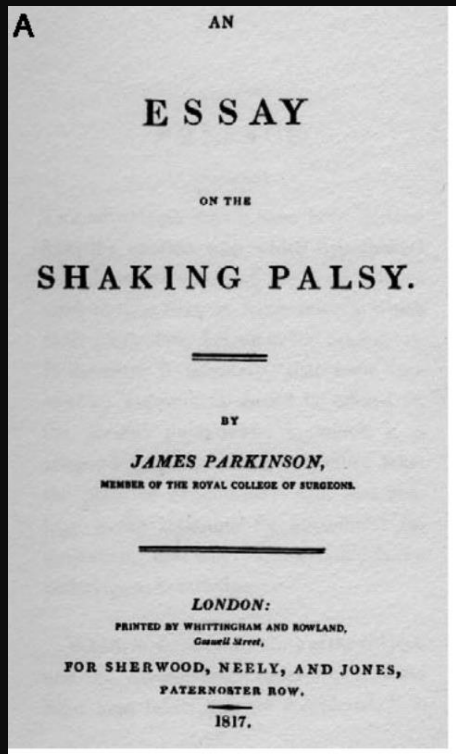
# Parkinson Disease

2024/5/26

# Parkinson Disease

- James Parkinson's seminal essay on 'the shaking palsy"



AN

ESSAY

ON THE

SHAKING PALSY.

BY

*JAMES PARKINSON,*

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

*LONDON:*

PRINTED BY WHITTINGHAM AND ROWLAND,
*Gunwell Street,*

FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.

1817.

FIG. 316.

Paralysis Agitans. *(After St. Leger.)*

# Parkinson Disease
## Epidemiology

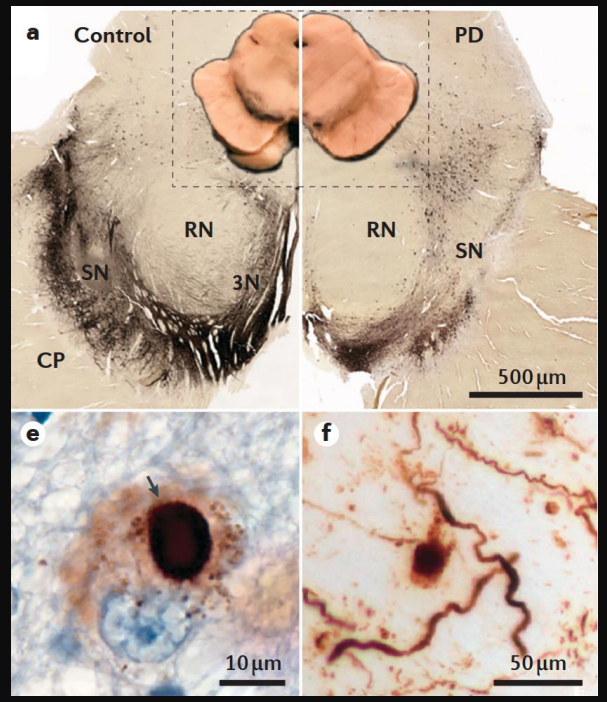
- Second-most common neurodegenerative disorder
- 2–3% of the population ≥65 years of age
- Incidence : 21 cases per 100,000 person-years
- Rare before 50 years, but incidence increases 5–10-fold from the sixth to the ninth decade of life
- Global prevalence: conservatively estimated at 0.3%
  - >3% in those >80 years of age

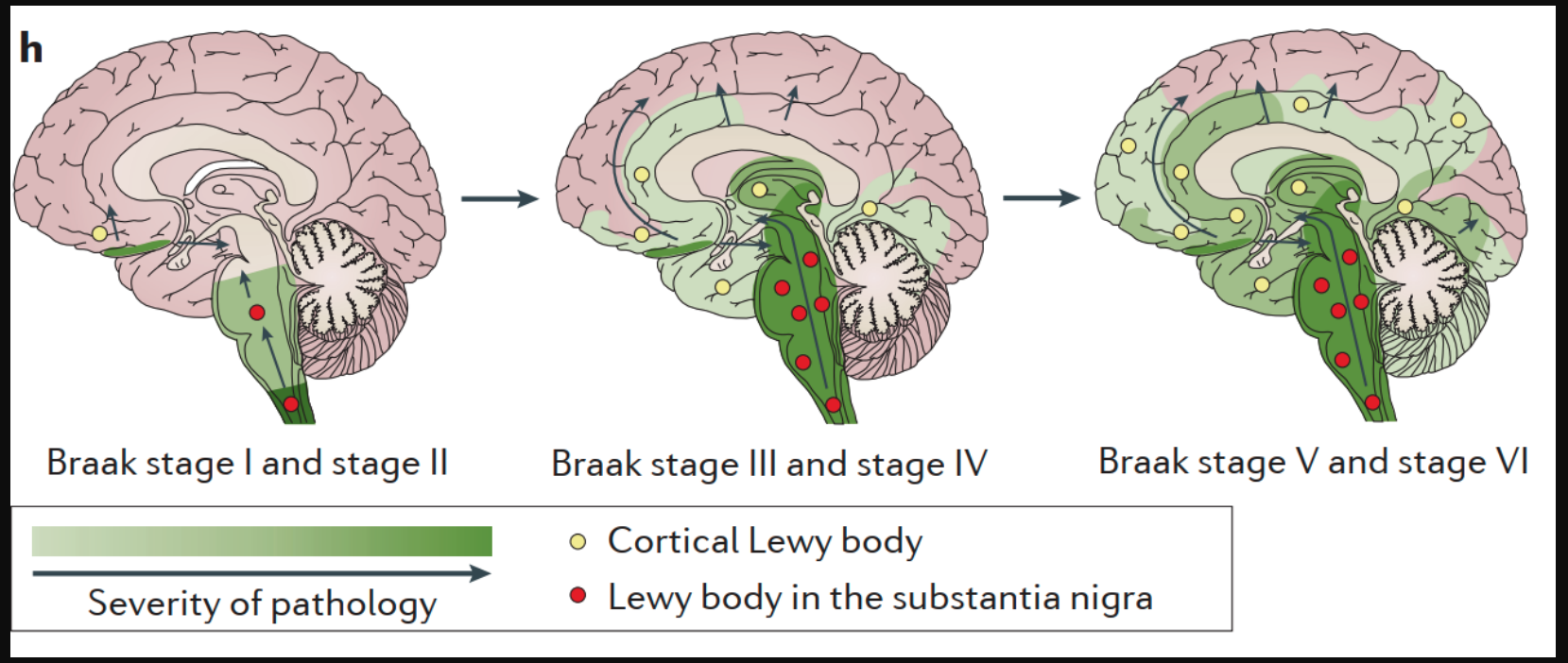
# Parkinson Disease
## Epidemiology

- Twice as common in men
- Gene–environment interactions
  - Incidence greater in individuals exposed to certain pesticides and traumatic brain injury
  - Incidence lower in smokers or caffeine users

# Parkinson Disease
## Mechanism

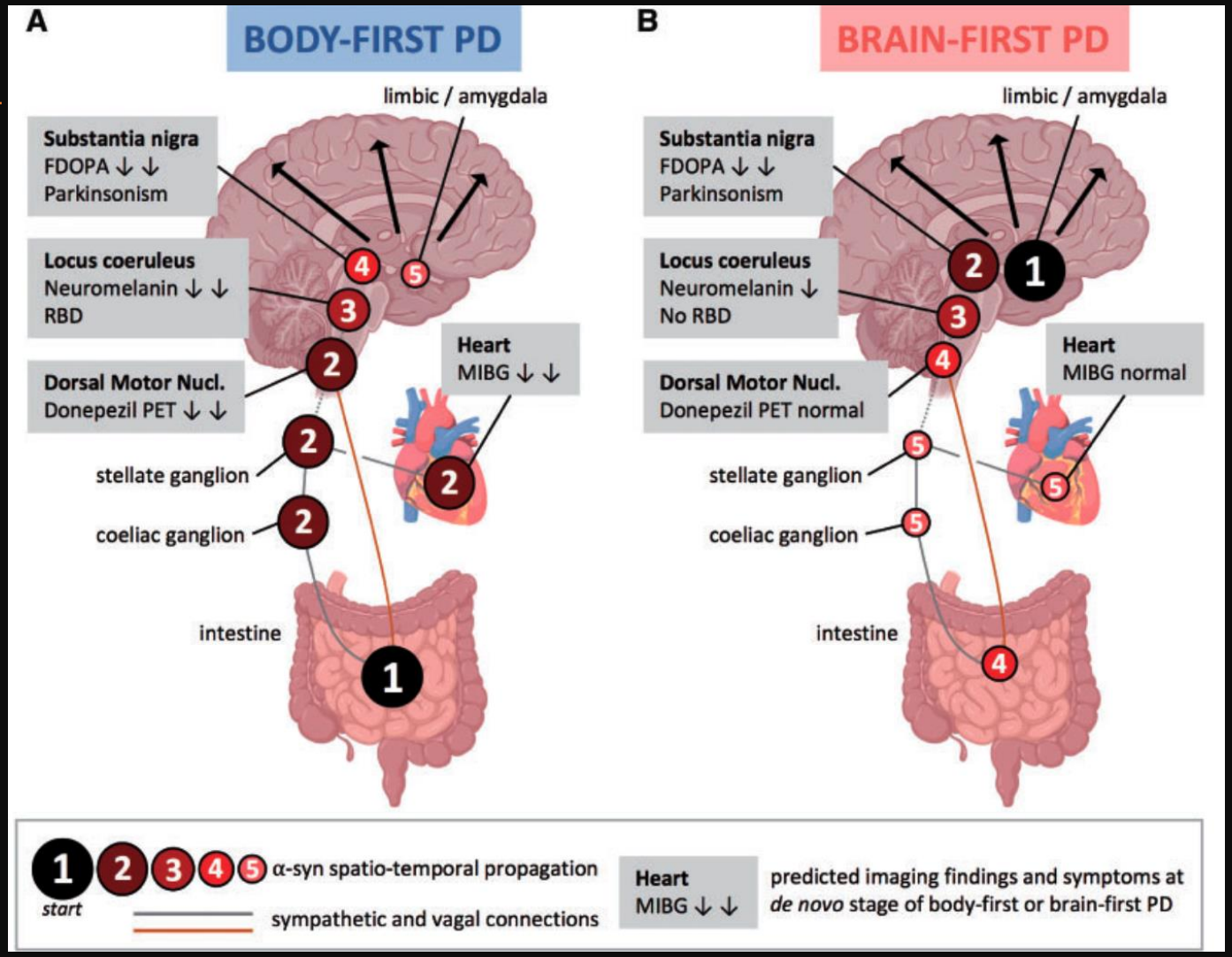
- Neuronal loss in specific areas of the substantia nigra
- widespread intracellular protein (α-synuclein) accumulation



