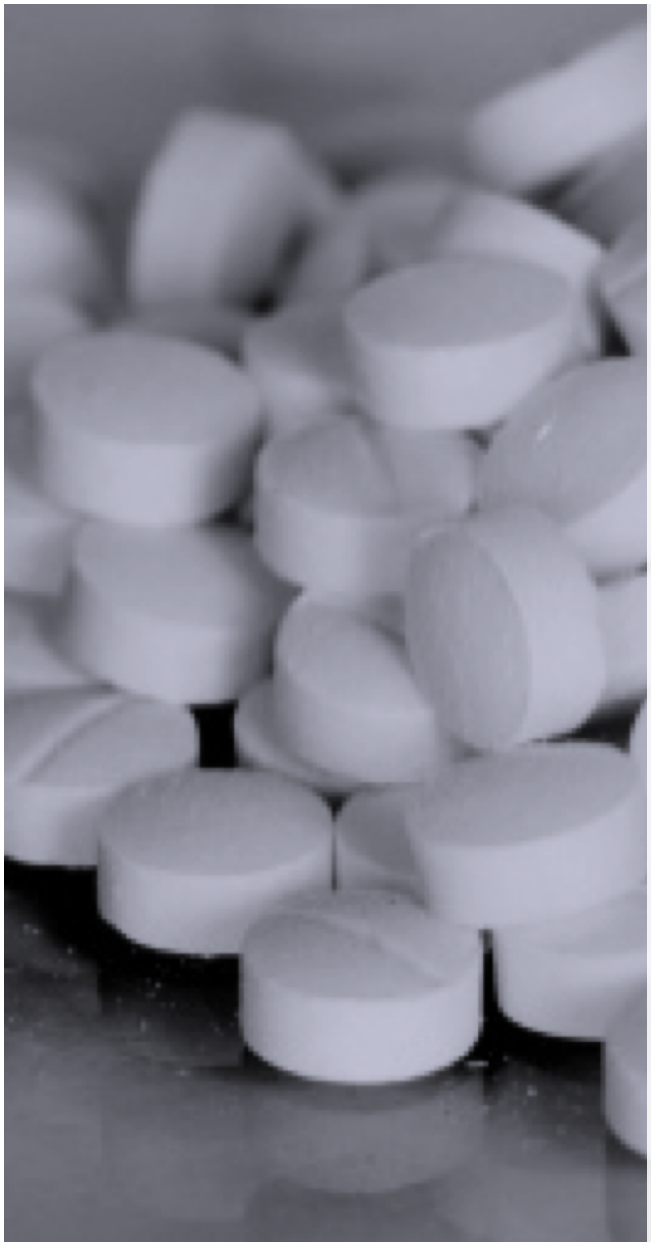
- Other symptoms: postural instability, gait impairment, nonmotor symptoms

Levodopa remains gold standard of therapy

Other therapies used alone or as adjunctive therapy

- Dopaminergic (i.e., dopamine receptor agonists, monoamine oxidase-B inhibitors, catechol-O-methyl transferase inhibitors)
- Non-dopaminergic (i.e., anticholinergic agents, amantadine)

Connolly BS, Lang AE. *JAMA.* 2014;311(16):1670-1683.



Treatment Goals

1

Symptomatic control of motor symptoms, as well as nonmotor and behavioral symptoms

