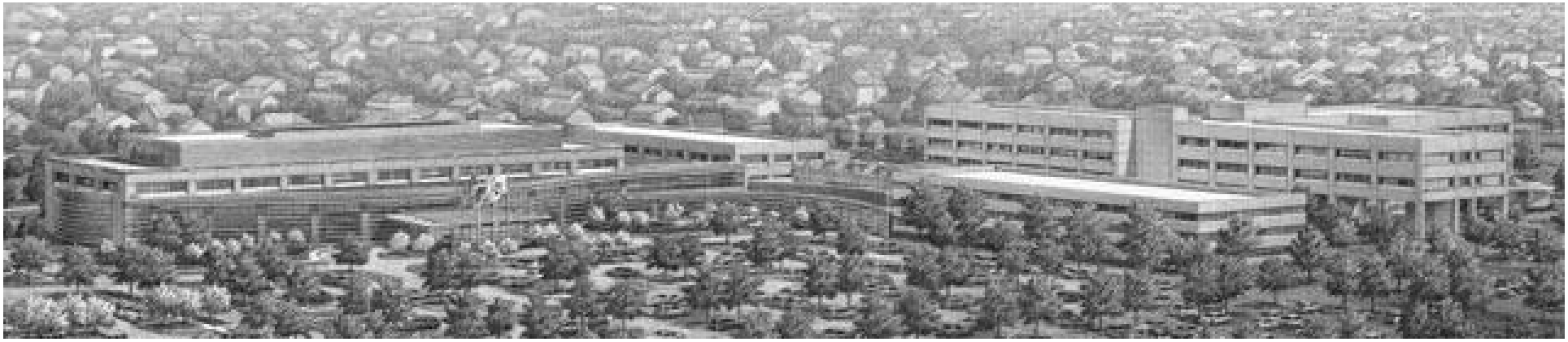


Updates in Parkinson's Disease

Ashvini P. Premkumar, MD
NorthShore Neurological Institute

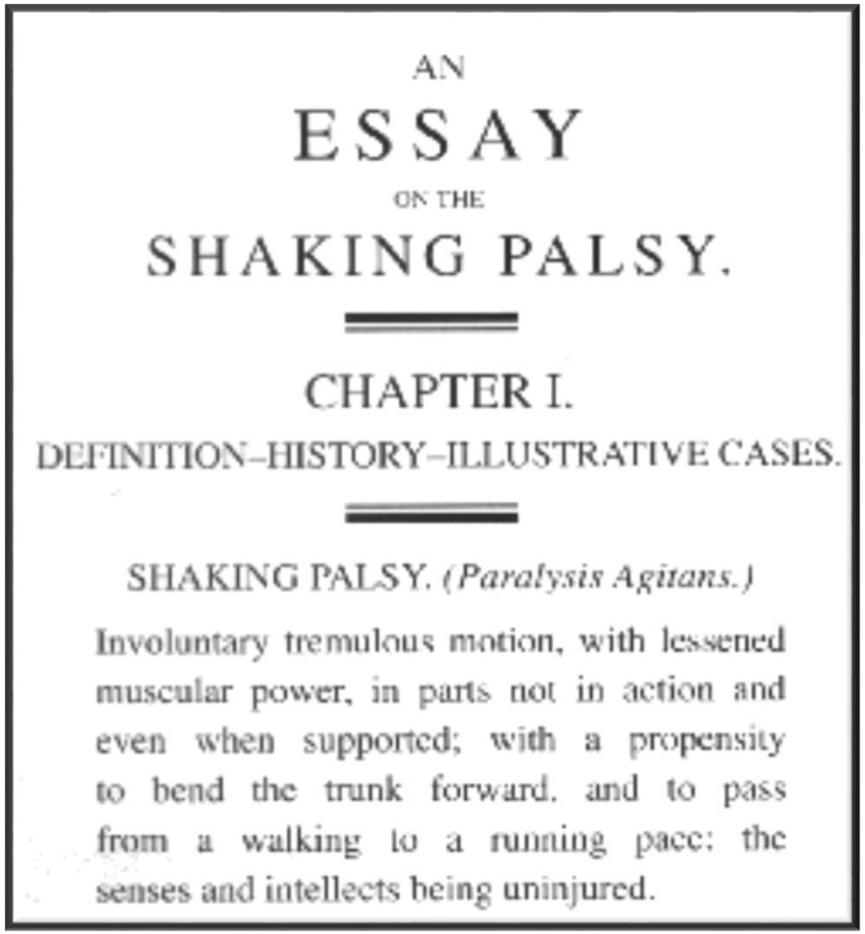
NorthShore University HealthSystem

NO DISCLOSURES

Objectives

- Be able to recognize nonmotor and motor manifestations of parkinson's disease
- Be able to recognize the pros/cons of different treatment strategies to optimize motor function
- Be able to recognize advanced surgical options

“The Shaking Palsy”



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 forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