# Parkinson Disease
## Mechanism

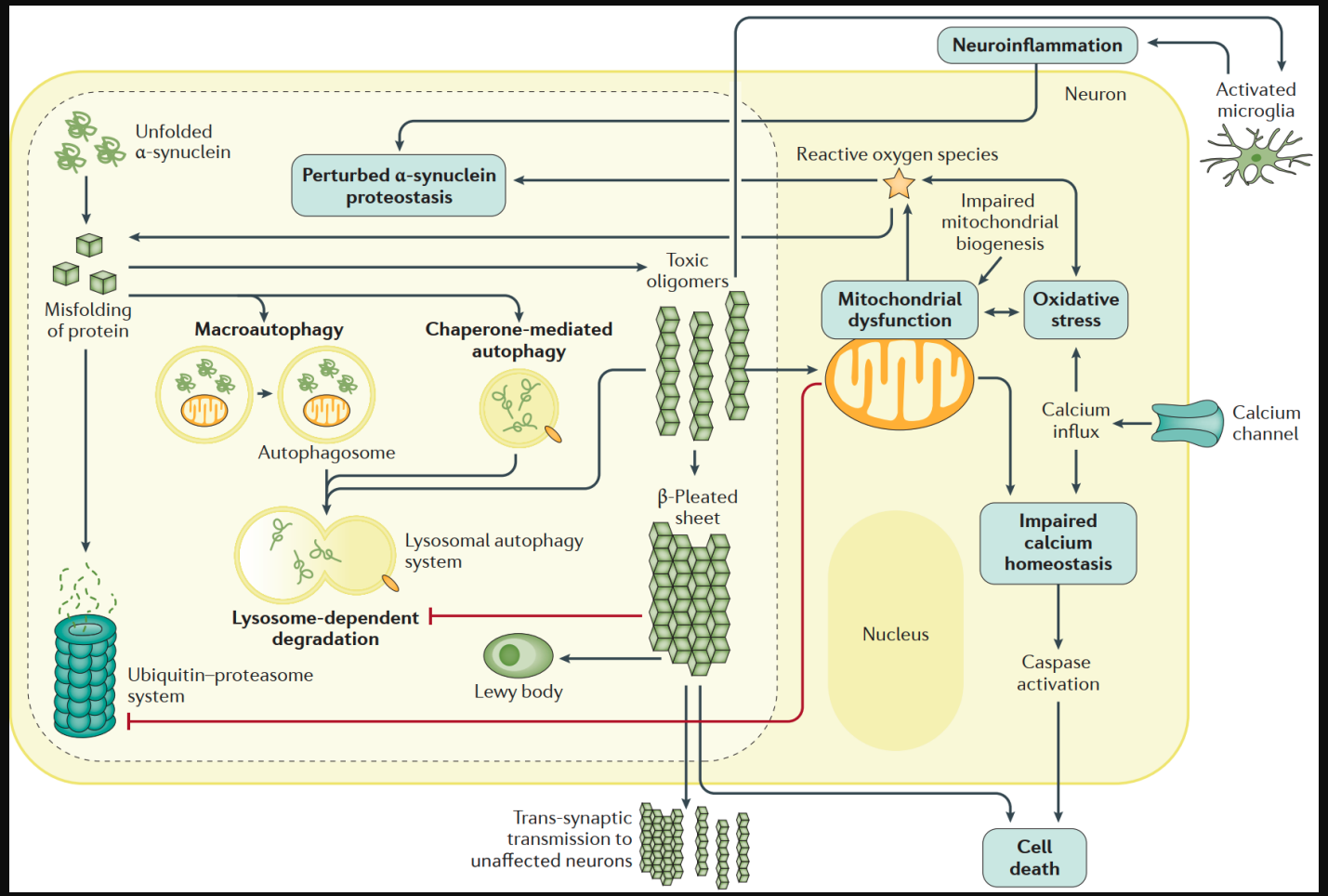
widespread intracellular protein (α-synuclein) accumulation



| | | | | | |
|---|---|---|---|---|---|
| ***Autosomal dominant Parkinson disease*** | | | | | |
| *PARK1* or *PARK4* | PARK-*SNCA* | 4q22.1 | *SNCA* | • 168601; 163890 (*PARK1*)<br>• 605543; 163890 (*PARK4*) | Missense mutations (*PARK1*) cause classic Parkinson disease phenotype. Duplication or triplication of this gene (*PARK4*) causes early-onset Parkinson disease with prominent dementia |
| *PARK8* | PARK-*LRRK2* | 12q12 | *LRRK2* | 607060; 609007 | Classic Parkinson disease phenotype. Variations in *LRRK2* include risk-conferring variants and disease-causing mutations |
| *PARK17* | PARK-*VPS35* | 16q11.2 | *VPS35* | 614203; 601501 | Classic Parkinson disease phenotype |
| ***Early-onset Parkinson disease (autosomal recessive inheritance)*** | | | | | |
| *PARK2* | PARK-*Parkin* | 6q26 | *PARK2* encoding parkin | 600116; 602544 | Often presents with lower limb dystonia |
| *PARK6* | PARK-*PINK1* | 1p36.12 | *PINK1* | 605909; 608309 | Psychiatric features are common |
| *PARK7* | PARK-*DJ1* | 1p36.23 | *PARK7* encoding protein deglycase DJ1 | 606324; 602533 | Early-onset Parkinson disease |
| *PARK19B* | PARK-*DNAJC6* | 1p31.3 | *DNAJC6* | 615528; 608375 | Onset of parkinsonism between the third and fifth decades of life |
| ***Complex genetic forms (autosomal recessive inheritance)***[§] | | | | | |
| *PARK9* | PARK-*ATP13A2* | 1p36.13 | *ATP13A2* | 606693; 610513 | Early-onset parkinsonism with a complex phenotype (for example, dystonia, supranuclear gaze palsy, pyramidal signs and cognitive dysfunction); also known as Kufor–Rakeb syndrome |
| *PARK14* | PARK-*PLA2G6* | 22q13.1 | *PLA2G6* | 256600; 603604 | PLAN (or NBIA2) is characterized by a complex clinical phenotype, which does not include parkinsonism in the majority of cases |
| *PARK15* | PARK-*FBXO7* | 22q12.3 | *FBXO7* | 260300; 605648 | Early-onset parkinsonism with pyramidal signs and a variable complex phenotype (for example, supranuclear gaze palsy, early postural instability, chorea and dystonia) |
| *PARK19A* | PARK-*DNAJC6* | 1p31.3 | *DNAJC6* | 615528; 608375 | Juvenile-onset parkinsonism that is occasionally associated with mental retardation and seizures |
| *PARK20* | PARK-*SYNJ1* | 21q22.11 | *SYNJ1* | 615530; 604297 | Patients may have seizures, cognitive decline, abnormal eye movements and dystonia |
| *PARK23* | Not yet assigned | 15q22.2 | *VPS13C* | 616840; 608879 | Young-adult-onset parkinsonism associated with progressive cognitive impairment that leads to dementia and dysautonomia |

