



MAKING GOOD DECISIONS DURING THE EARLY AND MIDDLE STAGES OF PARKINSON'S DISEASE

PETER LIN, MD

MOVEMENT DISORDERS SPECIALIST

VALLEY PARKINSON CLINIC

LOS GATOS, CA

PARKINSON'S DISEASE: DEFINITION

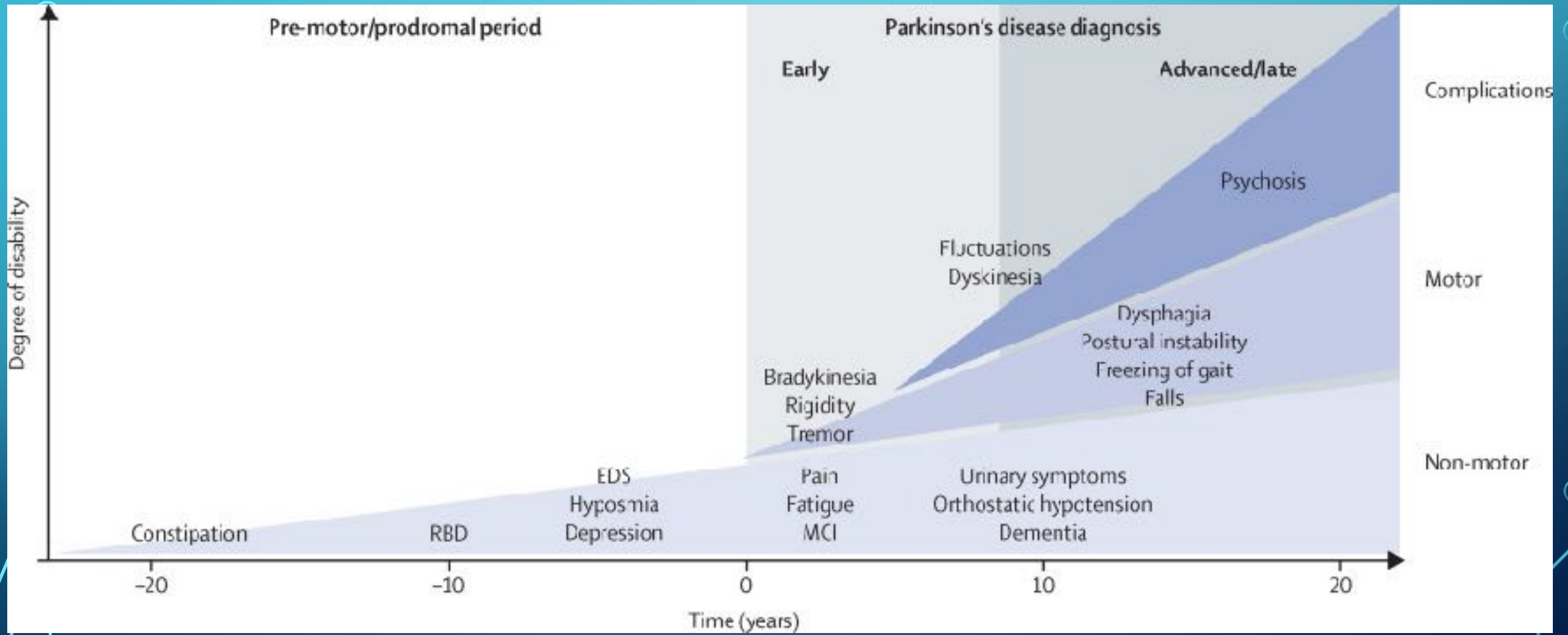
- Parkinson's Disease is a chronic neurodegenerative condition that spans several decades
- There is likely not a single Parkinson's disease but Parkinson's disease(s)
- Similar symptoms and signs allow for making diagnoses
- Symptoms may differ over time and dominate the picture

PARKINSON'S IS A MARATHON

- A long trajectory
- Requires endurance
- Challenging
- There can be obstacles along the way



