How to start therapy in early PD

XXIV World Congress of Neurology, Dubai 2019

Ryosuke Takahashi

Department of Neurology, Kyoto University Hospital, Japan

Email: ryosuket@kuhp.kyoto-u.ac.jp

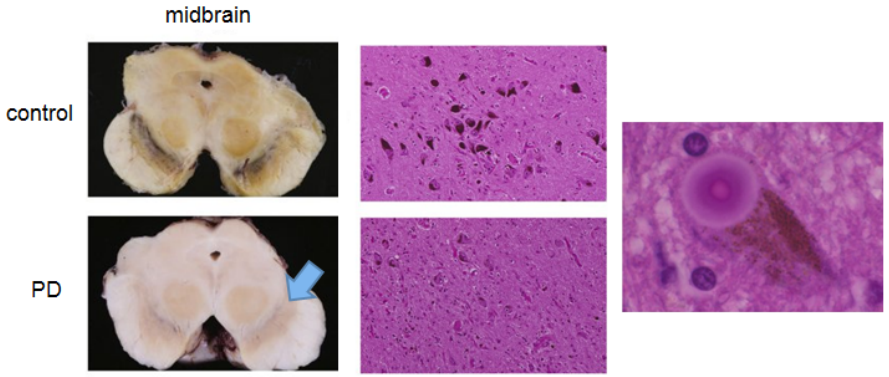
Learning Objectives

After the lecture, the audience will be able to

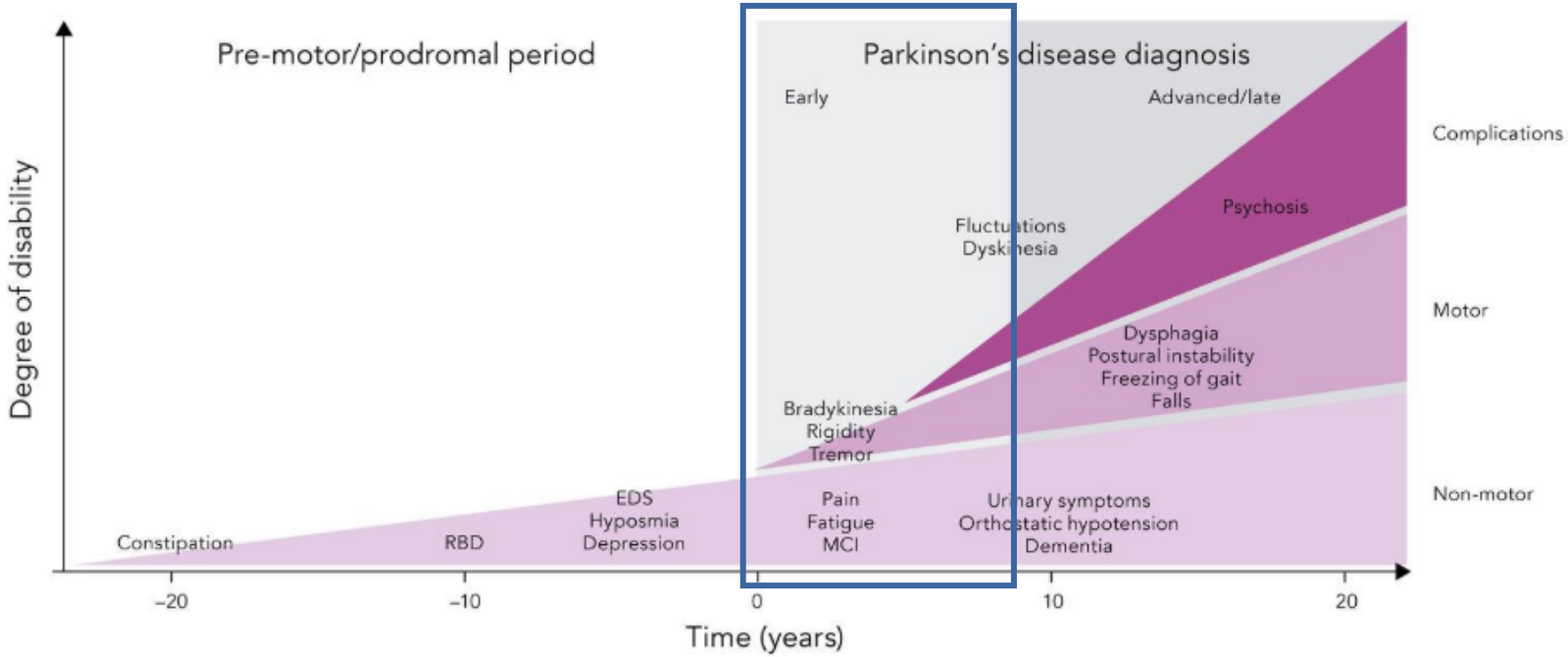
- Describe when to start treatment of early PD
- Describe the benefit and risk of L-dopa therapy
- Describe the benefit and risk of L-dopa sparing therapy

PD; Parkinson's disease

Aggregation of α-synuclein (α-Syn), called Lewy body, is pathological hall mark



Clinical symptoms and time course of Parkinson's disease progression



Kalia LV et al. Lancet. 2015; 386(9996): 896-912.

Parkinson's disease (PD) is a neurodegenerative disease which is characterized by dopaminergic neuronal death and abnormal aggregation of α-synuclein (α-syn) proteins, called Lewy body.

History of drug therapy for PD

AN
ESSAY
ON THE
SHAKING PALSY.

CHAPTER I.

DEFINITION–HISTORY–ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

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.

1817

Belladonna Alkaloid

1860

Anti-cholinergics

1950

L-dopa

1967

Dopmaine agonist

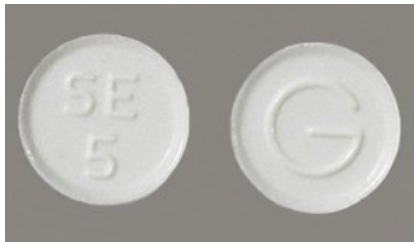
1975

DBS, LCIG, etc.