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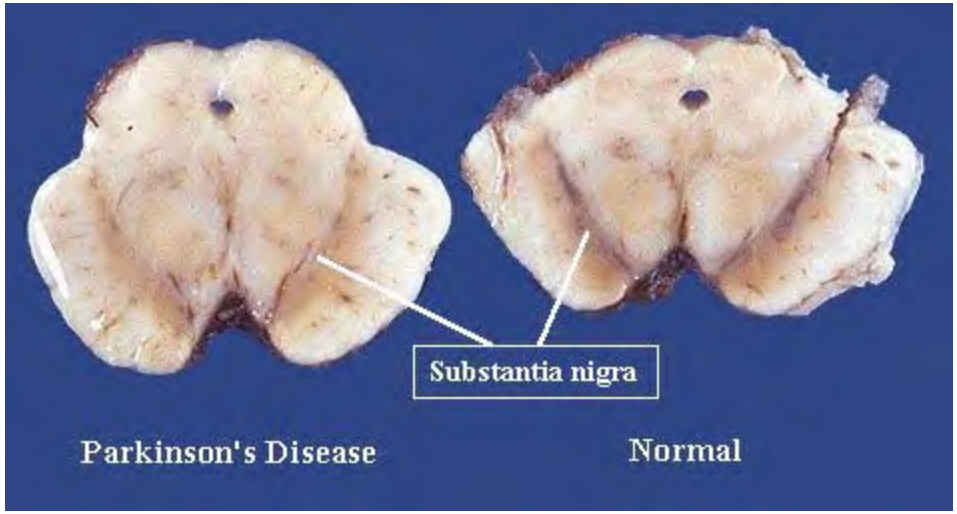
Parkinson’s disease



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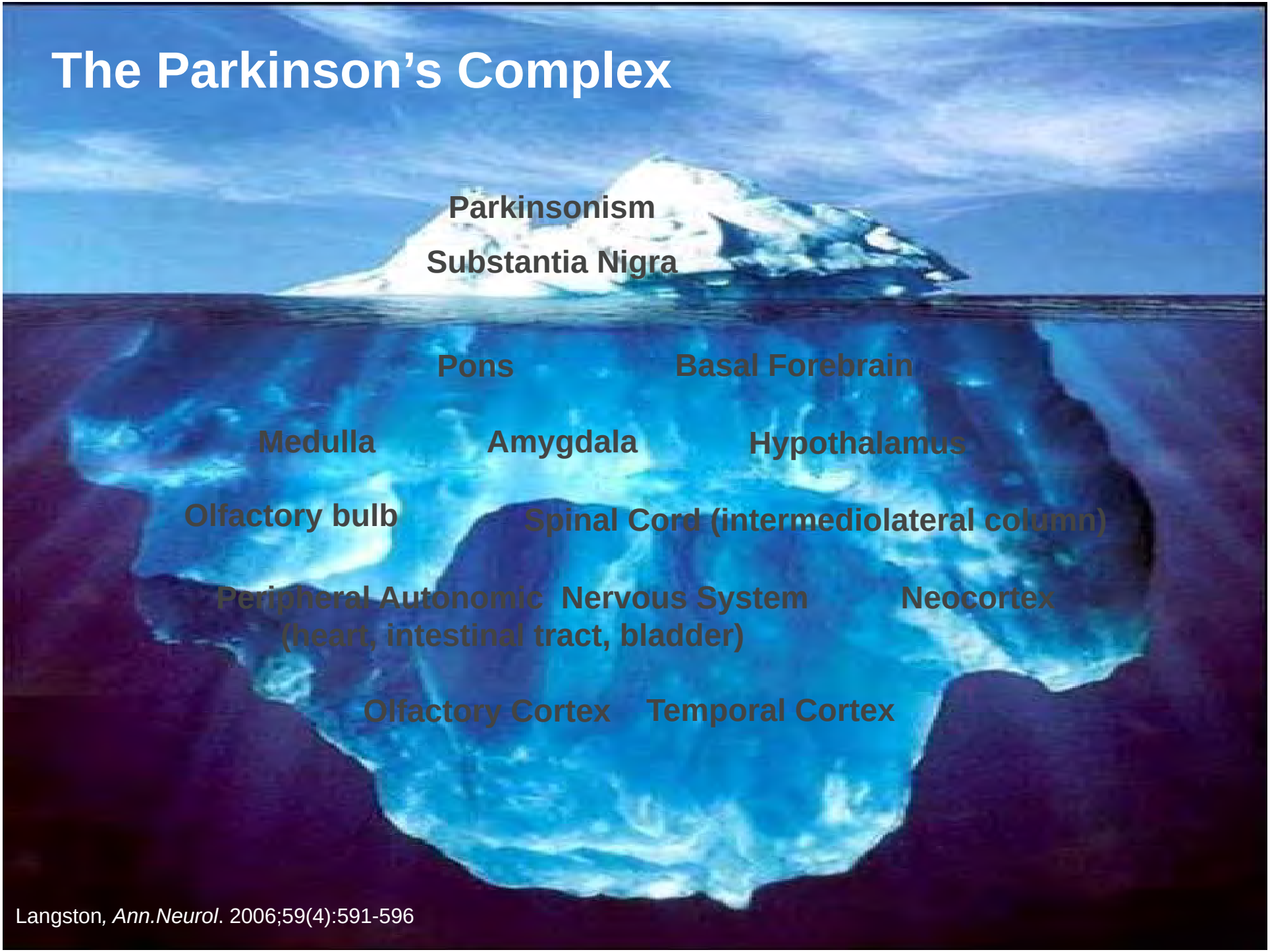
The Parkinson's Complex



Langston, *Ann.Neurol*. 2006;59(4):591-596

Symptoms of Parkinson's disease

Features of Parkinson's Disease	
Motor	
Bradykinesia	
Rigidity	
Tremor	
Postural Instability	

Chaudhuri K. et al, Lancet, 2006

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Symptoms of Parkinson's disease

Features of Parkinson's Disease	
Motor	**Nonmotor**
Bradykinesia	Alteration in memory, mood, and thinking (neuropsychiatric)
Rigidity	Sleep Disorders
Tremor	Autonomic Symptoms
Postural Instability	Gastrointestinal Symptoms
	Sensory Symptoms

Chaudhuri K. et al, Lancet, 2006

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Question: What impacts patients' quality of life the most when surveyed?