2

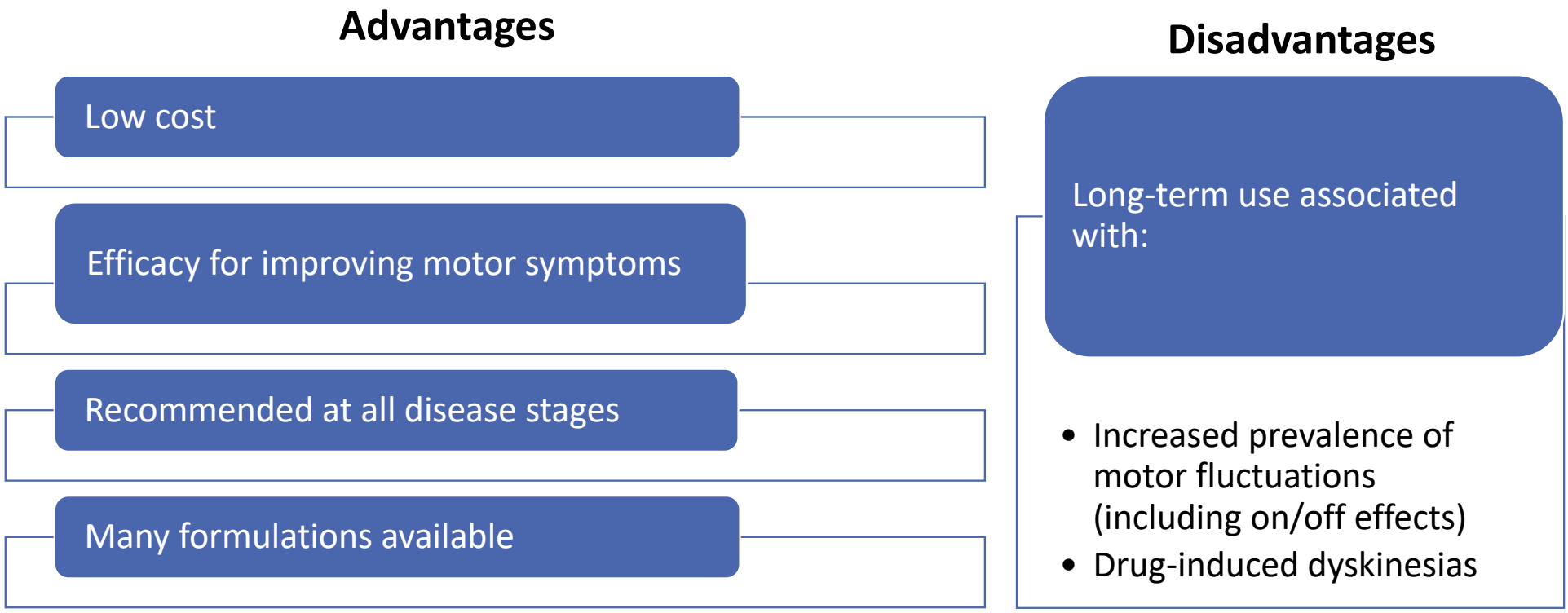
Prevention of treatment-related complications

Treatment Initiation

- No treatments that slow down neurodegenerative process[1-2]
- Optimal time frame for starting therapy has not been clearly defined[1-2]
- Treatment initiation is recommended when parkinsonian signs begin to negatively impact patient's life[1-2]
- PD LIFE observational study showed improvements in quality of life in patients treated with dopaminergic medications vs untreated cohort[3]

1. Connolly BS, Lang AE. *JAMA.* 2014;311(16):1670-1683. 2. National Institute for Excellence in Care. *Parkinson's Disease in Adults: Diagnosis and Management.* 2017.
3. Grosset D et al *JNNP* 2007;78(5):465-469.

Advantages and Disadvantages of Levodopa: Gold Standard



Arguments Used to Delay Levodopa in Early PD

Levodopa is primarily responsible for dyskinesias and motor fluctuations

- Chronic exposure associated with motor response oscillations
- Induces drug-induced dyskinesias in a dose-dependent fashion

Early treatment with DAs postpones motor fluctuations + dyskinesias

- Used to spare the daily dose of levodopa

Levodopa efficacy is lost with prolonged use

Levodopa is toxic and increases neurodegeneration

Vlaar A HA, et al. *Pract Neur.* 2011;11(145-152).

