



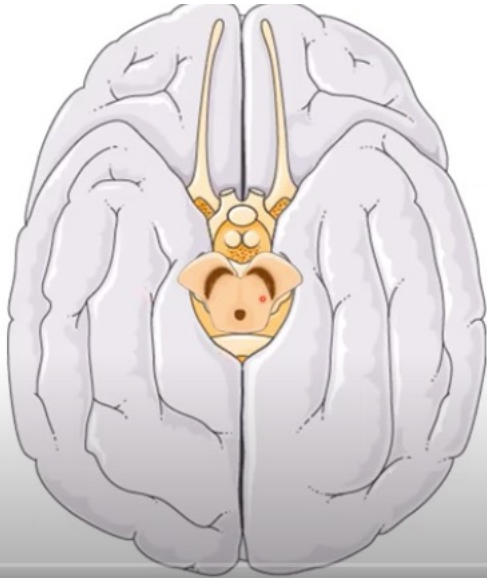
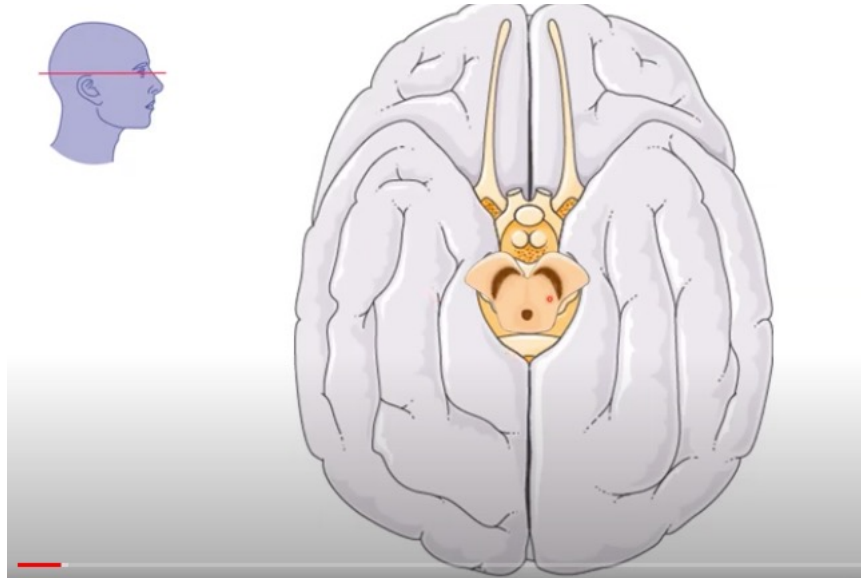
## Getting the best treatment for your Parkinson's Disease