PARKINSON'S DISEASE IS TYPICALLY RECOGNIZED BY **MOTOR** SYMPTOMS BUT THERE ARE ALSO MANY NONMOTOR SYMPTOMS



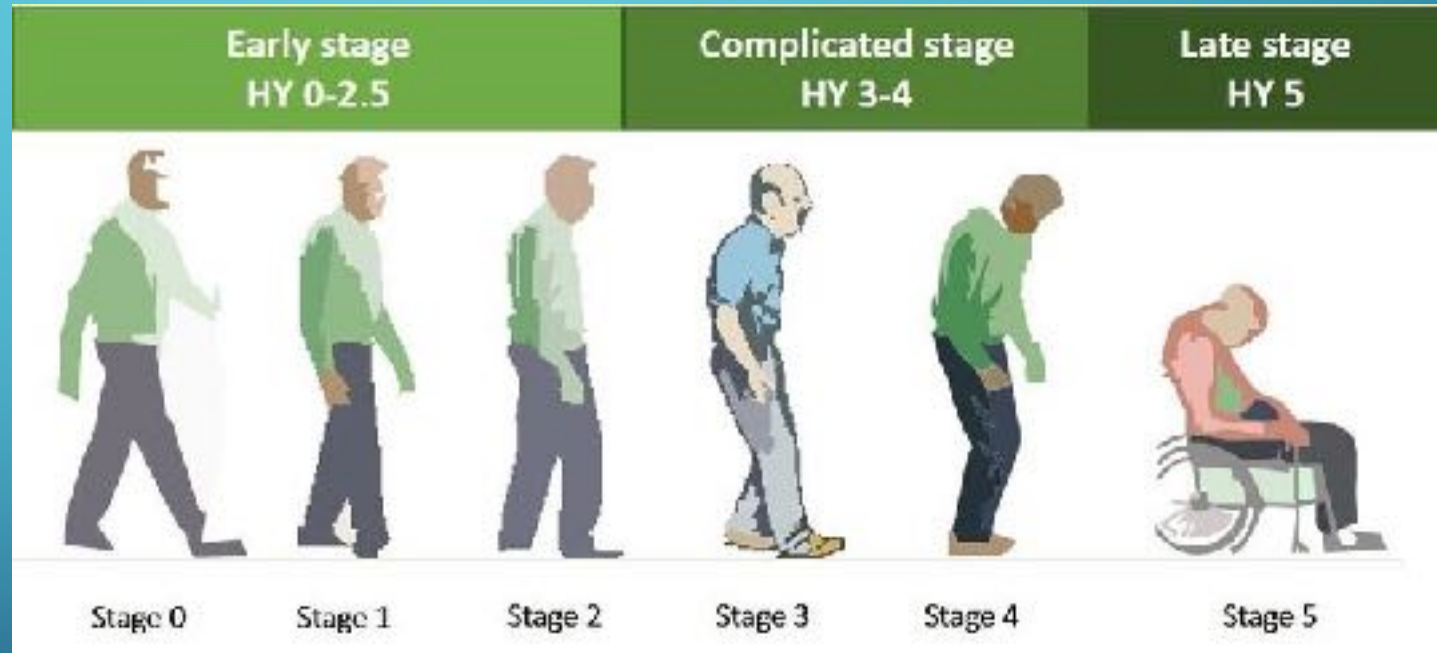
Kalia and Lang, 2015

STAGING OF PARKINSON'S DISEASE

- How is Parkinson's Disease staged?
- Clinical staging: Hoehn and Yahr (1967)
- Staging by time of disease
- Parkinson's disease likely precedes appearance of motor symptoms (premotor phase)

HOEHN AND YAHR CLINICAL STAGING

- Hoehn and Yahr H&Y Scale (1967)
- Progression to impairment of gait is a notable marker
- May be more useful for research studies



STAGES OF PARKINSON'S: BY YEARS

- Early (5-10 years)
- Middle (10-20 years)
- Advanced (20 years +)

EARLY STAGE

- First decade
- First 5 years often referred to as the “Honeymoon Period”
- Medications are typically reliable
 - Minimal wearing-off
 - No feeling of “ON”
 - Missing medications may not be noticed
 - Doses tend to be low (one tablet of Sinemet three-four times a day)
- Patients may be on one or no medications

“HONEYMOON” CATCHPHRASE: ABANDON?

- It is important to remember that not every patient with Parkinson’s will have the same symptoms, course or response to medications
- Some experts have recommended abandoning the term “Honeymoon Period” altogether
- Alternative terms suggested include “early untreated PD” or “initial treatment phase without response fluctuations”

Journal of Parkinson's Disease 13 (2023) 323–328
DOI 10.3233/JPD-225064
IOS Press

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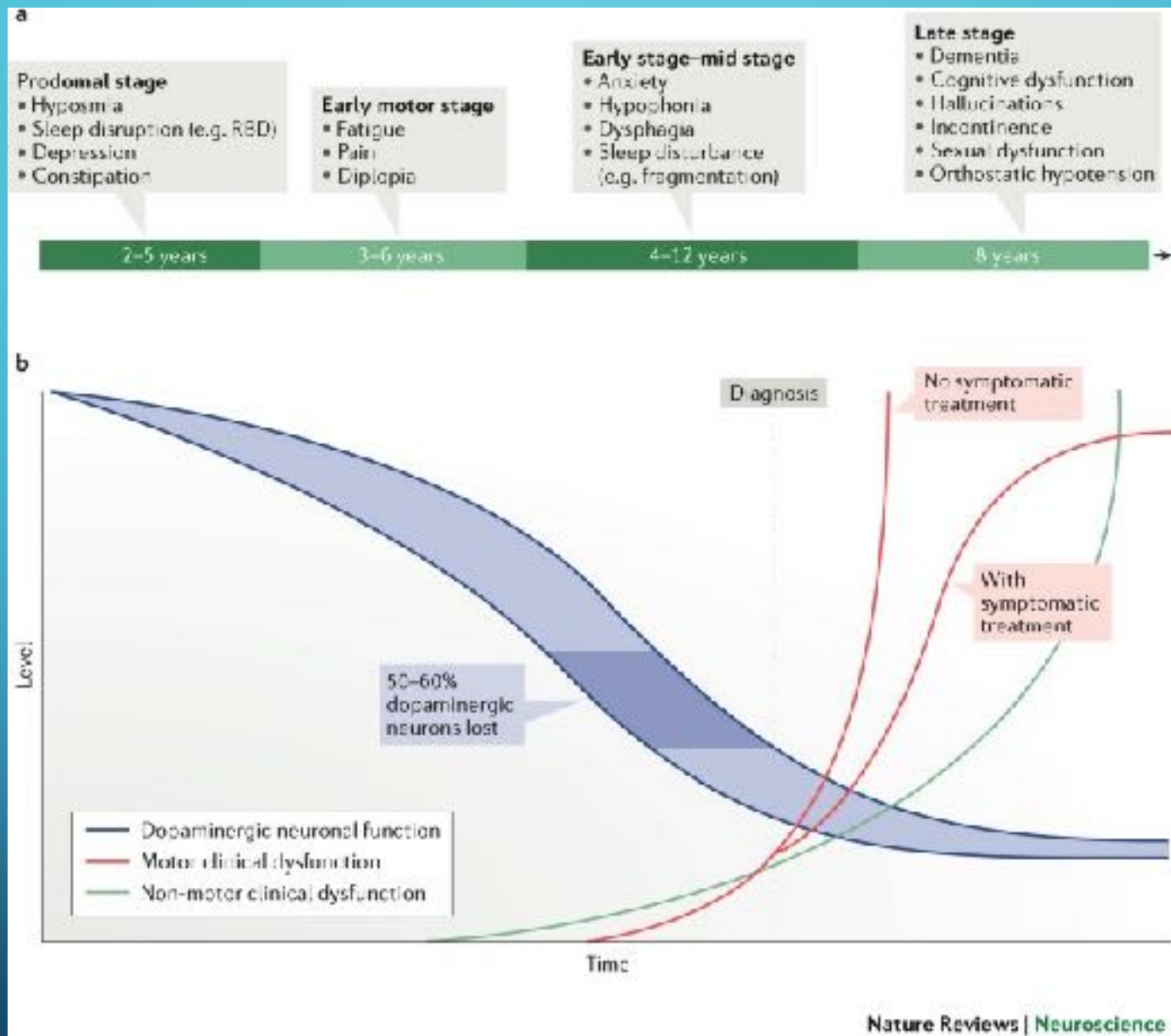
Commentary

The Early Treatment Phase in Parkinson’s Disease: Not a Honeymoon for All, Not a Honeymoon at All?