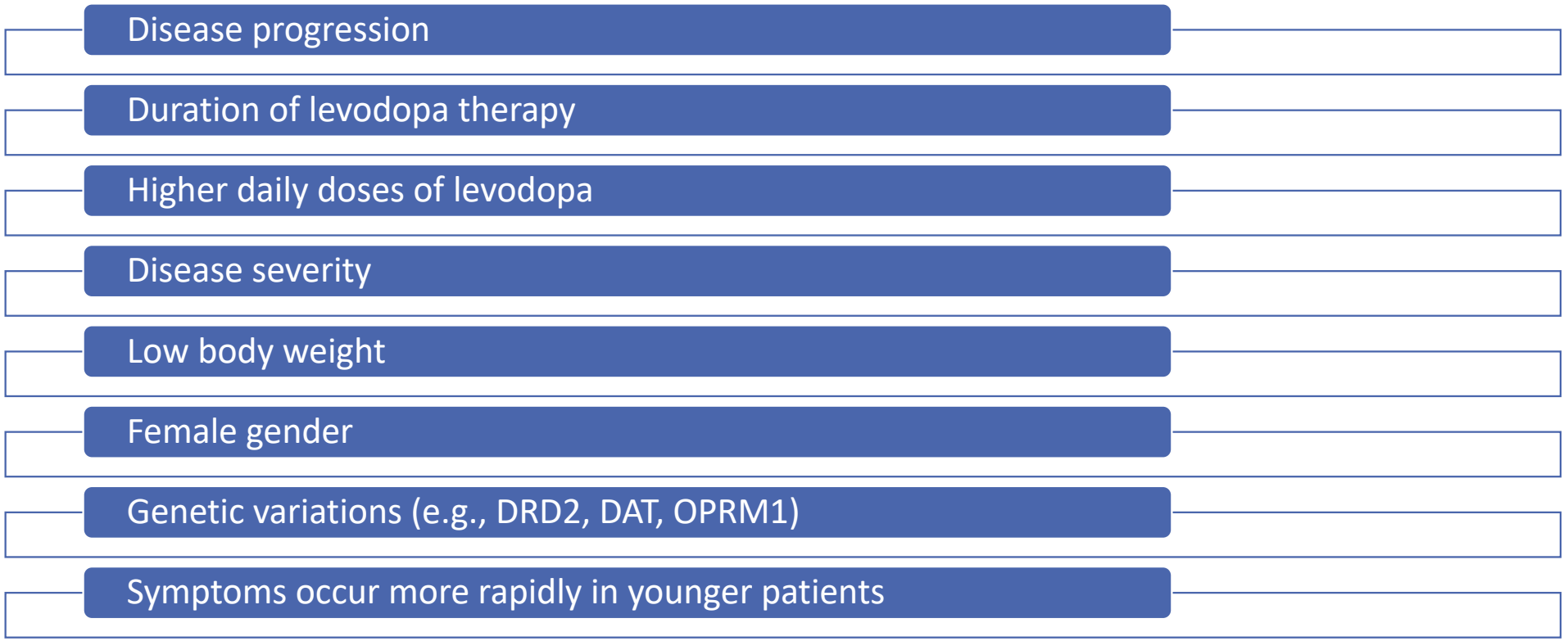
Types of Levodopa-Related Motor Complications

Clinical Pattern	Mechanism	Symptoms
Wearing off	90-minute half-life Presynaptic stage	▪ Re-emergence of parkinsonian motor problems prior to next dose ▪ Patients can become aware of 'end-of-dose' effect ▪ Becomes predictable over time (e.g. 3-4 hours after dose) — Early morning akinesia — Progresses to more unpredictable fluctuations
Dose failure, delayed or partial on response	Gastric emptying Intestinal absorption Blood-brain barrier transport	▪ L-dopa dose fails to provide expected benefit ▪ Benefit can be delayed by minutes or hours or may be absent
Random on-off	Striatal pharmacodynamic changes	Rapid, erratic transitions between periods with and without symptom improvement
Dyskinesias		May occur in the on state, peak-dose, beginning, or end-of-dose