A. Motor
B. Non-motor
C. Both equally

Question: What impacts patients' quality of life the most when surveyed?

A. Motor
B. Non-motor
C. Both equally

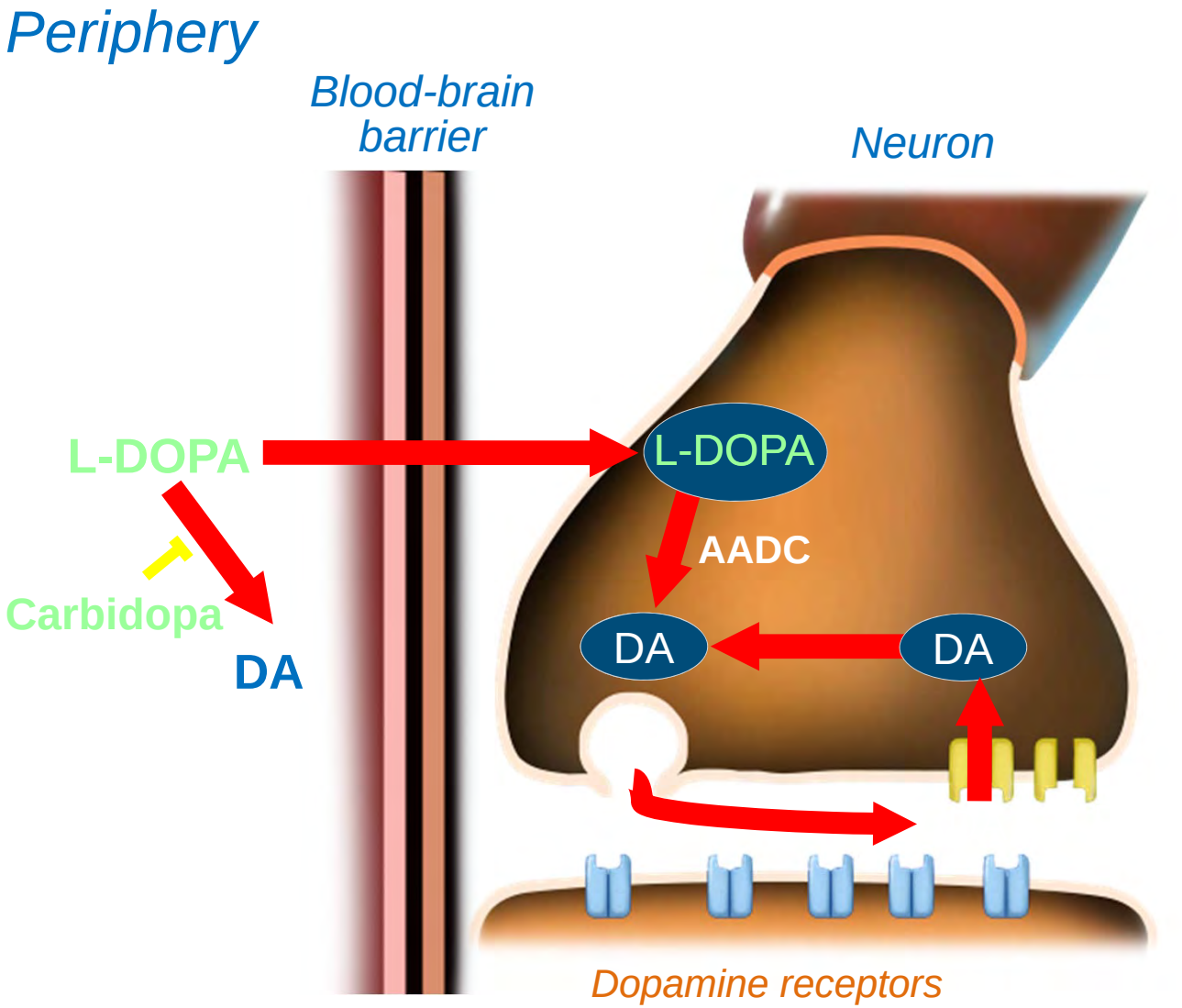
Tenets of Best Medical Treatment

- **Individualized** care
- Based on comprehensive assessment of both motor and nonmotor symptoms
- Understanding the importance of life individual circumstances
- Accounting for severity of disease

Foundation of current pharmacologic treatment strategies

- Current methods are aimed at treating the downstream effects of the disease process
- The goal of treatment is to increase the amount of dopamine
- Drugs targeted at other neurotransmitters

L-Dopa in PD



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Does Levodopa eventually stop working?

A. Yes
B. No

Does Levodopa eventually stop working?

