OPTIMIZING INITIAL TREATMENT STRATEGY FOR PARKINSON'S DISEASE

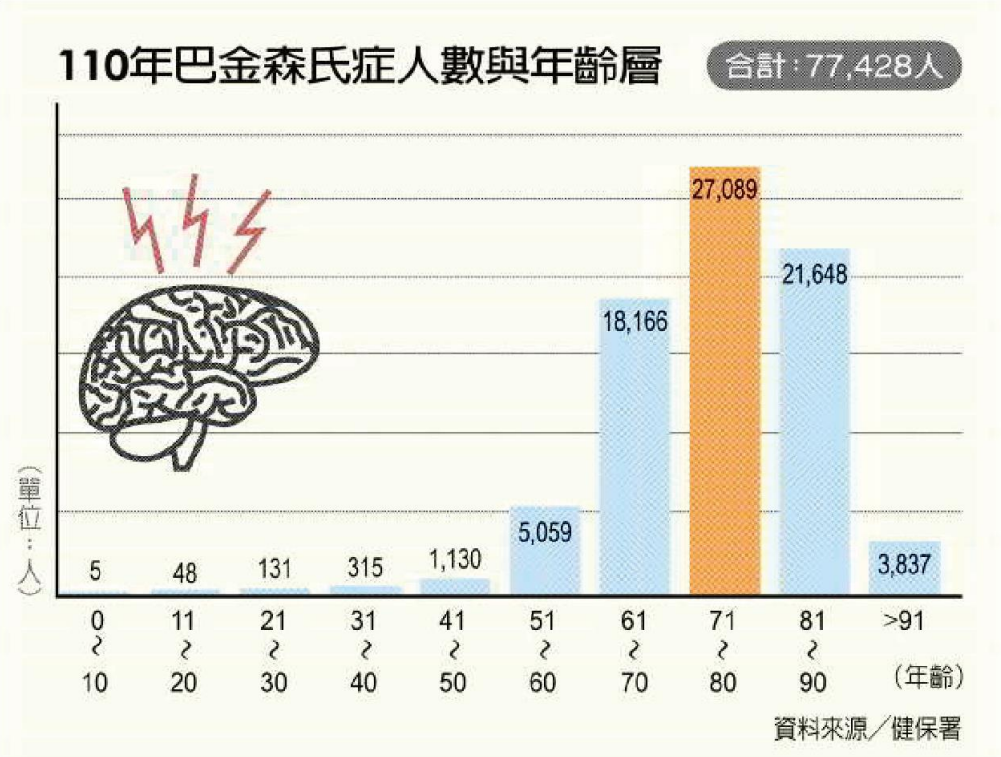
PC-TW-105615-04-Sep-2023

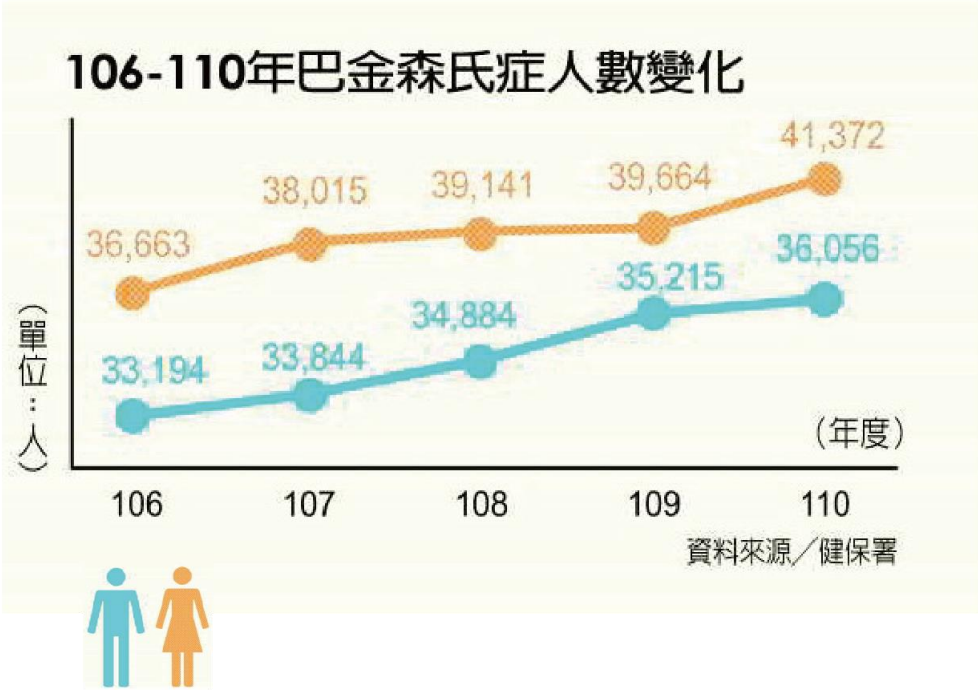
- DISCLOSURE: I HEREBY DISCLOSE THAT MY RELATIONSHIP WITH BOEHRINGER INGELHEIM INCLUDES: SPEAKER.

巴金森病 (Parkinson’ s disease)

巴金森病(巴病)是除了阿茲海默症之外最普遍的神經退化性疾病，
是一種進行性的動作障礙疾病。

巴金森病友年增2千人

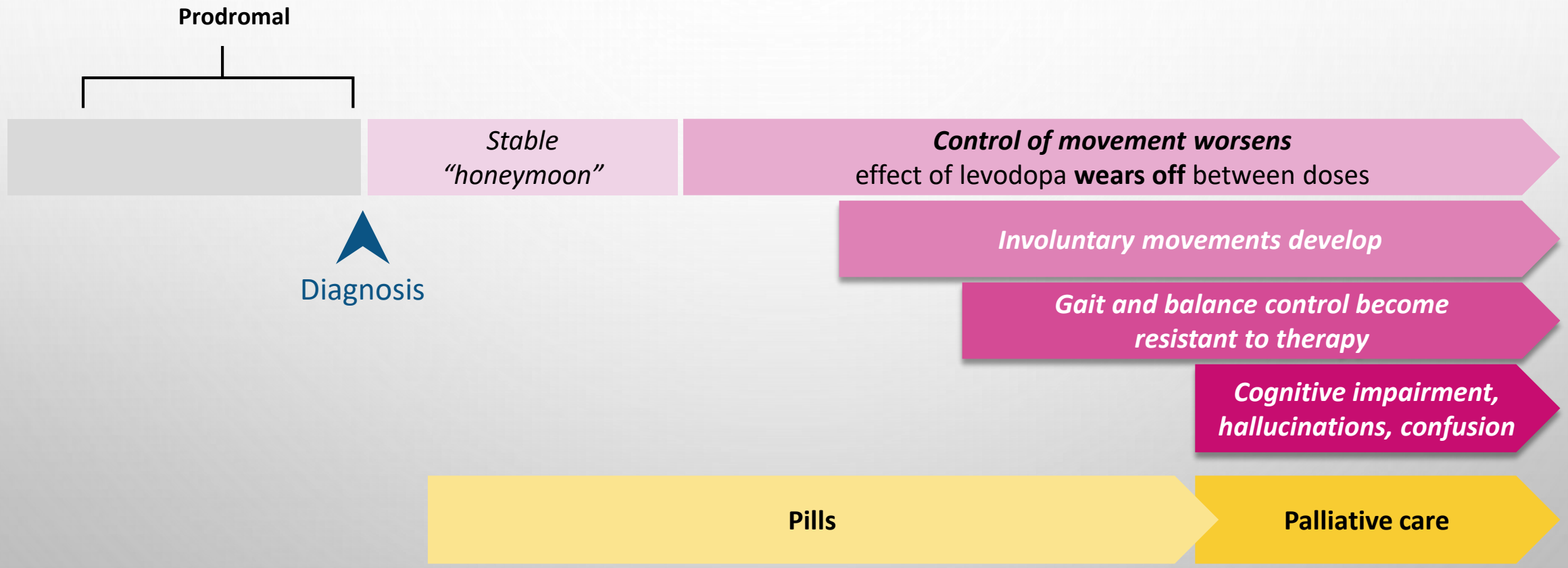




PC-TW-105615-04-Sep-2023

巴金森病 (PARKINSON’ S DISEASE) 的疾病分期與進展

巴金森病 (Parkinson’ s disease) 的進展與治療



Antonini A, Jenner P. Nat Rev Neurol 2018;14(12):693-694.

巴金森病的治療目標
根據二個國際學會所發表的診療指引

Control motor symptom — A

Prevent motor complication — B

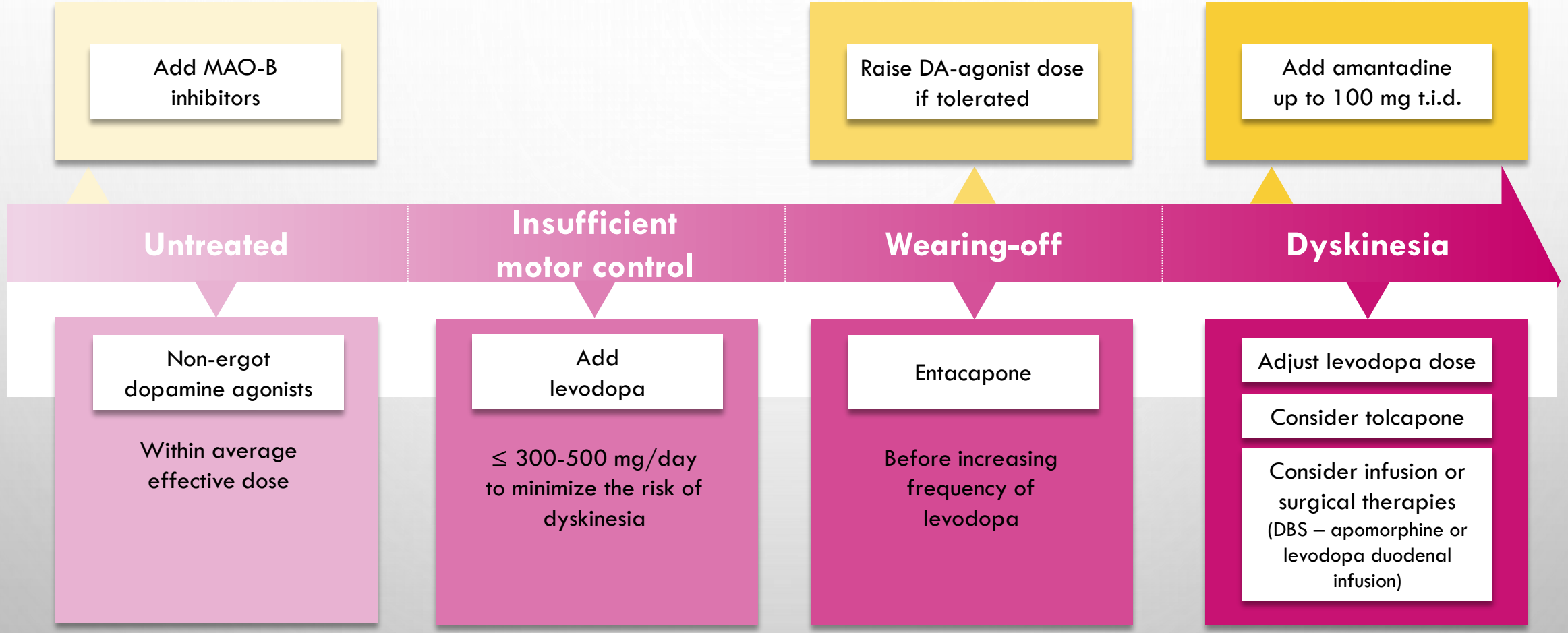
Improve non motor symptom — C

EFNS EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

International Parkinson and Movement Disorder Society

1. Fox SH, et al. Movement Disorders. 2011;26(S3):S2-S41. 2. Ferreira JJ, et al. Eur J Neurol. 2013 Jan;20(1): 5-15.

巴金森病 (PARKINSON’S DISEASE) 的治療建議 ALGORITHM

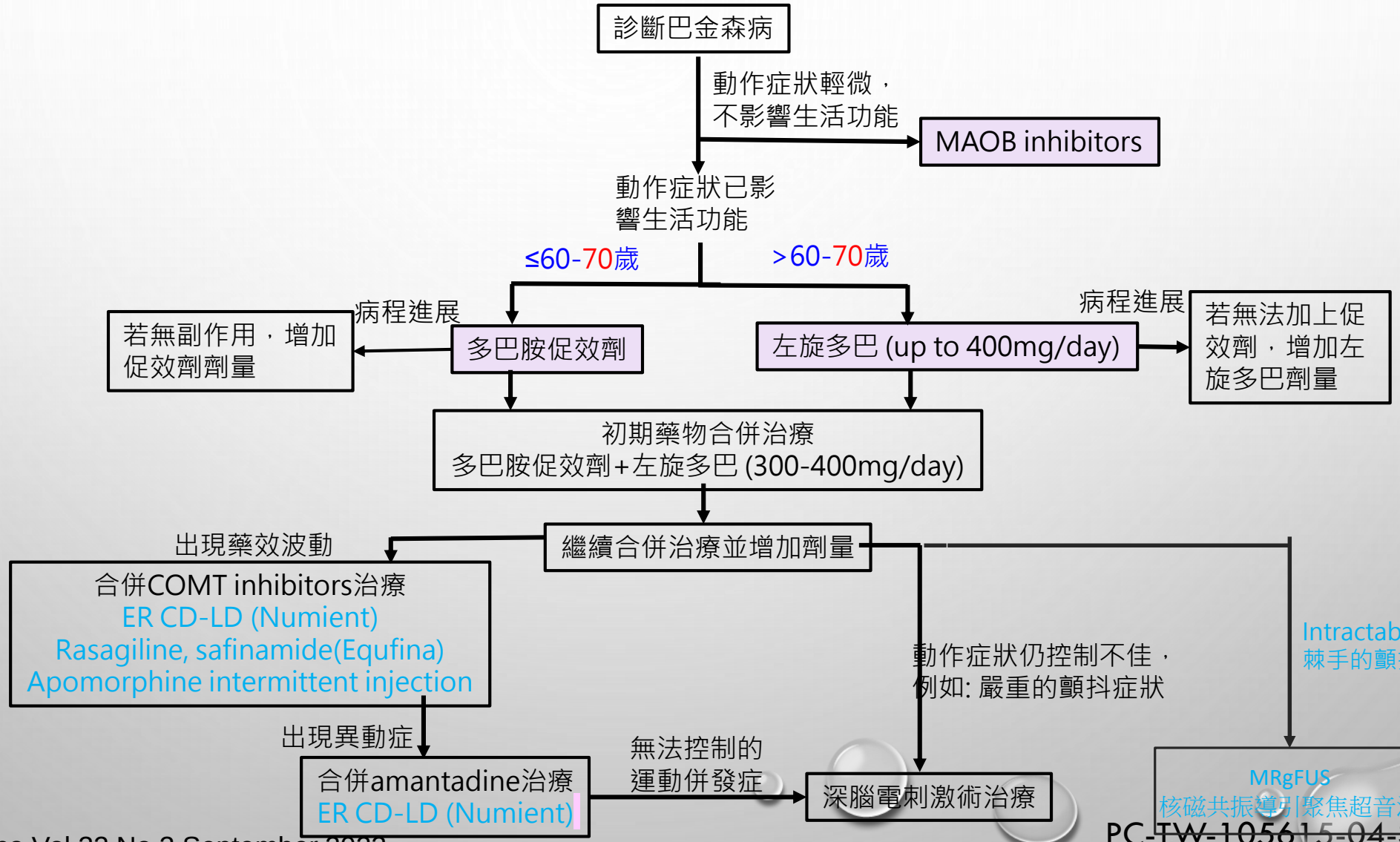


DA, dopamine agonist; DBS, deep brain stimulation; MAO-B, monoamine oxidase-B.

Antonini A, et al. Neurol Sci 2008;29:S371–4.

2023年版台灣巴金森病治療建議

-起始治療年齡放寬70歲



PC-TW-105615-04-Sep-2023

2023年版台灣巴金森病治療建議

-起始治療年齡放寬70歲

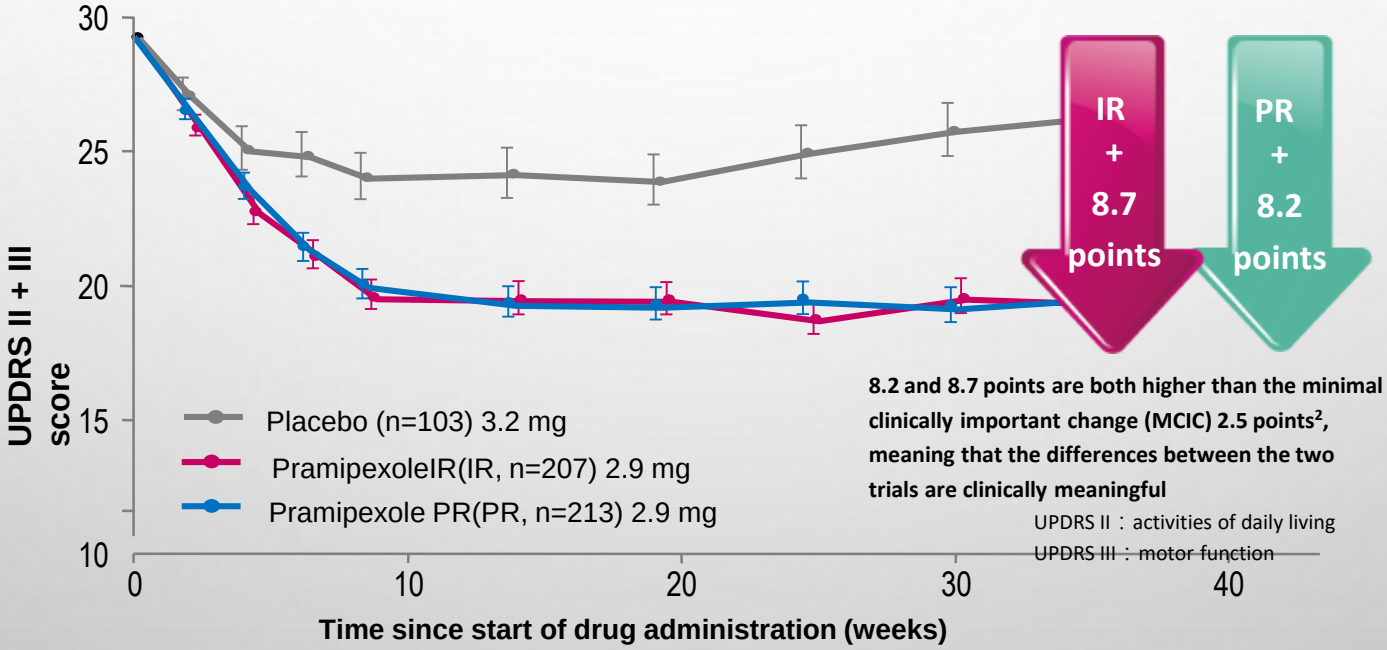
70歲以下巴金森病病人首選使用多巴胺促效劑

當病患出現動作症狀的不適，並影響到生活功能時，即早開始使用多巴胺製劑(左旋多巴或是多巴胺促效劑) 的治療可維護生活品質。有鑑於長期使用左旋多巴會有較高運動併發症的風險，因此，建議對於年齡較輕(≤ 60-70 歲) 的患者，因為預期餘命較長，治療時間較久，日後累積藥物用量將會較高，因此建議首選使用多巴胺促效劑至治療劑量，追蹤治療期間，若動作症狀改善幅度不夠，可再加上對動作症狀的改善效果較顯著之左旋多巴做為合併治療，可維持300-400mg/ 日或6mg/kg/ 日*

*Acta Neurologica Taiwanica Vol 32 No 3 September 2023

Mirapex® IR 或PR劑型改善UPDRS(Ⅱ+Ⅲ)
可以顯著改善病人的運動功能進而提昇生活品質

- At 33 weeks, the adjusted mean decrease was 8.7 for IR and 8.2 for ER vs 1.2 in the placebo group (p<0.0001), excluding post–levodopa rescue data, and 8.8 for IR and 8.6 for ER vs 3.8 in the placebo group (p<0.0001), including levodopa-rescued patients.