# Parkinson Disease
## Mechanism

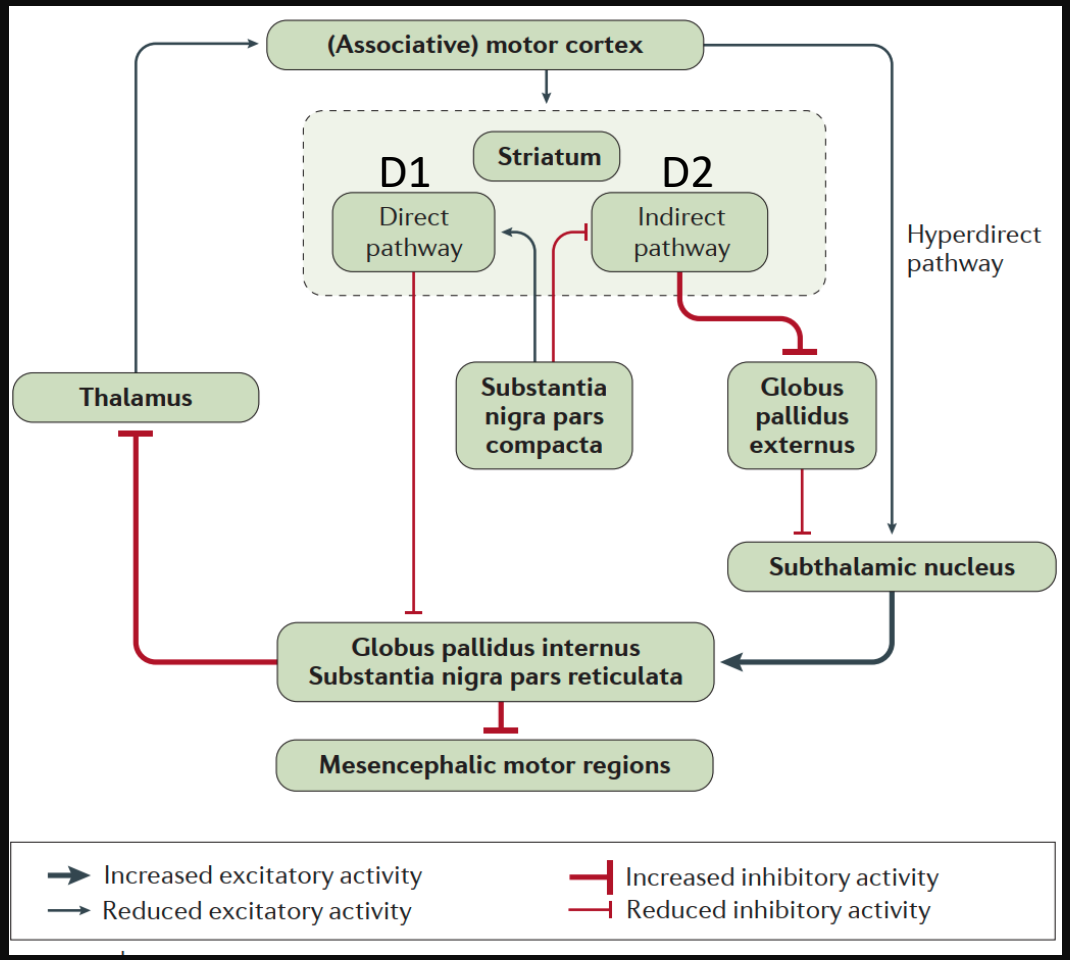
- α-Synuclein proteostasis
- Mitochondrial dysfunction
- Oxidative stress
- Neuroinflammation



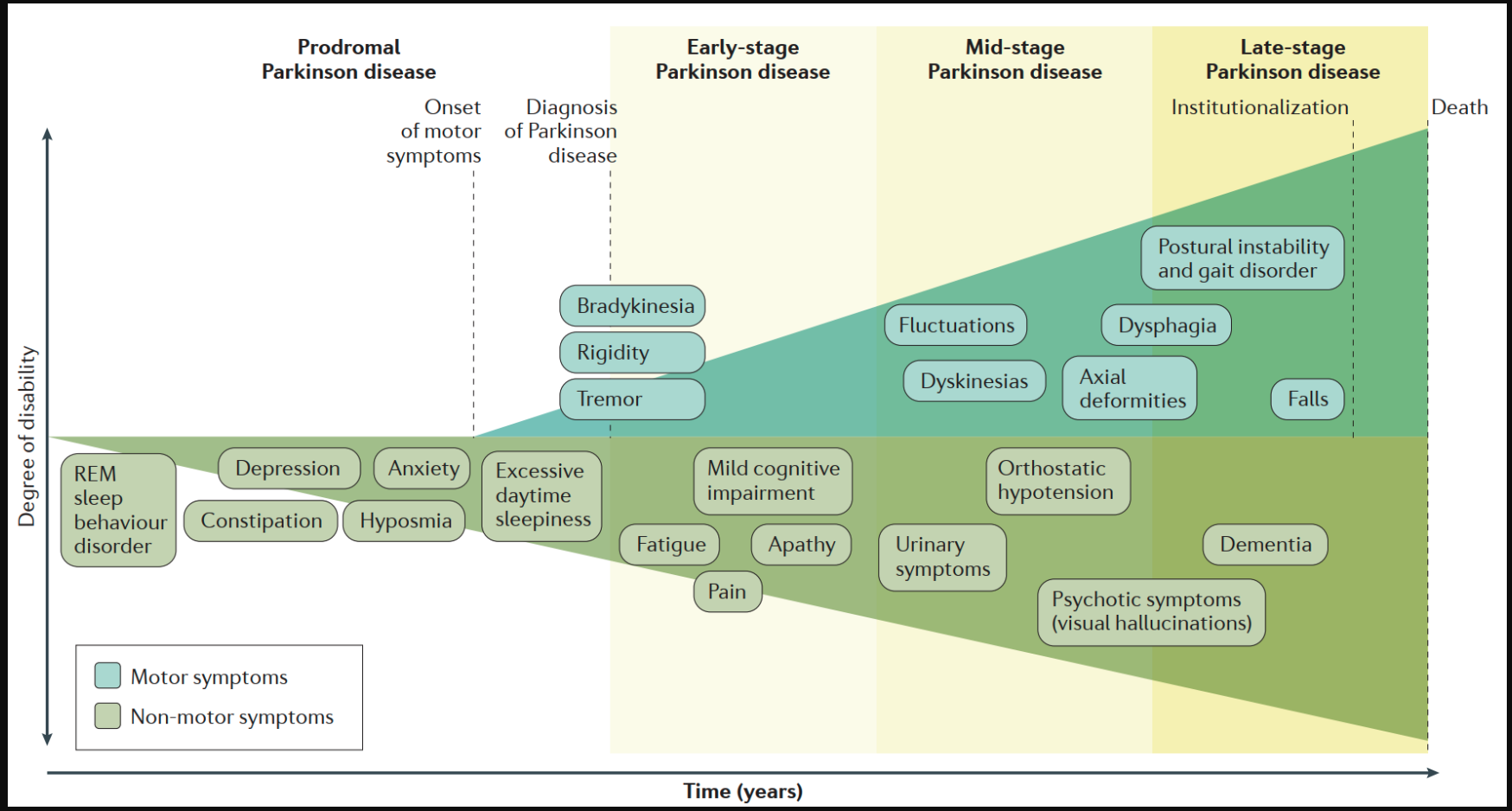
# Parkinson Disease
## Mechanism

Motor cortex circuitry activity changes in Parkinson disease

D1-mediated direct pathway activity reduced
D2-mediated indirect pathway activity increases