Leila Montaser Kouhsari, MD, PhD

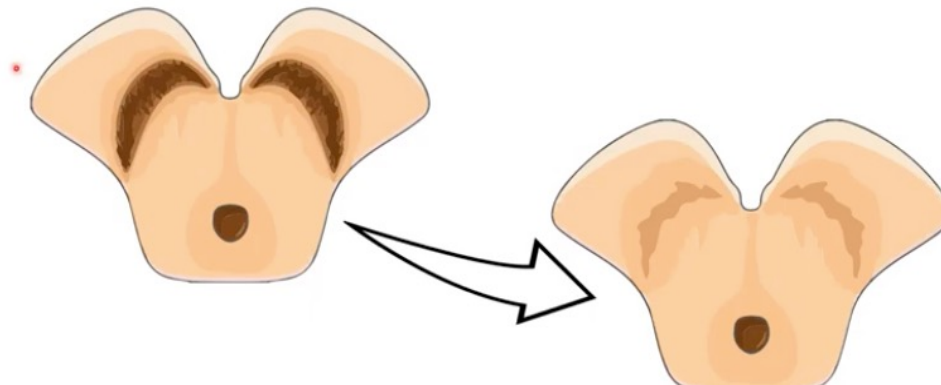
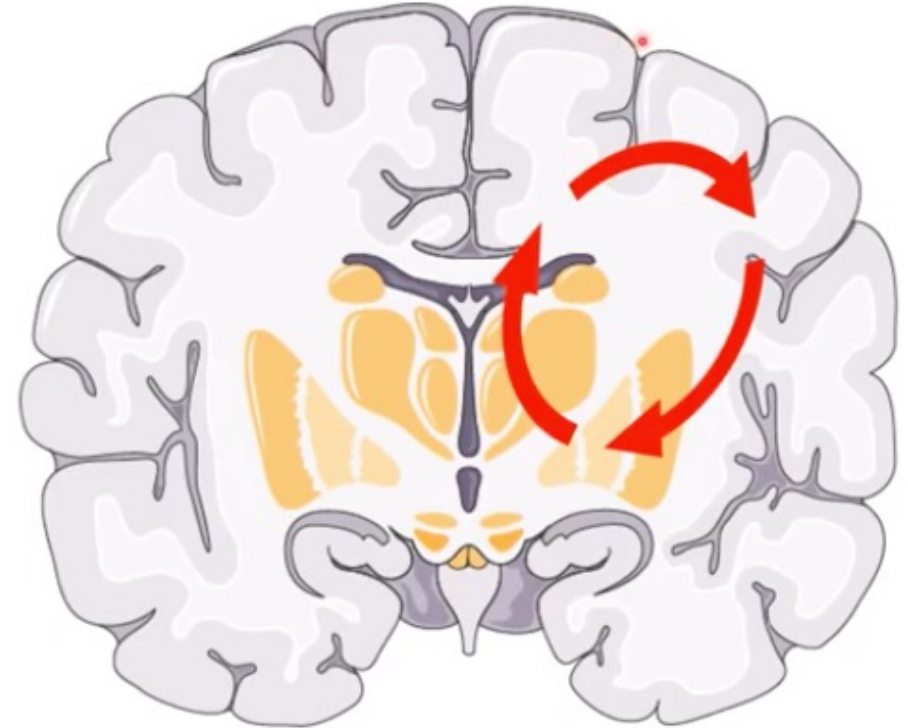
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# Parkinson's Disease



Substantia Nigra



# Parkinsonism comprises four cardinal motor features

- **Bradykinesia** (slow and small movements). Reduced blink, face expression, and gesturing. Soft voice. Difficulty getting out of chair, shuffling steps, reduced arm swing, freezing
- Tremor (usually resting) “pill rolling”, often involves thumb
- Rigidity (different from spasticity)
- Postural changes. Imbalance, falls; stooped flexed posture

# Common non-motor symptoms in Parkinson's Disease

## Early non-motor symptoms

- **Cognitive impairment**
- Constipation
- Anosmia
- Sleep disorders (RBD)
- Depression/Apathy
- Anxiety

## Late non-motor symptoms

- **Dementia**
- Psychosis
- Orthostatic hypotension
- Dysphagia

# Available treatments for motor symptoms in PD

## REVIEW

### International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease

Susan H. Fox, MRCP, PhD,<sup>1,2\*</sup> Regina Katzenschlager, MD,<sup>3</sup> Shen-Yang Lim, MD, FRACP,<sup>4</sup> Brandon Barton, MD, MS,<sup>5,6</sup>  
Rob M. A. de Bie, MD, PhD,<sup>7</sup> Klaus Seppi, MD,<sup>8</sup> Miguel Coelho, MD,<sup>9</sup> Cristina Sampaio, MD, PhD,<sup>10,11</sup>  
on behalf of the Movement Disorder Society Evidence-Based Medicine Committee