1. Poewe W, et al. Neurology. 2011;77(8):759-66.
2. Hauser RA, et al. Mov Disord. 2011 Apr;26(5):813-8

PC-TW-105615-04-Sep-2023

早期巴金森病的動作症狀顫抖

- Early PD patients

87.8% present with tremor

Rest tremor

69.6%

Postural tremor

50%

Kinetic tremor

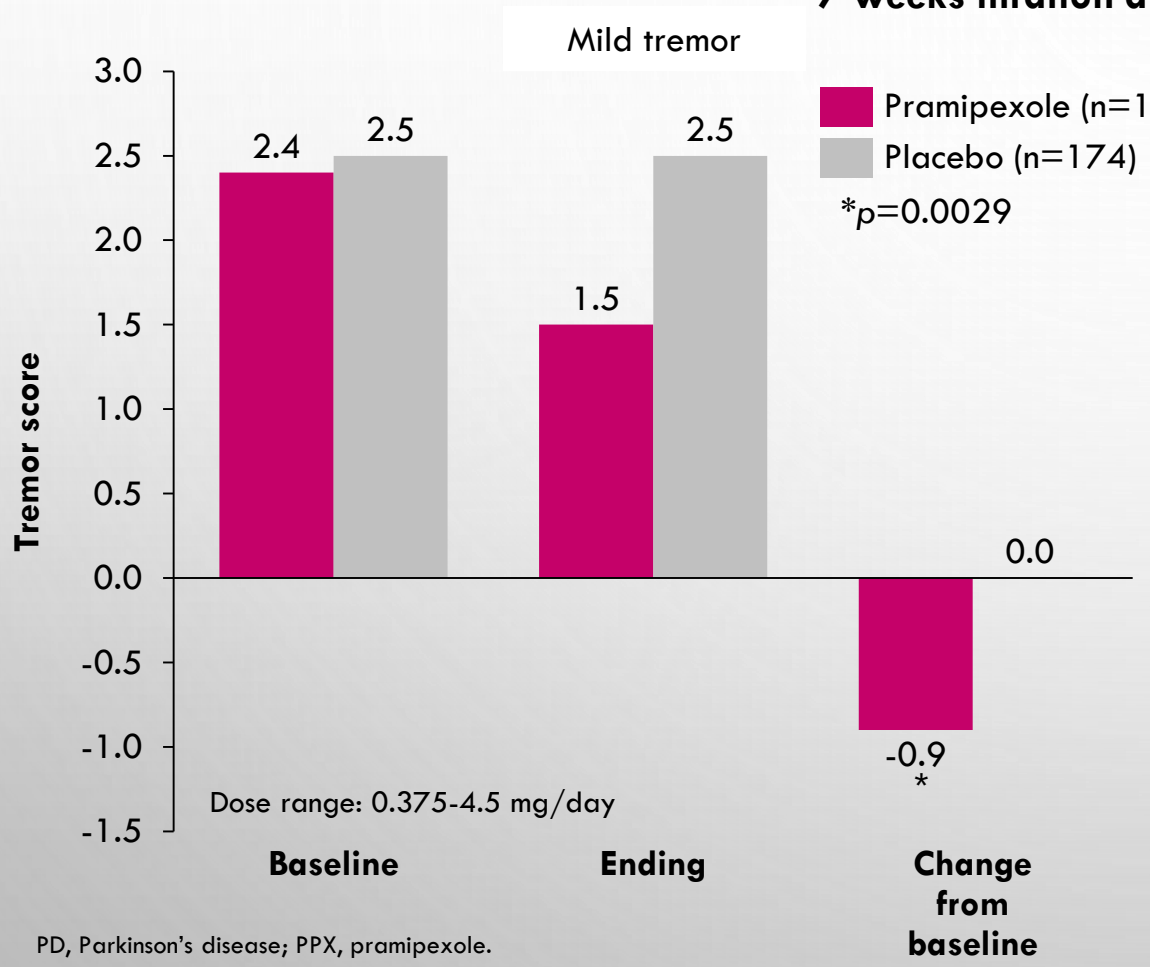
50%

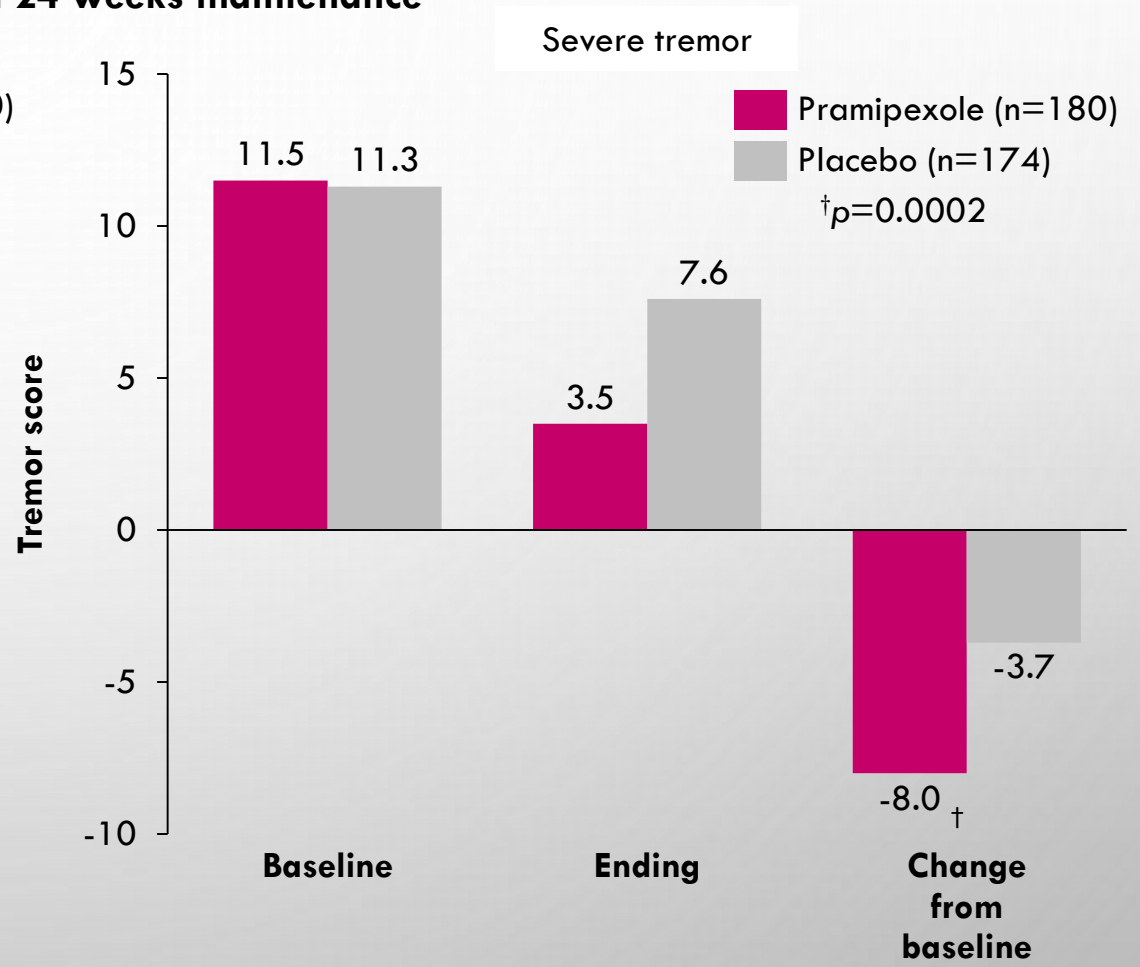
PD, Parkinson's disease

Pasquini J, et al. BRAIN 2018: 141; 811–821.

MIRAPEX® 可明顯改善巴金森病患者的輕微或嚴重顫抖

7 weeks titration and 24 weeks maintenance





PD, Parkinson's disease; PPX, pramipexole.

Moller JC, et al. Mov Disorders, 2005,20:602-610.

Adapted from table 4. Moller JC, et al. Mov Disorders, 2005,20:602-610.

PC-TW-105615-04-Sep-2023

MIRAPEX®用於治療早期巴金森病的隨機對照研究

Pramipexole trials in early Parkinson's disease

Study, year	Study design	Treatment arms	Primary endpoint	Primary endpoint findings
Hubble et al, 1995	Randomized, double-blind, parallel-group, placebo-controlled phase II, multicentre, 8-week study (n=56)	Pramipexole up to 4.5mg/day Placebo	UPDRS II and III scores	Pramipexole group showed significant improvement over placebo on UPDRS II score at the end of 9 weeks (p=0.002). The group were not significantly different on UPDRS III score but the pramipexole group had a greater improvement than placebo (p=0.10)
Shannon et al, 1997	Randomized, double-blind, parallel-group, placebo-controlled, multicentre, 31-week study (n=335)	Pramipexole up to 4.5 mg/day Placebo	UPDRS II and III scores	UPDRS II and III scores were significantly lower in the pramipexole group ꢀs placebo starting from the third week of the titration phase until the end of the maintenance phase (week 31) [p<0.001]
Parkinson Study Group, 1997	Randomized, double-blind, placebo-controlled, multicentre, 11-week study (n=264)	Pramipexole 1.5, 3.0, 4.5 or 6.0 mg/day Placebo	UPDRS III scores	At 10 weeks, patients treated with pramipexole showed a significant improvement compared with placebo of about 20% in the total UPDRS score compared with baseline (p<0.005)
Parkinson Study Group, 2000	Randomized, double-blind, parallel-group, placebo-controlled, multicentre, 4-year study (n=301)	Pramipexole 1.5, 3.0 or 4.5 mg/day Carbidopa/levodopa 75/300, 112.5/400 or 150/600 mg/day in three doses	Occurrence of the first motor complication (wearing-off at end of dose, 'ON-OFF' fluctuation, dyskinesia)	Results after 2 years: at the end of the maintenance phase (23.5 months) 28% of patients in the pramipexole group had motor complications vs. 51% of patient in the levodopa groups (p<0.001) Results after 4 years: 52% of patients in the pramipexole group had the first motor complications vs. 74% of patients in the levodopa groups (p<0.0001)
Navan et al, 2003	Randomized, double-blind, placebo-controlled, multicentre, 3-month study (n=30)	Pramipexole up to 1.0 mg three times daily Pergolide Placebo	Tremor Index and UPDRS III score	Both pramipexole and pergolide had significantly greater effects than placebo on tremor and UPDRS II scores vs. placebo. No significant difference was found be tween the two active treatment groups

PD, Parkinson's disease; UPDRS, the unified Parkinson's disease rating scale.

Antonini A, et al. CNS Drugs 2010;24(10):829-41.

運動性併發症嚴重影響病人的生活品質

The incidence of motor complications reach 50%-90% after an average of 5.15 years of levodopa treatment[1]

.

Patients with Dyskinesias

Quality of Life

Significantly poorer[2]

P=0.004

Patients with Dyskinesias

More Severely Disabled[3]

P=0.001

Patients with Motor Fluctuations

Medical Expenditures

Doubled[4]

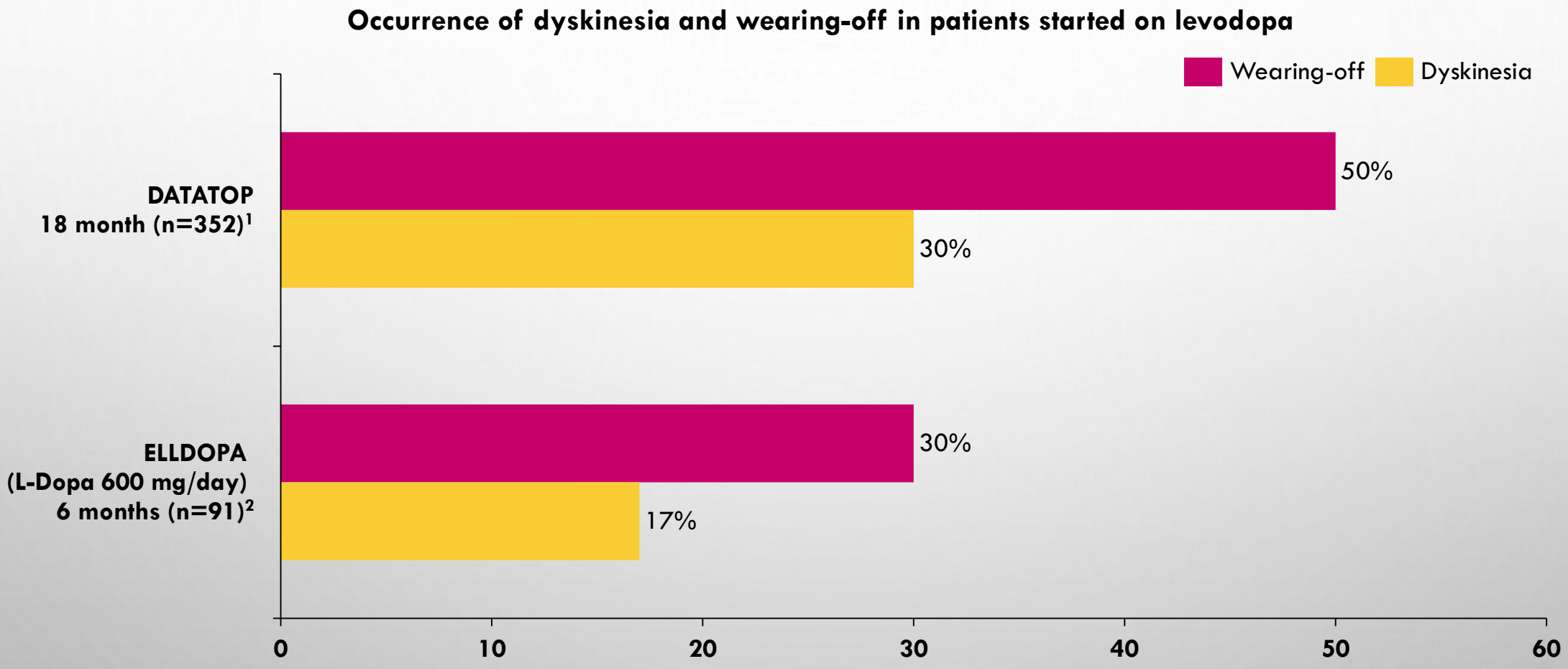
Motor complications were the main reason for hospital admissions[5]

Motor Complications (37%) > Motor and Psychiatric Complications (25%) > Psychosis (24%)

*Motor complication including: UTI, bronchitis, concussion etc

1..Zhang et al. BMC Research Notes 2014, 7:65
2.. Damiano AM, et al. Quality of Life Research. 2000; 9: 87-100.
3. Schrag A, et al. Brain. 2000; 123: 2297-2305.
4. Dodel RC, et al. Pharmacoeconomics. 1998; 14 (3): 299-312.
5. Klein C，et al. J Neural Transm. 2009 Nov;116(11):1509-12.

DATATOP 和 ELLDOPA 二項研究結果顯示藥效漸退 (WEARING-OFF) 和異動症 (DYSKINESIA) 是 LEVODOPA 治療上的主要問題



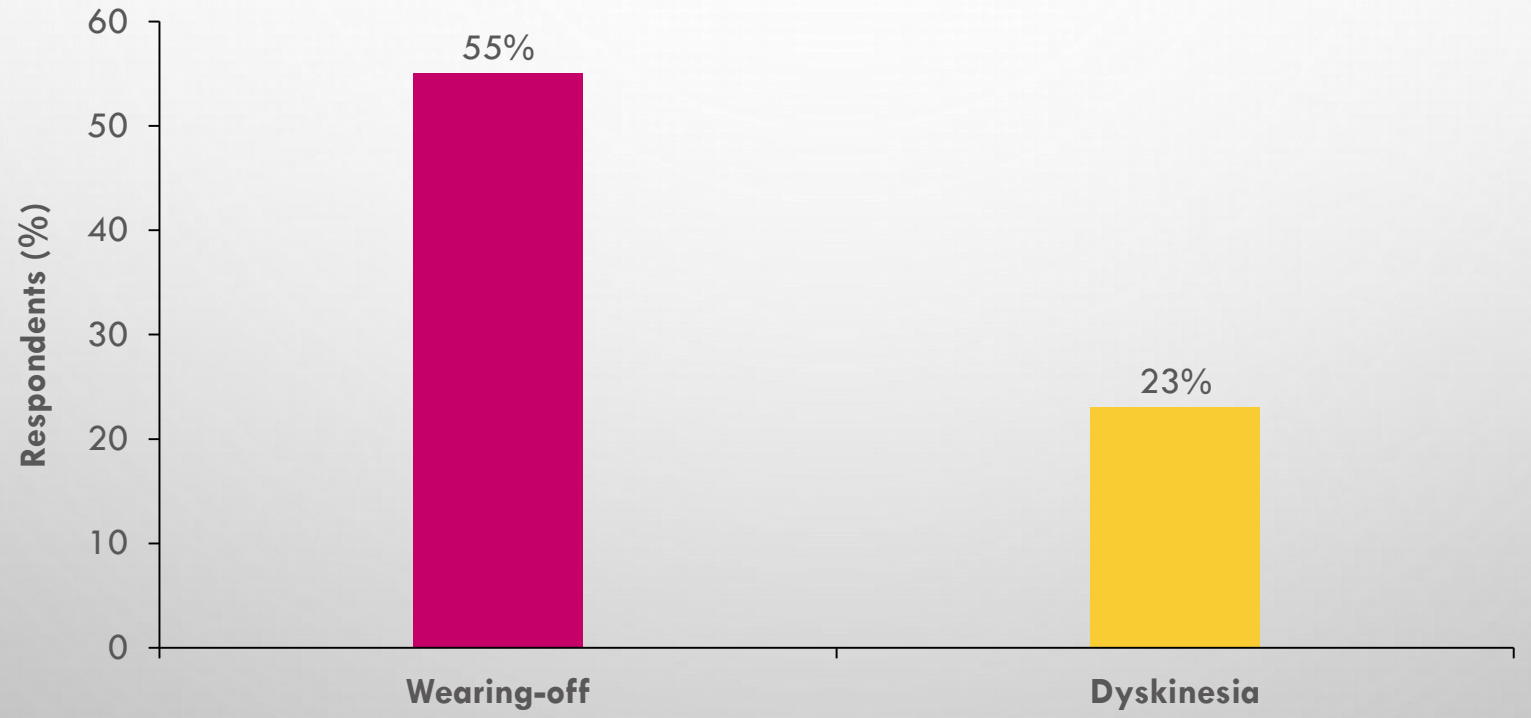
L-Dopa, levodopa.