Araeeli Alonso-Canevas^{a,b,c,*}, Jos Voeten^e, Larry Gifford^d, Omotola Thomas^e, Andrew J. Lees^f
and Bastiaan R. Bloem^g

WHY IS THERE A “HONEYMOON PERIOD”?

- Surviving nigrostriatal neurons can buffer fluctuations in levodopa levels
- Motor symptoms may not show up until 60% of neurons are lost
- With continued degeneration, buffering capacity is lost and the motor symptoms began to match medication fluctuations
- Motor complications herald the beginning of middle stage



“GOOD” DECISIONS

- Clinical decision making may vary depending on many factors including individual patient features, physician choice, etc.
- There are few algorithms to guide medication selection or adjustment
- Often, what works and causes minimal problems is the best solution

DECISIONS IN THE EARLY STAGE

1. To start medication or not
2. Which medication to start?
3. Exercise and diet
4. Clinical trials

TO START MEDICATION OR NOT?

- Medication should be started to treat **symptoms**
- Symptoms that limit daily function should be a threshold for treatment
- "Limiting function" is very subjective
- Delaying medications does not change the progression of disease

WHICH MEDICATION TO START?

- Levodopa (Sinemet)

- Dopamine agonists

- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine patch (Neupro)

- MAO Inhibitors

- Selegiline (Eldepryl)
- Rasagiline (Azilect)

- Amantadine (Symmetrel)s

- Adenosine Receptor Antagonist

- Istradefylline (Nourianz)

- Anticholinergic

- Trihexyphenidyl (Artane)
- Benztropine

CHOICE OF MEDICATION

- Medication selection is guided by a variety of factors
 - Age
 - Comorbid conditions or side effect avoidance
 - Cost
 - Convenience of dosing
 - Medication interactions
- Medication selection is best decided by active discussion between the patient and the physician

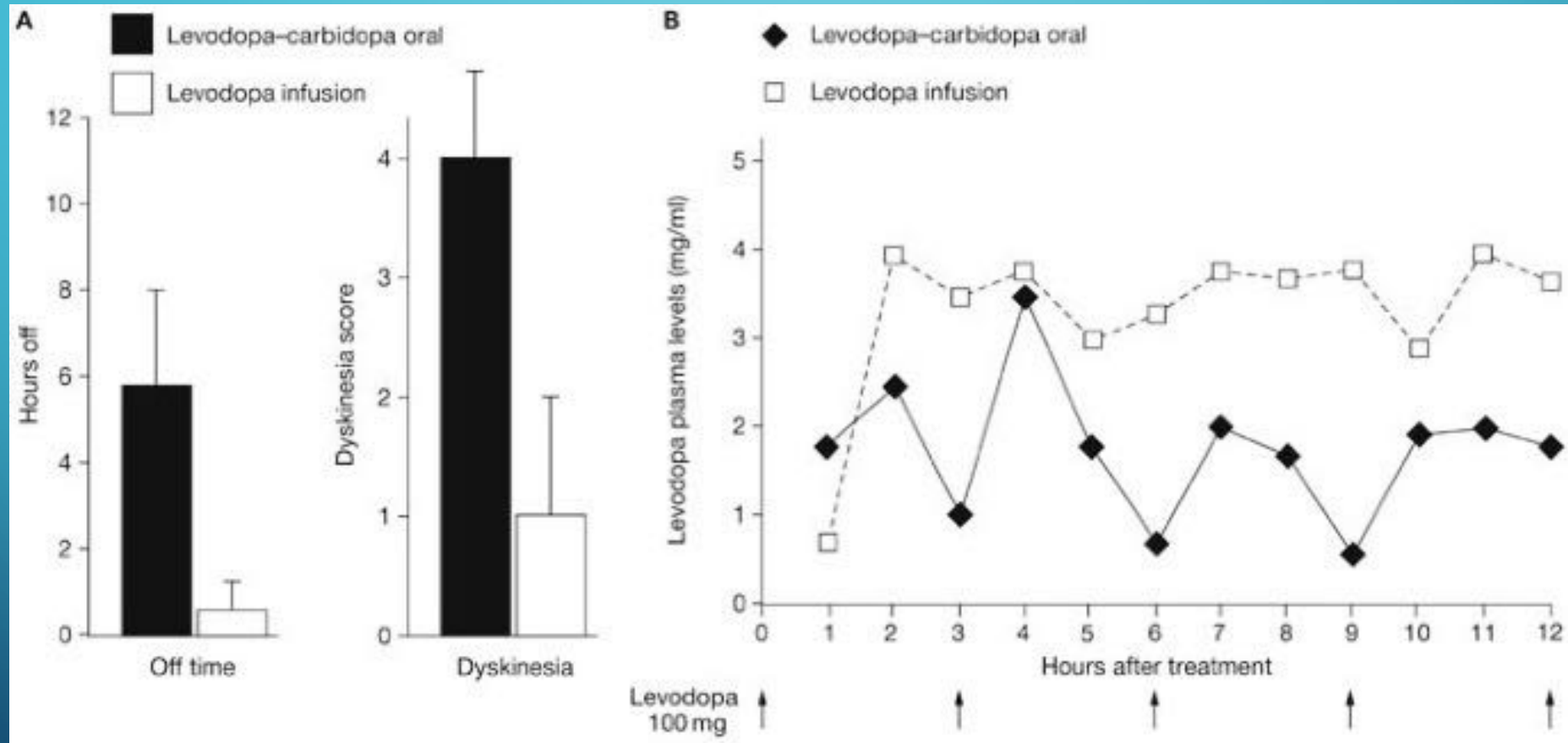
LEVODOPA CONTROVERSY

- Levodopa (Sinemet) is the most effective medication for the majority of symptoms
- However, levodopa is associated with the development of involuntary movements (dyskinesias) over the next 5-7 years
- Dyskinesias can be difficult to treat because the options are limited (lowering dose, Amantadine or surgical treatment)
- Concern for complications has led to a “levodopa-phobia” in the field