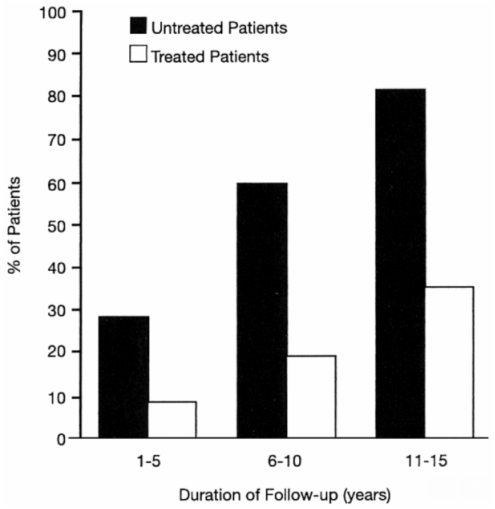
2002~

1989

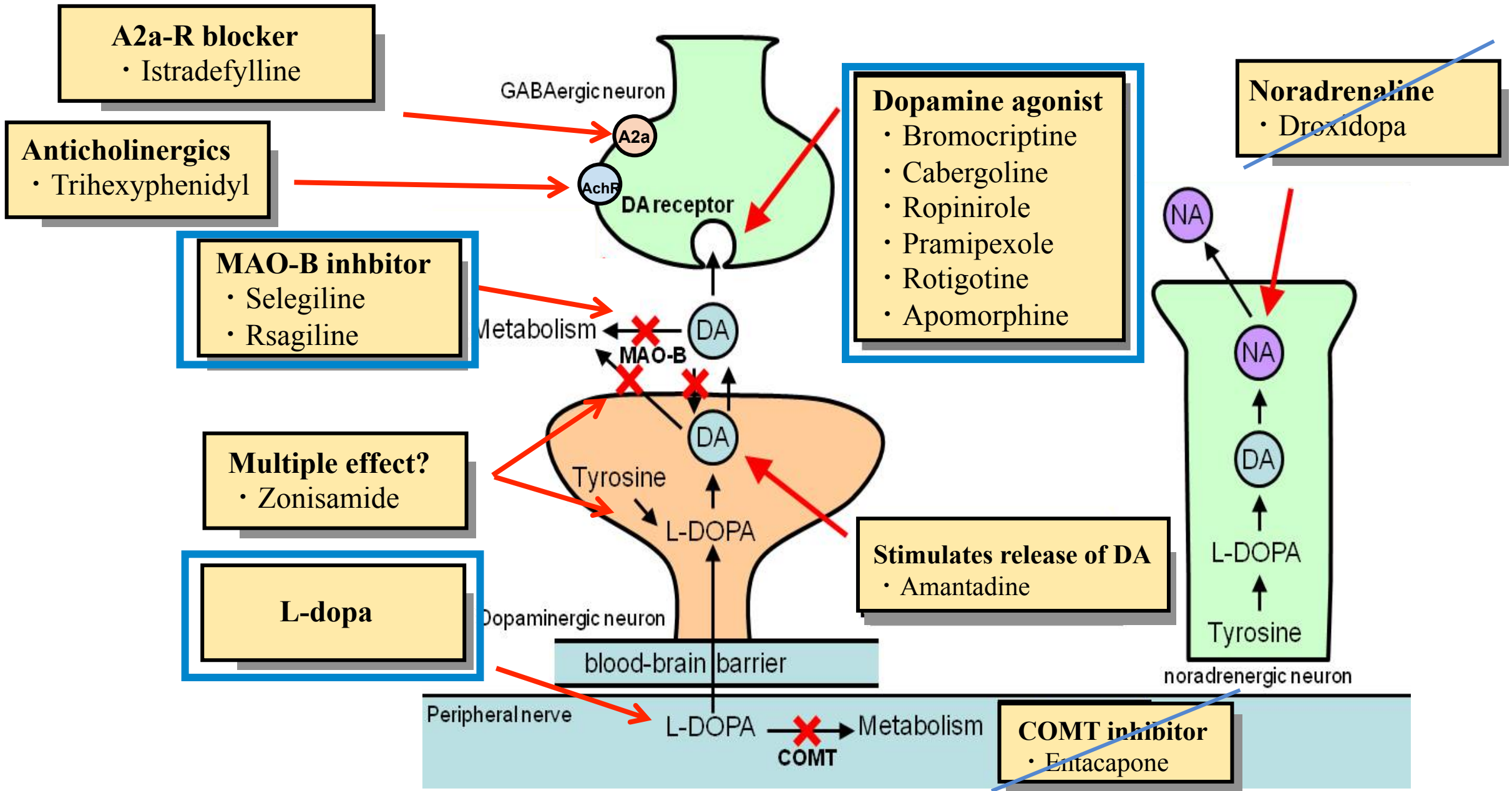
MAO-B inhibitor



L-dopa therapy has a huge impact on PD prognosis!



Sites of action of drug therapies for PD



NICE guideline 2017

Pharmacological management of motor symptoms（Monotherapy）

■Potential benefits and harms of dopamine agonists, Levodopa and MAO-B inhibitors

	Levodopa	Dopamine agonists	MAO-B inhibitors
Motor symptoms	More improvement in motor symptoms	Less improvement in motor symptoms	Less improvement in motor symptoms
Activities of daily living	More improvement in activities of daily living	Less improvement in activities of daily living	Less improvement in activities of daily living
Motor complications	More motor complications	Fewer motor complications	Fewer motor complications
Adverse events	Fewer specified adverse events*	More specified adverse events*	Fewer specified adverse events*

Abbreviation: MAO−B, monoamine oxidase B.

* Excessive sleepiness, hallucinations and impulse control disorders.

First-line treatment

Offer L-dopa for the early stage PD patients with moderate to severe motor symptoms.

DA or MAO-B inhibitor for the early stages PD patients with mild to moderate motor symptoms.

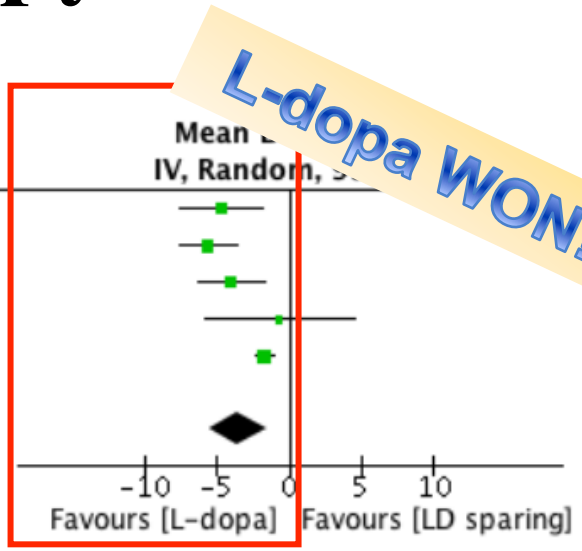
NICE（National Institute for Health and Care Excellence）. Parkinson's disease in adults. published 19 July 2017.

L-dopa vs other therapy

UPDRS-PartIII

Study or Subgroup	LD Mean	LD SD	LD Total	LD sparing Mean	LD sparing SD	LD sparing Total	Weight	Mean Difference IV, Random, 95% CI
Holloway 2004	-3.4	12.3	150	1.3	13.3	151	18.2%	-4.70 [-7.59, -1.81]
Oertel2006PELMOPET	-2.8	7.8	146	2.8	9.8	148	22.5%	-5.60 [-7.62, -3.58]
Rascol 2000 FK056study	-4.8	8.3	89	-0.8	10.1	179	21.2%	-4.00 [-6.27, -1.73]
Storch 2013	-7.2	7.2	18	-6.5	8.3	17	10.1%	-0.70 [-5.86, 4.46]
USA Olanow 1995	3.3	1	21	5	1.1	19	28.1%	-1.70 [-2.35, -1.05]
Total (95% CI)			**424**			**514**	**100.0%**	**-3.51 [-5.53, -1.48]**