1. Parkinson Study Group. Ann Neurol 1996;39(1):37-45. 2. Parkinson Study Group. N Eng J Med 2004;351:2498-508.

使用 LEVODOPA 治療最大的挑戰是藥效漸退 (WEARING-OFF)

Short, online patient survey collected data from **300** respondents with moderately advanced disease

Q: What is the biggest challenge with levodopa therapy?

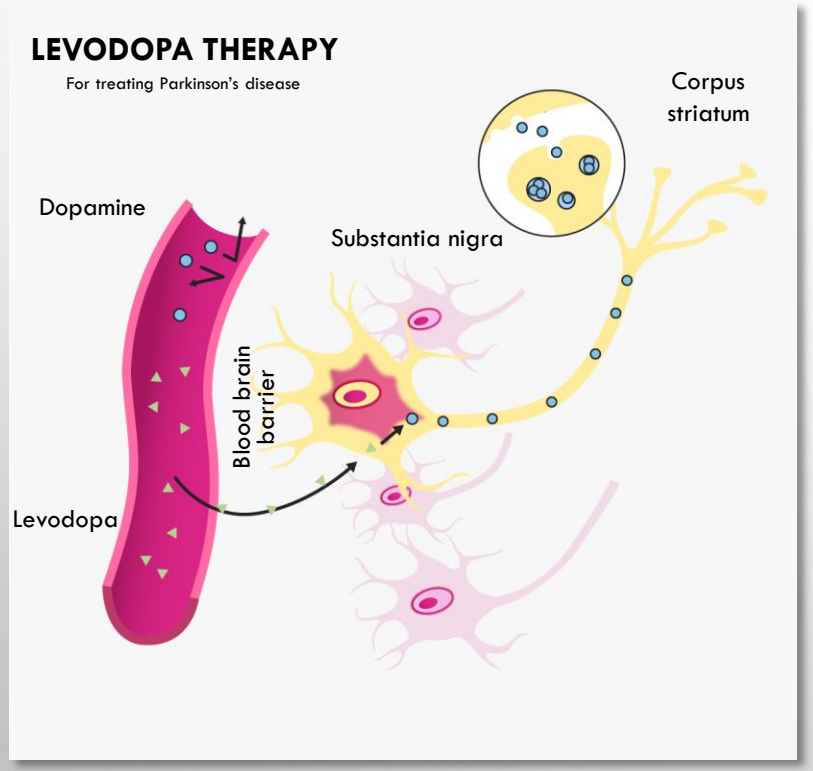


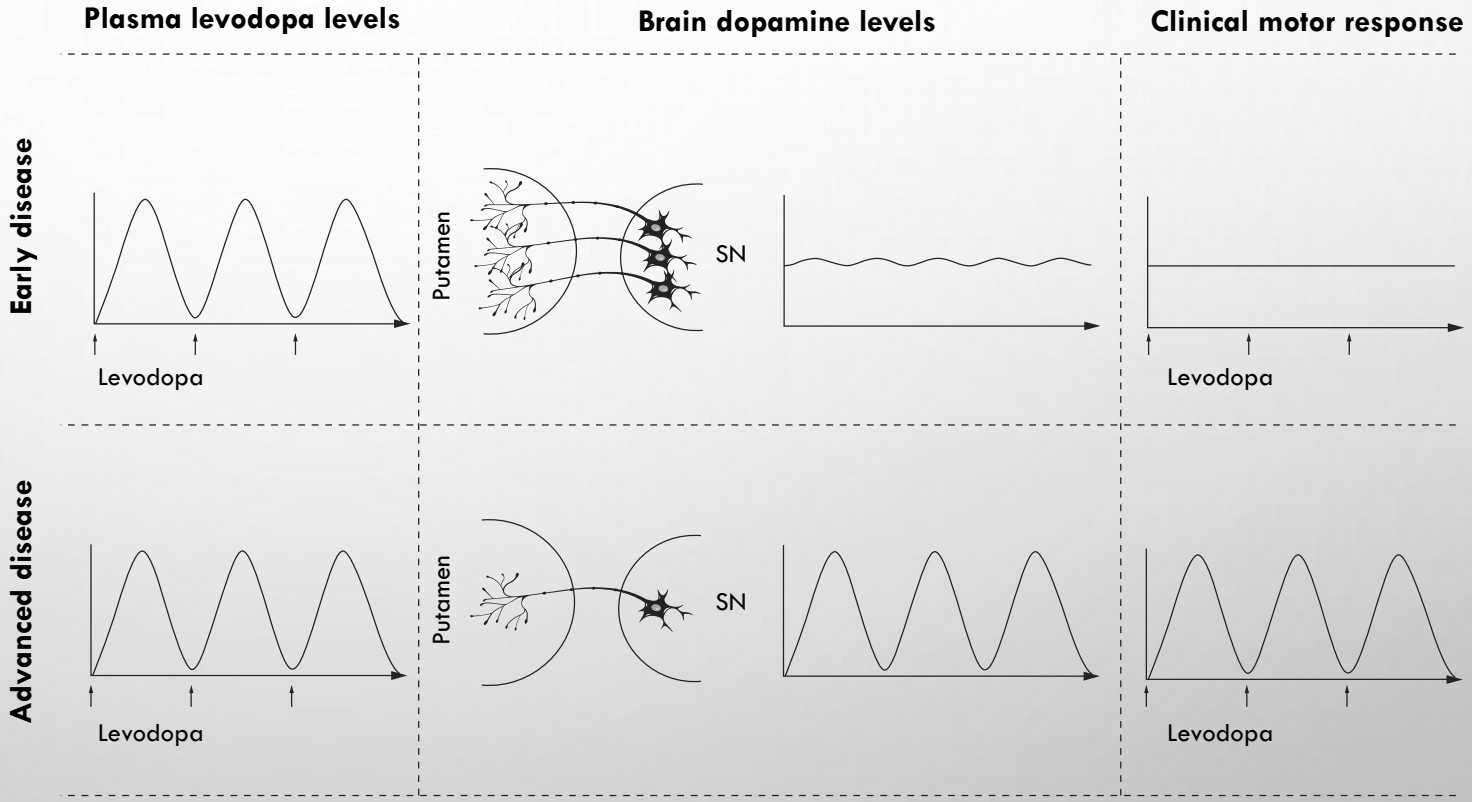
PD, Parkinson's disease.

Lieberman AN, et al. Eur J Neurol 2004; 11(Suppl 2): 109

巴金森病發生運動性併發症的原因

Loss of dopamine nerve terminals is associated with shortening in levodopa response The evolution of levodopa-associated motor fluctuations

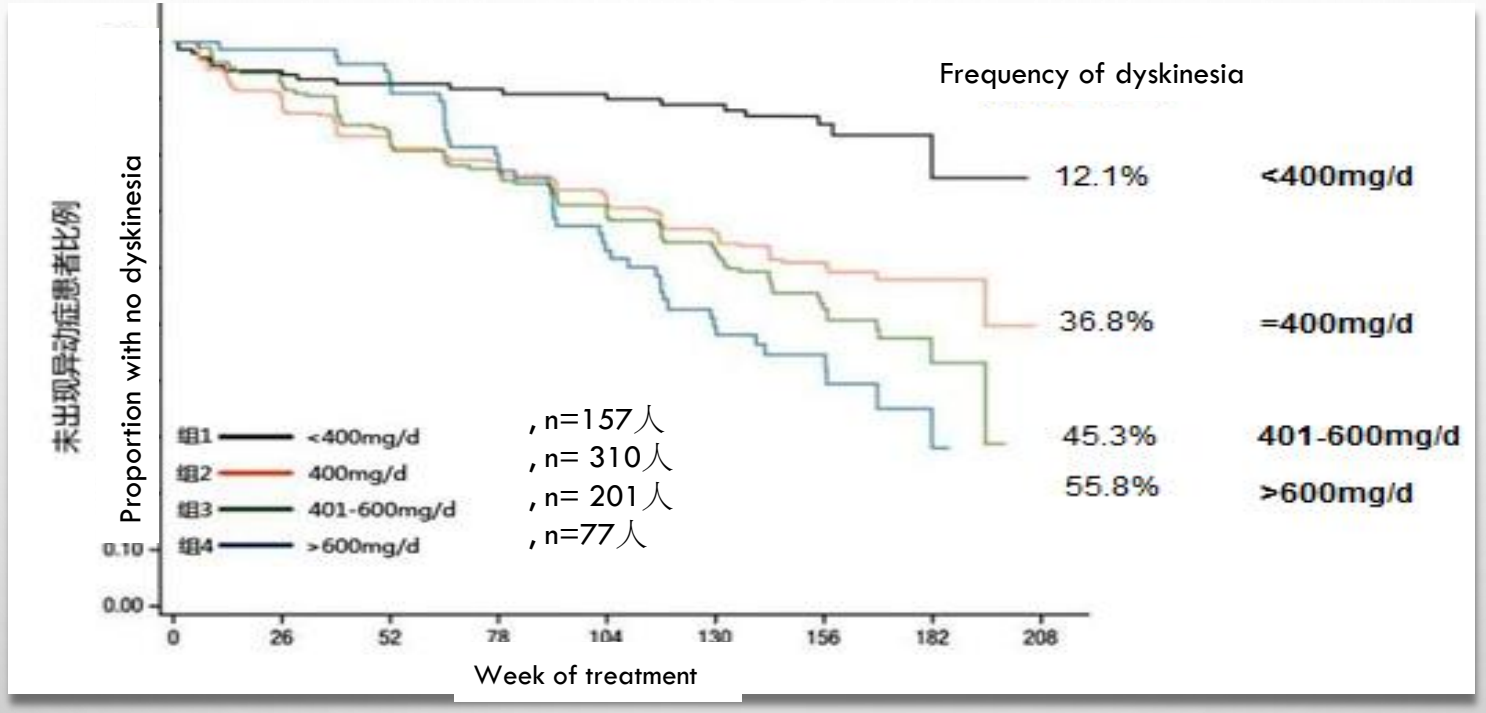




Poewe W, et al. Clin Interv Aging. 2010;5:229-38.

高劑量L-DOPA是運動併發症的獨立風險因素

- **STRIDE-PD study shows the risk of dyskinesia increased in a dose-dependent manner**
- **Analysis shows that high dosage of L-dopa is a risk factor for motor complications**

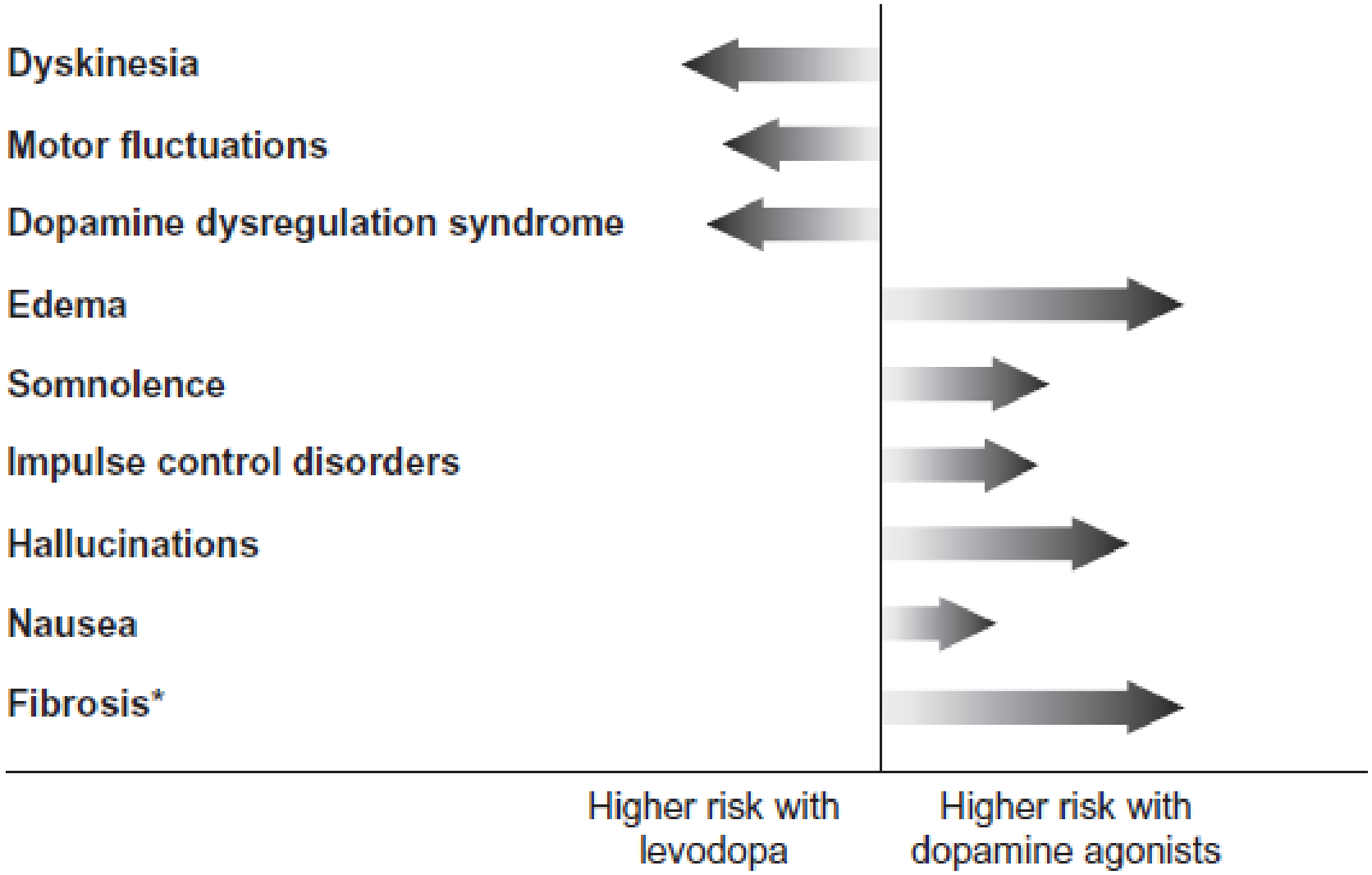


- **We suggest avoiding doses greater than 400 mg/day when not clinically necessary**
- **In order to reduce the risk of motor complications, polypharmacy using concurrent drugs, such as DA and** MAOB inhibitors**, may be preferable to continuously increasing the L-dopa dose**

——STRIDE-PD investigators

Warren Olanow C, et al. Mov Disord. 2013 Jul;28(8):1064-71.

使用DA治療顯著降低異動症的風險



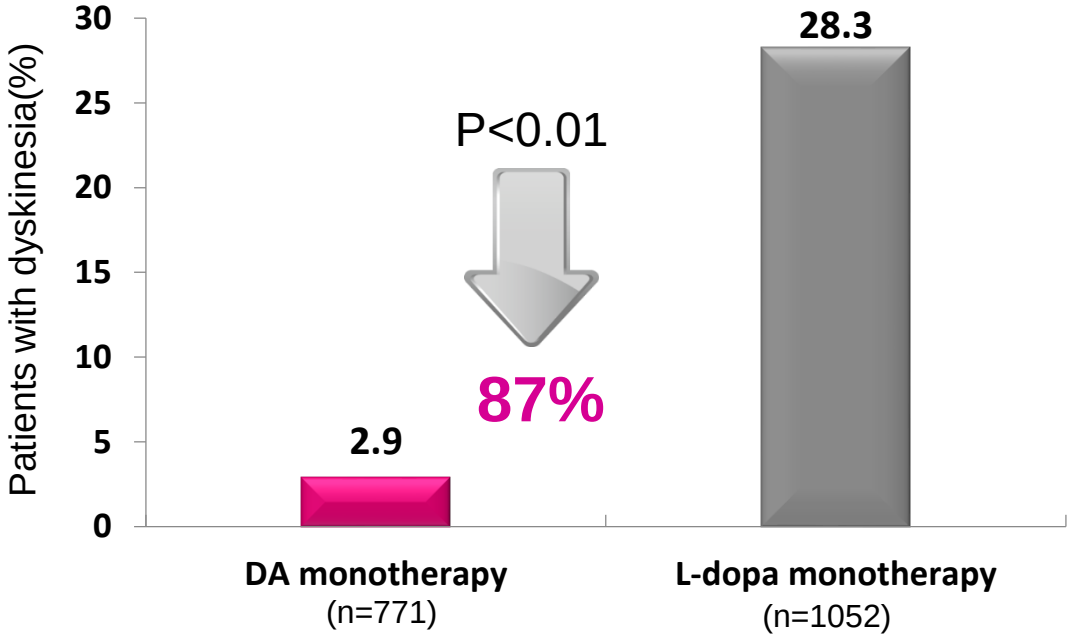
Poewe W, et al. Clin Interv Aging. 2010;5:229-38

使用DA治療顯著降低異動症的風險

Long-half-life advantage of DAs

Dopamine receptor agonists	$T_{1/2}$
Pramipexole	8-12h
Ropinirole	3-6h
Piribedil	2-5h
Levodopa	1-1.5h

Meta-analysis: Lower risk of dyskinesia in DA-treated patients[2]

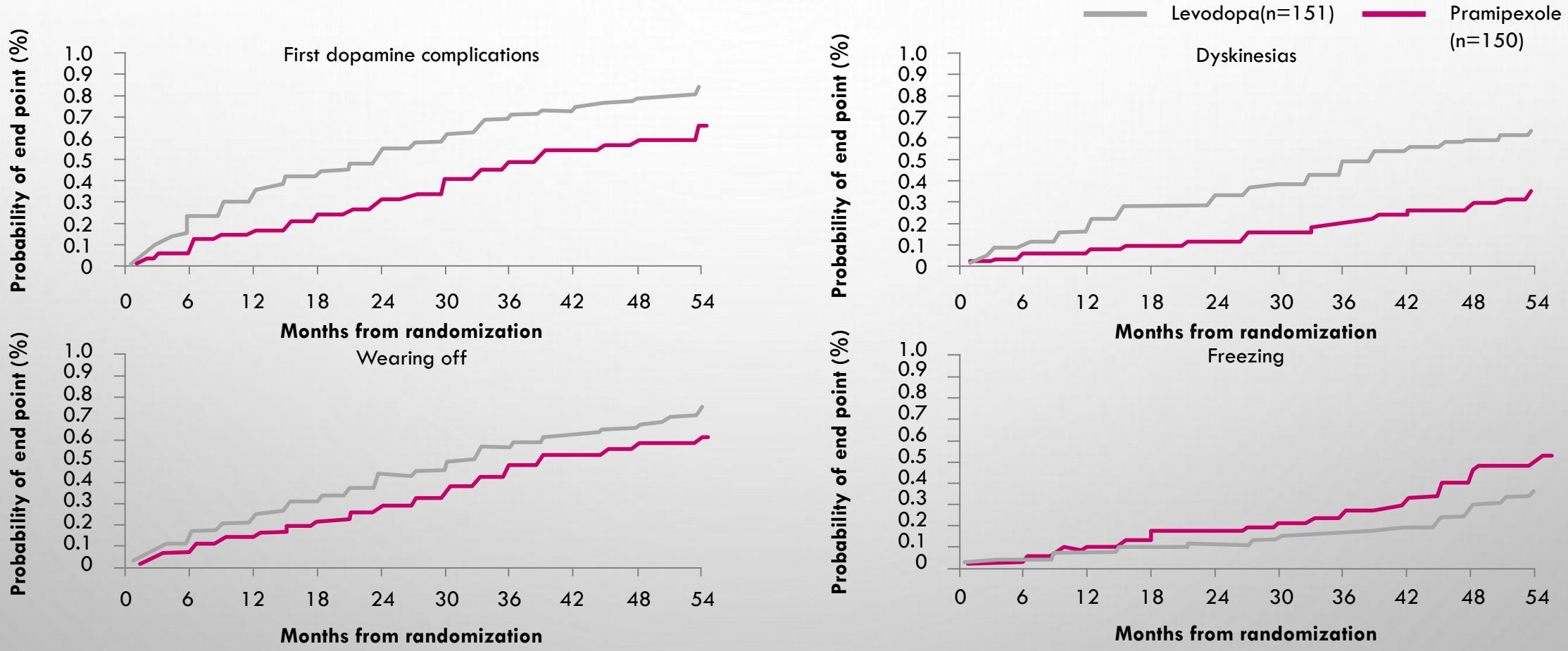


- Ten RCTs were included in the meta-analysis, involving 2223 early PD patients in total, Studies that allowed the open-label administration of levodopa in the DA arm during the trial were included only if the number or the percentage of patients who developed dyskinesia before the administration of levodopa was provided. The study shows a striking number of 87% lower odds for dyskinesia in the DA-treated versus the levodopa-treated patients.