CONTINUOUS DOPAMINERGIC STIMULATION

- Animal and clinical studies suggest continuous and not pulsatile stimulation of dopamine receptors may reduce the risk of developing dyskinesia
- Only limited medication formulations allow for continuous stimulation
- Continuous stimulation options tend to be more expensive
 - Neupro patch
 - Ropinirole or Mirapex Extended Release
 - Subcutaneous levodopa or Apomorphine infusion (coming soon)

PULSATILE LEVODOPA COULD LEAD TO DYSKINESIAS



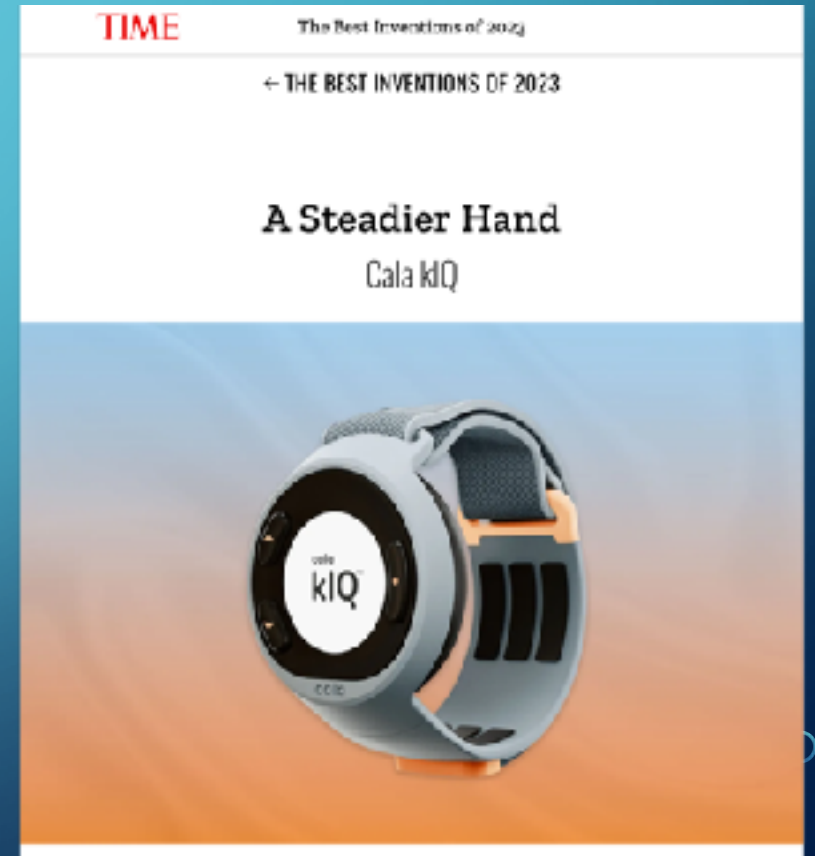
Olanow et al., 2006

AVOID LEVODOPA?

- In many cases, levodopa eventually is the best medication for most patients
- Trial and error approach with other medications could be feasible
- No real consensus as to which medication to start with

TREMOR DOMINANT PARKINSON'S

- Cala KiQ device may be useful for rest tremor in some patients
- Is a neuromodulation treatment and not medication
- Not covered currently.



EXERCISE

- Exercise is recommended at all stages of PD if possible
- 3 to 4 hours a week of moderate to severe intensity exercise has been the only proven intervention to slow progression of PD
- More important to pick exercises that are enjoyable to sustain motivation and interest
- Examples: Swimming, dancing, boxing, yoga, tai-chi, bicycling, taiko drumming

Exercise and physical activity can improve many motor and non-motor Parkinson's symptoms:



Aerobic Activity

3 days/week for at least 30 mins per session of continuous or intermittent at moderate to vigorous intensity

TYPE: Continuous, rhythmic activities such as brisk walking, running, cycling, swimming, aerobics class

CONSIDERATIONS: Safety concerns due to risks of freezing of gait, low blood pressure, blunted heart rate response. Supervision may be required.



Strength Training

2-3 non-consecutive days/week for at least 30 mins per session of 10-15 reps for major muscle groups; resistance, speed or power focus

TYPE: Major muscle groups of upper/lower extremities such as using weight machines, resistance bands, light/moderate handheld weights or body weight

CONSIDERATIONS: Muscle stiffness or postural instability may hinder full range of motion.



Balance, Agility & Multitasking

2-3 days/week with daily integration if possible

TYPE: Multi-directional stepping, weight shifting, dynamic balance activities, large movements, multitasking such as yoga, tai chi, dance, boxing

CONSIDERATIONS: Safety concerns with cognitive and balance problems. Hold on to something stable as needed. Supervision may be required.



Stretching

>2-3 days/week with daily being most effective

TYPE: Sustained stretching with deep breathing or dynamic stretching before exercise

CONSIDERATIONS: May require adaptations for flexed posture, osteoporosis and pain.