# Parkinson Disease
## Clinical & diagnosis

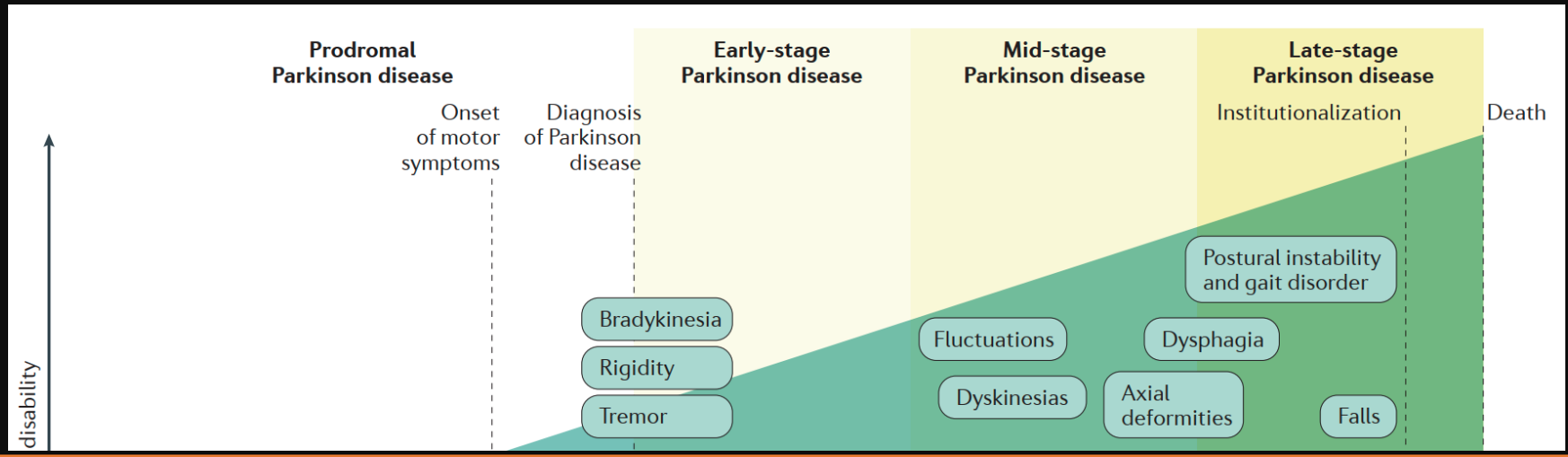


# Parkinson Disease
## Clinical & diagnosis

### BRT

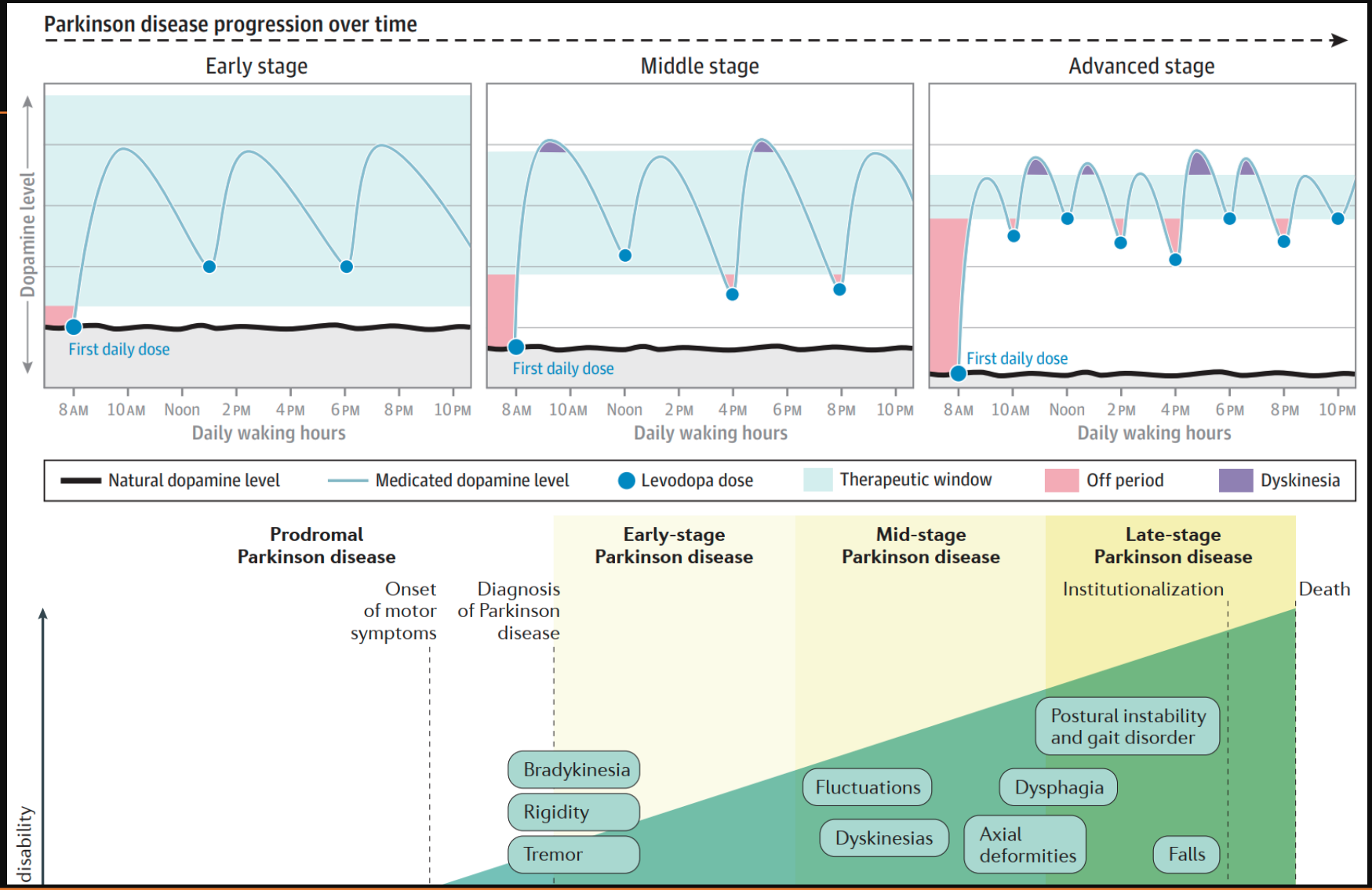
Bradykinesia = slowness of movement and a decrement in amplitude or speed (or progressive hesitations or halts) as movements are continuedI