1. Foley P, et al. J Neural Transm (Vienna). 2004 Oct;111(10-11):1375-446.
2. Chondrogiorgi M, et al. Eur J Neurol. 2014 Mar;21(3):433-40.

Mirapex® 能降低運動性併發症的風險

CALM-PD: Cumulative probability of reaching the first dopaminergic complication, the individual complications wearing off, dyskinesias and freezing treatment assignment



Holloway RG, et al. Arch Neurol. 2004;61(7):1044-1053.

Mirapex®預防運動性併發症的風險的臨床實證

CALM-PD
Study results

Pramipexole vs. Levodopa

2 Years[1]	6 Years[2]
Dopaminergic motor complications	
Significantly less with **pramipexole**	Significantly less with **pramipexole** • 90% of patients had added Levodopa

1. Parkinson Study Group. JAMA. 2000, 284: 1931-1938. 2. Parkinson Study Group CALM Cohort Investigators. Arch Neurol. 2009;66(5):563-70.

Mirapex®預防異動症的風險的臨床實證

- TREATMENT WITH PPX HAS OVERALL BEEN ASSOCIATED WITH (V.S. PLACEBO)
  - SIGNIFICANTLY BETTER IMPROVEMENT IN MOTOR FUNCTION
  - IMPROVED DAILY FUNCTION
- INCIDENCE OF DYSKINESIA
  - PPX V.S. PLACEBO: GENERALLY MORE PREVALENT
  - PPX V.S. OTHER DAS: COMPARABLE
  - PPX V.S. LEVODOPA: SIGNIFICANTLY LOWER
- MECHANISM: POTENTIAL INVOLVEMENT OF NON-PPX-RELATED FACTORS IN THE DEVELOPMENT OF DYSKINESIA

Hindawi Publishing Corporation
Parkinson's Disease, Volume 2012, Article ID 473769, 8 pagesdoi:10.1155/2012/473769

及早使用 Mirapex® 可有效改善PD的早期症狀並降低運動困難的風險發生

約有 40% 接受 LEVODOPA 的 PD 病人，隨著病程進展與藥效漸退 (WEARING OFF)逐漸增加 LEVODOPA 的使用劑量與頻次，在治療4-6 年後會出現運動困難 (DYSKINESIA)，進而影響生活品質

Armstrong MJ, Okun MS.JAMA.2020 Feb 11;323(6):548-560.

Mirapex®可預防或延緩運動併發症

可預防/延緩藥效波動（F）或運動困難（D）之藥物

藥物類別	藥物	療效		安全性	臨床意義	
		F	D		F	D
多巴胺促效劑	Pramipexole IR	有			臨床上有用	
非麥角類 (Nonergot)	Ropinirole IR	證據不足	有		具研究意義	臨床上有用
麥角類 (ergot)	Cabergoline	有		專業監控下，具有可接受的風險	臨床上有用	
	Bromocriptine	證據不足	可能有效		具研究意義	臨床上可能有用
	Pergolide	證據不足	可能有效		具研究意義	臨床上可能有用
COMT 抑制劑	Entacapone	無			無臨床意義	
MAO-B 抑制劑	Selegiline	證據不足	無		具研究意義	無臨床意義

1. Fox SH, et al. Mov Disord. 2018 Aug;33(8):1248-1266.

多巴胺促效劑 (DOPAMINE AGONIST，DA) 如何造成連續多巴胺刺激

Longer plasma half-life[1]

DA agonists have longer plasma half-life than levodopa; therefore, they are expected to have a favorable effect on motor complication.

Steady stimulation of dopamine receptors[2]

Rapidly cross the blood-brain barrier and ensure steady stimulation of dopamine receptors, preventing the occurrence of postsynaptic modifications leading to the onset of dyskinesia.

Smaller fluctuation[3]

The peak and valley fluctuation with DA agonists are smaller than levodopa and they can provide relatively constant receptor stimulation, which is consistent with the CDS theory.

CDS, continuous dopaminergic stimulation; DA, dopamine agonist.

1. Kondo T. J Neurol. 2002; 249 (Suppl. 2): II/25–II/29. 2. Jenner P. Neurology. 2004;62(Suppl. 1):S47-55. 3. Jenner P, et al. Clinical therapeutics.2009;31(11):2698-2711.

Mirapex®用於治療晚期巴金森病與動作障礙的隨機對照研究

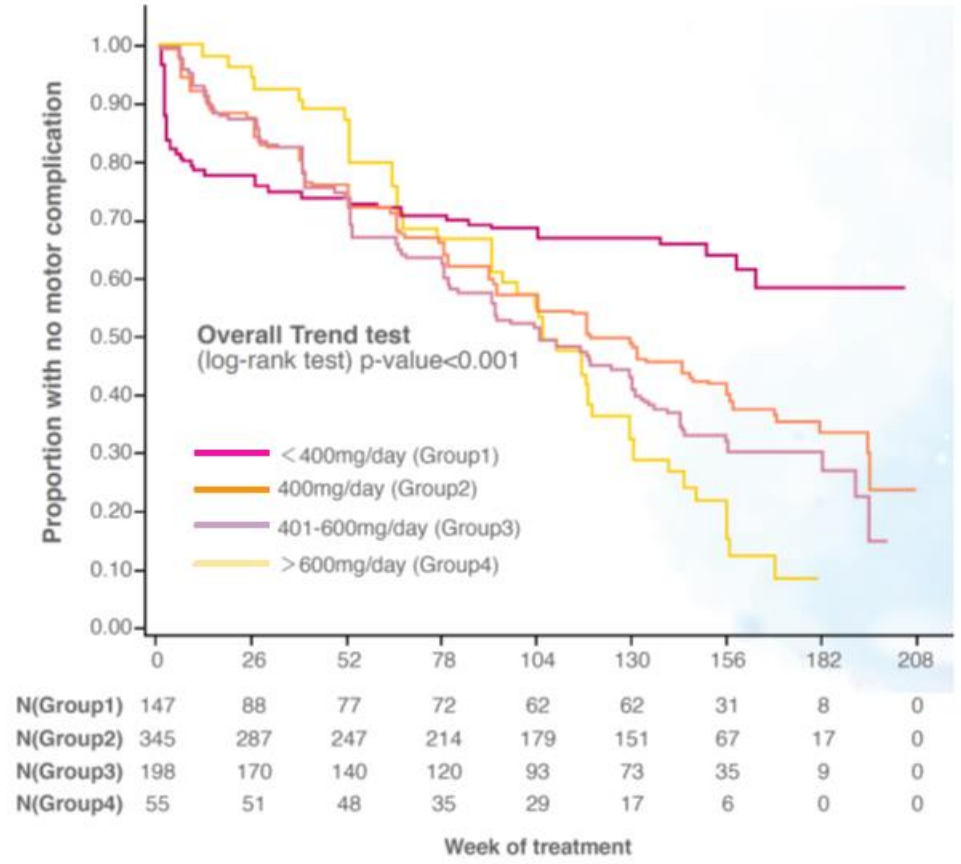
Pramipexole trials in advanced Parkinson's disease

Study, year	Study design	Treatment arms	Primary endpoint	Primary endpoint findings
Wermuth. 1998	Randomized, double-blind, placebo controlled, multicentre, 11-week study (n=69)	Pramipexole up to 5.0 mg/day Placebo	Total UPDRS score	At the end of the maintenance period, the total UPDRS score was significantly improved in pramipexole group as compared with placebo (p=0.0184)
Lieberman, et al. 1997	Randomized, double-blind, placebo-controlled, multicentre, 31-week study (n = 360)	Pramipexole doses of 0.35-4.5 mg/day Placebo	UPDRS II mean 'ON' and 'OFF' periods and UPDRS III score mean 'ON' periods	At 31 weeks, UPDRS II ($p < 0.0001$) and III (p=0.01) scores were significantly lower in the pramipexole group vs. placebo
Pinter, et al. 1999	Randomized, double-blind, placebo-controlled, multicentre, 11-week study (n= 78)	Pramipexole up to 5.0 mg/day Placebo	Total UPDRS score	At the end of the maintenance period, the total UPDRS score was significantly improved in pramipexole group vs. placebo (p=0.0002)
Guttman. 1997	Randomized, double-blind, placebo-controlled, multicentre, 9-month study (n= 247)	Pramipexole up to 4.5 mg/day Bromocriptine up to 30 mg/day Placebo	UPDRS II and III score	At the end of the maintenance period, the UPDRS II (p=0.0002) and III (p=0.0006) scores were significantly improved in the pramipexole group vs. placebo
Mizuno, et al. 2003	Randomized, double-blind, placebo-controlled, multicentre, Japanese 12-week study (n=313)	Pramipexole up to 4.5 mg/day Bromocriptine up to 22.5 mg/day Placebo	UPDRS II mean 'ON' and 'OFF' periods and UPDRS III score mean 'ON' periods	At the end of the maintenance period, the UPDRS II and III scores were significantly improved in the pramipexole and bromocriptine groups vs. placebo (p<0.001)

PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale.

Antonini A, et al. CNS Drugs 2010;24(10):829-41.

已經以L-DOPA治療的病人加入MIRAPEX的時機? 如何加?



- 根據 STRIDE-PD post hoc analysis 結果顯示，Levodopa < 400mg/day 可以降低 motor fluctuation 的發生，而且發生 dyskinesia和wearing-off 的風險比使用 400 mg 以上的組別有顯著地降低。所以如果先使用 Levodopa 的病患，在 Levodopa 劑量接近 400 mg/day時就可以考慮加上 Mirapex。

- 如果每天已經使用超過 400 mg 的 Levodopa，劑量可依照 1:100 等劑量當量換算，適量地把 Levodopa 換成 Mirapex，減少motor-fluctuation 的發生。

1. Warren O, C, Kieburtz, K, Rascol, O, et al. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov. Disord., 2013; 28(8), 1064-1071.
2. Sebastian S, Brit M,et al 2 Levodopa Equivalent Dose Conversion Factors: An Updated Proposal Including Opicapone and Safinamide, Mov Disord Clin Pract. 2020 Mar 16;7(3):343-345.

已經使用L-dopa的病人加入Mirapex® ，可協助控制動作症狀

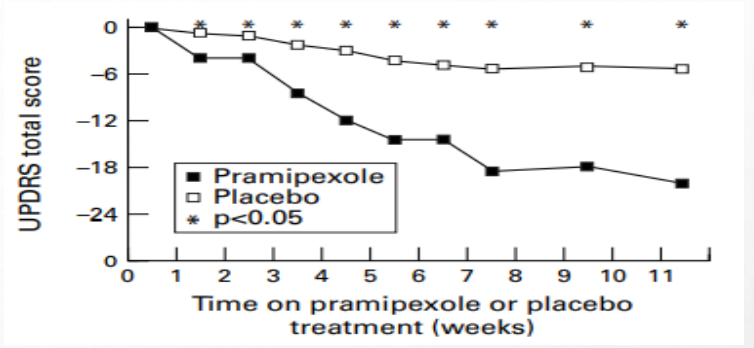
多中心、雙盲、安慰劑對照、前瞻性隨機試驗
(78位Advanced PD病人, 11周)

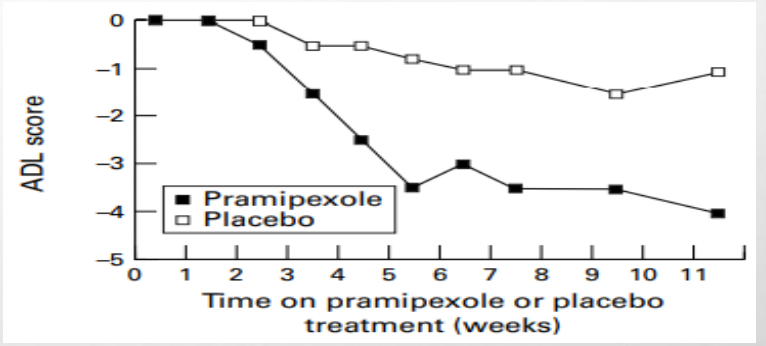
UPDR總分及各項量表變化

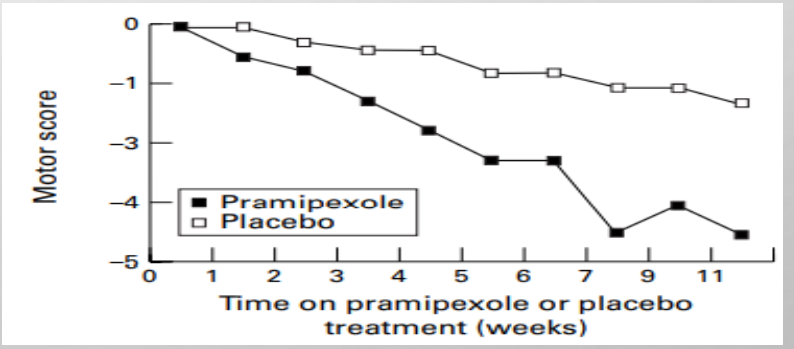
UPDRS total score, UPDRS II, III, IV
(p<0.01)

平 均 Pramipexole 劑 量
3.59±1.79 mg/day

	Pramipexole (n=33)			Placebo (n=44)			
	Mean change (SD)	Mean % change	Median change	Mean change (SD)	Mean % change	Median change	p Value
UPDRS total score	20.1 (16.0)	37.3	20.0	5.9 (12.8)	13.1	5.25	0.0002
UPDRS part I	0.7 (1.6)	27.0	0.0	−0.1 (1.0)	−1.0	0.0	0.128*
UPDRS part II	4.4 (4.7)	32.2	4.0	1.1 (3.4)	7.5	1.0	0.0034
UPDRS part III	13.2 (11.0)	39.4	14.0	4.5 (9.5)	15.3	5.0	0.0008
UPDRS part IV	1.8 (2.6)	23.2	1.0	0.4 (2.1)	1.2	0.0	0.0092







UPDRS: Unified Parkinson Disease Rating Scale (分數越高，症狀越嚴重)
ADL: Activities of daily living
平均Levodopa劑量537.5±314.4 mg/day

Pinter MM et al. *J Neurol Neurosurg Psychiatry.* 1999 Apr;66(4):436-41

PC-TW-105615-04-Sep-2023

已經使用L-dopa的病人加入Mirapex® ，可協助控制動作症狀並減少運動性併發症與L-dopa用量

多中心、雙盲、安慰劑對照、隨機分派試驗
(354位已接受Levodopa治療之病人，31周)

使用pramipexole的病患UPDRS各項量表 (p<0.05)

UPDRS II (average of on and off),
UPDRS III (on state)

平均Levodopa劑量減少103 mg
(p=0.001)