Fox et al. 2018



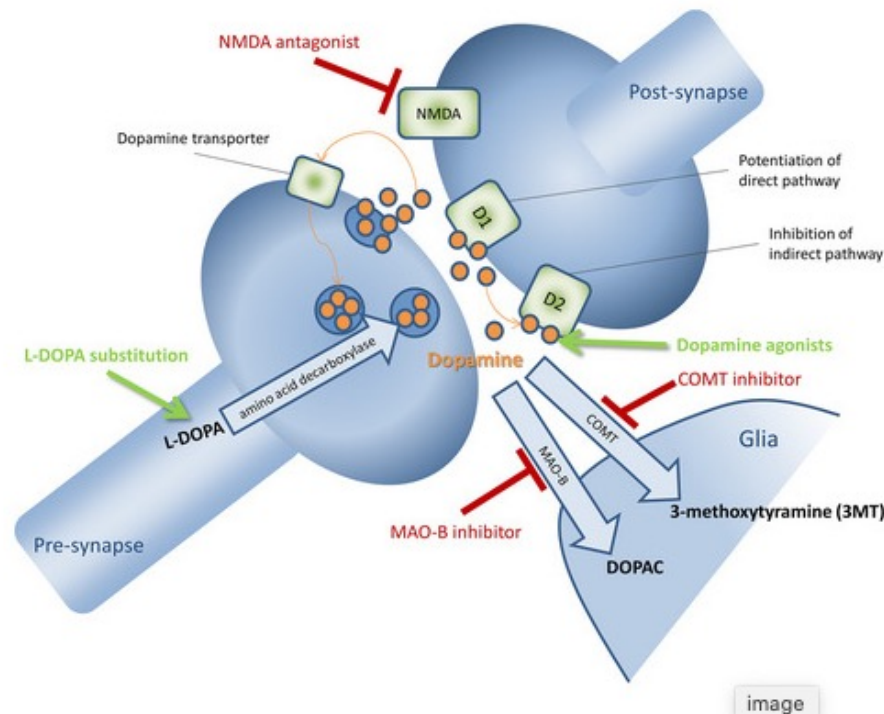
# Treatment of motor symptoms

- No effective neuroprotective agent



# Treatment of motor symptoms

- **Monotherapy (efficacious):**
  - **Carbidopa-Levodopa (Sinemet)**





# Does early treatment with Levodopa increase motor complications?

ORIGINAL ARTICLE

## Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

Constant V.M. Verschuur, M.D., Sven R. Suwijn, M.D., Judith A. Boel, Ph.D., Bart Post, M.D., Ph.D., Bas R. Bloem, M.D., Ph.D., Johannes J. van Hilten, M.D., Ph.D., Teus van Laar, M.D., Ph.D., Gerrit Tissingh, M.D., Ph.D., Alexander G. Munts, M.D., Ph.D., Guenther Deuschl, M.D., Anthony E. Lang, M.D., Marcel G.W. Dijkgraaf, Ph.D., et al., for the LEAP Study Group\*



# Leap study

- Multicenter, double-blind study in early PD
- Patients divided into Early or delayed group
- Early group: on Carbidopa/levodopa 25/100 mg TID at baseline
- DELAYED group: Carbidopa/levodopa started at 40 weeks
- Investigated response to therapy at the end of the 80 weeks



# Leap study

- Primary outcome: no significant motoric difference between the two groups at the end of 80 weeks
- Secondary outcome: no significant differences in motor fluctuations, dyskinesia, depression or cognitive scales
- Weeks 4 to 40: symptomatic benefit of Carbidopa-Levodopa
- Weeks 44 to 80: absence of disease-modifying effect of Carbidopa-Levodopa





Are motor complications primarily related to the duration of levodopa therapy or disease-related factors?



Motor fluctuations and dyskinesias are not associated with the duration of levodopa therapy, but rather with longer disease duration and higher levodopa daily dose.

Hauser et al. 2007



# Available preparations of Carbidopa-Levodopa

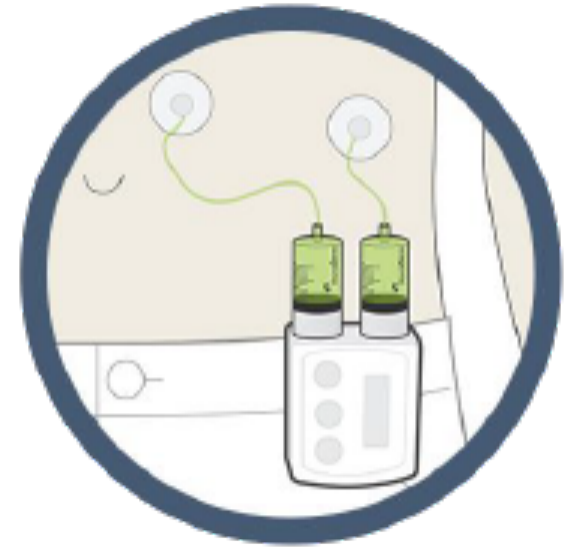
- Carbidopa-Levodopa immediate release (Sinemet)
- Orally dissolving (Parcopa)
- Carbidopa-Levodopa controlled release (Sinemet CR)
- Combination with entacapone (Stalevo)
- IR/CR (Rytary)
- Levodopa intestinal gel (Duopa): delivered directly to the small intestine via a J tube, continuously released during the day, 47% complications