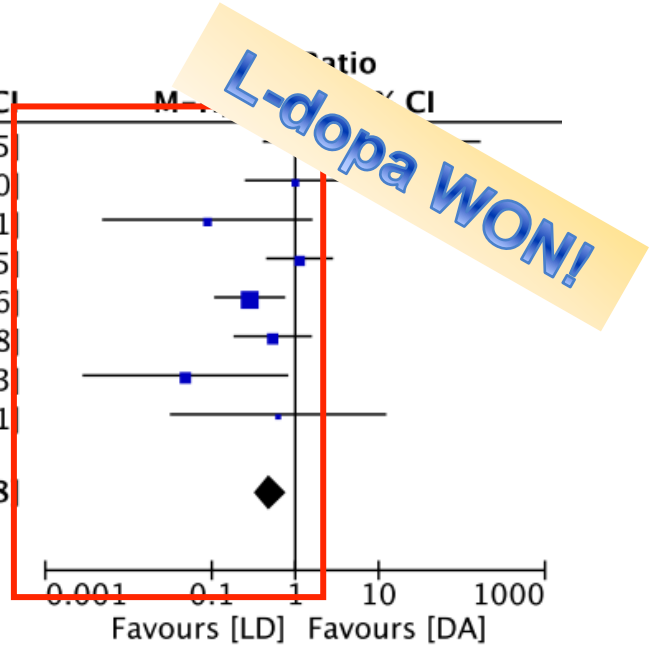
Heterogeneity: $Tau^2 = 3.69$; $Chi^2 = 18.61$, df = 4 (P = 0.0009); $I^2 = 79\%$
Test for overall effect: Z = 3.40 (P = 0.0007)



Psychotic symptom

Study or Subgroup	LD Events	LD Total	DA Events	DA Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Herskovits 1988 Argentina	3	29	0	31	0.7%	8.32 [0.41, 168.45]
Holloway 2004	4	150	4	151	6.7%	1.01 [0.25, 4.10]
Oertel2006PELMOPET	0	146	5	147	9.4%	0.09 [0.00, 1.61]
PKDS009	10	208	9	211	14.6%	1.13 [0.45, 2.85]
Rascol 2000 FK056study	5	89	31	179	33.4%	0.28 [0.11, 0.76]
SydneyMultiple Hely 1994	6	64	10	62	15.8%	0.54 [0.18, 1.58]
UK-PDRG Lees 2001	0	249	10	262	17.6%	0.05 [0.00, 0.83]
USABromocriptine Weiner 1993	1	9	1	6	1.8%	0.63 [0.03, 12.41]
Total (95% CI)		**944**		**1049**	**100.0%**	**0.50 [0.32, 0.78]**
Total events	29		70			

Heterogeneity: $Chi^2 = 12.60$, df = 7 (P = 0.08); $I^2 = 44\%$
Test for overall effect: Z = 3.02 (P = 0.002)

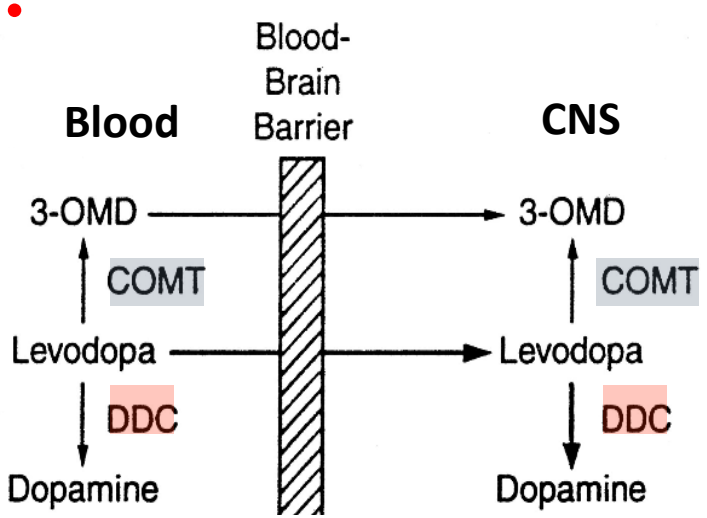


Guideline for treatment of Parkinson's disease 2018 in Japan

Levodopa (L-dopa)

✓ Advantages

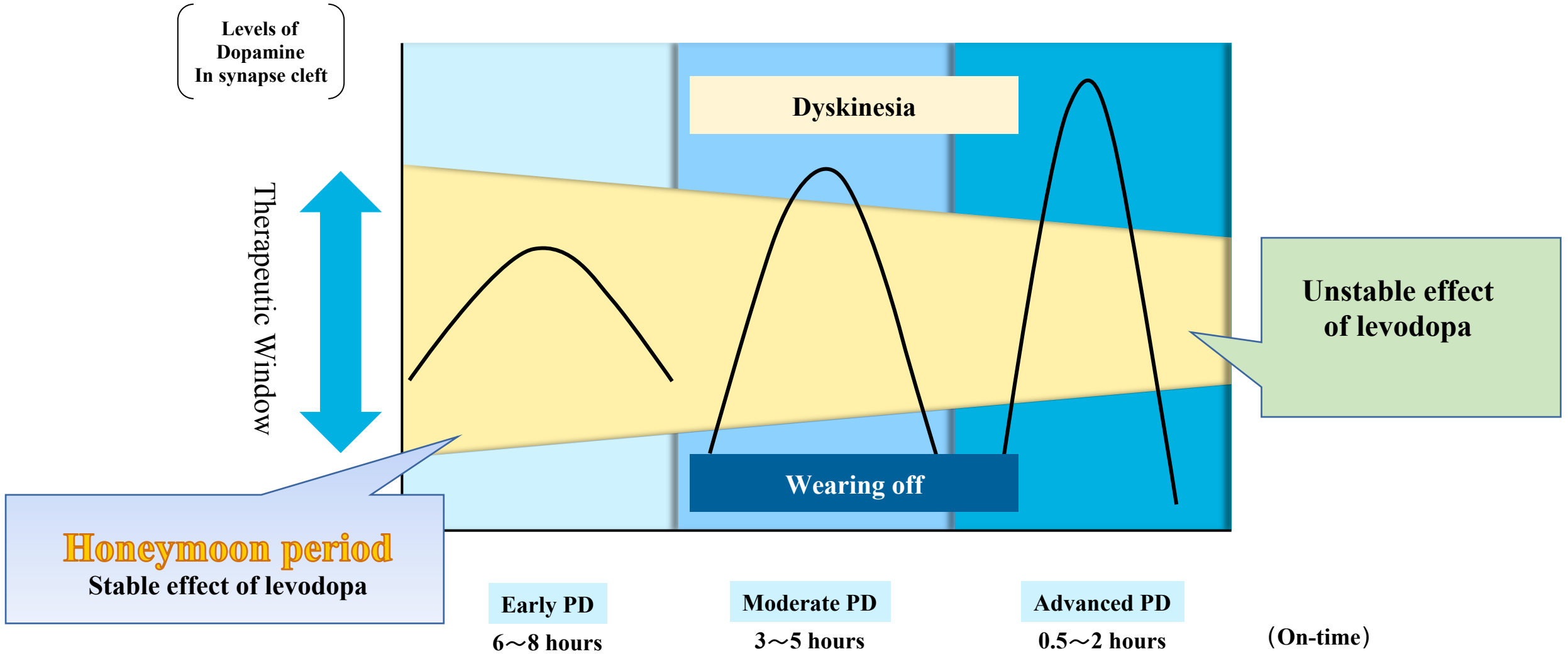
- L-dopa improves QOL and life expectancy.
- **The most effective therapy & gold standard!**
- Safety is assured.
- Inexpensive.