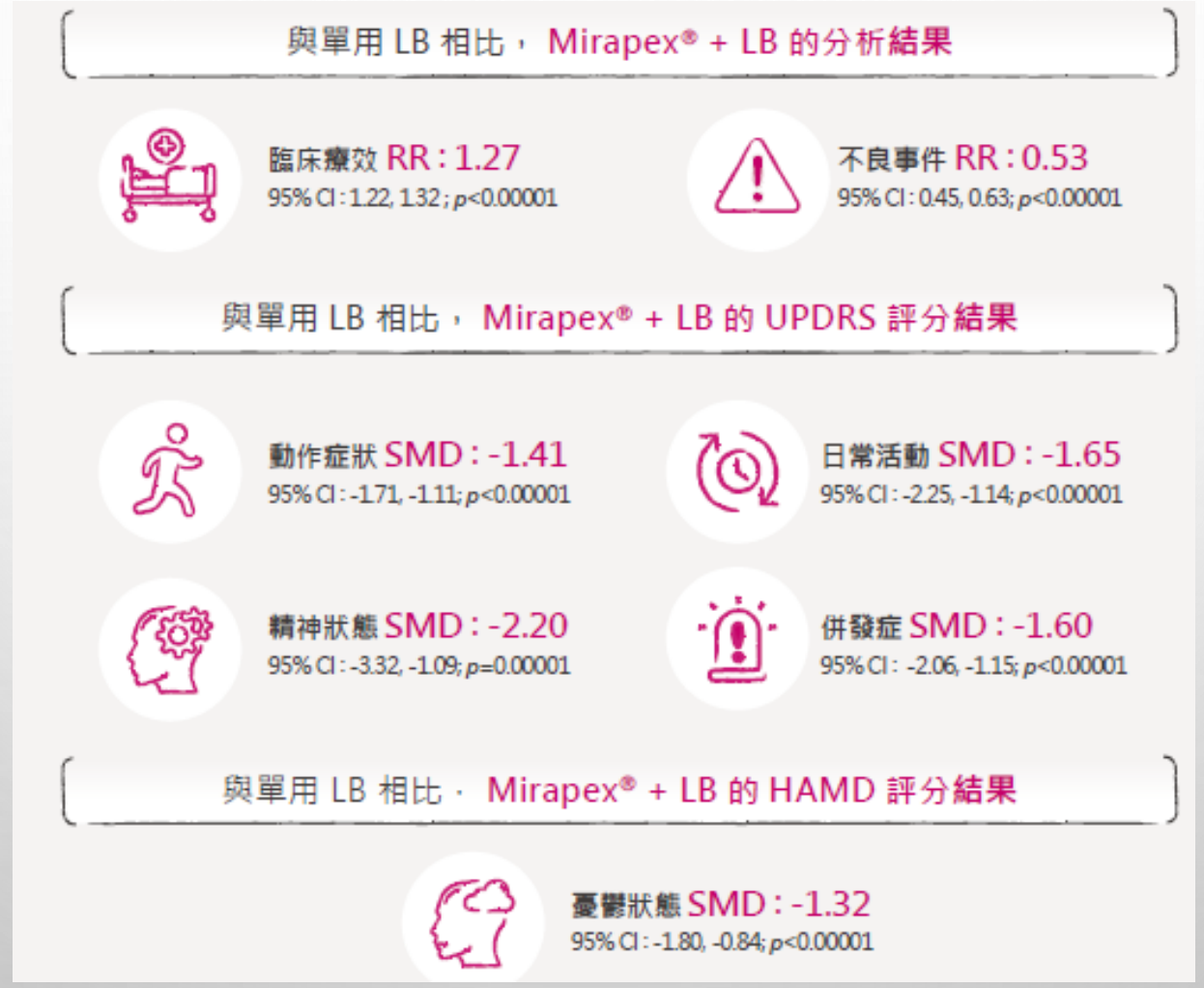
平均Pramipexole劑量3.7 mg/day

	Pramipexole	Placebo	*P*
Primary endpoints			
UPDRS Part II (average of *on* and *off*)[a]	−4.3 (4.6)	−1.80 (4.2)	0.0001
UPDRS Part III *on*[a]	−10.3 (12.0)	−4.43 (11.1)	0.0001
Secondary endpoints*			
UPDRS II AUC (average of on and *off*), change[a]	−88.9 (85.3)	−39.5 (80.4)	0.0001
UPDRS III AUC (during *on*), change[a]	−209.7 (223.6)	−98.6 (218.3)	0.0001
UPDRS IV, i.e. motor complications, change[a]	−1.1 (2.3)	−0.5 (2.2)	0.0114
UPDRS total score, change[a]	−16.4 (16.5)	−7.0 (15.3)	0.0001
UPDRS II during on, change[a]	−2.5 (4.1)	−1.2 (3.8)	0.0007
Average change of *off* time during waking hours (Percentage)[a]	−16.2 (21.6)	−1.0 (25.9)	0.0001
Timed-walking test (sec), Final[a]	26.1 (38.9)	32.8 (50.2)	0.0334
UPDRS I[b]			0.020
Missing	0 (0.0)	0 (0.0)	
Increase	22 (12.6)	43 (23.9)	
No change	74 (42.5)	69 (38.3)	
Decrease	78 (44.8)	68 (37.8)	
Daily levodopa dose[b]			0.001
Increase	5 (2.9)	8 (4.4)	
No change	101 (58.0)	149 (82.8)	
Decrease	68 (39.1)	23 (12.8)	

[a]Values are expressed as mean (SD).
初始平均Levodopa劑量637.7 mg/day

Möller JC et al. Mov Disord. 2005 May;20(5):602-10

Mirapex® 與 LB (levodopa/benserazide) 合併治療的療效與安全性優於單獨使用 LB (levodopa/benserazide)



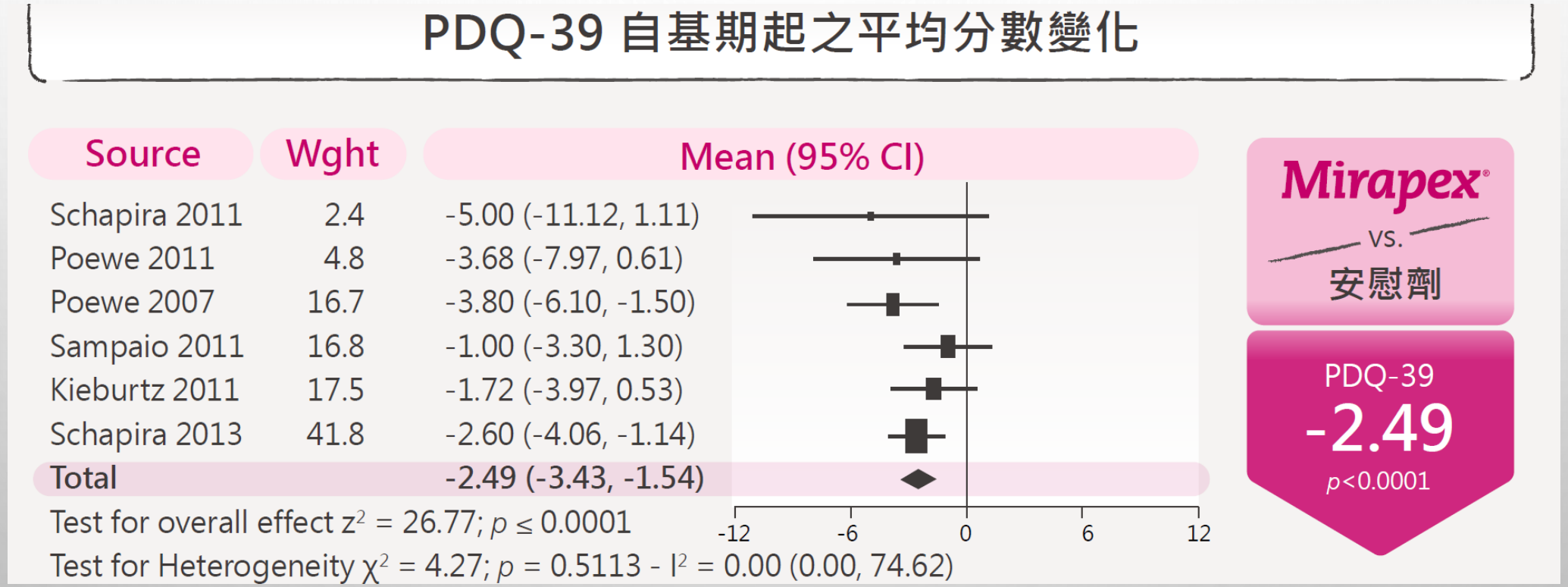
CI, confidence interval; HAMD, Hamilton depression rating scale; PD, Parkinson's disease; RR, risk ratio; SMD, standardized mean difference; UPDRS, The Unified Parkinson's Disease Rating Scale

Jiang DQ, et al. Naunyn Schmiedebergs Arch Pharmacol. 2021;394(9):1893-1905.

Mirapex® 可有效改善早期及晚期 PD 病人的生活品質

收錄 6 項試驗的統合分析，
以 PDQ-39 評估 PD 病人的生活品質
至少 2,000 位早期及晚期 PD 病人

PDQ-39 自基期起之平均分數變化

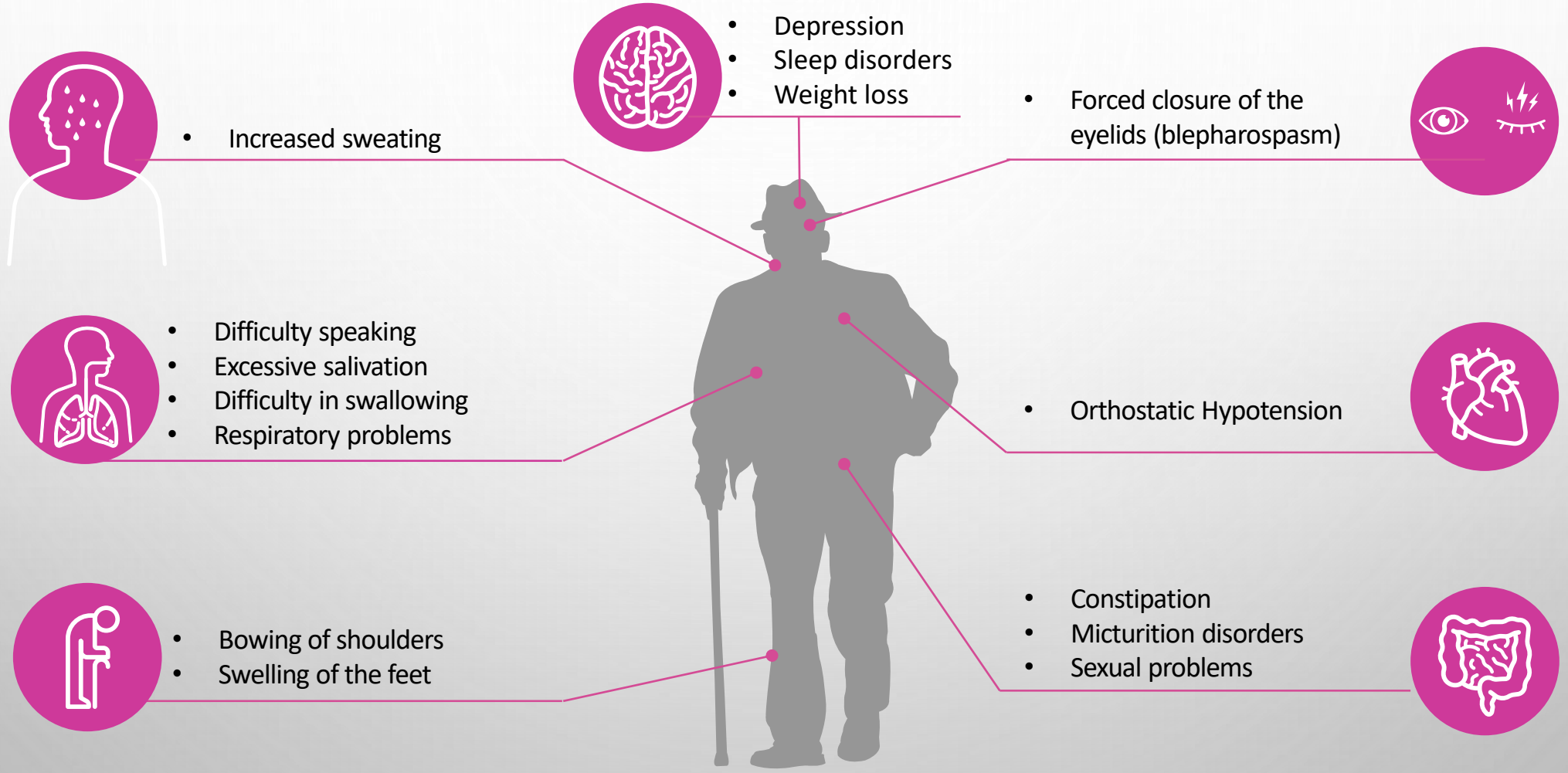


CI, confidence interval; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire; QoL, quality of life

Tao Li, et al. BMC Neurol. 2022 Aug 25;22(1):320.

PC-TW-105615-04-Sep-2023

非運動 (NON-MOTOR) 症狀在巴金森病人也十分常見

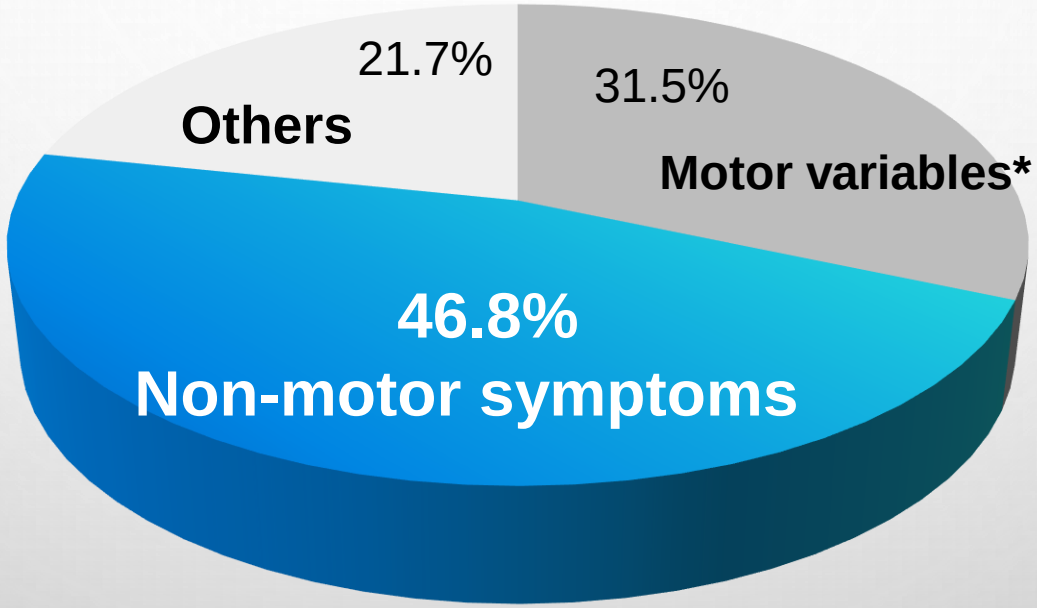


Chaudhuri KR, Schapira AH. Lancet Neurol 2009;8(5):464-74.

PC-TW-105615-04-Sep-2023

非運動症狀對PD病人的生活品質的影響更甚於運動症狀

Short-form Health Survey (SF-36) Physical Summary Scores[1]



Motor variables*：Including motor symptoms and motor complications

Müller B, et al. Parkinsonism Relat Disord. 2013 Nov;19(11):1027-32.

PC-TW-105615-04-Sep-2023

運動性併發症會明顯的增加非運動症狀並影響病人的生活品質

The study used clinical examination of 10 NMS quantified using a visual analogue scale (VAS) in motor-defined on (NMS_{on}) and off state (NMS_{off}) combined with motor assessments and self-ratings at home in 100 patients with advanced PD.

On state **Off state**

NMS fluctuated in conjunction to motor fluctuations with more frequent and severe symptoms.

Fluctuations between on and off states of NMS

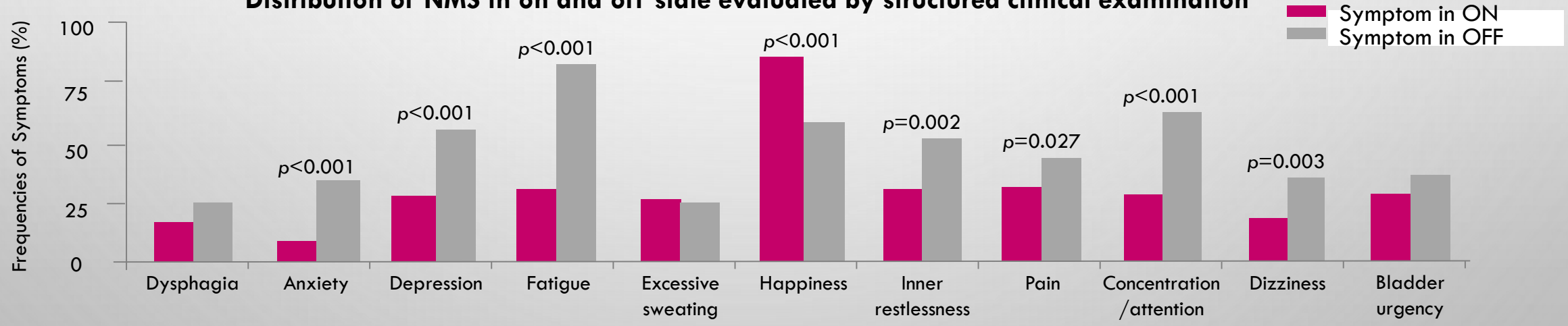
HRQOL

Depression p=0.009

Anxiety p=0.049

Pain p=0.049

Distribution of NMS in on and off state evaluated by structured clinical examination



HRQOL, health-related quality of life; NMS, nonmotor symptoms; PD, Parkinson's disease; VAS, visual analogue scale.

Storch A, et al. Neurology. 2013 Feb 26;80(9):800-9.

巴金森病人的憂鬱症狀

- **50%** PD PATIENTS EXPERIENCE SOME FORM OF DEPRESSION
- **40%** EXPERIENCE ANXIETY DISORDER
- DECREASED ENDOGENOUS PRODUCTION OF SEROTONIN, NORADRENALINE AND DOPAMINE.
- DEPRESSION IN PD RESULTS IN
  - INCREASED SEVERITY OF DISABILITY
  - DECREASED QUALITY OF LIFE

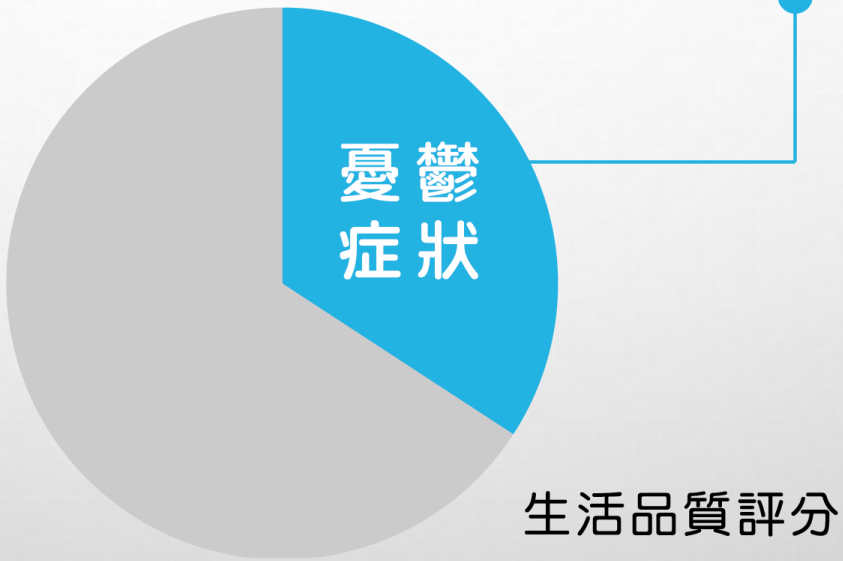
Müller B, et al. Parkinsonism Relat Disord. 2013 Nov;19(11):1027-32.