A. Yes
B. No

Levodopa

- Early introduction of levodopa is associated with early appearance of levodopa related motor complications
  - These complications include dyskinesias and wearing off
  - Younger patients appear to be at higher risk
- In 4-6 years, about 40 percent will develop manifestations of this phenomenon
  - However, in the majority the motor complications were mild and not disabling

Ahlskog JE et al, Movement Disorders, 2001

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Treatment of Motor complications
Initiation of dopaminergic therapy

- In early 2000s, studies indicated that treating with dopamine agonist before levodopa delays the onset of motor complications
- Recently, long term usefulness of this strategy has been challenged
- Lancet 2014
  - Randomly assigned 1620 people with early PD to levodopa-sparing therapy (DA or MAOBI) or levodopa
  - 7 years of follow-up, self-reported scores on scales measuring mobility and QoL showed small but persistent benefits of starting treatment with levodopa rather than the other drugs

Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

*PD MED Collaborative Group**

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Levodopa - Pros and Cons

- Starting levodopa at diagnosis was associated with a better quality of life.
- Early levodopa therapy MAY normalize basal ganglia physiology
- Fewer neuropsychiatric side effects

- Early levodopa may be associated with motor complications

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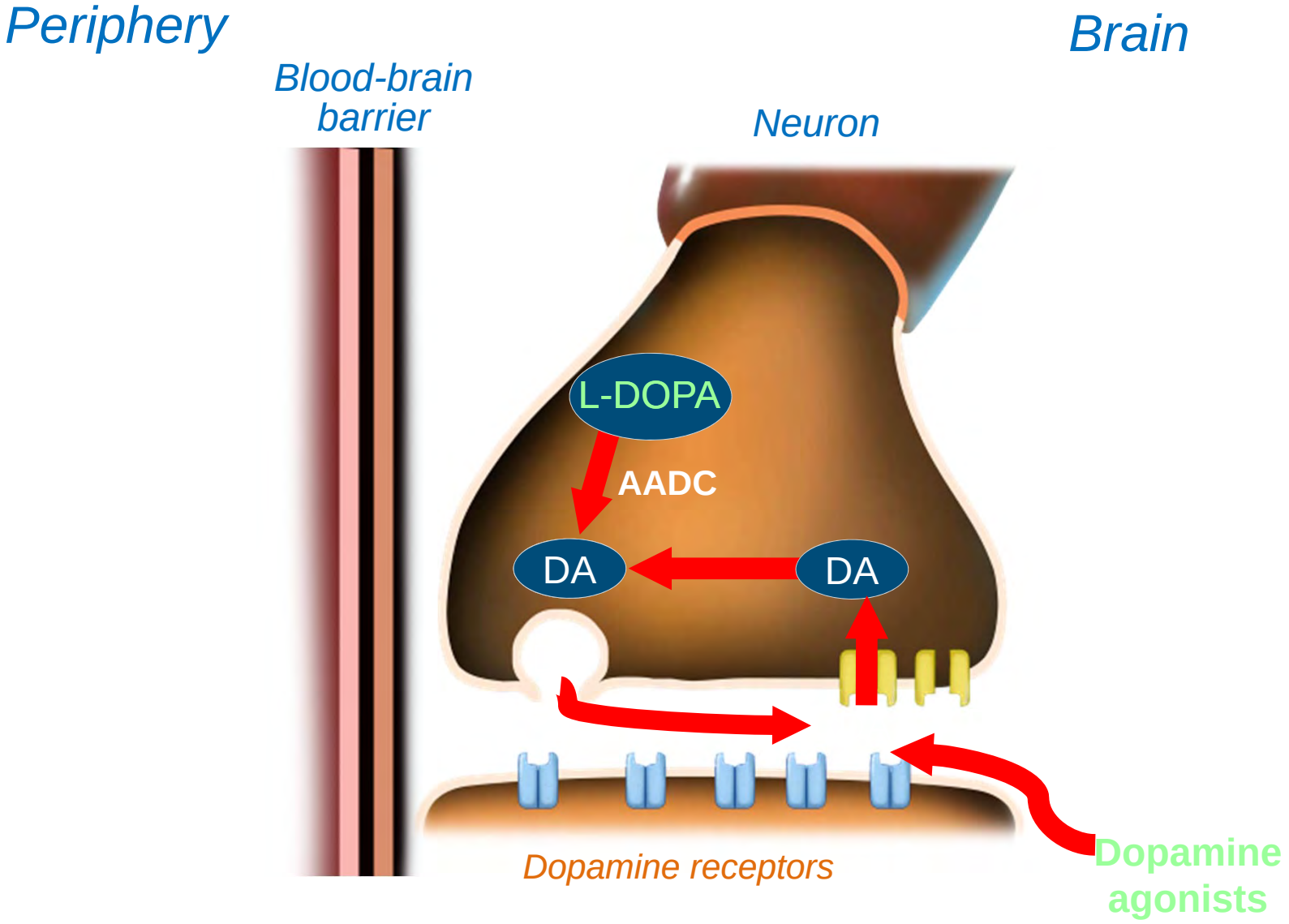
Medical Management of PD



Available Dopamine Agonists

- Pramipexole (*Mirapex*)
- Ropinirole (*Requip*)
- Rotigotine (*Neupro Patch*)
- Apomorphine (injection)
- Extended Release formulations provide more continuous dopaminergic stimulation and improved compliance