✗ Limitations

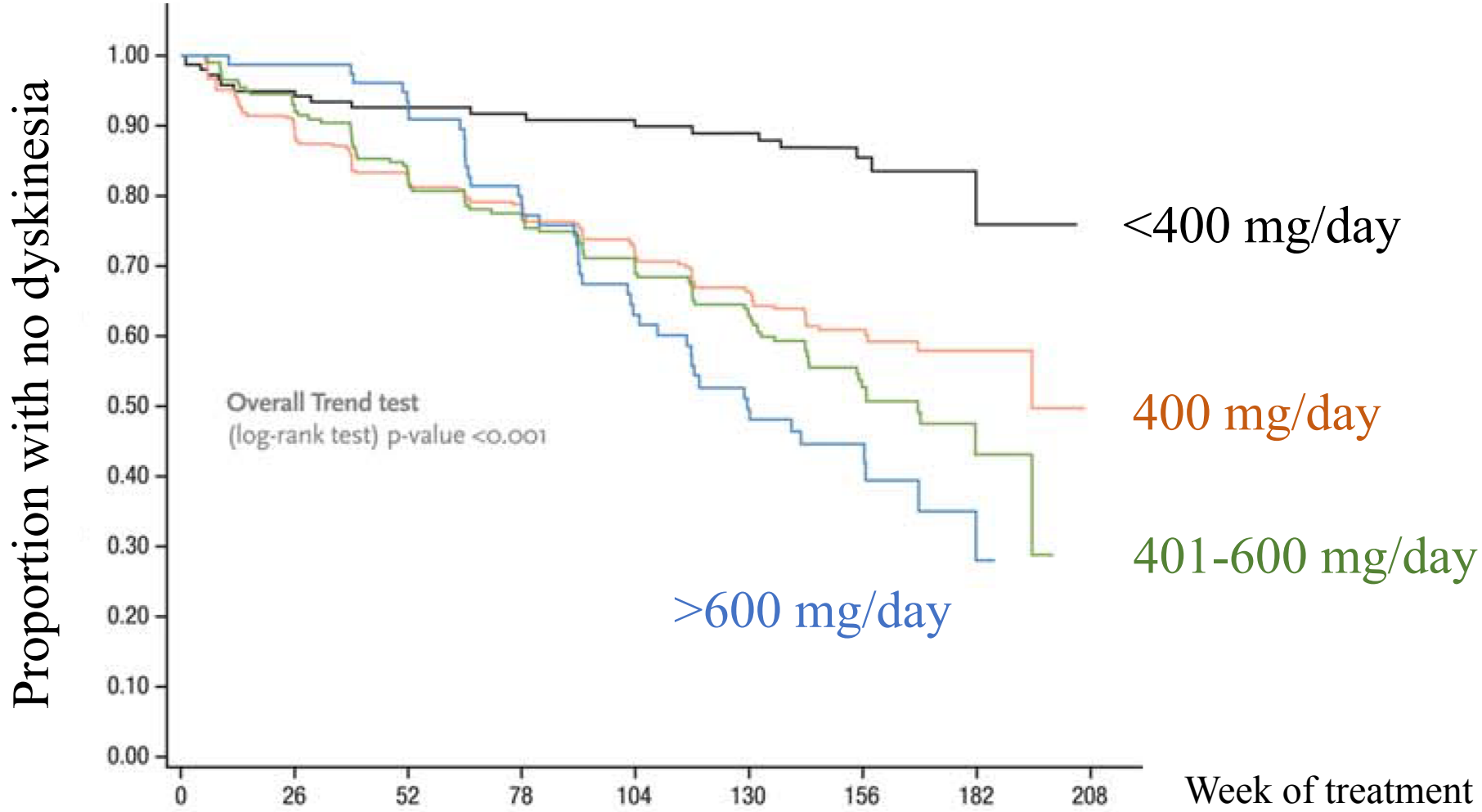
- Short half-life in plasma (60-90 min).
- **Long term use of L-dopa causes motor fluctuations and dyskinesia**

Levodopa treatment and Motor complications (Wearing off and dyskinesia)



Kenichi K. et al. Parkinson's disease Textbook for General Practitioners and Residents. Tokyo: Aruta Press ;2012, p107 partially modified

The risk of developing dyskinesia increased in an L-dopa dose-dependent manner.

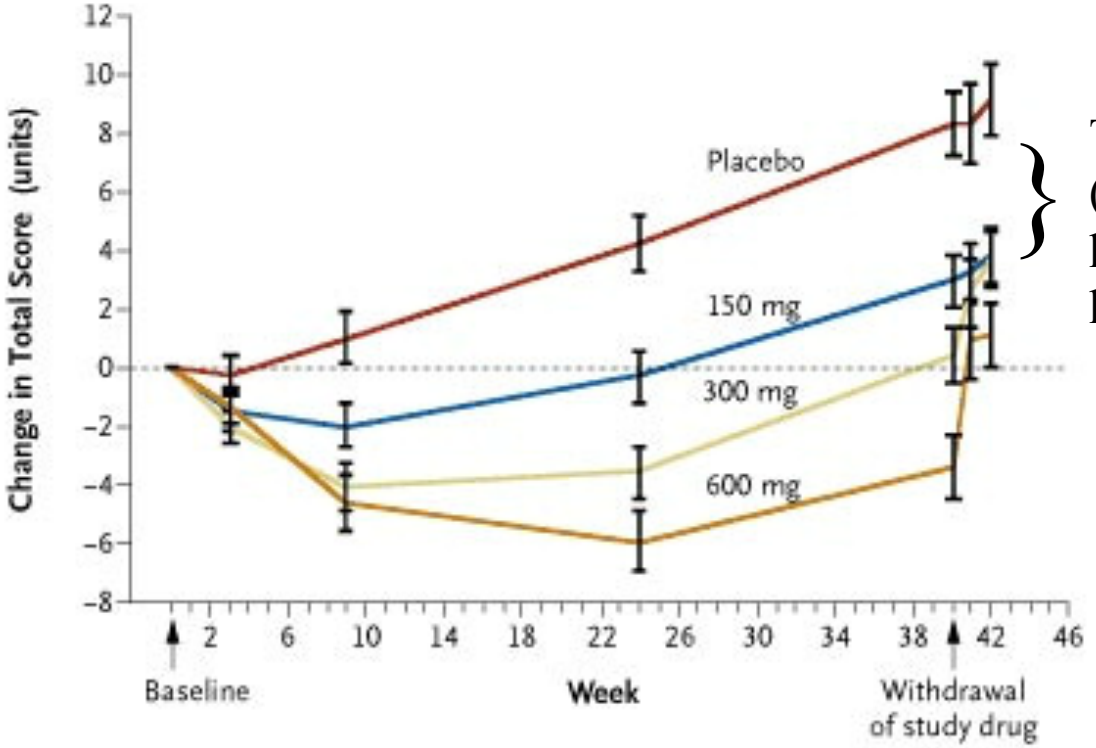


Warren Olanow C, et al. Mov Disord. 2013

When should L-dopa treatment be initiated in the course of the disease ?