憂鬱症是影響PD病人的生活品質最重要的非運動症狀

80.7% 的PD患者問卷自評#存在憂鬱症狀[1]

憂鬱症狀對生活品質評分*的影響[2]占**34.2%**

比重最高



#NMSQuest：評估PD患者非運動症狀的患者自評問卷，共包含30項非運動症狀

- ***SF-36量表：**是國際普遍認可的生活品質評估工具，包含生理功能(PF)、生理職能(RP)、軀體疼痛(BP)、總體健康(GH)、活力(VT)、社會功能(SF)、角色限制-情感(RE)、精神健康(MH)等8個方面，共36個問題

1.Cosentino C,et al.Arq Neuropsiquiatr. 2013;71(4):216-9.
2.Qin Z, et al. Clin Neurol Neurosurg. 2009 Nov;111(9):733-7.

PC-TW-105615-04-Sep-2023

巴金森病病人因其他病症就醫件數，以憂鬱症為最多

110年因巴金森氏症就醫者前10年（100年-109年）
囚憂鬱、便祕、睡眠障礙及非動作症狀等就醫件數

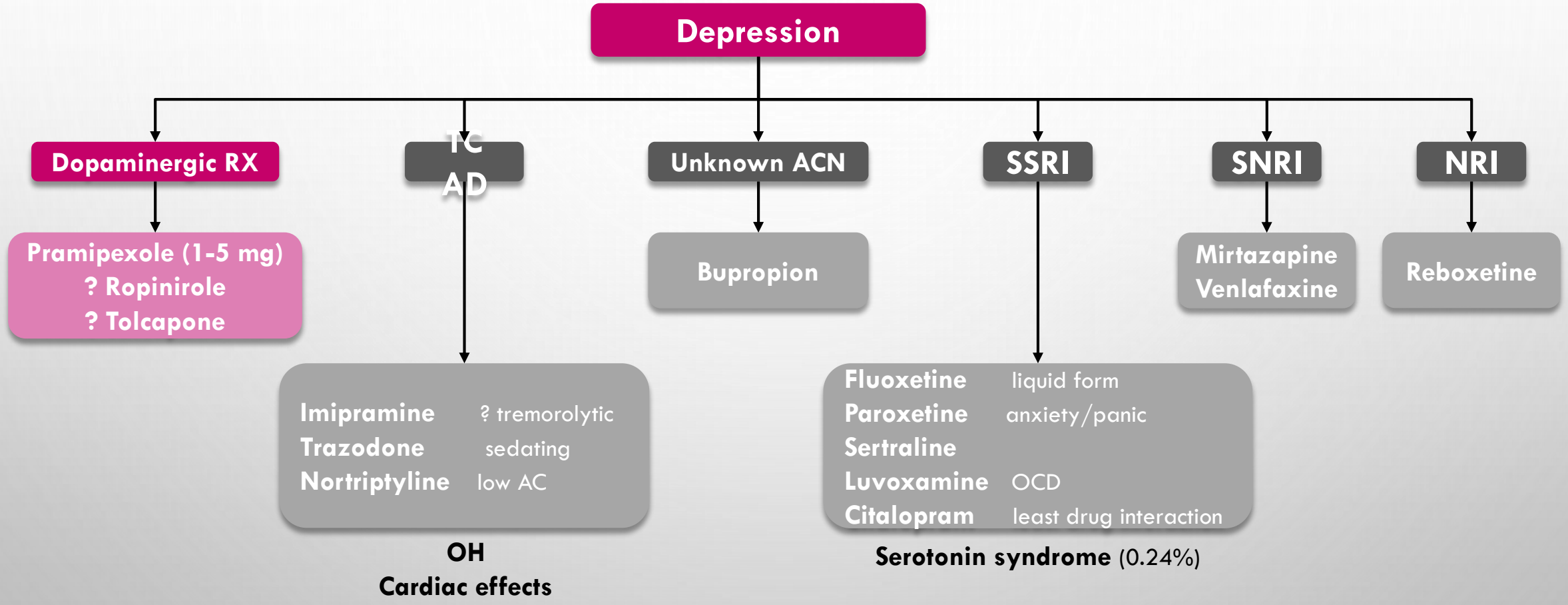
單位：件

年度	憂鬱症	便秘	睡眠障礙 睡眠障礙	快速動眼 系統異常	自律神經	夜尿
100	30,565	13,837	22.175	5.461	1,583	420
101	33.273	15,966	23.042	5.950	1.825	496
102	35,631	16,801	22,880	6,108	2,156	621
103	36,770	17,680	23,232	6,099	2,276	664
104	38,875	19,165	21,115	3,385	2,482	874
105	39.817	21,957	24,642	101	892	1,185
106	39.920	22,878	24,880	175	906	1,383
107	39.986	22.700	25.669	303	1.123	1,673
108	39 694	24.695	25,530	319	1,227	1,666
109	38,711	24.869	23.918	308	1.534	1,753
合計	373,242	200,548	237,083	28,209	16,004	10,735

資料來源健保署
•本項巴金森氏症採主診斷1CD-10-0v前三碼為：G20.G21:ICD-9-CM：3320.3321.33392。110年巴金森氏症就醫院所層級人數統計
•憂鬱主診新為ICD-10-CN前三碼：F32、F33、F34:ICD-9-0M：296.2、296.3、296.82、296.99、298、300.4、301.10、30.12、301.13、311。
•便秘主診斲為1O-10-0前三碼：K59：100-9-CM：564.0。醫學中心27,382
•睡眠障儗主診斷為ICD-10-CM：647.0、647.01、647.09、647.20、647.50~-647.54~G47.5g、G47.61、647.69、
區域醫院29,216C47.8、G47.9:ICD-0-0M：780.50、780.52、780.55、780.56、 791.59。地區醫院17.267
•快速動眼睡眠障凝主診斷為ICD-10-04：647.52：IC-9-C4:780.59。
•自主神經系統墨常主診新為ICD-10-0前前三碼：690：ICD-9-CN前三碼：333、337、742.8。墓層院所39.707
•夜尿主診新為ICD-10-C4:R35.1、N39.44：I0D-9-CM：788.35、788.43。合計77,428
•母群體為110年因巴金森氏症就醫者共77.428人

2022/03/27聯合報元氣周報, 巴金森病健保大數據

DOPAMINE AGONISTS- BETTER CHOICE FOR MANAGEMENT OF PD DEPRESSION

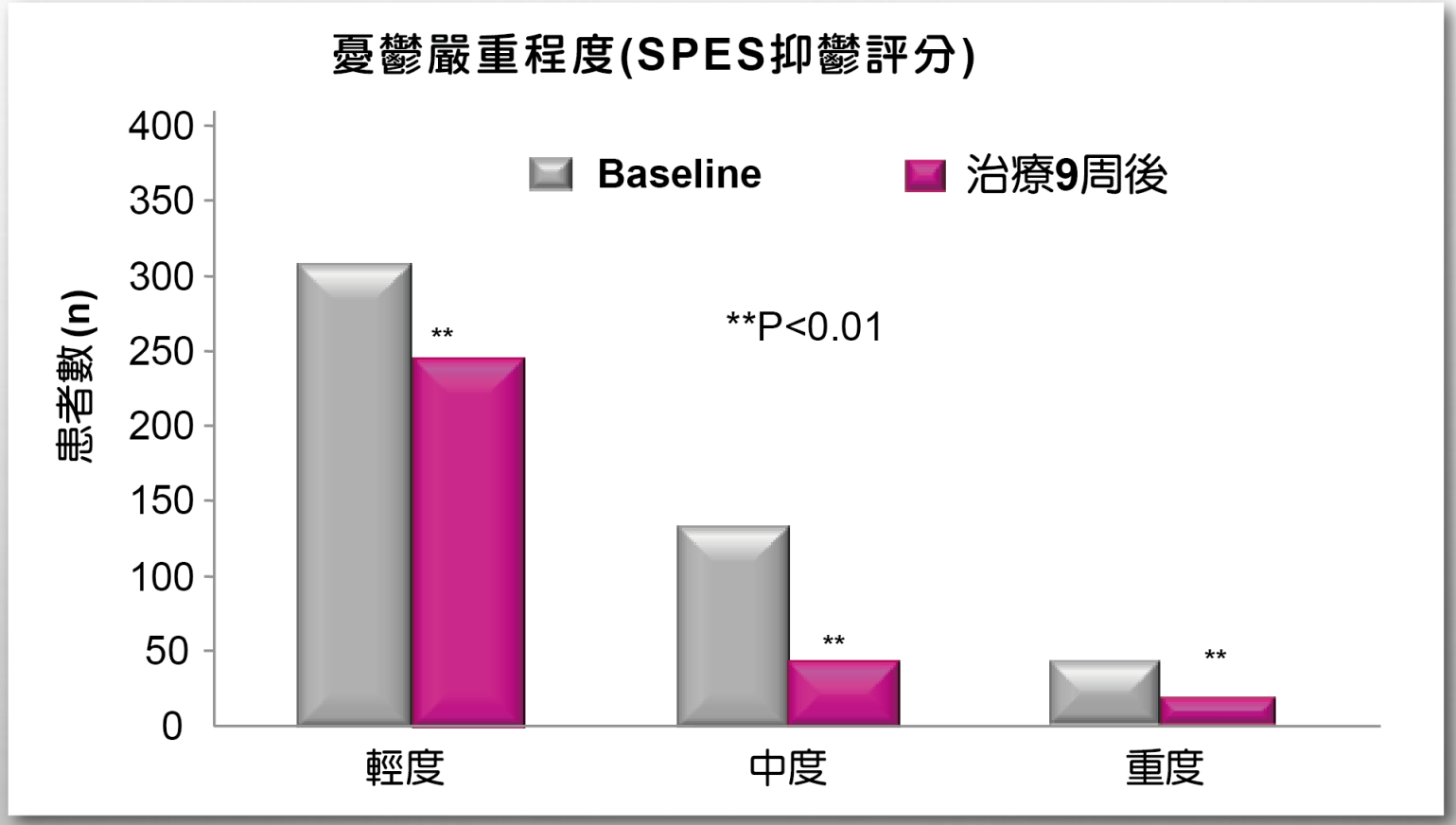


AC, attentional control; NRI, norepinephrine reuptake inhibitor; OCD, obsessive-compulsive disorder; OH, orthostatic hypotension; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors.

Antonini, et al. J Neurology, 2006

Mirapex® 對各階段PD憂鬱均可有效改善

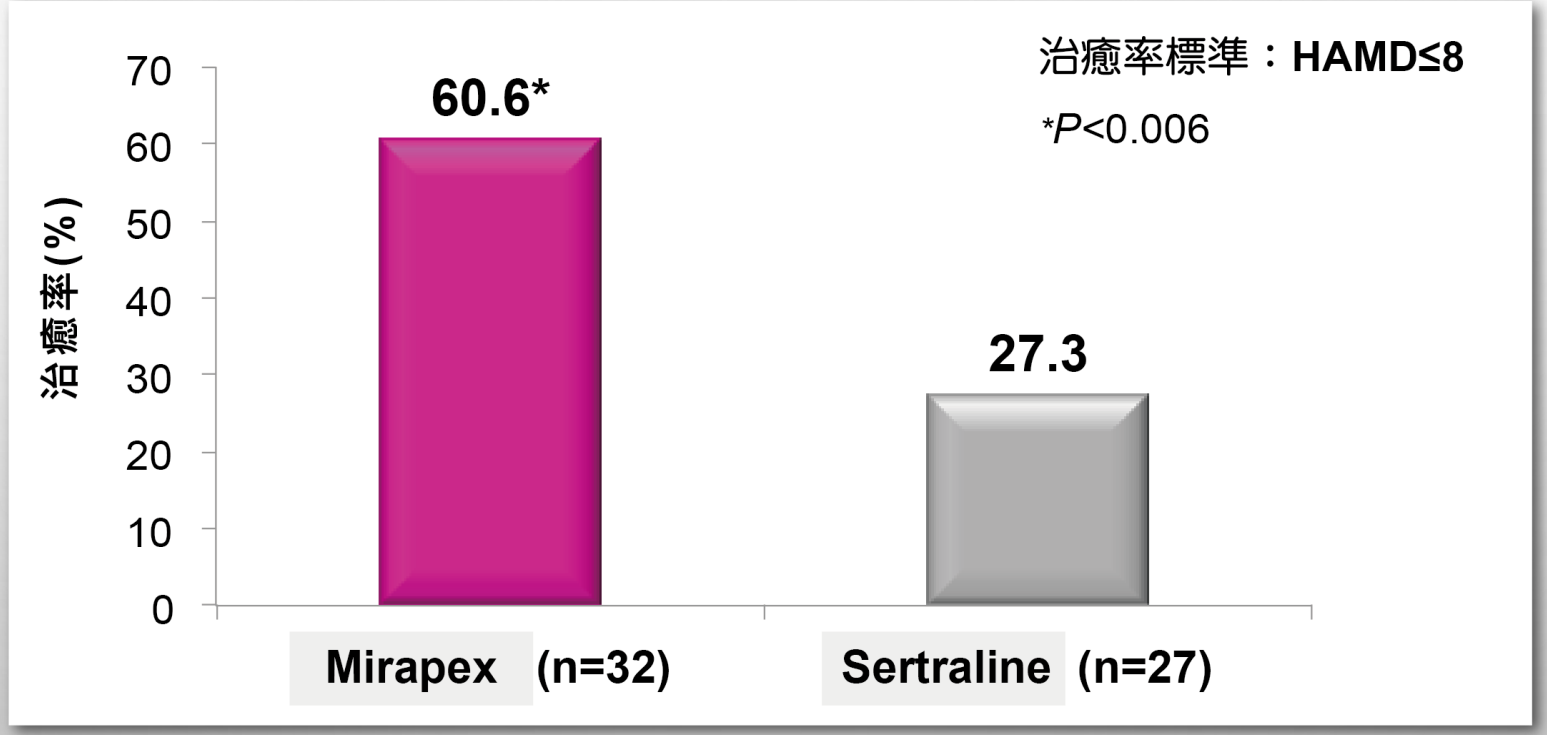
- 一項前瞻性、開放性研究，對PD伴發憂鬱患者(n=657)，給予Mirapex治療，並根據療效和耐受性調整Mirapex劑量，最大劑量4.5mg/天(平均劑量為1.0±0.6mg/d)。治療9周，評估治療前後患者的憂鬱改善情況



Lemke MR, et al. J Neuropsych Clin Neurosci. 2005; 17: 214-220
注：上述研究為上市後支持性臨床研究.

Mirapex® 改善PD患者併發的憂鬱，療效優於SERTRALINE

- 一項隨機、對照研究，為期14周，對PD伴重度憂鬱患者(n=67)分別給予Mirapex (平均劑量3.24mg/d) 和Sertraline (平均劑量48.1mg/d)，比較兩種藥物的憂鬱治癒率

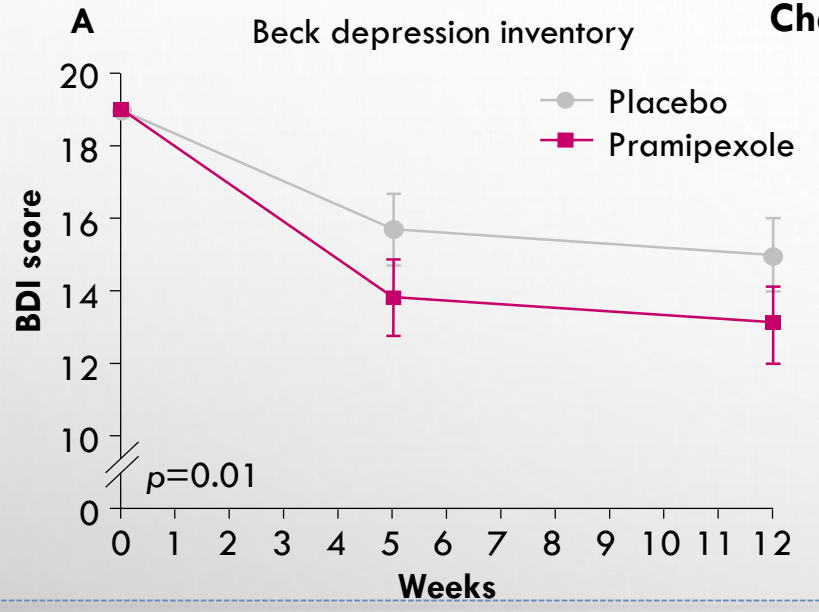


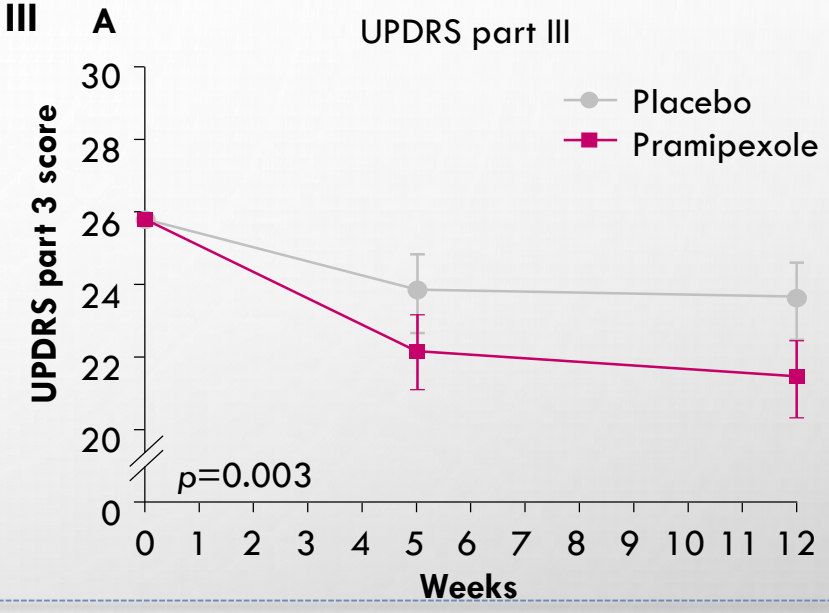
Barone P, et al. J Neurol 2006;253(5):601-7.

Mirapex® 改善PD憂鬱，80%歸因於直接抗憂鬱效應

Pramipexole 同時具有控制動作症狀及憂鬱問題 (平均劑量為2.18 ± 0.83 mg/day)。

Change in BDI and UPDRS part III





BDI, Beck depression inventory; PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale.

