Parkinson’s disease treatment: Maintaining function

J. Eric Ahlskog, Ph.D., M.D.
Mayo Clinic, Rochester, Minnesota
No conflicts of interest to disclose

No off-label drug advice
CASE

55 year old right-handed commercial pilot

- Subtle sx, age 43: reduced right arm swing, mild micrographia, toes curling
- Age 48: mildly reduced right hand dexterity (e.g., brushing teeth), right leg stiffness & subtle gait change
- Age 54-55: Requiring more use of left hand to pilot; stopped flying 6 months ago

TREATMENT: One tablet carbidopa/levodopa t.i.d.: No perceived benefit

EXAM: Mild hypomimea, right limb rigidity, reduced right arm swing, slowed right alternate motion rate, mild gait change, slight rest tremor, right limbs
OUTCOME, 9 months later

- On 3 of the 25/100 carbidopa/levodopa tablets 3X daily (1 hr ac & 2 hr pc) : Markedly improved
- Exam: Slight R foot slapping with walking; R hand alternating movements mildly slowed
- Flight simulator: “…highest flight simulation scores ever in his career…”

RETURNED TO COCKPIT WITHOUT RESTRICTION
Medical treatment of Parkinson’s disease
Symptomatic PD treatment

**Stocchi** *(Neurodegenerative Dis. 2010)*:

“...treatment of PD should be started with rasagiline and/or with long-acting DA agonists.”

**Olanow** *(Neurology 2009)*:

“Initiate symptomatic therapy with an MAO-B inhibitor and/or a dopamine agonist...”

**Schapira** *(Annals of Neurology 2008)*:

“For most PD patients, we would advocate the initiation of either an MAO-B inhibitor or a dopamine agonist.”
Symptomatic drug choices

**Rasagiline or selegiline (MAO-B inhibitors)**
- Modest symptomatic benefit
- Poor evidence for neuroprotective effect

**Dopamine agonists**
- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro patch)

**Carbidopa / levodopa**
Initial carbidopa / levodopa vs agonist

Carbidopa/levodopa
- More efficacious, by far
- Will be required within a few years at most
- Much cheaper
  (except regular pramipexole, ropinirole, Requip XL)
- Quicker to response
- Easier to use

Dopamine agonist
- Lower risk of dyskinesias*
- Lower risk of fluctuations*

* But dyskinesia & fluctuation risks markedly increase after carbidopa/levodopa added
Unique dopamine agonist side effects

- Pathological behaviors (About 25% frequency if therapeutic doses) (Hassan, Park Rel Dis 2011; 17:260-4)
  - Gambling
  - Hypersexuality
  - Spending
  - Eating
- Hallucinations, delusions (paranoia)
- Somnolence (driving)
- Edema
PD drugs for symptoms
Cost online per tablet / patch

Cheapest price on GoodRx.com, including with coupon

MAO-B inhibitors:
- Selegiline $1
- Rasagiline $19.50

Dopamine agonists:
- Pramipexole 0.25mg $0.25
  - ER 1.5mg $6.31
- Ropinirole 1mg $0.19
  - XL 2mg $0.33
- Rotigotine patch 4mg $19

Carbidopa/levodopa
(dopamine precursor) $0.19

No revenue streams, hence few advocates
My choice: Carbidopa/levodopa
Carbidopa/levodopa: Regular or...?

Stalevo (carbidopa/levodopa plus entacapone)
- No advantages in early PD
- Expensive: $1.56 per tablet (vs $0.19 for carbidopa/levodopa)
- Increased levodopa side effects (e.g., dyskinesias)

Sustained-release (Sinemet CR)
- Complex interactions with food
- Only partially bioavailable; slow kick-in
- Prolongs levodopa only 60-90 minutes

Rytary: Costly and not needed in early PD
Initiating Carbidopa / Levodopa*
Immediate-release 25 / 100 tablets

Take at least 1 hour before & 2 hours after meals

- Begin: ½ to 1 tablet three times daily
- Advance weekly by ½ tablet, all doses, guided by response
- Point of diminishing returns: 2 ½ tablets 3 times daily (in new patients); max = 3 tabs each dose
- Settle on best dose; if several doses equally effective choose lowest

* My scheme
Why carbidopa/levodopa on empty stomach?