ELLDOPA study **prospective, randomized, double-blind study** (NEJM, 2004)

Subject：Patients with PD, who had received a diagnosis of Parkinson's disease within the past two years and had no treatment for the symptom（Yahr Ⅰ～Ⅱ）

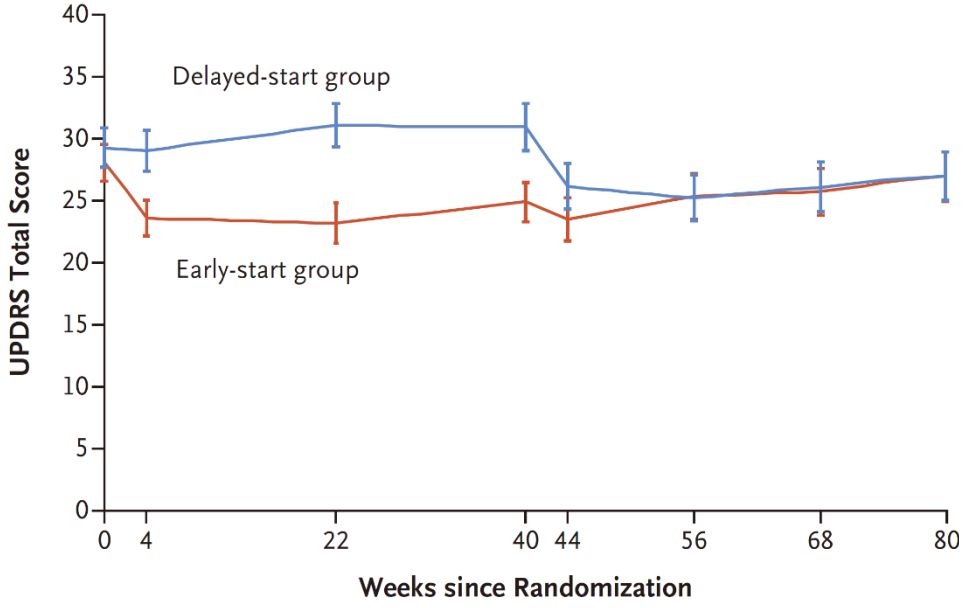


The gaps of UPDRS score (placebo vs L-dopa treated groups) had remained even after the L-dopa had washed out.

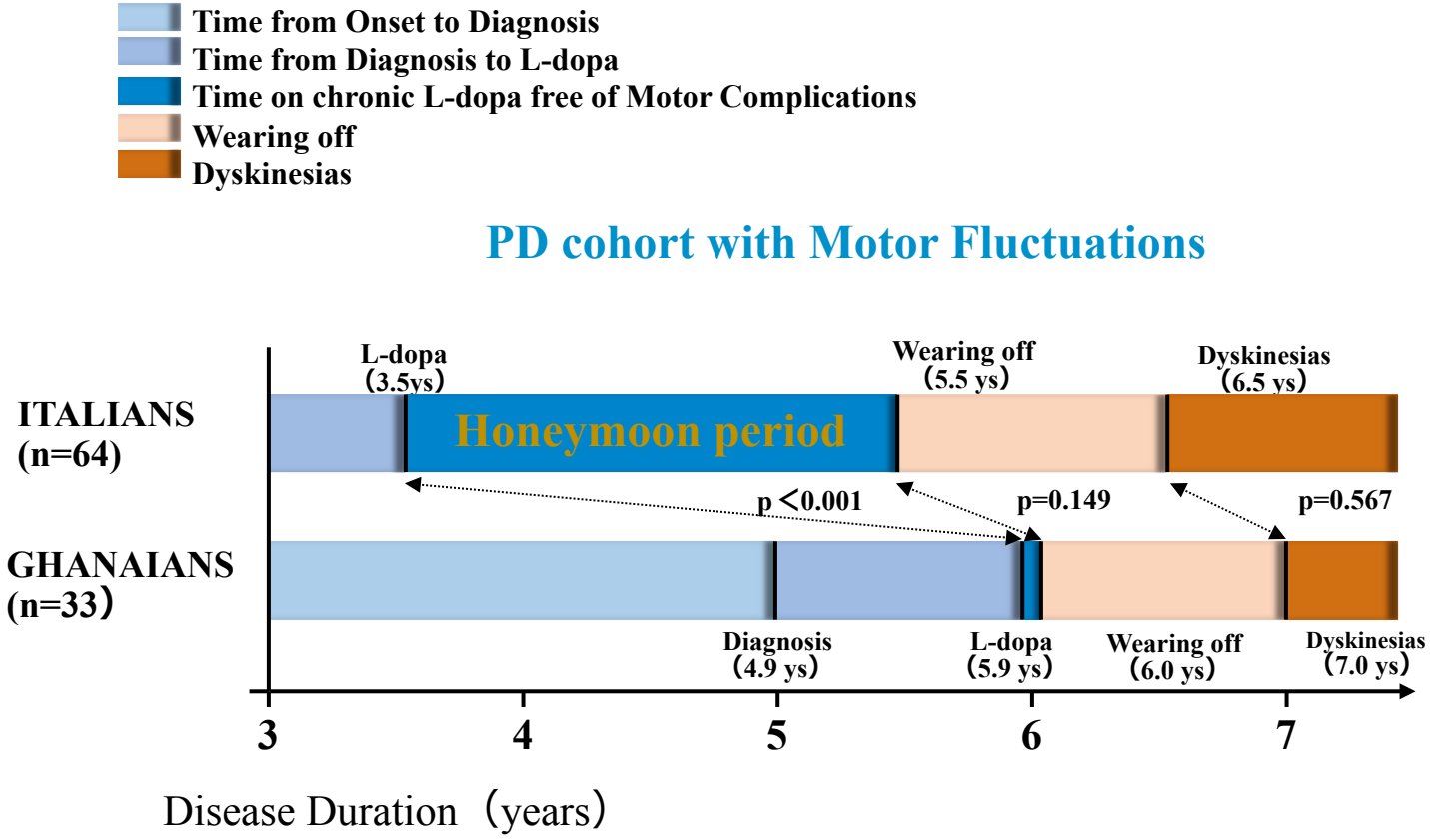
No merits in delaying the start of L-dopa treatment

There were no apparent evidence of disease modifying effect and toxicity of early levodopa treatment.

LEAP study



N Engl J Med. 2019 Jan 24;380(4):315-324.