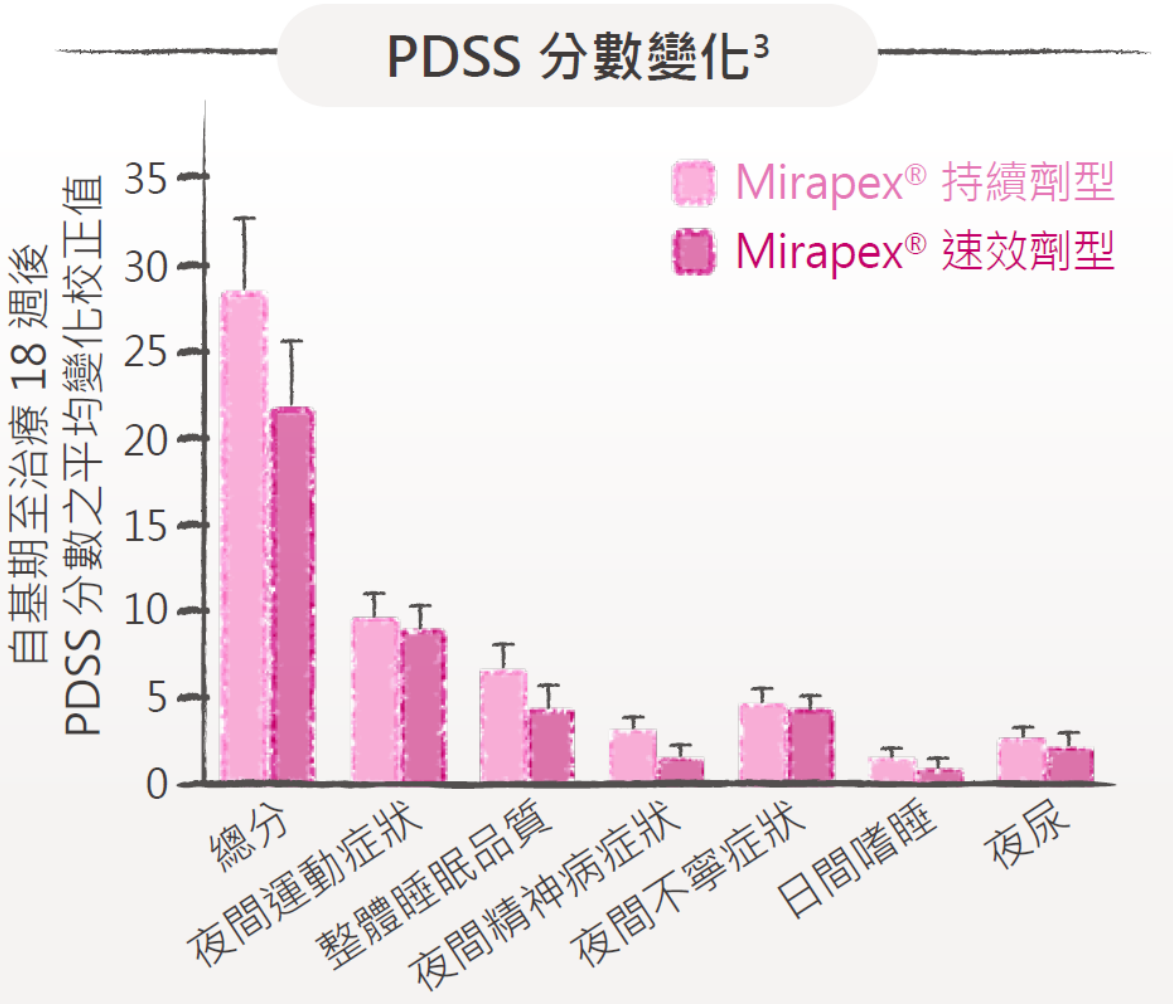
Barone P, et al. Lancet Neurol 2010;9:573-80.

Mirapex®可改善 PD 病人睡眠障礙症狀及整體睡眠品質

- 探索性、回溯性研究[3]
- 以 PDSS* 評估 Mirapex® 改善夜間症狀的效果[3]

橫跨 14 國、嚴重型 PD 病人且患有睡眠障礙
(PDSS 總分 <90) (n=119)[3]

PDSS, Parkinson's Disease Sleep Scale



改善睡眠障礙的各種症狀

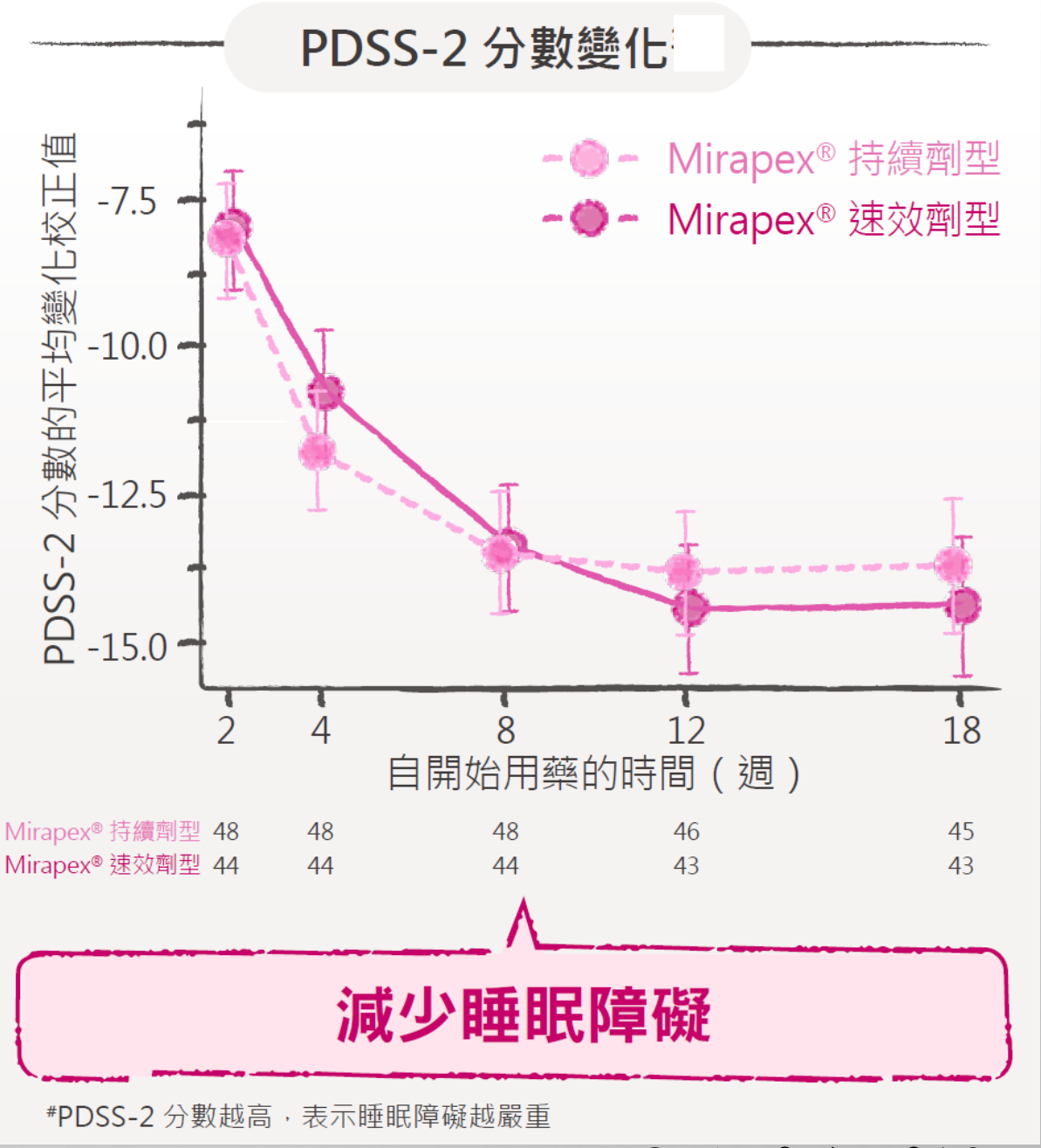
*PDSS 分數越高表示症狀越輕微或越少出現

3. Xiang W, et al. Drug Des Devel Ther. 2018 Jul 4;12:2017-2024.

Mirapex®可改善 PD 病人睡眠障礙症狀及整體睡眠品質

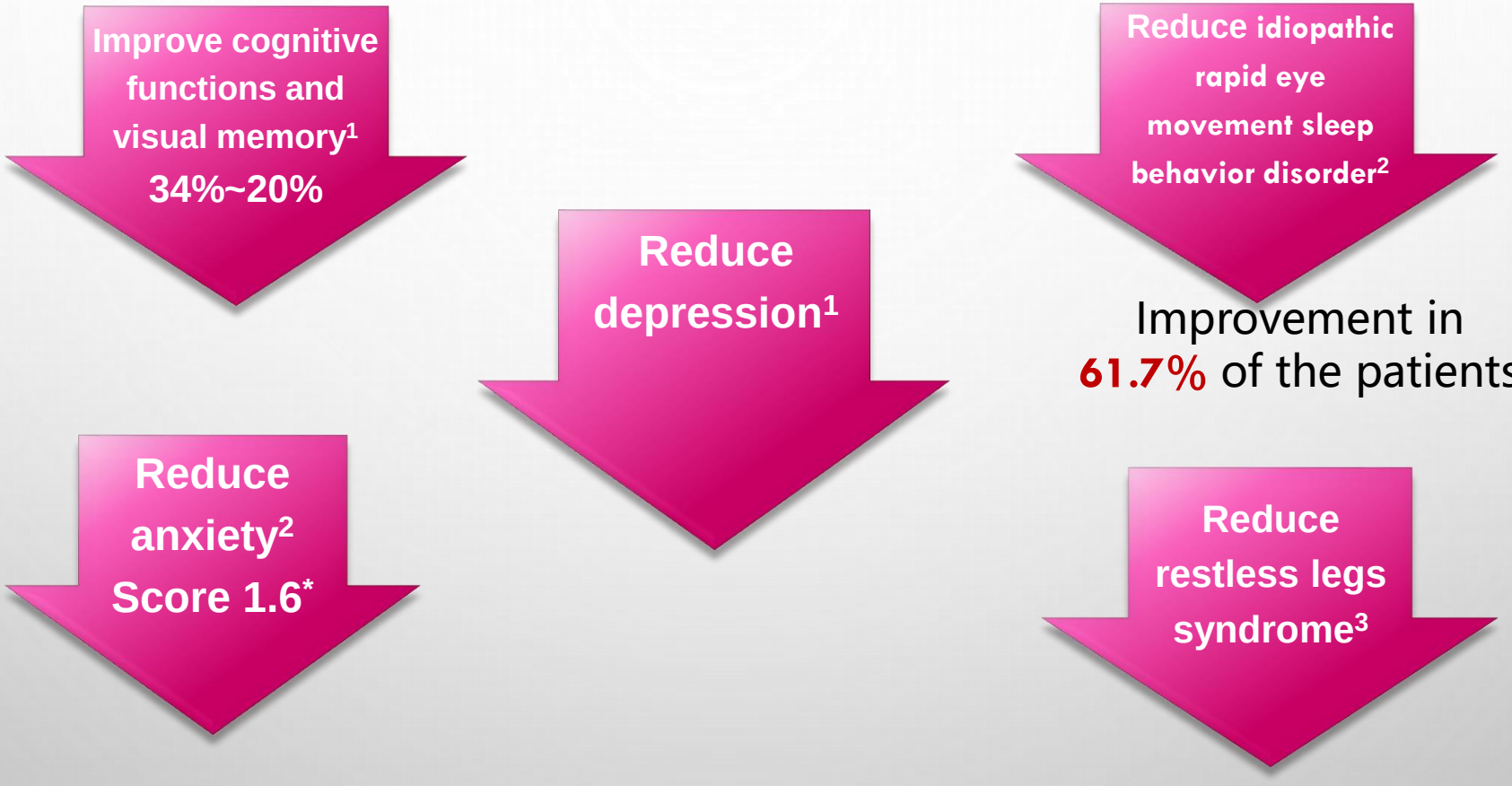
- 多中心、隨機分配、第四期探索性先導研究[2]
- 以 PDSS-2# 評估 Mirapex® 改善夜間症狀的效果[2]

中國、嚴重型 PD 病人且患有睡眠障礙（PDSS-2 總分 ≥18）(n=98)[2]



2. Zhou H, et al. Parkinsons Dis. 2021 Mar 3;2021:8834950.

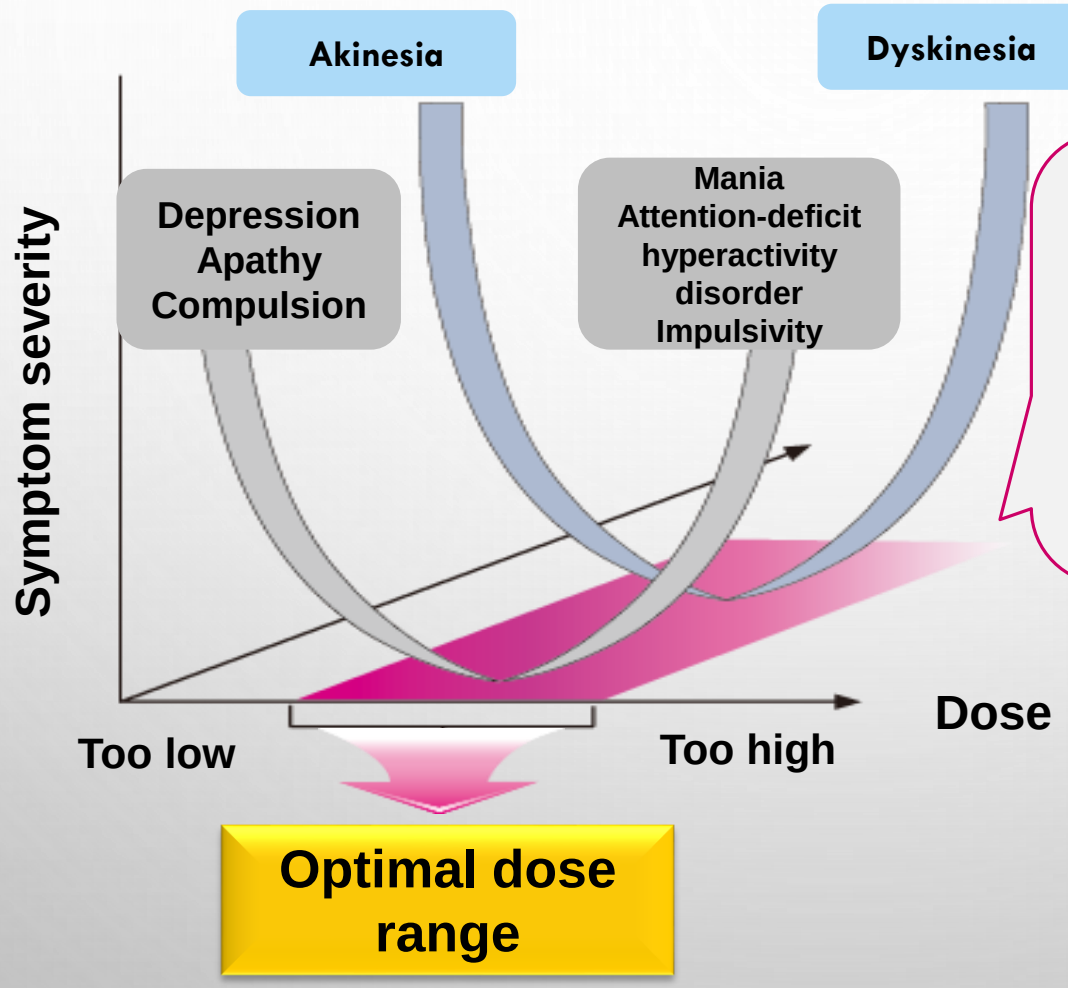
Mirapex® 改善許多非動作症狀



*Hamilton Anxiety Scale (HAMA)

1.Fedorova NV, et al. Neurosci Behav Physiol. 2007 Jul;37(6):539-46
2.Sasai T, et al. Parkinsonism Relat Disord. 2013 Feb;19(2):153-7.
3.Mirapex PI

適切的調整藥物劑量對於PD的治療是很重要的



Dopaminergic stimulation and/or medication are primarily **titrated to achieve optimal motor symptom control**, **leaving the other circuits at risk of overdosing or underdosing.**

Volkmann J, et al. Nat Rev Neurol. 2010; 6(9): 487-98.

Meta-analysis 建議為確保療效與延後Levodopa的使用DA一定要用到最適切的劑量

European Journal of Neurology 2014, 21: 433–440 doi:10.1111/ene.12318

Dopamine agonist monotherapy in Parkinson's disease and potential risk factors for dyskinesia: a meta-analysis of levodopa-controlled trials

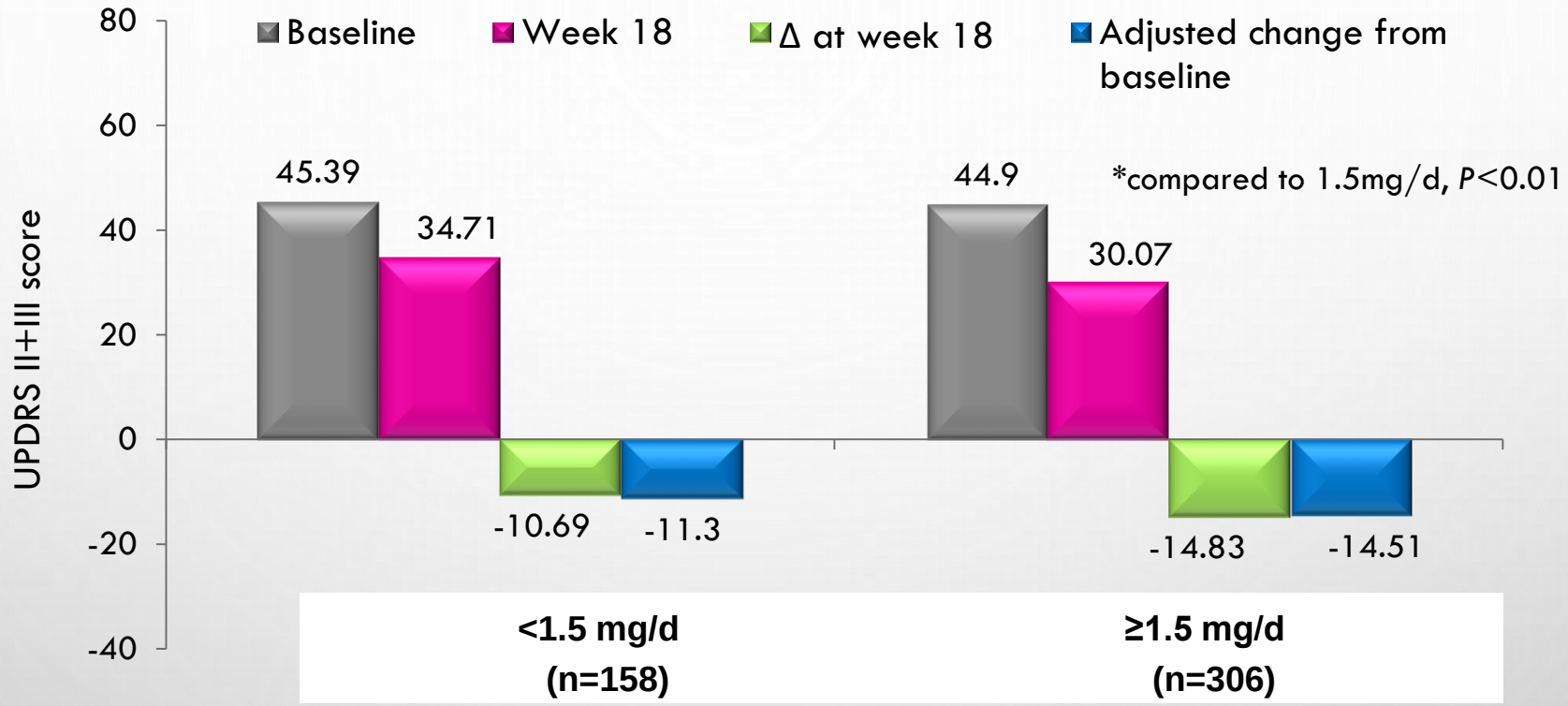
M. Chondrogiorgi[a], A. Tatsioni[b], H. Reichmann[c] and S. Konitsiotis[a]
[a]Department of Neurology, University of Ioannina, Ioannina; [b]Department of Internal Medicine, University of Ioannina, Ioannina, Greece; and [c]Department of Neurology, Medical School, University of Dresden, Dresden, Germany

10 RCTs were included in the meta-analysis, monotherapy with DAs in early PD is suggested at doses that ensure efficacy and delay the need for L-dopa.

in a dose-related manner. As the dose and treatment duration with DAs are factors independent of the risk of dyskinesia, monotherapy with DAs in early PD is suggested at doses that ensure efficacy and delay the need for levodopa, always following an adequate evaluation of the risks DAs can pose in individual patients.