Patients identify fluctuating response to medication as most bothersome symptom

Aquino CC, Fox SH. *Mov Disord.* 2015;30(1):80-89. Politis M et al. *Mov Disord.* 2010;25(11):1646-1651

Risk Factors for Motor Complications



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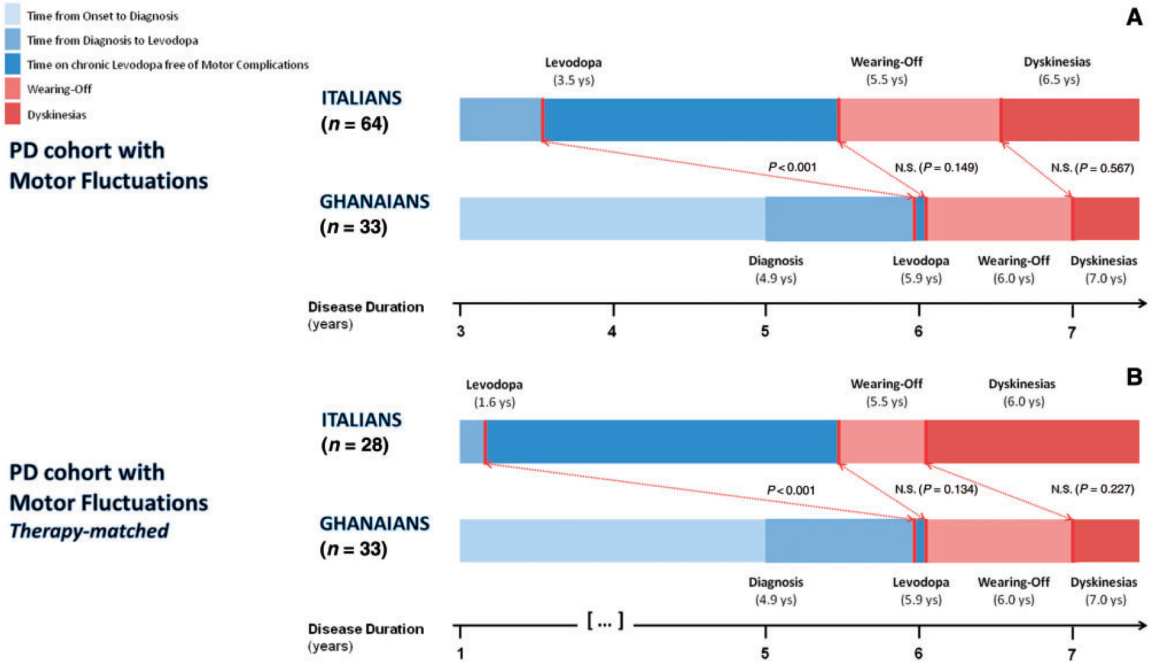


Relationship between initiation of levodopa therapy and onset of motor fluctuations, and between initiation of levodopa therapy and onset of dyskinesias

Cilia R, et al.. *Brain.* 2014;137(Pt 10):2731-2742.