+ at least one of: Rigidity and/or rest Tremor



# Parkinson Disease

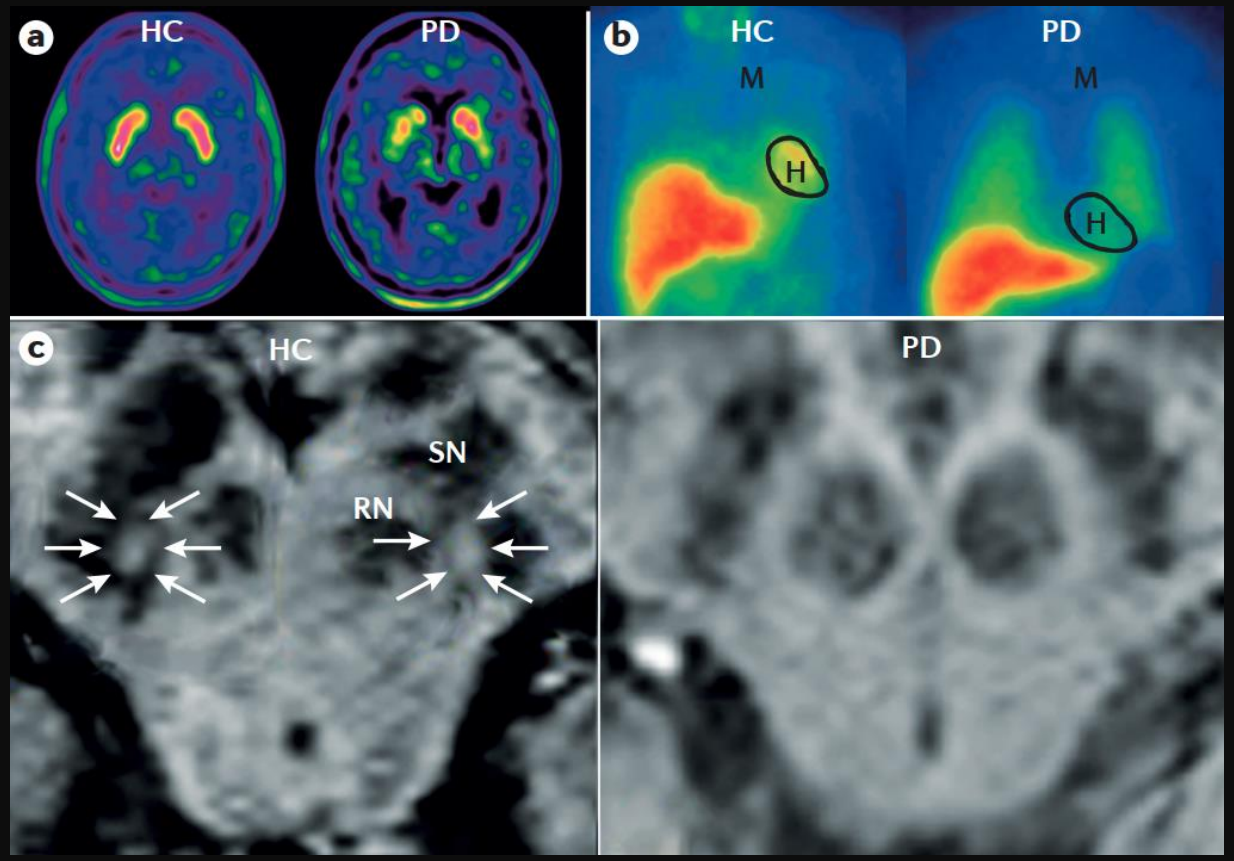
## Clinical & diagnosis



# Parkinson Disease
## Clinical & diagnosis - Image

18F-labelle l-DOPA

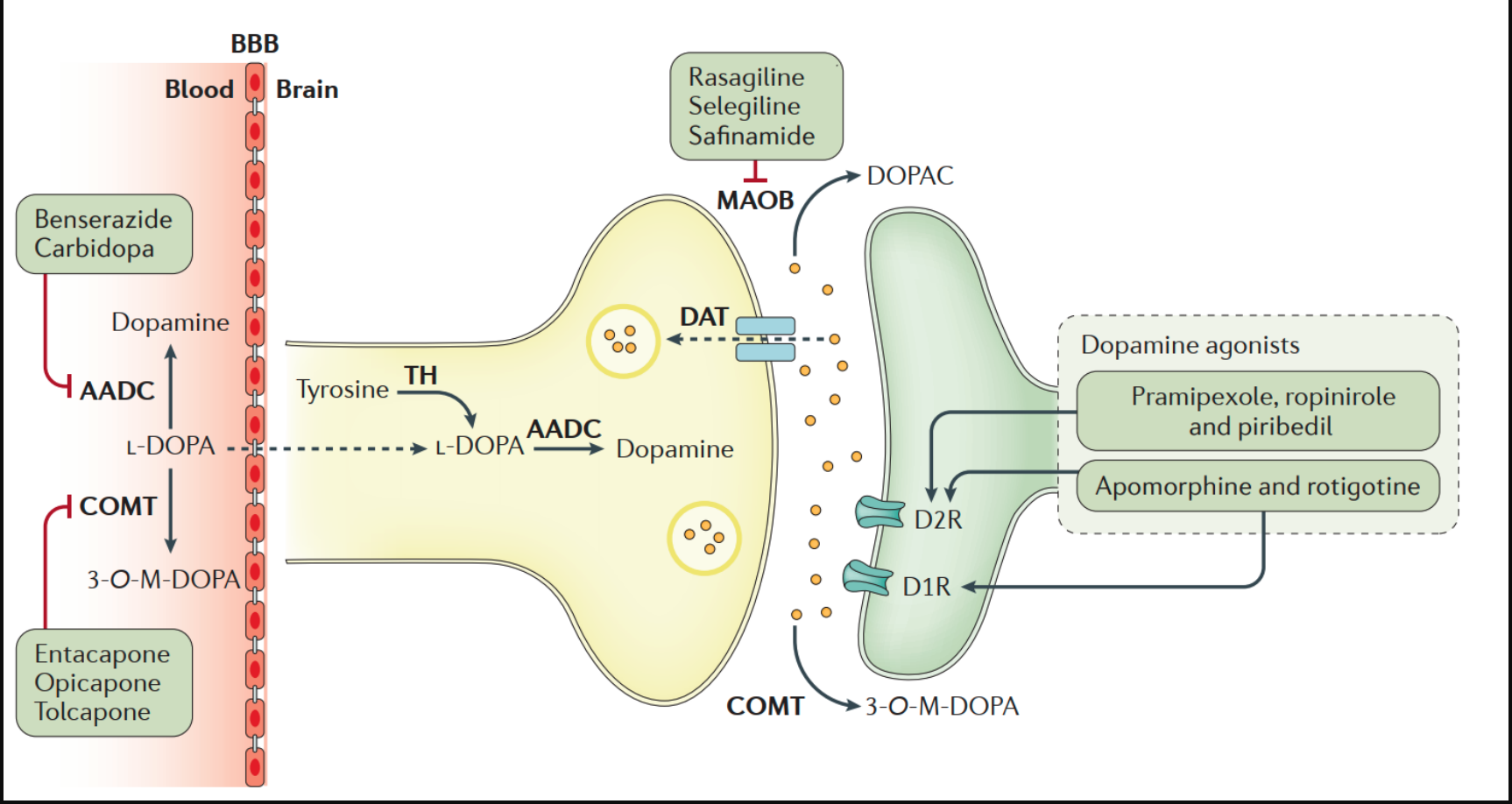
MRI SWI



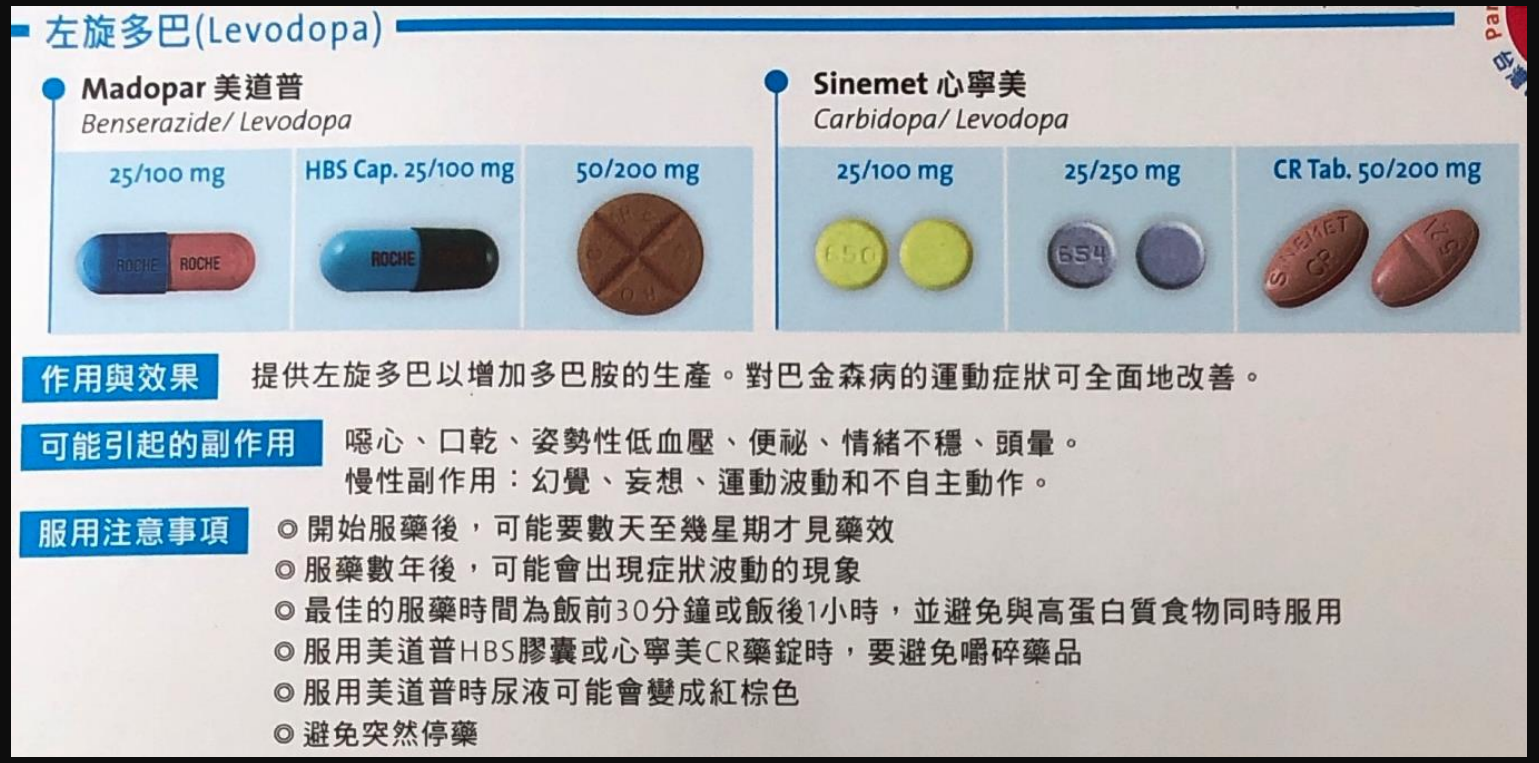

MIBG SPECT
Cardiac sympathetic denervation in PD

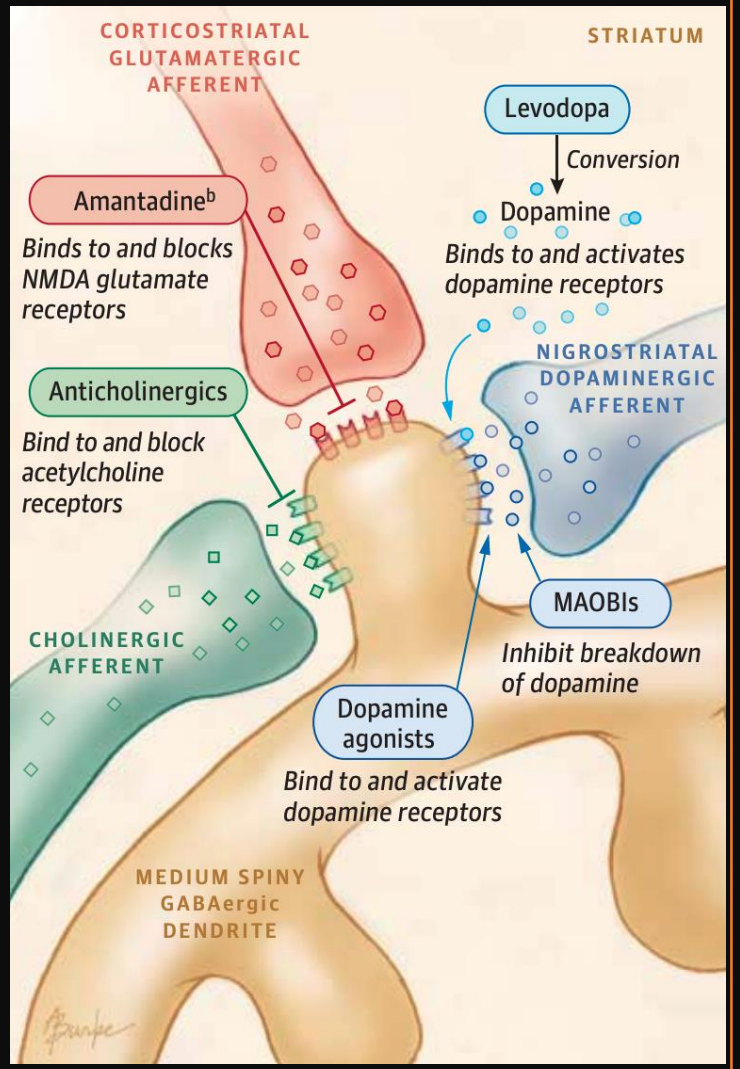
# Parkinson Disease

## Treatment - Motor



# Parkinson Disease
## Treatment



# Parkinson Disease
## Treatment

**作用與效果**

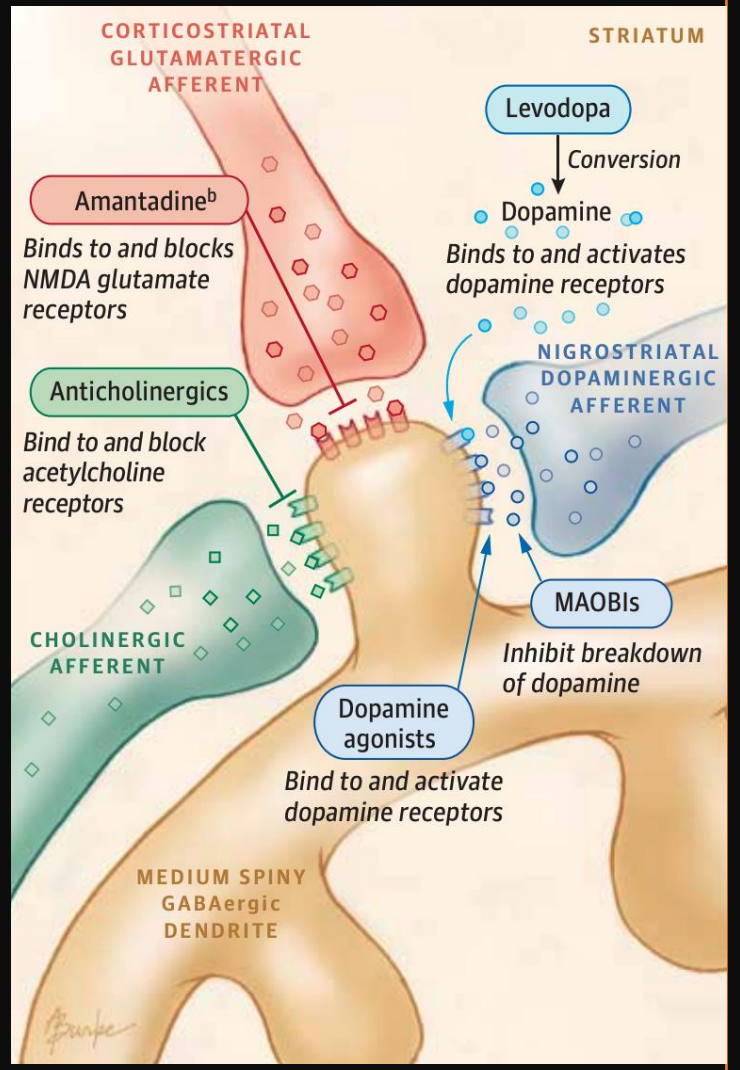
**Requip Tab. 力必平 / Mirapex Tab. 樂伯克 / Butin Tab. 伯汀錠：** 模仿多巴胺來刺激多巴胺接受體，以代替腦內不足的多巴胺。對巴金森病的運動症狀可全面地改善。**APO-go Pen Injection 帕特捷筆型注射劑：** 模仿多巴胺來刺激多巴胺接受體，以代替腦內不足的多巴胺。主要用在改善巴金森病後期症狀波動的現象。**Neupro Transdermal Patch 紐普洛穿皮貼片劑：** 模仿多巴胺來刺激多巴胺接受體，以代替腦內不足的多巴胺。對巴金森症的症狀可全面地改善。

**可能引起的副作用**

嗜睡、幻覺、暈眩、失眠、頭痛、意識混亂、噁心、便秘、口乾、衰弱無力、姿態性低血壓、異常衝動(如：賭博、性慾、購買慾、食慾增強等)