# Under development preparations of Carbidopa-Levodopa

## Neuroderm:

- Continuous subcutaneous infusion of liquid Levodopa/Carbidopa (60/7.5 mg/mL) through a non-surgical mini-pump system
- Causing a stable blood level of Levodopa
- Low dose of up to 360 mg levodopa infused via one infusion site
- High dose of up to 720 mg levodopa infused via two infusion sites
- Reduction in off-time and on-time dyskinesia





# Inhalational Levodopa powder (Inbrija)

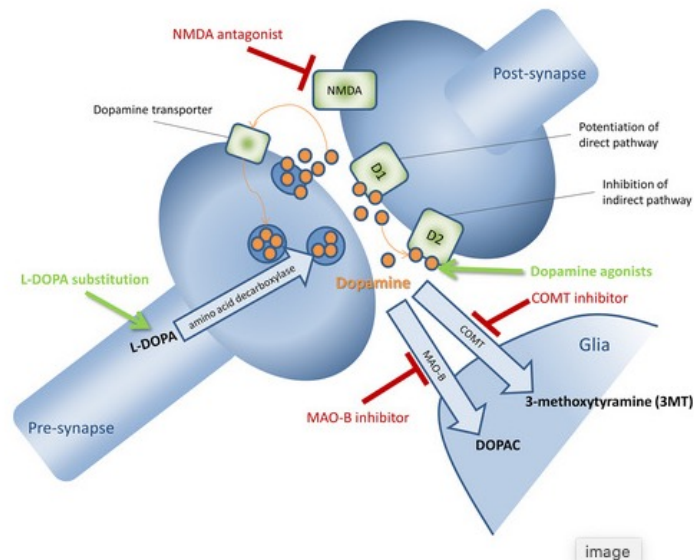
- FDA approved in 12/2018, 2 caps per dose
- SPAN-PD, multicenter, double-blind and placebo-controlled
- PD patients with  $\geq 2$  h off-time/day
- 42mg, 84mg or placebo, up to 5 x day, 12-week study
- Significant change in UPDRS after 30 min (low and high dose), and after 60 min (high dose)
- Side effects cough, throat irritation, sputum discoloration and URI
- No change in PFT





# Treatment of motor symptoms

- **Monotherapy (efficacious):**
  - Levodopa-Carbidopa
  - **Dopamine agonists (Pramipexole, Ropinirole, Rotigotine)**