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

Summary of L-dopa therapy

■ L-dopa is most effective drug and gold standard in PD therapy
■ No evidence showed either toxicity or disese-modifying effect of L-dopa

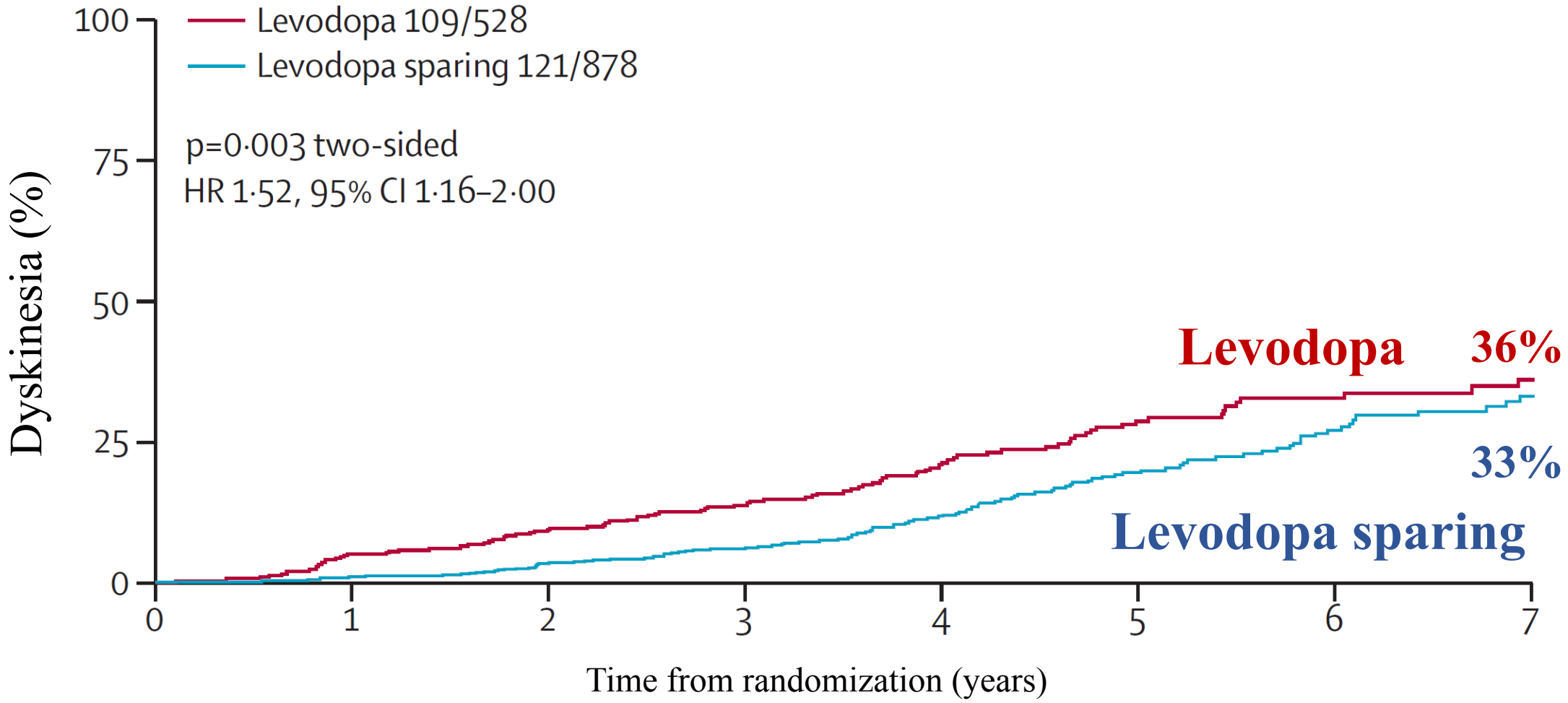
■ Long-term use of L-dopa increases the risk of motor fluctuation
■ Motor fluctuation occurs in a L-dopa dose-dependent manner

→**Patients (≦ 70 years old)** should be treated with drugs except for L-dopa, or low-dose L-dopa (less than 300-400mg)

Patients (> 70 years old) should be treated with L-dopa as a first choice to maintain their QOL

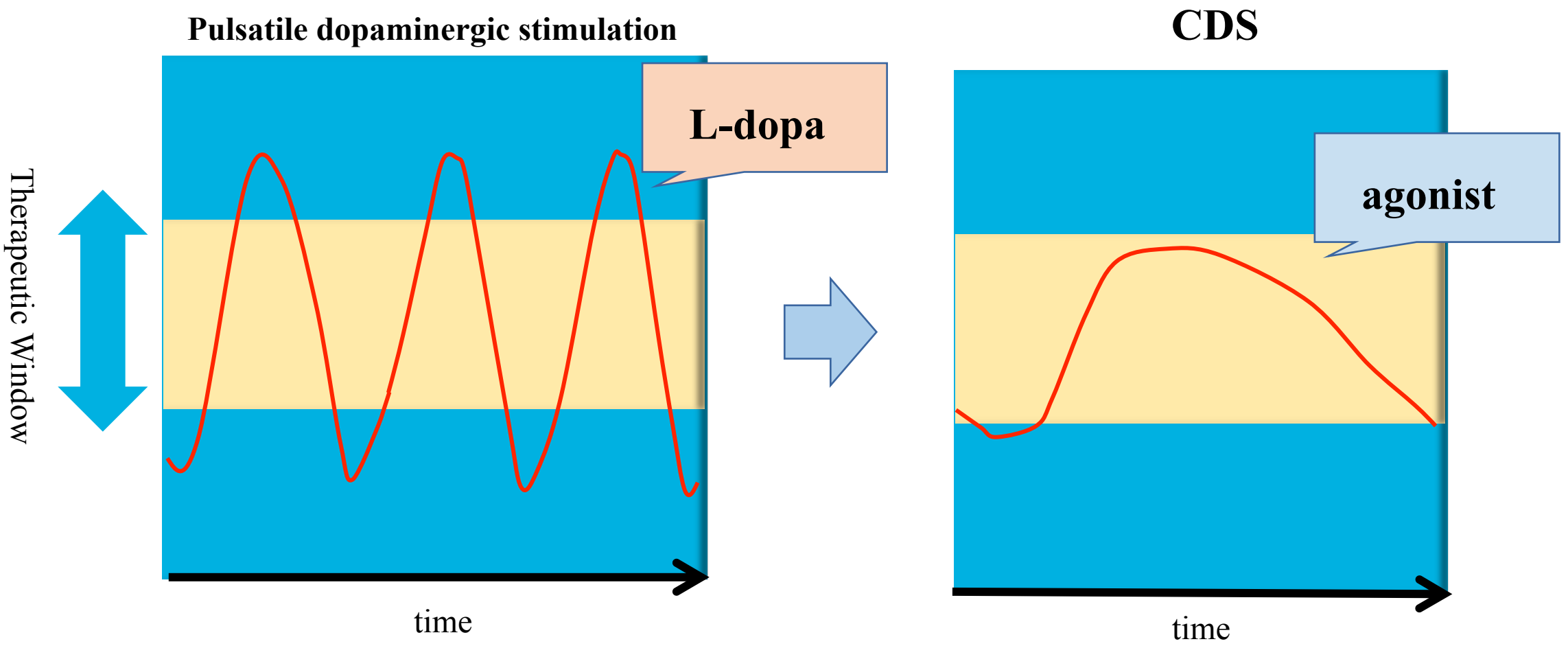
Levodopa sparing therapy avoids motor complications