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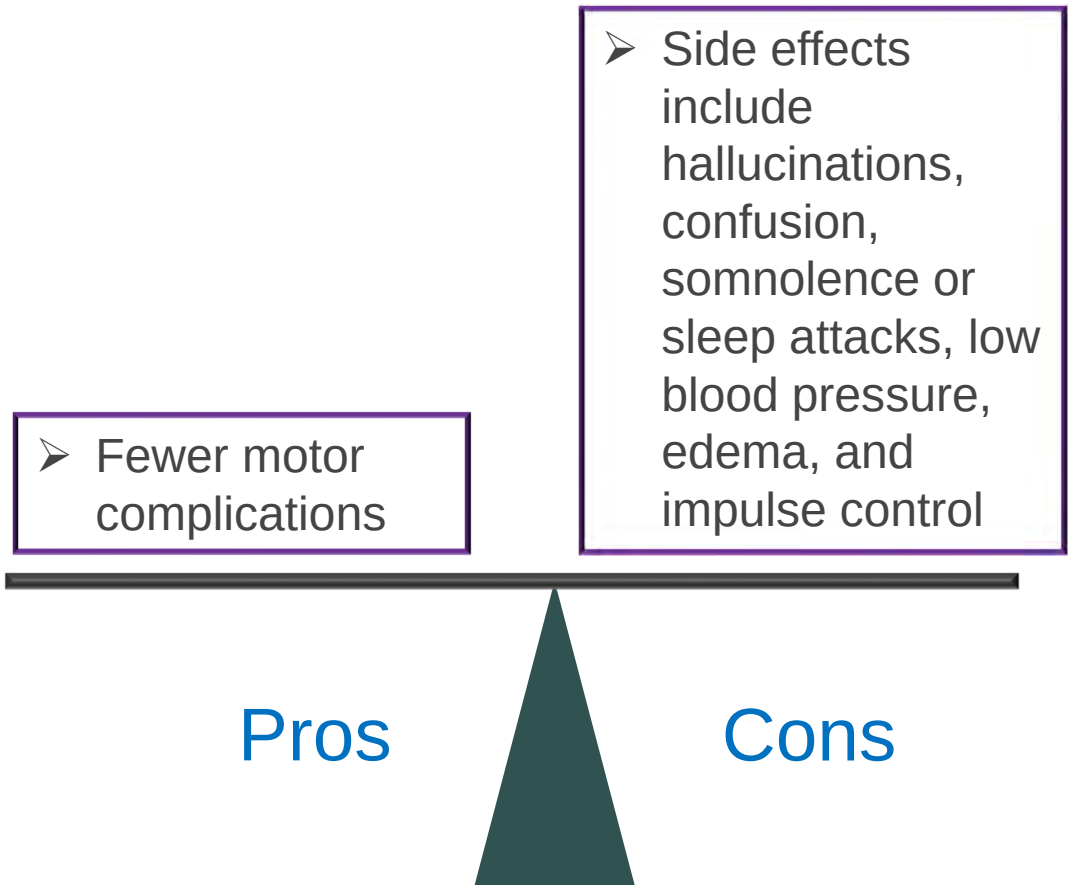
Dopamine agonists

- Can be used as the sole therapy in mild to moderate disease
- Used as adjunctive therapy in more advanced disease
- Levodopa is typically required in 2-5 years after diagnosis

Dopamine Agonists - Pros and Cons



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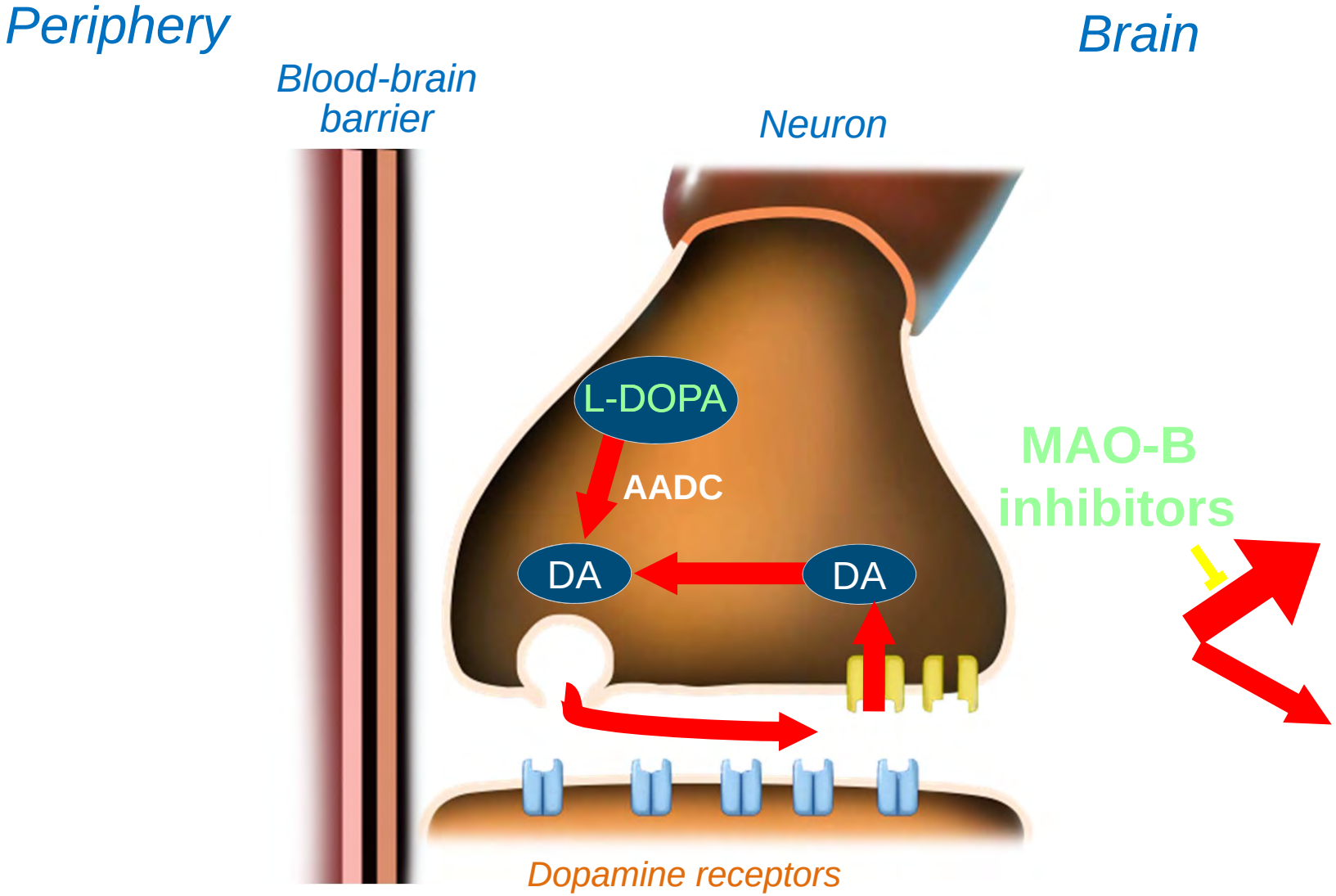
Medical Management of PD