Fox et al. 2018



# Dopamine agonist vs Levodopa

## Long-term Effect of Initiating Pramipexole vs Levodopa in Early Parkinson Disease

Parkinson Study Group CALM Cohort Investigators, Arch neurology 2009

## Ten-Year Follow-Up of Parkinson's Disease Patients Randomized to Initial Therapy with Ropinirole or Levodopa

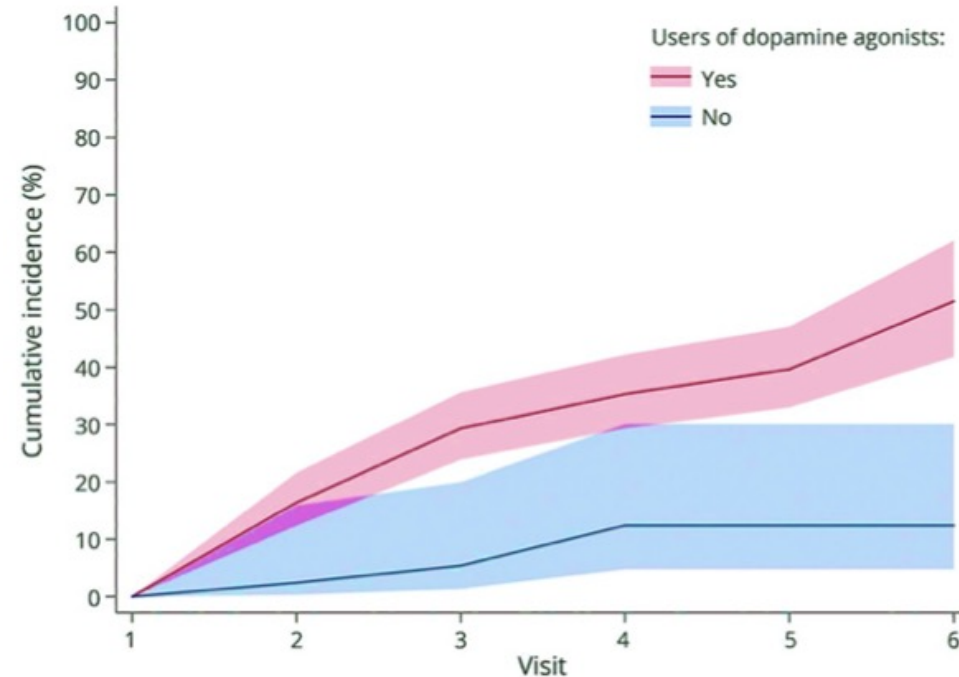
Hauser et al., Movement Disorders 2007



# Dopamine agonists side effects

## Impulse control disease (ICD):

- Pathological gambling
- Compulsive eating
- Compulsive shopping
- Hypersexuality



**Cumulative incidence (95% CI) of ICDs at each visit**



- 5-years cumulative incidence of ICDs 51.5%

# Dopamine agonists side effects

- Excessive daytime sleepiness
- Hallucinations
- Orthostatic hypotension
- Pedal edema
- They can be addictive; 1/3 of patients can have withdrawal symptoms even when the tapering is done very slowly
- These symptoms are subtle, including panic attack, agitation, fatigue, dysphoria, sleep disturbance, suicidality, restlessness, and generalized pain



# Treatment of motor symptoms

- No effective neuroprotective agent
- Monotherapy (efficacious):
  - Levodopa-Carbidopa
  - Dopamine agonists: (Pramipexole, Ropinirole, Rotigotine)
  - **MAO-B inhibitors (Selegiline, Rasagiline)**



# MAO-B inhibitors

- Extend half-life of dopamine by inhibiting its breakdown
- **Selegiline** metabolized to levoamphetamine
  - Not suitable to be given late during the day since can cause insomnia
- **Rasagiline** does not have amphetamine metabolites
- **Safinamide (Xadago)**
  - Potent, highly selective reversible MAO-B inhibitor
  - Blocks voltage-dependent Na and Ca channels
  - Reduces neuronal glutamate release
  - **Ineffective as monotherapy but has shown to increase on-time \***



# Treatment of motor symptoms

- No effective neuroprotective agent
- Monotherapy (efficacious):
  - Levodopa-Carbidopa
  - Dopamine agonists (Pramipexole, Ropinirole, Rotigotine)
  - MAO-B inhibitors (Selegiline, Rasagiline)
  - **Amantadine (likely efficacious)**



# Amantadine

- NMDA and nicotinic antagonist
- Need to be careful to prescribe it in the elderly and patients with kidney disease
- Side effects: constipation, dry mouth, dizziness/orthostatic hypotension, leg swelling, nausea, livedo reticularis



# Newer versions of Amantadine

- Gocoveri (Extended-release capsules):
  - Once at night (placebo-controlled trial)\*
  - Decreases levodopa-associated dyskinesia and off-time
  - Costly
- Osmolex (The combination of IR and ER):
  - Not specifically approved for dyskinesia
  - Less expensive than Gocoveri



\* Pahwa et al., 2017, Oertel et al. 2017



# Treatment of motor symptoms

- No effective neuroprotective agent
- Monotherapy (efficacious):
  - Levodopa-Carbidopa
  - Dopamine agonists: (pramipexole, Ropinirole, Rotigotine)
  - MAO-B inhibitors: (Selegiline, Rasagiline)
  - Amantadine (likely efficacious)
  - **Anticholinergic (likely efficacious):** can help tremor, has side effects so reserved for young patients





# Motor fluctuations (efficacious)

- Dopamine agonists: (Pramipexole, Ropinirole, Rotigotine)
- Levodopa extended-release
- Levodopa intestinal gel (Duopa)
- **COMT inhibitors (Entacapone, Tolcapone, Opicapone)**



# COMT inhibitors

- Prolong the effect of Levodopa by inhibiting catechol-O-methyltransferase
- Entacapone (Comtan): given with each dose of Sinemet, peripheral inhibition of COMT
- Tolcapone: given 3 time a day, peripheral and central inhibition of COMT
  - Fulminate hepatotoxicity reported in 4 patients with 3 deaths
  - Liver enzyme monitoring is needed
- FDA approved Opicapone (Ongentys) to use in April 2020
  - Peripheral COMT inhibitor, once daily
  - Increases daily on-time \*
  - Non-inferior to (Entacapone)