PD-MED study
Initial treatment: L-dopa vs DA or MAOB-I



PD Med Collaborative Group, et al. Lancet. 2014

Continuous Dopaminergic Stimulation (CDS)



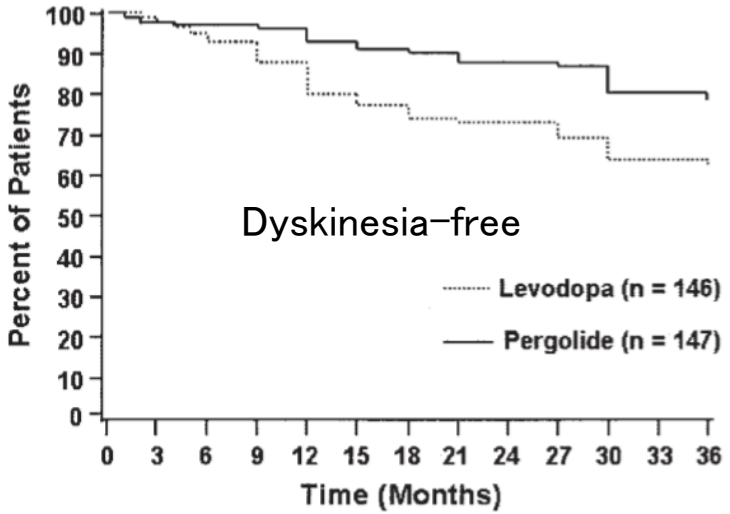
Motor fluctuation due to L-dopa is caused by **long-term, non-physiological, and pulsatile dopaminergic stimulation.**

CDS is important to reduce motor fluctuation.

Dopamine agonists

Initial treatment with dopamine agonists had a significantly lower incidence of motor complications compared with L-dopa.