**服用注意事項**

**Requip Tab. 力必平 / Mirapex Tab. 樂伯克：** ◎ 部分病患可能會有『突然入睡』的現象。◎ 服藥後數星期之內，要避免駕駛或從事需要高度集中注意力之工作。◎ 服用力必平持續性Requip PD 錠及樂伯克持續性Mirapex PR.時，要避免嚼碎藥品。**Butin Tab. 伯汀錠：** ◎ 可能引起血壓下降，須注意血壓變化。**APO-go Pen Injection 帕特捷筆型注射劑：** ◎ 患者應能夠辨識自己即將出現斷電症狀，且有能力於需要時可自行注射，或者有負責照顧的人可為其施打本藥。**Neupro Transdermal Patch 紐普洛穿皮貼片劑：** ◎ 貼片不可裁剪，一旦從包裝袋中取出即使用。◎ 一張貼片勿使用超過24小時，應貼在清潔、乾燥、無傷口或毛髮的皮膚表面，同一部位應間隔至少14天。



# Parkinson Disease
## Treatment

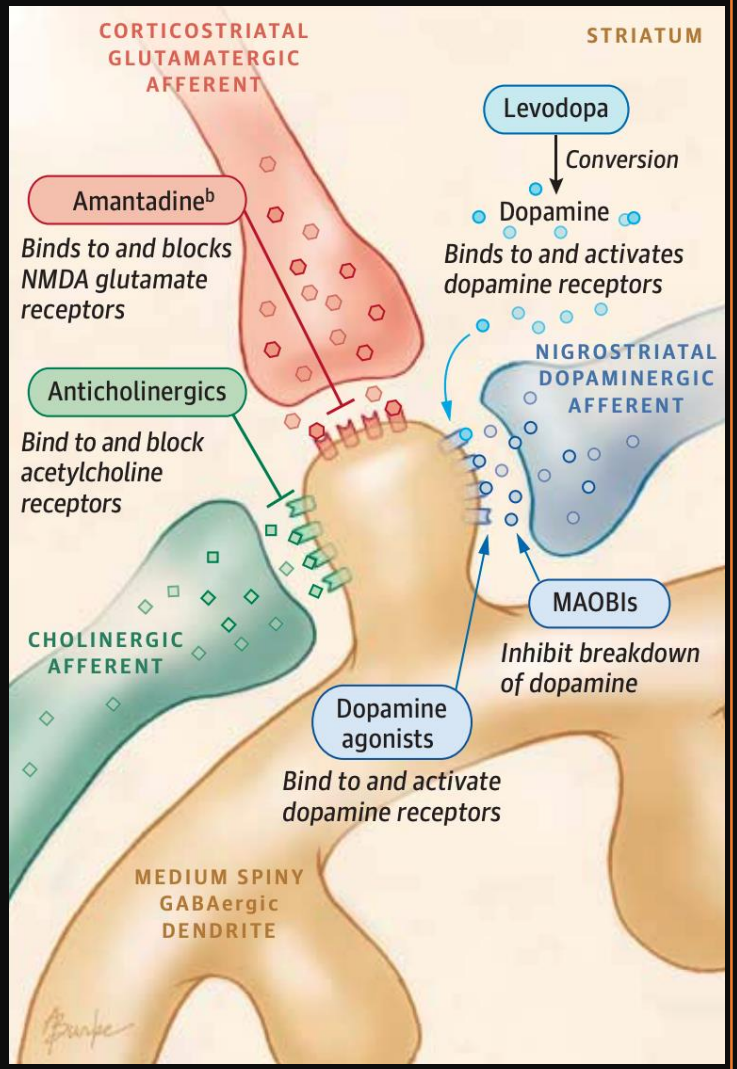
### B型單胺氧化酵素抑制劑(MAO-B Inhibitors)

- **Azilect Tab. 易助力** *Rasagiline* — 1 mg
- **Parkryl Tab. 巴可癒** *Selegiline* — 5 mg

**作用與效果** 提抑制MAO-B酵素對多巴胺的分解，以增加進入腦內的多巴胺。改善左旋多巴的藥力，以減少症狀波動的現象，並減少左旋多巴藥物的用量。

**可能引起的副作用** 失眠、不自主動作、口乾、姿勢性低血壓、便祕、情緒不穩、昏眩

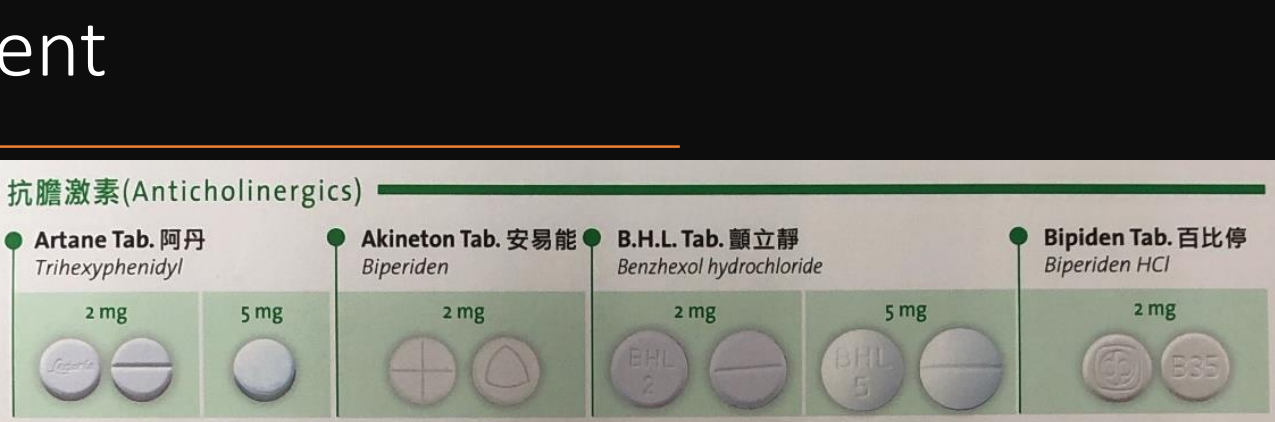
**服用注意事項**
- ◎ 避免晚上服藥以減少失眠。
- ◎ 服藥期間不宜攝取含有高酪酸胺(tyramine)食物，如：乳酪類、煙燻製品、香腸、醃漬品、魚干、紅酒、啤酒、酪梨、起司等。