\* Less et al. 2017

# Motor fluctuations (efficacious)

- Dopamine agonists: (Pramipexole, Ropinirole, Rotigotine)
- Levodopa extended-release
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- COMT inhibitors (Entacapone, Tolcapone, Opicapone)
- **Adenosine A2A antagonist (Istradefylline(Nourianz)): (likely efficacious)**



# Motor fluctuations (efficacious):

- Dopamine agonists (Pramipexole, Ropinirole, Rotigotine)
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- COMT inhibitors (Entacapone, Tolcapone, Opicapone):
- MAO-B inhibitors (Rasagiline, Safinamide)
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- **Zonisamide: low dose 50 mg/day (Murata et al. 2015)**



# Motor fluctuations (efficacious):

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- Zonisamide: low dose 50 mg/day (Murata et al. 2015)
- **Apomorphine**



# Apomorphine

- It is not an opiate, highly potent, a nonselective dopamine agonist
- Can not be used orally
- Subcutaneous injection (Apokyn) is FDA approved in 2004 for acute motor offs but found to be hard to use during off-time
- Side effects: potent emetic (needs to be premedicated with antiemetics), orthostatic hypotension
- Apomorphine film for sublingual use (Kynmobi) approved in 2020: up to five times a day, at doses ranging from 10 mg to 30 mg, potent and fast-acting \*



# Motor fluctuations (efficacious):

- Dopamine agonists (Pramipexole, Ropinirole, Rotigotine)
- Levodopa extended-release
  - Levodopa intestinal gel (Duopa)
- COMT inhibitors (Entacapone, Tolcapone, Opicapone):  
prolong the effect of levodopa
- MAO-B inhibitors (Rasagiline, Safinamide)
- Adenosine A2A antagonist (Istradefylline): likely efficacious
- Zonisamide: low dose 50 mg/day ( Murata et al. 2015)
- Apomorphine
- **Deep Brain Stimulation (DBS)**



# Dyskinesia (efficacious)

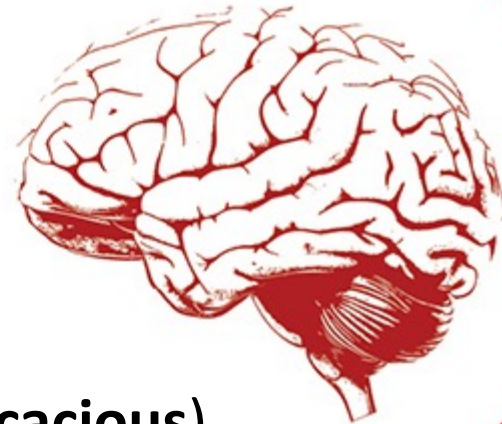
- Amantadine
- Levodopa gel intestinal infusions (likely efficacious)
- Clozapine
- Unilateral pallidotomy
- DBS





# Treatment of PD as an adjunct in early or stable PD

- Dopamine agonists: (pramipexole IR, ER, ropinirole IR, rotigotine)
- MAO-B inhibitors: (Rasagiline, **saquinamide: non-efficacious** )
- Anticholinergic (likely efficacious)
- Amantadine (likely efficacious)
- Zonisamide
- **Adenosine A2A antagonist (Istradefylline (Nourianz)): non-efficacious**
- COMT inhibitors (tolcapone: but risky so not useful, **entacapone: non-efficacious**)



## Get Involved

We rely on the energy, skill and passion of our **volunteers, advocates and fundraisers** to make life better for people with Parkinson's and advance research toward a cure.



### Engage

- Moving Day
- Parkinson's Revolution
- Educational Programs

### Educate

- Aware in Care Ambassador
- Education Program Volunteer

### Advise

- People with Parkinson's Council
- Research Advocate

# Moving Day San Francisco

**Saturday, April 23<sup>rd</sup>**

The Great Meadow at Fort Mason

[www.MovingDaySanFrancisco.org](http://www.MovingDaySanFrancisco.org) for more info or to register!



# Revolution San Francisco

- **February 26th**— Location TBD
- In-person, outdoor spin class (COVID safe)
- Appx 30 in-person riders plus virtual options



[www.PDRevolutionSF.org](http://www.PDRevolutionSF.org) for more info or to register!



# We're Here For You



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