MAOB Inhibitors

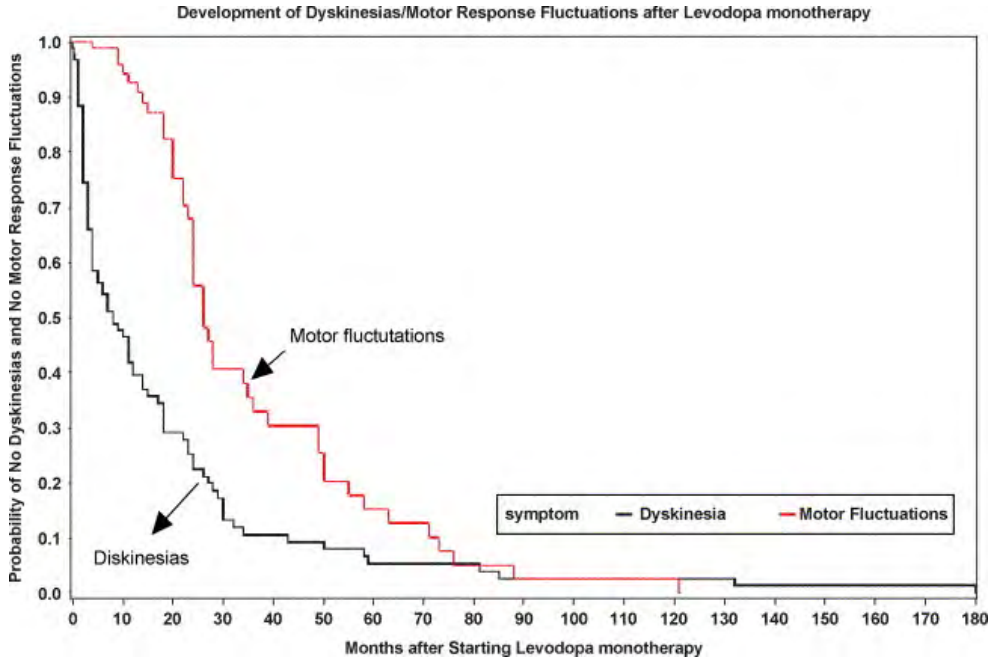
- Rasagaline (*Azilect*)
- Selegeline (*Eldepryl, Zelapar*)
- Safinimide (xadago)
- It is generally felt that MAOB inhibitors are less effective
- Used as sole therapy in mild disease and adjunctive therapy in moderate disease
- Due to a long half-life, once daily dosing is possible with a side effect profile similar to placebo

Non-Dopaminergic Therapy

- Anticholinergic agents (examples of which are trihexiphenidyl)
- Mainly effective for drooling and tremor
  - Unfortunately not as effective for rigidity, bradykinesia, and balance
- Side effects include confusion, dry mouth, constipation, urinary retention, and cognitive impairment
- Amantadine is another medication useful for tremor and dyskinesia