# Parkinson Disease
## Treatment

### 抗膽激素(Anticholinergics)

| Artane Tab. 阿丹 *Trihexyphenidyl* | Akineton Tab. 安易能 *Biperiden* | B.H.L. Tab. 顫立靜 *Benzhexol hydrochloride* | Bipiden Tab. 百比停 *Biperiden HCl* |
|---|---|---|---|
| 2 mg / 5 mg | 2 mg | 2 mg / 5 mg | 2 mg |



**作用與效果** 抑制乙醯膽素的作用，增加腦內多巴胺的活性。改進僵硬、顫抖、流口水等症狀。

**可能引起的副作用** 意識錯亂、口乾、視覺模糊、小便困難、便祕、失憶、心悸。

**服用注意事項** ◎服藥後，請勿開車或操作危險機械及從事需要集中注意力的工作。

### COMT抑制劑(COMT Inhibitors)

**Comtan Tab. 諾康停** *Entacapone* 200 mg

**作用與效果** 抑制COMT酵素對多巴胺的分解，以增加進入腦內的多巴胺。
改善左旋多巴的藥力，以減少症狀波動的現象，並減少左旋多巴藥物的用量。

**可能引起的副作用** 噁心、不自主動作、腹瀉。

**服用注意事項** ◎必須與左旋多巴藥物(Madopar 或 Sinemet)一起服用才能有效。
◎必要時須監測肝功能指數。

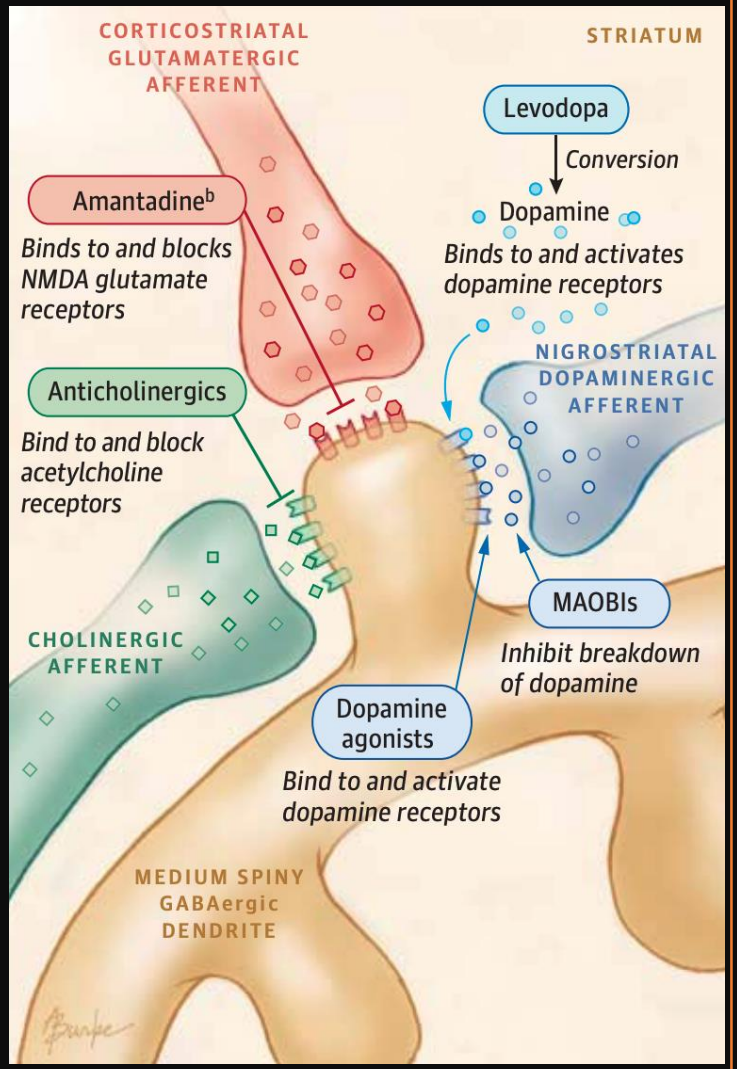
### Amantadine 金剛胺

**PK-Merz Tab. 麥斯克** *Amantadine* 100 mg

**作用與效果** 刺激多巴胺的釋出，以增加腦內多巴胺的活性。紓解巴金森病的症狀。

**可能引起的副作用** 口乾、皮膚斑點、腳腫脹、幻覺、姿勢性低血壓。

**服用注意事項** ◎ 盡量於黃昏前服藥以避免失眠。
◎ 開車或操作機械時須小心。



# Parkinson Disease
## Treatment – non motor

### Depression

| | | | | |
|---|---|---|---|---|
| Dopamine Agonists | Pramipexole | Efficacious | Acceptable risk without specialized monitoring | Clinically useful |
| Tricyclic antidepressants | Nortriptyline | Likely efficacious | Acceptable risk without specialized monitoring[b] | Possibly useful |
| | Desipramine | Likely efficacious | Acceptable risk without specialized monitoring[b] | Possibly useful |
| | Amitriptyline | Insufficient evidence | Acceptable risk without specialized monitoring[b] | *Possibly useful*[c] |
| Selective serotonin reuptake inhibitors/selective serotonin norepinephrine reuptake inhibitors | Citalopram | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | Sertraline | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | **Paroxetine** | insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[d] |
| | Fluoxetine | Insufficient evidence | Acceptable risk without specialized monitoring[e] | *Possibly useful*[c] |
| | **Venlafaxine** | *Efficacious* | *Acceptable risk without specialized* | *Clinically useful* |
| Nonpharmacological interventions | **rTMS** | *Insufficient evidence* | *Acceptable risk without specialized monitoring*[f] | *Possibly useful (short term)* |
| | **CBT** | *Likely efficacious* | *Insufficient evidence*[g] | *Possibly useful* |

# Parkinson Disease

## Treatment – non motor

### Apathy

**TABLE 3.** Interventions to treat apathy in PD

| Intervention | | | | |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| Dopamine agonists | **Piribedil**[a] | *Likely efficacious* | *Acceptable risk without specialized monitoring* | *Possibly useful* |
| | **Rotigotine** | *Unlikely efficacious* | *Acceptable risk without specialized monitoring* | *Investigational* |
| Acetylcholinesterase inhibitors | **Rivastigmine** | *Efficacious* | *Acceptable risk without specialized monitoring*[b] | *Possibly useful* |

# Parkinson Disease
## Treatment – non motor

ICD

**TABLE 4.** Interventions to treat impulse control and related disorders in PD

| Intervention | | | | |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | Efficacy | Safety | Practice implications |
| N-methyl-D-aspartate (NMDA) antagonists | Amantadine[a] | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |
| Anti-opioids | **Naltrexone**[b] | *Insufficient evidence* | *Insufficient evidence* | *Investigational* |
| Nonpharmacological interventions | **CBT**[b] | *Likely efficacious* | *Insufficient evidence*[c] | *Possibly useful* |

# Parkinson Disease

## Treatment – non motor

### Dementia

**TABLE 5.** Interventions to treat dementia and nondementia cognitive impairment in PD

| Intervention | | Efficacy | Safety | Practice implications |
|---|---|---|---|---|
| Drug class/intervention strategy | Drug/intervention | | | |
| **Dementia** | | | | |
| Acetylcholinesterase inhibitors | **Donepezil** | Insufficient evidence | Acceptable risk without specialized monitoring[a] | *Possibly useful*[b] |
| | **Rivastigmine** | Efficacious | Acceptable risk without specialized monitoring[a] | Clinically useful |
| | Galantamine | Insufficient evidence | Acceptable risk without specialized monitoring[a] | *Possibly useful*[c] |
| N-methyl-D-aspartate (NMDA) antagonists | Memantine | Insufficient evidence | Acceptable risk without specialized monitoring | Investigational |

# Parkinson Disease

## Treatment – non motor

### Psychosis

| Drug | Efficacy | Safety[a] | Practice implications |
|---|---|---|---|
| Clozapine | Efficacious | Acceptable risk with specialized monitoring | Clinically useful |
| **Olanzapine** | *Not efficacious* | Unacceptable risk | *Not useful* |
| Quetiapine | Insufficient evidence | Acceptable risk without specialized monitoring | *Possibly useful*[b] |
| **Pimavanserin** | *Efficacious* | *Acceptable risk without specialized monitoring*[c] | *Clinically useful* |