DIET

- Mediterranean Diet
 - Fruits, Vegetables, Whole Grains
 - Seeds, Nuts, Olive Oil
 - Plant based foods
 - Seafood, dairy, Chicken/Turkey/Eggs
 - Avoid red meat and sweets
- High fiber
- Drink plenty of water
- Consume alcohol in moderation
- May avoid taking Sinemet with high protein meals (30 min. before or after meal)

CLINICAL TRIALS

- Clinical trial opportunities exist for both early and middle stage patients
- Depending on the stage, patients may participate in neuroprotective trials or symptomatic treatment trials
- Most studies do not interfere with clinical treatment by your neurologist

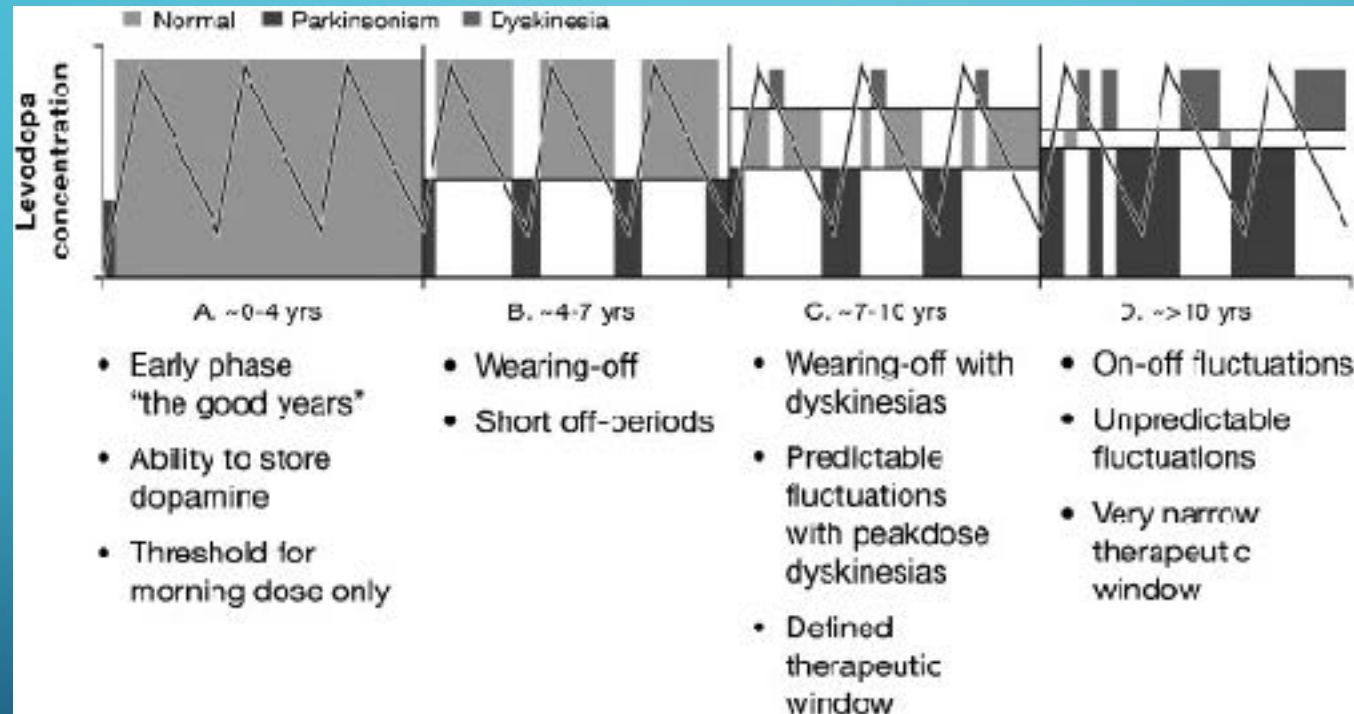
EARLY STAGE CLINICAL TRIALS

- Many trials focus on patients who are not on symptomatic therapies or have not started therapy
- May allow for access to treatments that prevent progression of Parkinson's (neuroprotection)
- But may restrict starting medications for symptomatic benefit