Medical Treatment of Advanced Disease-Fluctuations and Dyskinesias

- Incidence of fluctuations and dyskinesias increase with advancing disease



Mazzella L et al., Parkinsonism and Related Disorders, 2005

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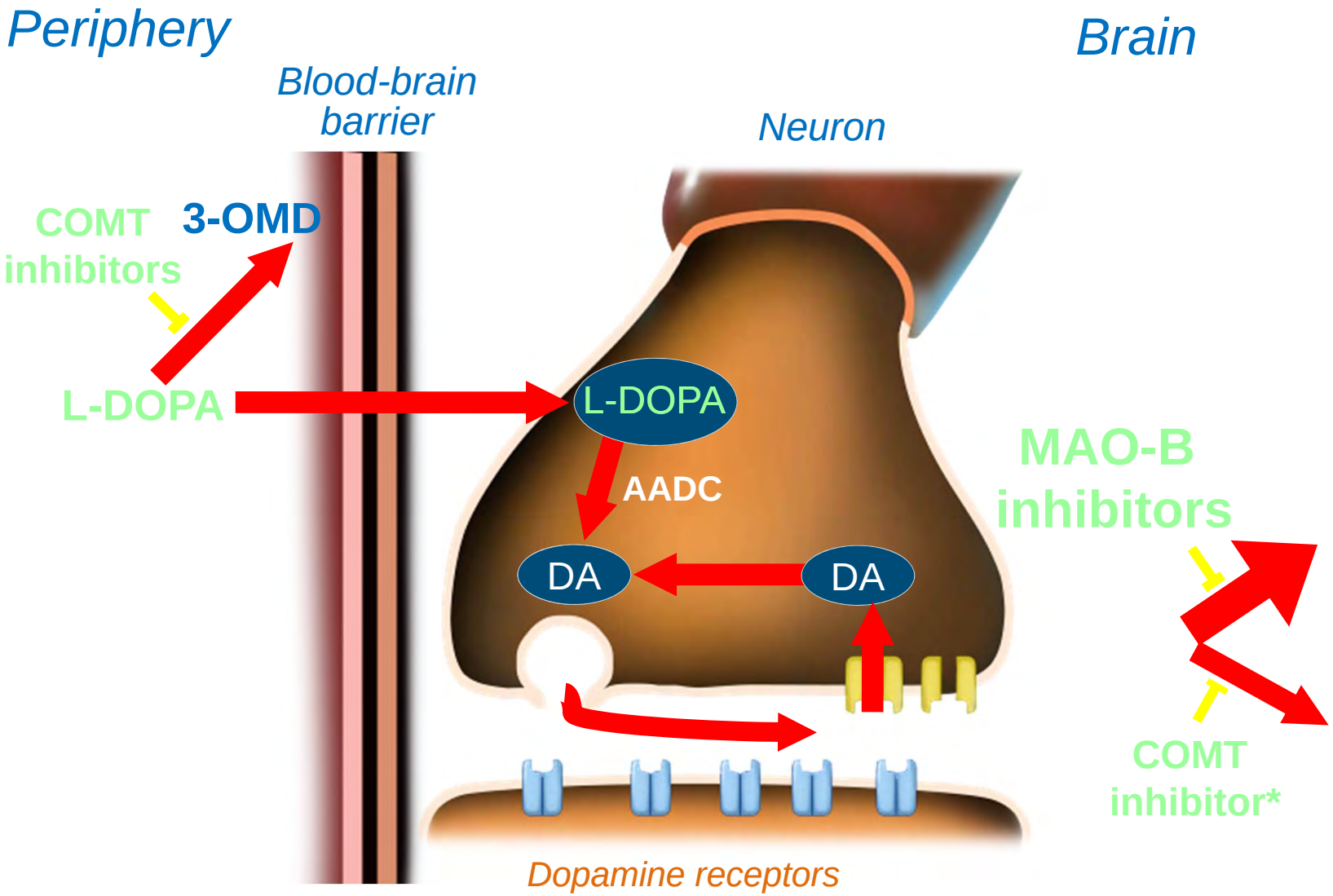
Treating fluctuations



Apomorphine

- Injectable dopamine agonist used for unpredictable severe wearing off periods
- Rapidly effective when injected under the skin
- Reaches full potency in 10 minutes-lasts 60 minutes
- Side effects of lightheadedness,nausea, dyskinesia, hallucinations, and injection site reaction

Treatment of Motor Fluctuations
Rytary (Dopaminergic therapy)

- Levodopa + carbidopa capsule, containing IR + ER pellets
- ADVANCE-PD (2013)
  - Randomized, double blind, placebo controlled study of 393 fluctuating PD patients comparing IR levodopa to Rytary
  - PD patients had at least 2.5 hours of “off” time underwent open label IR treatment, followed by 6 weeks open label Rytary dose conversion, then all randomized to 13 weeks double blind IR vs ER vs placebo
  - Primary endpoint: Off time
  - Results: Rytary reduced daily OFF time by 1.17 hours compared to IR levodopa
    - Reduced dosing frequency (3 per day vs 5 x /day)
    - FDA approved 2015

Lancet Neurol. 2013 Apr;12(4):346-56. doi: 10.1016/S1474-4422(13)70025-5. Epub 2013 Feb 26.

Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial.

Hauser RA[1], Hsu A, Kell S, Espay AJ, Sethi K, Stacy M, Ondo W, O'Connell M, Gupta S; IPX066 ADVANCE-PD investigators.

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Treatment of Motor Fluctuations
Inbrija (Dopaminergic Therapy)

- Inhaled levodopa
- FDA approved 12/2018 for the treatment of OFF periods in PD
  - 351 patients enrolled, randomized to placebo; 60mg or 84mg dose
  - Assessed at 12 weeks
  - Use up to 5 times per day for Off periods
  - Primary endpoint: Change in UPDRS iii, 30 min post dose
  - Results: Ibrija improved UPDRS scores by nearly 4 points compared to placebo (between-group difference -3·92 [-6·84 to -1·00]; p=0·0088)
  - Onset of action as early as 10 minutes, duration approx 60 min
  - Caution: lung disease; apparatus

Lancet Neurol. 2019 Feb;18(2):145-154. doi: 10.1016/S1474-4422(18)30405-8.

Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial.

LeWitt PA[1], Hauser RA[2], Pahwa R[3], Isaacson SH[4], Fernandez HH[5], Lew M[6], Saint-Hilaire M[7], Pourcher E[8], Lopez-Manzanares L[9], Waters C[10], Rudzínska M[11], Sedkov A[12], Batycky R[12], Oh C[12]; SPAN-PD Study Investigators.

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Motor Fluctuations
AP-CD/LD "Accordian Pill"

- Pill with multilayer films containing IR + IR/ER LD
- Phase II study of 34 PD patients showed AP-CD/LD was safe and reduced OFF time by 45% (nearly 2 hours) and reduced total number of levodopa doses (Lewitt et al. MovDisor.2014)
- Phase III study (ACCORDANCE)
  - 462 patients
  - Open label: 6 weeks of stabilization of levodopa dose, 6 weeks of conversion to AP
  - Randomized to double blind, 13 week tx with IR levodopa OR AP
- Primary endpoint: change in OFF time
- Phase 3 study completed enrollment

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Treatment of Dyskinesia
Amantadine

- Amantadine: Robust evidence for dyskinesia suppressing effects
- Glutamate antagonists
- New formulations of Amantadine (Gocovri – FDA approved 2017; Osmolex 2018)
  - RCT of 126 PD with dyskinesia randomized to ER Amantadine vs Placebo
  - Primary endpoint: Dyskinesia rating scale
    - Results: At 12 weeks, ER formulation reduced dyskinesia by -20.7 for ER vs -6.3 placebo (treatment difference -14.4, 95% confidence interval -20.4 to -8.3, P < .0001); ER formulation improved OFF Time by 0.6 hours
    - Note: No direct comparison between ER and immediate release

JAMA Neurol. 2017 Aug 1;74(8):941-949. doi: 10.1001/jamaneurol.2017.0943.

ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial.

Pahwa R[1], Tanner CM[2,3], Hauser RA[4], Isaacson SH[5], Nausieda PA[6], Truong DD[7], Agarwal P[8], Hull KL[9], Lyons KE[1], Johnson R[10], Stempien MJ[10].

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Surgical/Advanced Treatment of PD

- Levodopa Intestinal Infusion (Duopa)
- Deep Brain Stimulation
- MRI guided focused ultrasound

Levodopa Intestinal Infusion (Duopa)

- Intrajejunal infusion (bypasses gastric emptying problems → less variable plasma concentrations than oral formulations)
- Available in Europe since 2004
- FDA approved 2015 for advanced PD
  - 12 week, double blind, sham controlled trial
  - Randomized 71 pts with advanced PD to LCIG vs oral C/L
  - Primary endpoint: OFF time
  - Results: showed a mean reduction in Off time of 4.04 hours vs 2.14 hours in placebo group; effects maintained for up to 24 months
- Option for advanced PD patients not interested in pursing DBS
  - Keep in mind: Adverse events related to Duopa therapy have been cited to occur ~ 80%

Lancet Neurol. 2014 Feb; 13(2): 141–149. PMID: 24361112
Published online 2013 Dec 20. doi: 10.1016/S1474-4422(13)70293-X

Double-Blind, Double-Dummy, Randomized Study of Continuous Intrajejunal Infusion of Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease

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Deep Brain Stimulation

- 1997: FDA approved thalamic DBS for ET and PD
- 2002: FDA approved STN and Gpi DBS for PD
- When compared to best medical therapy, DBS:
  - ”On time” 4.6 hours per day
  - Higher rate of clinically meaningful motor improvement and improved quality of life (PDQ39)
- So what’s new?
  - Timing of surgery; target selection, surgical procedure , new technical developments

DBS – Timing

- Can early intervention preserve functional capacity?
- EARLY-STIM trial (2013)
- Effects of DBS at mid stage rather than later stage PD
  - 251 PD patients with symptom onset 4 years or more but motor complications < 3 years; average disease duration of 7.5 years , randomized to STN DBS + BMT vs BMT alone
    - Results: PDQ 39 improved by 26 % in DBS group and worsened by 1% in medical therapy group
    - Secondary outcomes: UPDRS III improved by 53% DBS vs 4% BMT and Med reduction 39% in stim group vs INC 21% in BMT
  - AE: depression more frequent in DBS group

N Engl J Med. 2013 Feb 14;368(7):610-22. doi: 10.1056/NEJMoa1205158.

Neurostimulation for Parkinson's disease with early motor complications.

Schuepbach WM[1], Rau J, Knudsen K, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider GH, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto JL, Bataille B, Maltête D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis JM, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y, Schade-Brittinger C, Deuschl G; EARLYSTIM Study Group.

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MRI-guided Focused Ultrasound for PD

- FDA approved for ET 2016
- FDA approved for tremor predominant PD 12/2018
  - 27 patients with tremor-predominant PD
  - Randomized in double blind, sham-controlled trial
  - Results: tremor scores improved 62% with FUS vs 22% with placebo; UPDRS motor

nt

JAMA Neurol. 2017 Dec 1;74(12):1412-1418. doi: 10.1001/jamaneurol.2017.3098.

Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial.

Bond AE[1], Shah BB[2], Huss DS[3], Dallapiazza RF[1], Warren A[1], Harrison MB[2], Sperling SA[2], Wang XQ[4], Gwinn R[5], Witt J[6], Ro S[6], Elias WJ[1].

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MRI-guided fUS for PD

- Things to consider
- Pros
  - Does not require surgical incision or generalized anesthesia
- Cons:
- Treatment effects and side effect profile/risk same as other “lesioning” procedures
  - Irreversible
  - Cannot be adjusted
  - Cannot be performed on both sides

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Future Treatments

- Subcutaneous Apomorphine
- Continuous subcuntaneous levodopa pump

Are there any disease modifying medications for Parkinson's disease

- Yes
- No

Are there any disease modifying medications for Parkinson's disease

- Yes
- No

REVIEW

Disease Modification in Parkinson's Disease: Current Approaches, Challenges, and Future Considerations

Anthony E. Lang, MD, FRCPC [1]* and Alberto J. Espay, MD, MSc [2]

[1]*Edmond J. Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada*
[2]*UC Gardner Neuroscience Institute and Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, Ohio, USA*

Summary

- Parkinson's disease cause both motor and nonmotor symptoms which impact patient's quality of life
- Motor fluctuations require multifaceted approach, with various medications- balancing benefits and side effects
- Advanced surgeries in the form of Intestinal infusion of Levodopa and Deep brain stimulation for treatment of advanced disease
- Great deal of research focused on neuroprotective therapies, improved surgical techniques, and better delivery of levodopa