Study Design

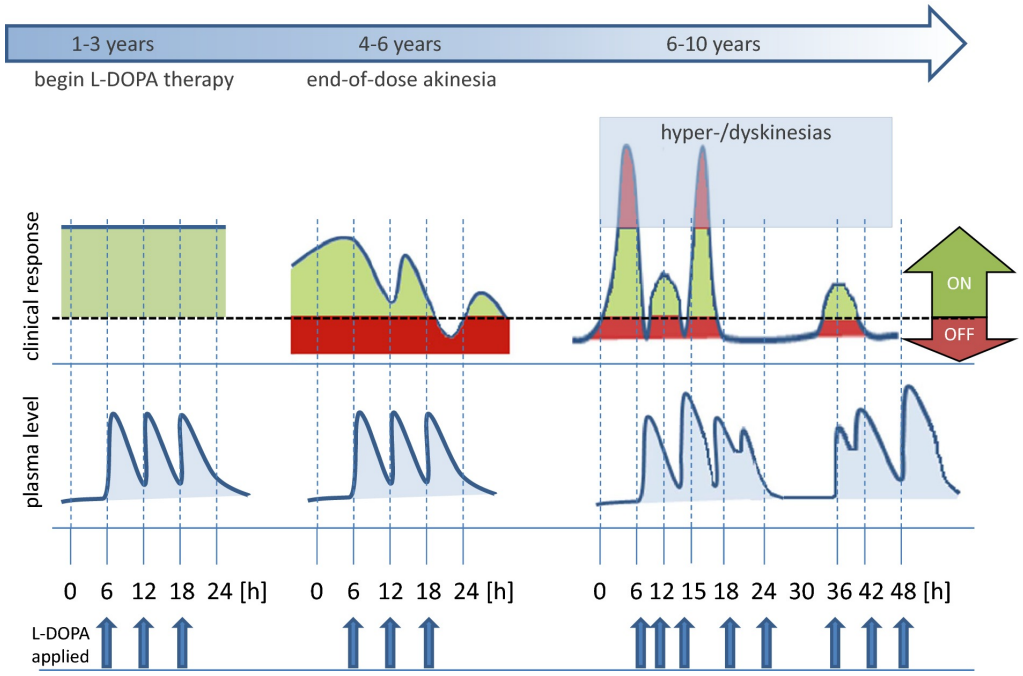
- Cross-sectional, case-control 4 year study
- Ghana cohort (n=91)
  - Baseline fluctuations (56%) dyskinesias (14%)
- Italian Control cohort (n=50)

RESULTS

- L-dopa introduced later in Ghana cohort
- Motor fluctuations and dyskinesias associated with longer disease duration and higher L-dopa dose

- Clinical response (on) is stable in first 1-3 years of therapy
- Short half-life (1.5 hrs)
  - After a dose of levodopa, plasma levels initially rise then fluctuate throughout the day
- Despite continuous plasma level responses, patients experience end-of-dose akinesia
  - Clinical responses are frequently lower and transgress into 'OFF'-phases with the reappearance of the cardinal motor symptoms and signs as well as of non-motor symptoms
- Progressive degeneration of nigrostriatal dopamine terminals may limit the normal physiologic uptake and release of dopamine
  - Results in pulsatile dopamine receptor stimulation and altered basal ganglia signaling pathways

Pharmacokinetic Profile of Levodopa May Contribute to Motor Fluctuations



Oertel W, Schulz JB. *J Neurochem.* 2016;139 Suppl 1:325-337.
Kuoppamaki M, et al. *Euro J Clin Pharmacol.* 2009;65(5):443-455.

Dopamine Receptor Agonists

Nonergot Agonists

- Pramipexole, ropinirole, rotigotine, apomorphine, piribedil
- Effective for all motor features of disease, first used as option in patients <70 years
- Can be used as monotherapy or as add-on therapy in later disease

Ergot derivatives

- Bromocriptine, cabergoline
- Associated with cardiac valvular fibrosis, heart failure, and rare cases of pleuropulmonary/retroperitoneal fibrosis

ADVERSE EFFECTS

- Neuropsychiatric adverse effects
- Impulse dyscontrol
- Daytime somnolence
- Sleep attacks

Associated with cardiac valvular fibrosis, heart failure, and rare cases of pleuropulmonary/ retroperitoneal fibrosis

- 782 patients randomised to L-dopa/decarboxylase inhibitor (DDCI), L-dopa/DDCI plus selegiline, or bromocriptine
- Main endpoints = mortality, disability, motor complications

- Disability scores, physical functioning, physical summary scores superior on L-dopa
- Differences in mortality rates and prevalence of dyskinesias, motor fluctuations, and dementia were not significantly different

Prevalence at final follow-up	L-dopa arm (n = 42)	Bromocriptine arm (n = 63)	Difference* (95% CI)	*p* Value
Any dyskinesia	58%	56%	−5.3% (−25%, 15%)	0.61
Moderate/severe dyskinesia	39%	35%	−6.0% (−25%, 13%)	0.51
Any fluctuations	50%	56%	5.1% (−15%, 25%)	0.61
Moderate/severe fluctuations	33%	35%	0.01% (−19%, 19%)	0.94

Prevalence of Motor Complications at Follow-up

Katzenschlager R, et al. *Neurology.* 2008;71(7):474-480.