Chondrogiorgi M, et al. Eur J Neurol. 2014 Mar;21(3):433-40

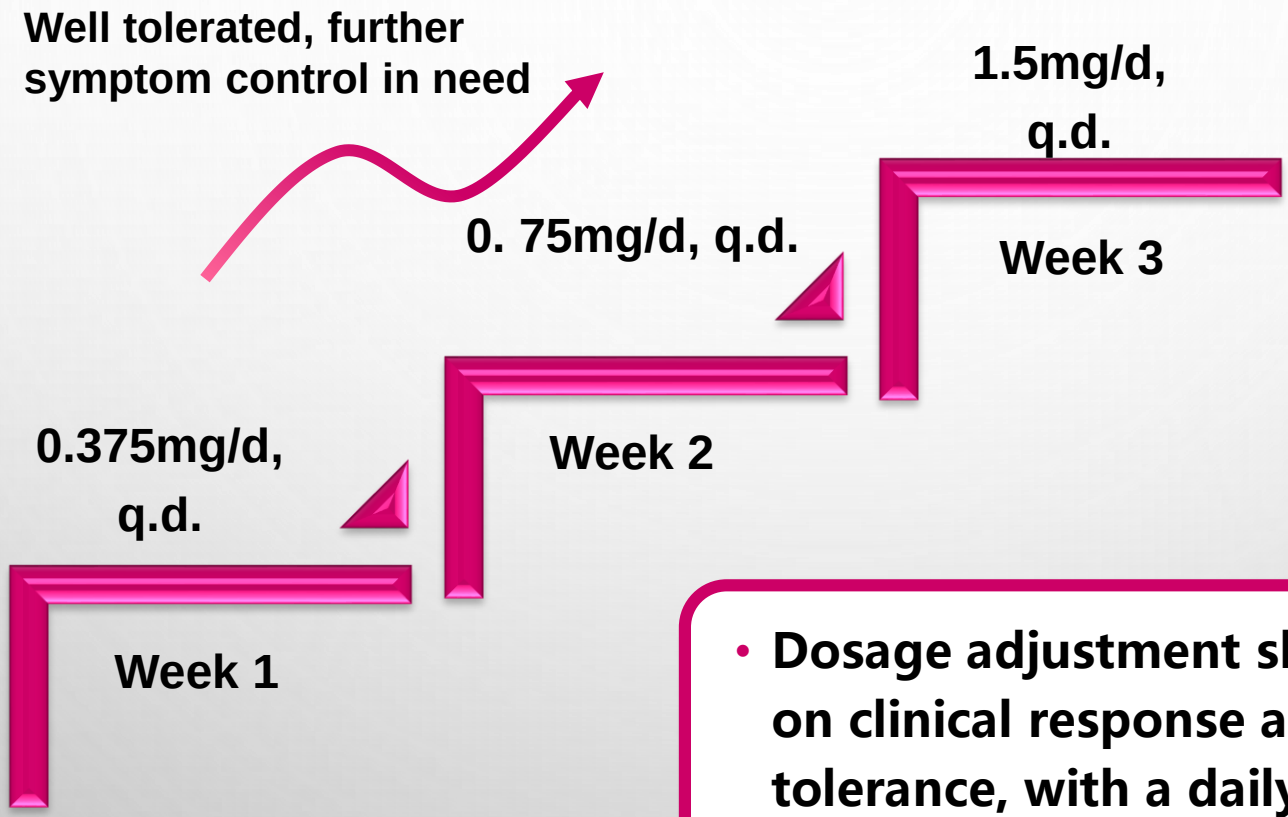
Mirapex® ≥1.5mg/d 有較佳的日常生活功能改善



- After 18 weeks of PPX treatment, PPX at both dose levels can improve motor function and daily activities with comparable AE rates (scores reduced by 11.30 and 14.51 relatively)
- **Patients receiving PPX≥1.5 mg/d showed a greater reduction in UPDRS II+III scores compared with those receiving PPX<1.5 mg/d, The adjusted difference was 3.21 (1.14, 5.28) (*P*=0.0025)**
- **These differences were greater than the minimal clinically important change (MCIC) of 2.5, thus indicating their clinical significance**

1. Wang Y, et al. Drug Des Devel Ther. 2016 Dec 23;11:83-89.
2.Hauser RA, et al. Mov Disord. 2011 Apr;26(5):813-8.

Mirapex® 為達最佳療效需依照病人臨床反應作個別的劑量調整



- **Dosage adjustment should be based on clinical response and drug tolerance, with a daily maximum dosage of 4.5mg**

1. Mirapex PI

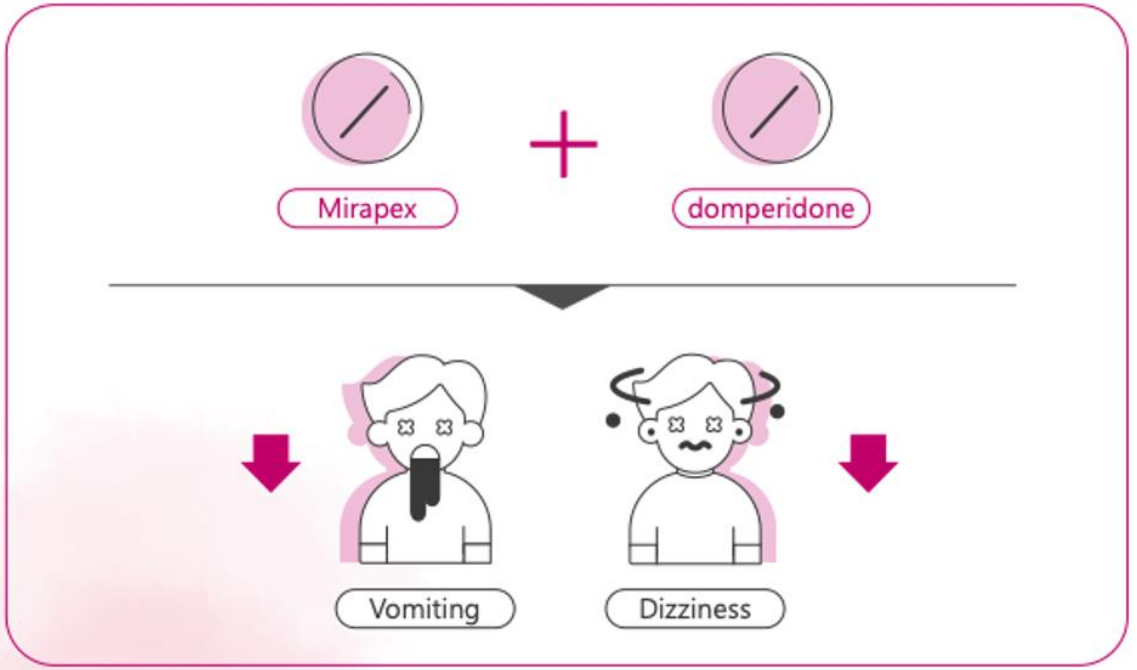
放心加藥

如何預防病人治療初期可能出現的暈眩嘔吐及噁心
讓Mirapex 充分發揮療效

Domperidone is a peripheral D_2 receptor antagonist and is used as a prokinetic and antiemetic of low therapeutic efficacy. It is the preferred drug to counteract levodopa-induced vomiting and constipation in patients with Parkinson disease as in recommended doses domperidone does not block central dopamine receptors (Critchley et al.,1985). There are isolated reports of domperidone-induced

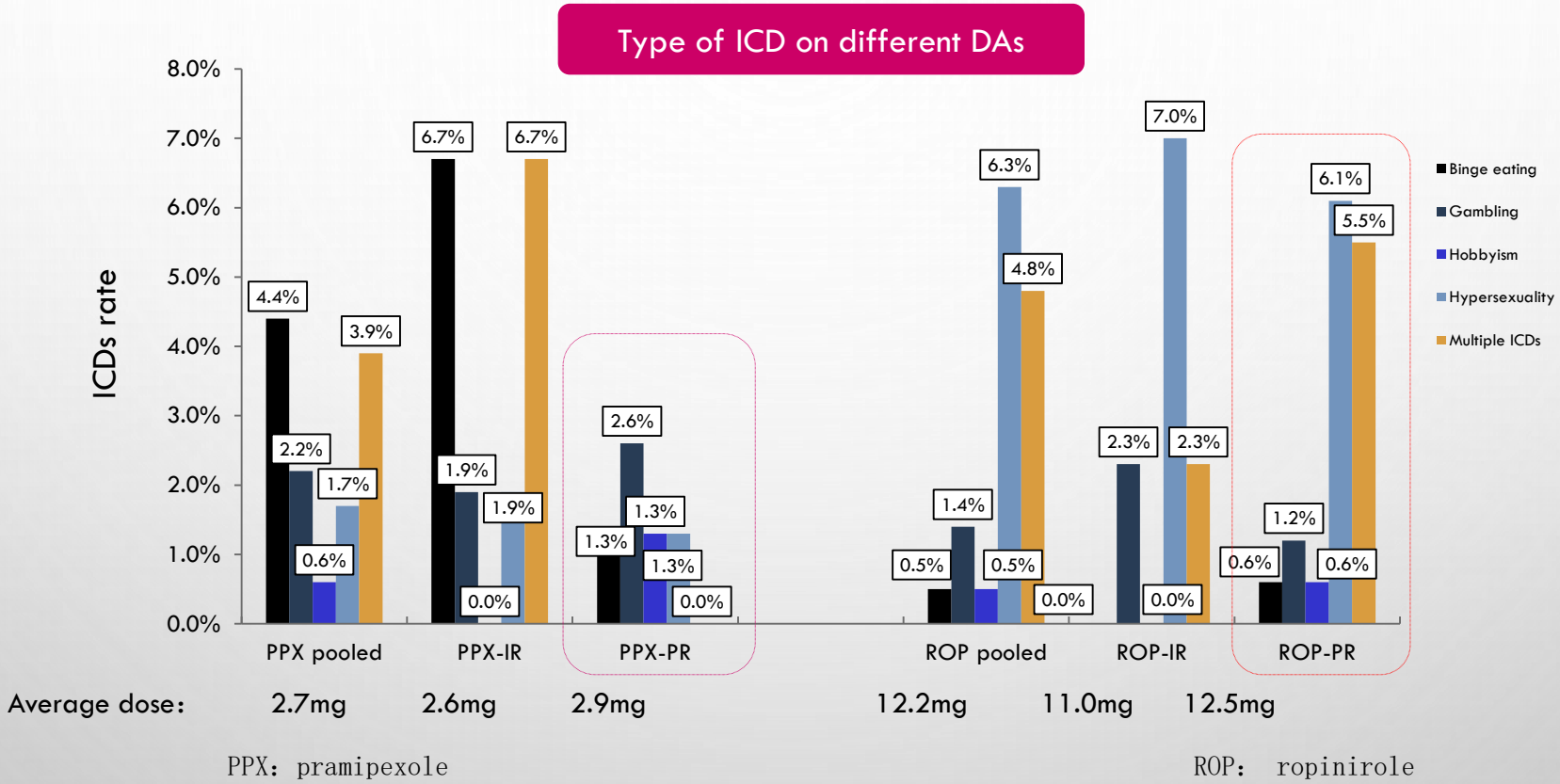
of bromocriptine (12, 60, 61).Domperidone also improved gastric emptying and alleviated GI symptoms,including nausea, vomiting, anorexia, and abdominal bloating, induced by levodopa. There is also an associated improvement in gastric emptying which was delayed by levodopa (62). The beneficial central effects of the anti-Parkinsonian drugs were not inhibited by domperidone, and no extra-pyramidal side effects attributable to domperidone were reported in any of these studies (62).

- 建議一開始處方 Mirapex 時可合併使用 domperidone，將有效減緩暈眩嘔吐及噁心等情形[1,2]。



1. Aggarwal, A, and Bhatt, M. Commonly used gastrointestinal drugs. Handb Clin Neurol 2014;120: 633-643.
2. Reddymasu, S C, Soykan, I, and McCallum, R W. Domperidone: review of pharmacology and clinical applications in gastroenterology. Am J Gastroenterol 2007;102: 2036-2045.

MIRAPEX® PR 衝動控制障礙發生風險比ROPINIROLE更低



- Dopamine agonist associated with ICDs included binge eating, gambling, hobbyism, and hypersexuality.
- The rate and risk of Multiple ICDs was **lower when using PPX-PR** compared to ROP-PR

*: non-head to head study comparison

Rizos A, et al. Eur J Neurol. 2016 Aug;23(8):1255-61.

台灣最新治療建議:

70歲以下巴金森病病人
首選使用DA
(如Mirapex至1.5mg)
可明顯改善動作症狀並
延緩藥效波動與異動症*

Mirapex®可以有效改善早期及晚期PD病人的生活品質

*Acta Neurologica Taiwanica Vol 32 No 3 September 2023
JAMA. 2020;323(6):548-560. doi:10.1001/jama.2019.22360
Tao Li, et al.BMC Neurol.2022 Aug 25;22(1):320

PC-TW-105615-04-Sep-2023

針對早期的PD病人
以 Mirapex0.375mg為起始劑量處方，並隔週觀察逐步調整至1.5mg以上。

一開始處方Mirapex時可和病人衛教可能產生的副作用，可增加病人的用藥信心與耐受度。

已經使用L-dopa的PD病人
建議在 <400mg/day時及早併用Mirapex，病人有改善時可逐漸降低L-dopa劑量，提升Mirapex劑量到≥1.5mg/day以上

仿單資訊

樂伯克® 持續性藥效錠 0.375 毫克 Mirapex® 0.375mg prolonged-release tablets
樂伯克® 持續性藥效錠 0.75 毫克 Mirapex® 0.75mg prolonged-release tablets
樂伯克® 持續性藥效錠 1.5 毫克 Mirapex® 1.5mg prolonged-release tablets

【適應症與用途】治療巴金森氏症的徵候與症狀。**【主成分】**Pramipexole**【用法用量】**MIRAPEX PR 錠劑為一天口服一次，空腹用藥或與食物併用均可。MIRAPEX PR 錠劑必須整顆吞服，不可嚼碎、壓碎或切割。若MIRAPEX PR錠劑的治療中斷過久，就可能必須重新調整治療劑量。初始劑量為0.375mg，一天一次。可根據療效與耐受性，逐漸調高劑量，但調整頻率不可多於每5至7天一次(not more frequently than every 5 to 7 days)，首先調至一天0.75 mg，然後每次增加0.75 mg，最多增至一天4.5 mg（最大建議劑量）。Mirapex 持續性藥效錠應以每天 0.75 毫克的速率調降，直到每日劑量降至 0.75 毫克為止。此後，每天應減少 0.375 毫克的劑量。在腎功能不全病人的用藥方法：Pramipexole 的清除須仰賴腎功能。肌酸酐清除率超過 50 ml/分鐘的病人無需降低每日劑量或用藥頻率。在中度腎功能受損（肌酸酐清除率在30至50 mL／分鐘）的病人，開始時必須每隔一天服用一次 MIRAPEX PR。須謹慎用藥，並仔細評估治療反應及耐受性，才可於一週後調高每日劑量，並進一步以每次0.375 mg的增幅將劑量調至最高一天2.25 mg。劑量調整頻率不可多於一週一次。MIRAPEX PR錠劑尚未在重度腎功能受損（肌酸酐清除率低於30mL／分鐘）或洗腎的病人進行研究，因此不建議在這些病人使用。**【禁忌症】**對pramipexole 或製劑中任一成分過敏者禁用。**【警語與注意事項】**請告知病人，Mirapex 可能具有鎮靜作用，包括困倦與於日常活動中睡著的可能性。因為困倦為可能造成嚴重後果的常見不良事件，病人在有足夠的使用經驗可供判斷 Mirapex 是否會影響其精神與／或運動功能之前，請勿開車或從事其他複雜的操作機械活動。請告知病人，若於治療期間任何時間出現困倦情況增加或於日常活動（例如談話或進食）期間出現睡著的新狀況時，在與醫生聯絡之前，請勿開車或從事可能具有危險性的活動。在臨床試驗與臨床經驗中，多巴胺拮抗劑可能造成全身性血壓調節作用受損，而導致起立型低血壓症（orthostatic hypotension），尤其在劑量調升期；在使用一種或多種可增加中樞多巴胺活性（central dopaminergic tone）的藥物與帕金森氏症的常用治療藥物（包括MIRAPEX PR）時，病人可能出現賭博衝動、性慾增加、花錢慾望強烈、暴飲暴食與／或其他強烈慾望，而且無法控制這些衝動。應考慮減少劑量／逐漸停藥。幻覺和意識混亂是帕金森氏症病人使用多巴胺促進劑和左多巴的已知副作用。與接受單一療法的早期帕金森氏症病人相比，以 Mirapex 併用左多巴治療的末期帕金森氏症病人出現幻覺的頻率較高。請告知病人可能會出現（大多為視覺上的）幻覺。病人應知道可能會出現幻覺且可能對其駕駛能力造成不良影響。**【不良反應】**在早期帕金森氏症病人的試驗中，以MIRAPEX PR 錠劑治療33週之後，最常見的不良事件（發生率≧5%且較安慰劑高）包括困倦、噁心、便秘、暈眩、疲勞、幻覺、口乾、肌肉痙攣與周邊水腫。在末期帕金森氏症病人（併用左多巴）所進行的試驗中，以MIRAPEX PR 錠劑治療18週期間最常出現（發生率≧5%且高於安慰劑組）的不良事件為運動困難、噁心、便秘、幻覺、頭痛與食慾不振。

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PIP052191-001