MIDDLE STAGE

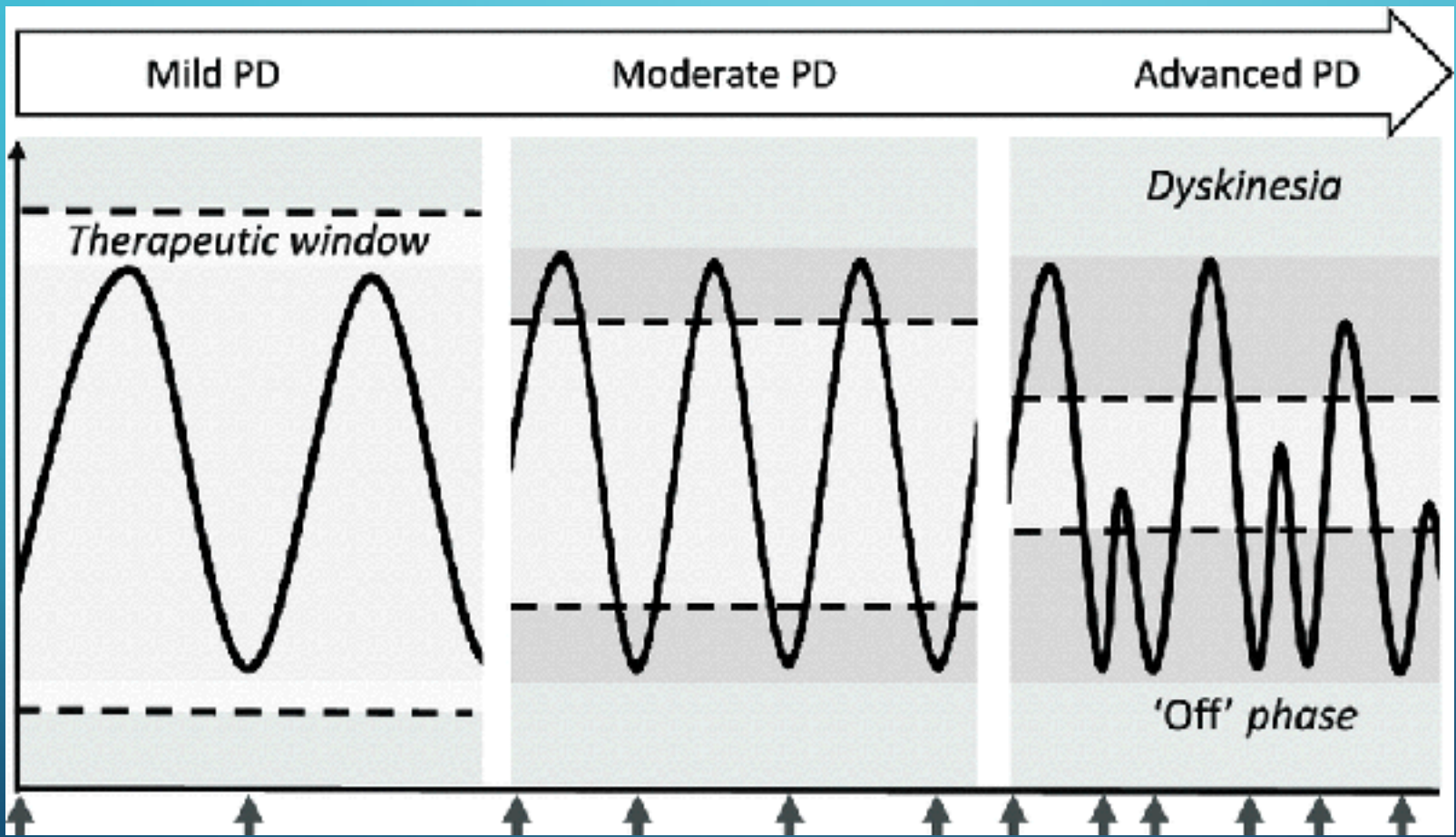
- Motor complications (fluctuations)
- Dyskinesias
- Loss of balance with falls
- Nonmotor symptoms