PELMOPET study

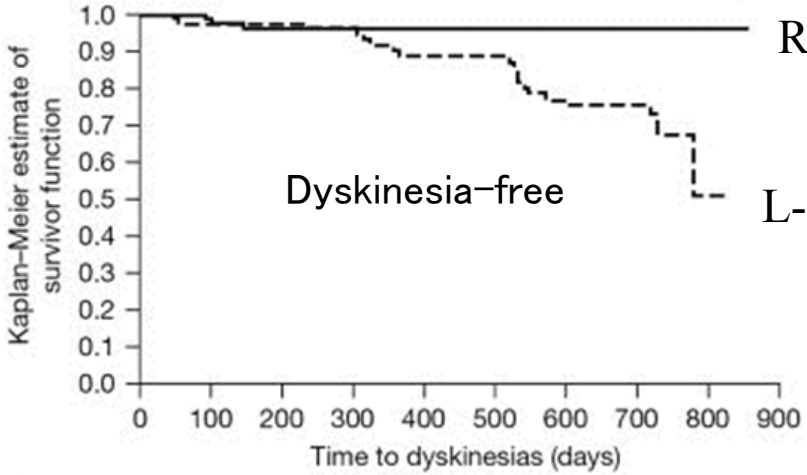


Pergolide

L-dopa

Movement Disorders, 2006

The REAL-PET study

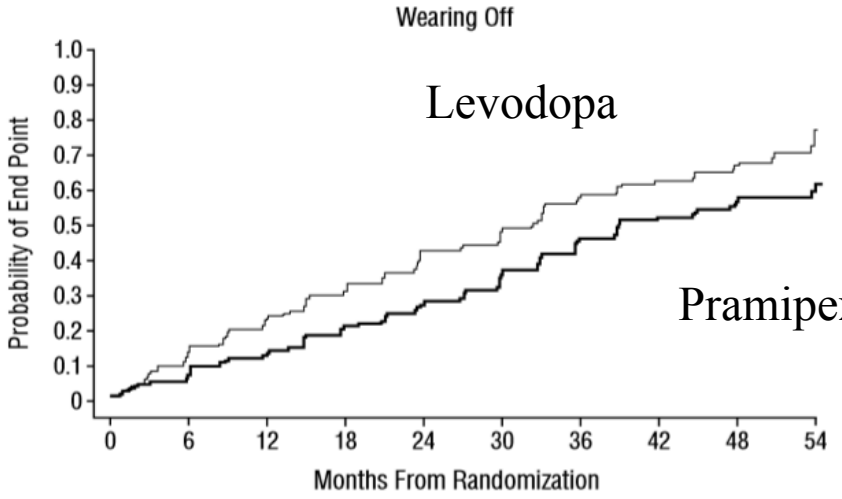


Ropinirole

L-dopa

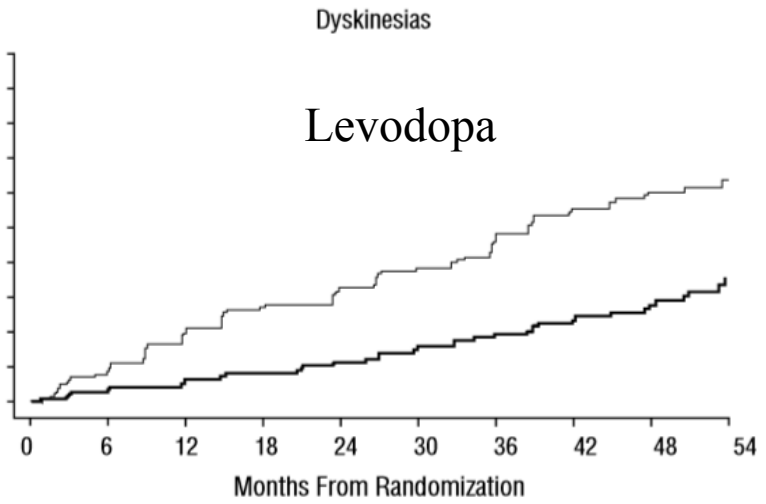
Whone AL et al. Ann Neurol, 2003

CALM-PD study



Levodopa

Pramipexole

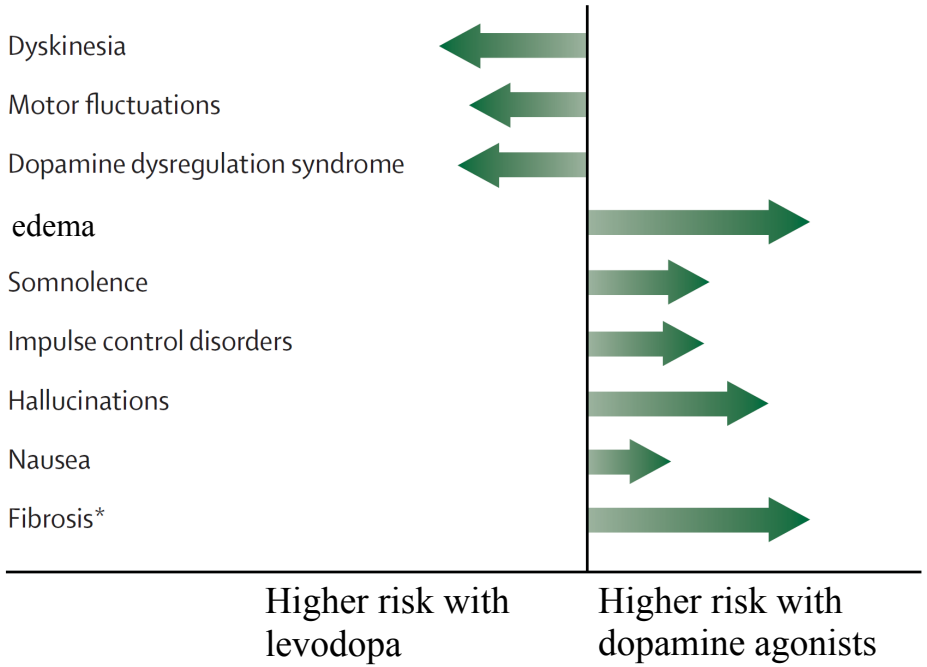


Levodopa

Pramipexole

JAMA, 2000

Comparison of the risk of adverse events associated with L-dopa vs dopamine agonists.



Antonini A, et al. Lancet Neurol. 2009

Common adverse effects

- Somnolence（ergot < non-ergot)
- Nausea（ergot < non-ergot)
- Hallucination
- Impulse control disorders (Pathological gambling, hypersexuality, compulsive buying)

Non-ergot dopamine agonists

- Sudden somnolence

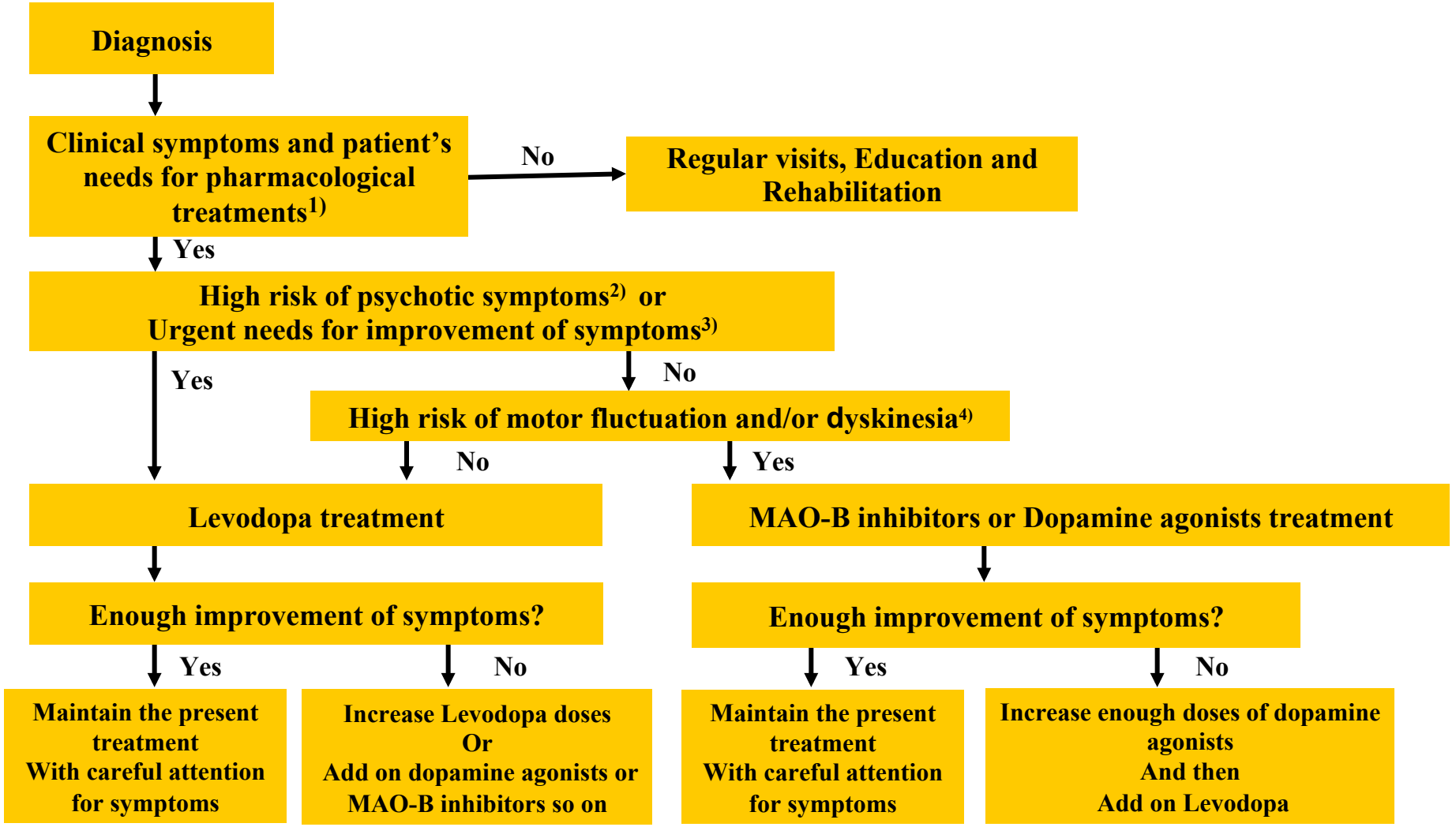
Avoid driving, machine operation, or work at height

Ergot dopamine agonists

- Increased risks of valvular heart disease, retroperitoneal fibrosis, and pulmonary fibrosis

⇒Ergot dopamine agonists are second-line drugs.
follow up echocardiogram every half or one year!

Treatment algorithm in the early stage of Parkinson's disease from Japanese PD guidline



1) Discuss the person's individual clinical symptoms, lifestyle circumstances and needs.
2) Elderly people and Dementia so on.
3) Severe motor symptoms (Hoehn & Yahr Stage 3 or more), High risk of fall so on.
4) Disease onset is less than 65 years old, so on.

Guideline for treatment of Parkinson's disease 2018 in Japan

Other medications

- Zonisamide

Efficacious for tremor

- Anticholinergics

Efficacious for tremor

Inexpensive

Consider use of zonisamide or anticholinergics tremor dominant PD in early stage

- Amantadine

Inexpensive

No evidence for improving ADL or motor symptom

Key Messages

- L-dopa remains gold standard of early PD.
- L-dopa could be neither toxic nor disease-modifying.
- Use sufficient amount of L-dopa to improve patient's QOL.
- Motor complications are L-dopa dose dependent.

- Consider dopamine agonist for young-onset PD in early stage to avoid motor complications, especially dyskinesia.
- Consider MAO-B inhibitor monotherapy for mild motor symptoms of PD.
- Consider use of zonisamide/anticholinergics for tremor dominant PD to save the amount of L-dopa therapy.

Reference

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