# Parkinson Disease
## PD evaluation - Motor

- MDS-UPDRS
  - Motor evaluation and characterizes the extent and burden of disease
  - Can be used in a clinical setting as well as in research
  - 4 parts
    - Part I: Non-Motor Aspects of Experiences of Daily Living
    - PartII: Motor Aspects ofExperiencesofDaily Living
    - **PartIII: Motor Examination**
    - **Part IV: Motor Complications**

# Parkinson Disease
## PD evaluation - Motor

- Rush Dyskinesia Rating Scale (RDRS)

Severity rating code: 0, absent; 1, minimal severity, no interference with voluntary motor acts; 2, dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor acts; 3, intense interference with movement control and daily life activities are greatly limited; 4, violent dyskinesias, incompatible with any normal motor task.

| Severity of worst dyskinesia observed | Dyskinesias present (more than one choice possible) | | | Most disabling dyskinesia (choose one) | | |
|---|---|---|---|---|---|---|
| | Chorea (C) | Dystonia (D) | Other (list) | C | D | Other |

# Parkinson Disease
## PD evaluation - Motor

- Unified Dyskinesia Rating Scale (UDysRS)

| Historical | Score | Objective | Score |
|---|---|---|---|
| 1. Time dyskinesia | | 16. Face | |
| 2. Speech | | 17. Neck | |
| 3. Chewing/Swallowing | | 18. Right Hand/arm/shoulder | |
| 4. Eating tasks | | 19. Left Hand/arm/shoulder | |
| 5. Dressing | | 20. Trunk | |
| 6. Hygiene | | 21. Right foot/leg/hip | |
| 7. Handwriting | | 22. Left foot/leg/hip | |
| 8. Doing hobbies/activities | | 23. Communication | |
| 9. Walking/balance | | 24. Drinking | |
| 10. Public/social | | 25. Dressing | |
| 11 Exciting situations | | 26. Ambulation | |
| 12 Time Off dystonia | | | |
| 13. Dystonia effects on activities (not pain) | | | |
| 14. Effect of Pain from dystonia | | | |
| 15. Dystonia pain severity | | | |
| | | | |
| Historical sub-score (sum) | | Objective sub-score (sum) | |
| | | | |
| Total UDysRS score (Historical + Objective): | | | |

# Parkinson Disease

## PD evaluation – Non motor

- Non-Motor Symptoms Scale for Parkinson's Disease (NMSS)
- 30-item , 9 dimensions
  - CV, Sleep/fatigue, Mood/cognition, Perceptual/hallucination, Attention/memory, GI, Urinary, Sexual function, Miscellaneous
- Severity and frequency of non-motor symptoms

# Parkinson Disease
## PD evaluation – Mood

### Depression

| | Sensitivity | Specificity | Cutoff score for screening in patients without PD | Cutoff score for screening in patients with PD | Sensitivity to change |
|---|---|---|---|---|---|
| HAM-D | ++ | ++ | 13/14 | 9/10 | + |
| MADRS | ++ | ++ | 6/7 | 14/15 | + |
| BDI | + | + | 9/10 | 13/14 | + |
| HADS | + | +/– | 7/8 | 10/11 | na |
| SDS | na | na | 50/51 | na | + |
| GDS 30 | ++ | ++ | 9/10 | 9/10 | na |
| GDS 15 | ++ | ++ | 2/3 | 4/5 | na |
| CSDD | na | na | 6/7 | na | na |
| CES-D | na | na | 15/16 | na | na |
| UPDRS part I | na | na | na | na | na |

# Parkinson Disease
## PD evaluation – Mood

### Anxiety

| Reference | Tool | Age | Type of anxiety reported | Individuals with Parkinson disease, n | Prevalence of anxiety in PD, % | MMSE score | H&Y score | "On"/ "off" status | Setting | Index test | Duration of motor symptoms, y | Tool specific cutoff | Sensitivity | Specificity | Likelihood ratio (+) | Likelihood ratio (−) | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 28 | BAI | 64.8 | Any anxiety | 342 | 34.0 | 28.5 | 2.0 (median) | "On" | Neurology and psychiatric clinics | M.I.N.I. (DSM-IV) | 8.2 (5.6) | 12/13 | 0.68 | 0.75 | 2.72 | 0.427 | 59 | 82 |
| 26 | GAI | 66.2 | Any anxiety | 58 | 28.0 | 29.1 | 2.5 (mean) | "On" | Neurology clinics | DSM-IV | 8.15 (NR) | 6/7 | 0.86 | 0.88 | 6.88 | 0.160 | NR | NR |
| 28 | HADS-A | 64.8 | Any anxiety | 342 | 34.0 | 28.5 | 2.0 (median) | "On" | Neurology and psychiatric clinics | M.I.N.I. (DSM-IV) | 8.2 (5.6) | 6/7 | 0.83 | 0.5 | 1.66 | 0.340 | 47 | 85 |

# Parkinson Disease
## PD evaluation – Cognition

Dementia associated with Parkinson's disease

- Diagnosis of Parkinson's disease
- Impairment in more than one cognitive domain
- Deficits severe enough to impair daily life
- Cognitive deficits: at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired freere call memory which usually improves with cueing)
- At least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness)

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# Parkinson Disease
## PD evaluation – Cognition

PD-MCI

- Cognitive deficits are not sufficient to interfere significantly with functional independence
- Level I (abbreviated assessment)
- Level II (comprehensive assessment)

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# Parkinson Disease
## PD evaluation – Cognition

### PD-MCI

Level1

| Assessment | Neuropsychological Tests[40] | Estimated Time of Test, min |
|---|---|---|
| Global cognition | MoCA[22,58] | 10 |
| | PD-CRS[24,59] | 15 |
| | SCOPA-COG[59,60] | 15 |
| | MDRS[23,59,61] | 20 to 30 |
| Estimated premorbid intelligence | NART[40] | 5 |
| | WTAR[40] | 5 |

Level2

| Cognitive Domain | Neuropsychological Tests[40] | Estimated Time of Test, min |
|---|---|---|
| Attention and working memory | WAIS-IV (or earlier version) Letter Number Sequencing | 5 |
| | WAIS-IV Coding (or earlier version) or other substitution task, written or oral | 5 |
| | Trail Making Test[a] | 5 to 10 |
| | Digit span backward or digit ordering | 5 |
| | Stroop color-word test | 5 to 10 |
| Executive function | Wisconsin Card Sorting Test (CST), or modified CST (Nelson's modification) | 15 |
| | Tower of London test–Drexel version, or Stockings of Cambridge (CANTAB) | 10 to 15 |
| | Verbal fluency test, such as letter fluency (COWAT or similar tests), category fluency (animals, supermarket, or similar), *or* alternating fluency tasks (if a well-standardized version is used). Not more than one verbal fluency test abnormality should be used to satisfy the MCI criterion of two abnormal test performances because of the strong relationship among these tests; 10 points Clock Drawing Test | 5 |
| Language | WAIS-IV (or earlier version) Similarities | 10 to 15 |
| | Confrontation naming task, such as Boston Naming Test (or short-form validated in PD) or Graded Naming Test | 5 to 15 |
| Memory[b] | Word list learning test with delayed recall and recognition conditions, such as Rey's Auditory Verbal Learning Test, California Verbal Learning Test, Hopkins Verbal Learning Test, and Selective Reminding Test | 10 to 20 |
| | Prose recall[3] test with a delayed recall condition, such as Wechsler Memory Scale-IV Logical Memory subtest (or earlier version) or Rivermead Behavioural Memory Test paragraph recall subtest | 10 to 15 |
| | Brief Visuospatial Memory Test–Revised (BVMT-R) | 10 to 15 |
| Visuospatial[c] function | Benton's Judgment of Line Orientation | 5 to 10 |
| | Hooper Visual Organization Test | 10 |
| | Clock copying (e.g., Royall's CLOX) | 5 |

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# Parkinson Disease
## PD evaluation – Non motor

Others:

- Neuropsychiatric inventory (NPI)
  - No obvious cut-off ?
- PDSS
  - 15 items
  - Insomnia, nocturia, nocturnal motor symptoms, etc
  - Visual analog scale (VAS) from 0 (severe or always present) to 10 (never or not present)
  - Below PDSS-total of 100 indicate abnormal sleep

# Parkinson Disease
## PD evaluation – Non motor

Others:

- Neuropsychiatric inventory (NPI)
  - No obvious cut-off ?
- Parkinson's disease sleep scale (PDSS)
  - 15 items
  - Insomnia, nocturia, nocturnal motor symptoms, etc
  - Visual analog scale (VAS) from 0 (severe or always present) to 10 (never or not present)
  - Below PDSS-total of 100 indicate abnormal sleep

# Parkinson Disease

## PD evaluation – Non motor

Others:

- Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (QUIP-RS)
  - 28-item patient-reported or clinician-rated scale
  - 0 (never) to 4 (very often)
  - Pathological gambling [PG ≥6], hypersexuality [HS ≥8], binge eating [CE ≥7], compulsive buying [CB ≥8]) , punding (≥7), hobbyism (≥7), compulsive medication use (CMU)
  - Vombined ICDs ≥10

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# Parkinson Disease

## PD evaluation – Non motor

Others:

- Parkinson's Disease Questionnaire (PDQ-39)
  - Assesses how often people with Parkinson's experience difficulties
    - 分數越高 生活品質越差
  - 8 dimensions of daily living