MOTOR COMPLICATIONS HERALD MIDDLE TO ADVANCED STAGES



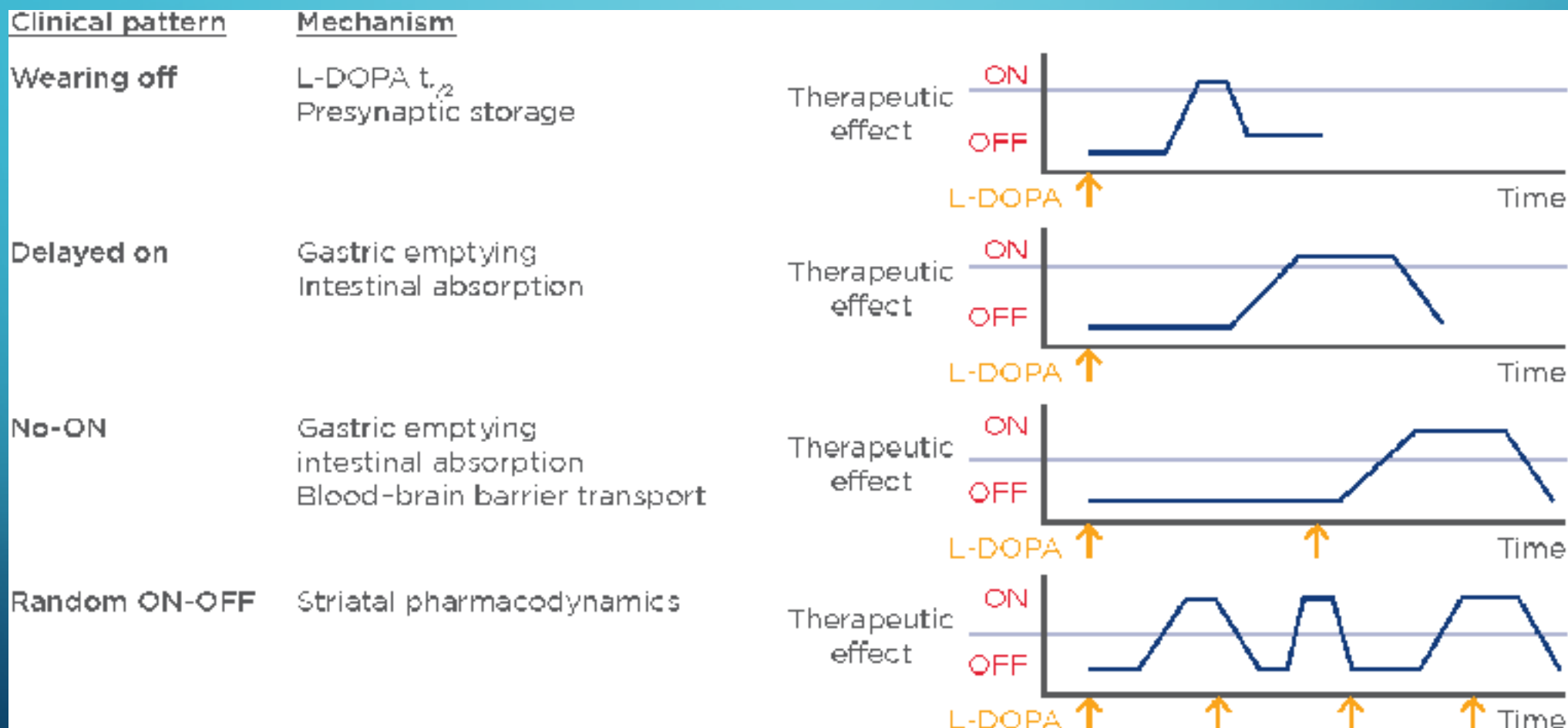
Nyholm, 2007

MIDDLE STAGE: NARROWING OF THE THERAPEUTIC WINDOW

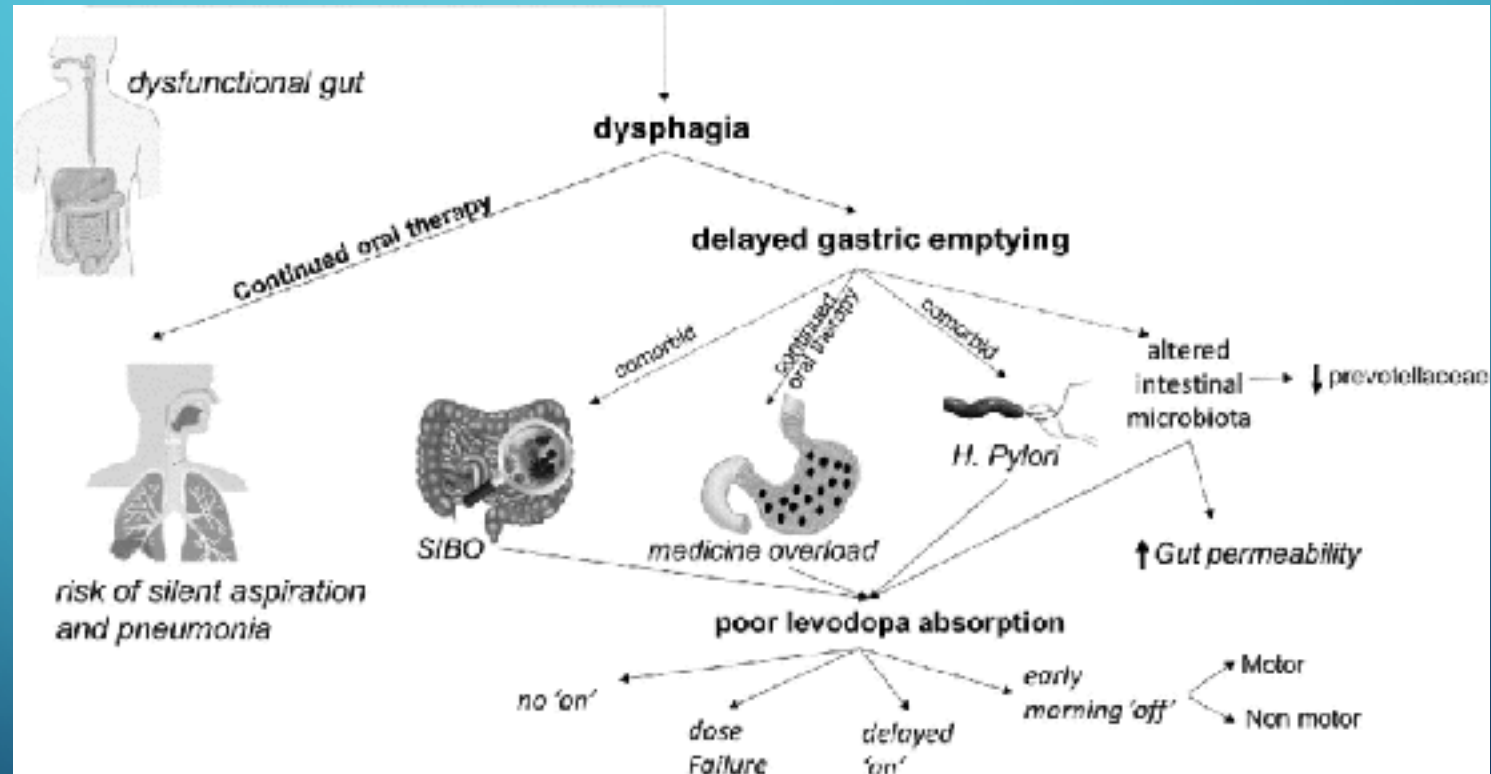


Keun et al., 2021

MOTOR FLUCTUATIONS



MOTOR FLUCTUATIONS ARE OFTEN DUE TO CHANGES IN GASTROINTESTINAL FUNCTION



Chaudhuri et al., 2016

DECISIONS IN THE MIDDLE STAGE

1. Maintain status quo or change medications (add or adjust)
2. Dyskinesia management and surgery
3. Nonmotor symptoms
4. Assistive devices
5. Clinical trials

MEDICATION ADJUSTMENTS

- Medication adjustment should be made to address changes in motor control but also keep in mind potential for side effects
- Often adding a dose helps improve control
- Adding medications can be helpful but can also introduce new risk
- Nonoral medications may be useful due to gastrointestinal issues

RESCUE MEDICATIONS

- One may choose to use rescue meds for OFF time rather than change daily schedule
- Using rescue meds as needed may avoid persistent dose escalation
- Rescue meds work faster since they are not absorbed through the GI system
- Rescue meds may be expensive

ON-DEMAND "RESCUE" THERAPIES

- Inbrija – inhaled levodopa for OFF time



- Apokyn – subcutaneous injection for OFF



DYSKINESIA

- Dyskinesias are involuntary movements triggered by medication doses
- Lowering the dose of levodopa or adding Amantadine is standard
- If dyskinesias are difficult to manage, surgical therapy may be warranted