Other Anti-Parkinsonian Therapies

Monoamine oxidase-B inhibitors

- Rasagiline, selegiline, safinamide*
- Can be used as monotherapy
- Disease-modifying effect?
- Can be added to levodopa to increase its bioavailability in patients ≥70 years and those experiencing motor symptoms on levodopa therapy

Anticholinergic agents

- eg, benztropine, trihexyphenidyl—older generation treatment
- No longer considered first line options

Amantadine

- Can be added to anticholinergic agents or levodopa in patients with severe motor symptoms
- Recent data suggest amantadine may improve both dyskinesia and motor fluctuations[1]

ADVERSE EFFECTS

MAOB-i
- Nausea
- Headaches
- Dyskinesia

Anticholinergics
- Memory impairment
- Confusion
- Hallucinations

Amantadine
- Visual hallucinations
- Livedo reticularis
- Peripheral edema

Pahwa R, et al. *JAMA Neurol.* 2017;74(8):941-949.

*Safinamide is EMA- and FDA-approved only as adjunctive therapy

COMT Inhibitors

Used in advanced disease when patients are experiencing motor fluctuations or on/off effect with long-term levodopa therapy

Entacapone[1]

- Adjunct to standard levodopa/DDCI preparations in adults with PD and end-of-dose fluctuations who are not stabilized
- Estimated duration effect of ~40 mins

Tolcapone[1]

- Combined with levodopa/DDCI in patients with idiopathic PD and motor fluctuations who do not respond to or are intolerant to other COMT inhibitors
- High risk for hepatoxicity

Opicapone[2-3]

- Adjunct to levodopa/DDCI in adults with PD end-of-dose fluctuations who are not stabilized
- Opicapone 50mg reduced off time by ~2 hours vs placebo (1 hour)

ADVERSE EFFECTS

- Dyskinesia, hallucinations, confusion, nausea, and orthostatic hypotension, hepatotoxicity, diarrhea
- COMT inhibitors may precipitate the emergence of L-DOPA dyskinesias[4]

1. Deane KH, et al. *Cochrane Data System Rev.* 2004(4):Cd004554. 2. Lees AJ, et al. *JAMA Neurology.* 2017;74(2):197-206.
3. Ferreira JJ, et al. *Lancet Neurology.* 2016;15(2):154-165; 4. Stocchi F, et al. *Ann Neurol.* 2010;68(1):18-27.

COMT Inhibitor Add-Ons

Increases central levodopa bioavailability, prolonging and enhancing its effect

Reasonable option for reducing end-of-dose wearing ‘off’ time

- Could also use dopamine agonist or MAO-B agents as add-on

Inhibition of COMT reduces methylation of L-dopa and dopamine

- Increases the plasma half-life of L-dopa
- Stabilises plasma L-dopa concentrations
- Prolongs therapeutic effect of each dose

Entacapone, tolcapone, opicapone licensed with EMA

Rascol O, et al. *Mov Disord.* 2015;30(11):1451-1460.

Summary

Levodopa remains gold standard of symptomatic therapy

- Highly effective in treating PD symptoms and is well tolerated
- Optimal time frame for starting therapy has not been clearly defined
- Treatment initiation is recommended when parkinsonian signs begin to negatively impact patient's life

Possible causes of motor fluctuations

- Short half-life
- Intestinal absorption
- Pulsatile dopamine receptor stimulation

Strategies to address wearing off

- Increase levodopa dose size and/or dose frequency
- Add or increase dopamine agonist dose
- Add MAO-B inhibitor
- Add COMT inhibitor