SURGERY

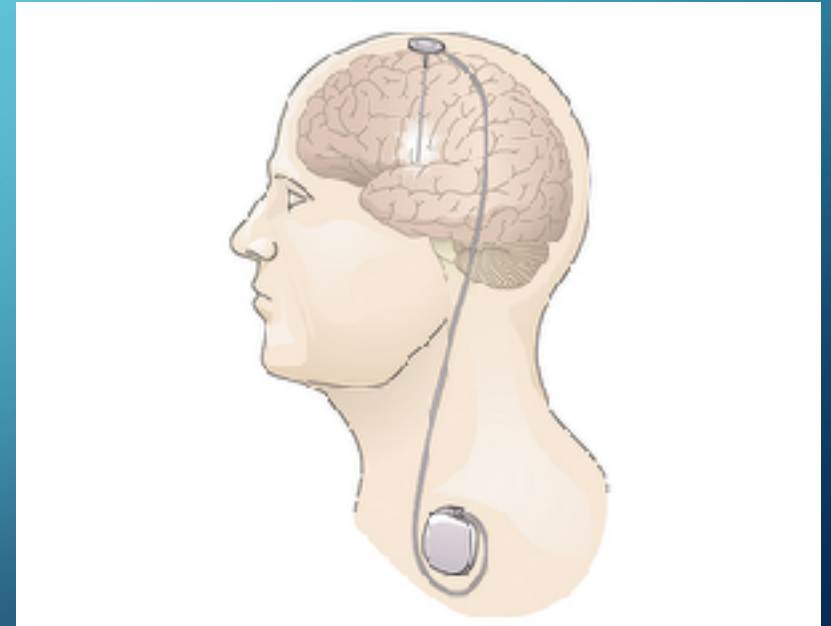
- When is the right time to pursue surgery?
- Typical Indications for surgery
 - Waning medication responsiveness
 - Complications of medications
 - Lack of significant cognitive or psychiatric symptoms
- Surgery may be invasive (DBS) or noninvasive (MRGFUS)

IS EARLY SURGERY AN OPTION?

- Not typically in the United States
- FDA approved in 2016 DBS for Parkinson's disease with at least 4 years of disease and at least 4 months of motor complications
- Some evidence (EARLYSTIM) that early DBS surgery slows rate of decline
- MR-Guided Focused Ultrasound (MRGFUS) is a noninvasive surgical procedure that can be used in early stage patients whose symptoms do not respond to medications (tremor predominant)

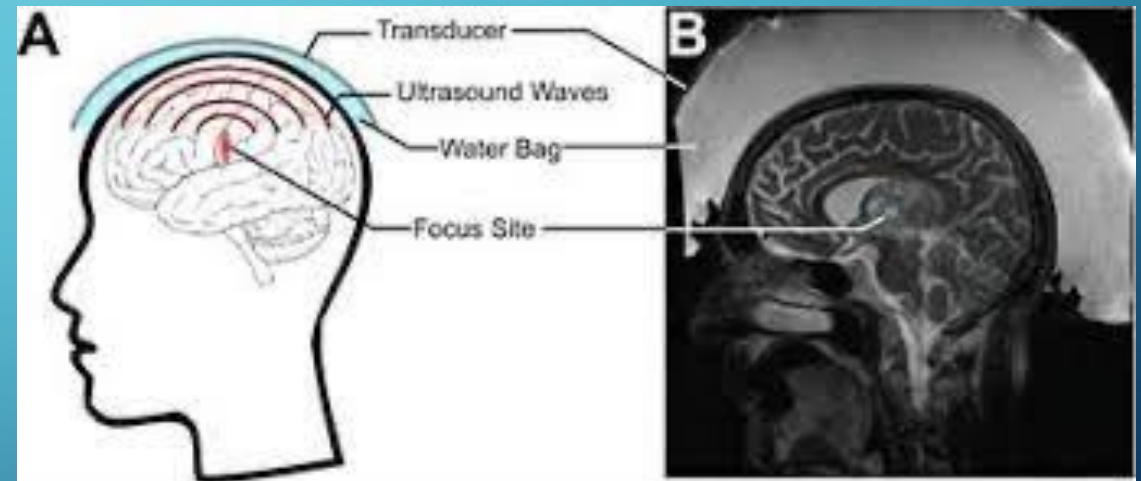
DEEP BRAIN STIMULATION

- A robust form of electrical therapy that is used to treat Parkinson's symptoms
- Implanted surgically
- Strict criteria for candidacy
- Adjustments are made in clinic based on symptoms



MR GUIDED FOCUSED ULTRASOUND (MRGFUS)

- A noninvasive lesion based therapy using MRI guidance and ultrasound waves
- Best for patients with unilateral tremor
- Bilateral surgeries can be performed separated > 6 months apart



NONMOTOR SYMPTOMS

- Cognitive
 - Memory
 - Visuospatial function
- Genitourinary
 - Nocturia
 - Erectile dysfunction
 - Incontinence
- Orthostatic hypotension
- Pain
- Changes in smell, taste
- Drooling, sweating
- Constipation
- Psychosis
 - Hallucinations
 - Delusions

ASSISTIVE DEVICES

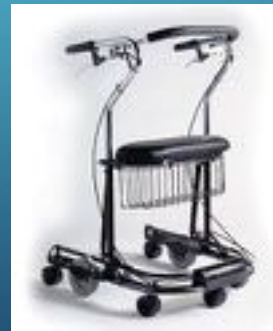
- Cane



- Walking poles



- Walker



ASSISTIVE DEVICES

- Walking may be limited by changes in balance, freezing or dyskinesias
- Uneven environments can present challenges and increase risk of falls
- Devices can facilitate safe navigation
- Occupational and physical therapy referrals can help selection

MIDDLE STAGE CLINICAL TRIALS

- Trials may focus on management of middle stage symptoms:
 - motor fluctuations
 - dyskinesias
 - nonmotor symptoms
- Are not precluded from neuroprotective treatments
- Some trials involve surgery or novel devices (Vibrotactile glove, DBS)

CLINICAL TRIALS: WHERE TO FIND?

- Michael J. Fox Foundation - <https://www.michaeljfox.org/join-study>
- <https://clinicaltrials.gov> – search for Parkinson’s disease
- Academic center websites: Stanford or UC San Francisco
- Ask your neurologist

GENERAL ADVICE ACROSS STAGES

- Recommend routine follow-up with your neurologist or a movement specialist
 - Quarterly (every 3 months)
 - More frequent if need to observe response to therapy
- Participation in support groups
- Stay active with regular exercise
- Pay attention to nonmotor symptoms as much as motor symptoms
- Follow up with primary medical doctor for health maintenance and screening