Levodopa is an amino acid

- Crosses the blood-brain-barrier carried by a molecular transporter
- Transporter binding sites can easily be saturated
- Dietary amino acids occupy those binding sites
Titration: Symptoms

**Motor**
- Walking most important
- Poor finger-thumb tapping (AMRs) → impaired writing, typing, brushing teeth, etc.
- Social interactions: masking, speech

**Non-motor**
- Sleep
- Anxiety (akathisia)

**Dystonias**
- Toes curling, calf cramping
- Chest or abdominal tightness (dyspnea?)
Orthostatic Hypotension

Check standing BP’s before & after starting carbidopa/levodopa

- Easy to miss; BP fluctuates with:
  - Levodopa administration
  - Meals
  - Time of day: worst in morning

- Approximate symptom threshold: 90/60
  If “dizzy” and BP > 90 / 60, then not due to low BP

Treatment: Check medication list
Motor Complications years later

Fluctuations
Dyskinesias
Levodopa Motor Fluctuations

For the first few years of PD, the levodopa benefit is unvarying & not tied to each dose

“Long-duration response”
Builds over a week

With advancing PD, the primary benefit is time-locked to each levodopa dose

“Short-duration response”
Lasts from one to a few hours
Short-duration response
Treatment of “Wearing Off”

• Consider two points in levodopa cycle:
  1. Time of peak-effect
  2. Time just before the next dose (end-of-dose)

• Adjust levodopa dose to capture best peak-effect
  
  60-90 minutes after a dose of immediate-release carbidopa/levodopa (or benserazide/levodopa)

• Adjust interval between doses to match response duration

• Use as many doses per day as necessary
1. Is dose adequate to capture optimum peak effect? (larger doses don’t last much longer)

2. Assess duration of response; set dosing interval to match (don’t worry about number of doses per day)
Short-duration levodopa responses less than 4 hours are problematic

Carbidopa/levodopa doses must be at least one hour before, and 2 hours after the end of meals

- Dietary protein inhibits the levodopa response
- Meals often explain “failed doses”

Options:

- Defer meals for important engagements
- Rytary (appears better than immediate-release plus CR carbidopa/levodopa)
- DBS

Theoretically, entacapone, dopamine-agonists should work, but modest effect in practice
Levodopa dyskinesias

- Chorea or choreo-dystonia
- Excessive levodopa effect
- Dopamine agonists may add to this

Distinguish from levodopa insufficiency, which includes:

1. Pure dystonia, especially if painful,
2. Akathisia (restlessness)

Video

1. Off-state with tremor
2. 30 minutes after levodopa (dyskinesias)
Dyskinesias

• Resolve with levodopa reduction
  Occasionally at expense of increased parkinsonism

• Dyskinesias are “short-duration” effect

Linked to each levodopa dose (not cumulative)
Long term issues...
Progression of Lewy pathology

- REM sleep disorder, dysautonomia (Stages 1-2)
- Smell loss (Stages 1-2)
- Levodopa-responsive motor symptoms (Stages 3-4)
- Dementia (Stages 5-6)
- Levodopa-refractory motor symptoms (Stages 5-6)

Braak PD stages
The long-term outcome: Parkinson’s disease progression

- Not dopamine-based
  - Dementia
  - Refractory motor responses
  - Dysautonomia (e.g., neurogenic bladder)

- Drug resistant
## Drugs to slow PD progression?

**RCT’s with N > 100**

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**Rasagiline (Azilect):** Clinical trial designs very complex & highly susceptible to multiple confounding factors *(Ahlskog & Uitti, Neurology 2010; 74:1143-8)*

**FDA panel, rasagiline:** 17:0 vote against approval as disease modifying

No proof of a neuroprotective effect with any drug, but...
Is vigorous exercise neuroprotective for Parkinson disease?

ABSTRACT
Parkinson disease (PD) is progressive, with dementia and medication-refractory motor problems common reasons for late-stage nursing-home placement. Increasing evidence suggests that ongoing vigorous exercise/physical fitness may favorably influence this progression. Parkinsonian animal models reveal exercise-related protection from dopaminergic neurotoxins, apparently mediated by brain neurotrophic factors and neuroplasticity (predicted from in vitro studies). Similarly, exercise consistently improves cognition in animals, also linked to enhanced neuroplasticity and increased neurotrophic factor expression. In these animal models, immobilization has the opposite effect. Brain-derived neurotrophic factor (BDNF) may mediate at least some of this exercise benefit. In humans, exercise increases serum BDNF, and this is known to cross the blood–brain barrier. PD risk in humans is significantly reduced by midlife exercise, documented in large prospective studies. No studies have addressed whether exercise influences dementia risk in PD, but exercised patients with PD improve cognitive scores. Among seniors in general, exercise or physical fitness has not only been associated with better cognitive scores, but midlife exercise significantly reduces the later risk of both dementia and mild cognitive impairment. Finally, numerous studies in seniors with and without dementia have reported increased cerebral gray matter volumes associated with physical fitness or exercise. These findings have several implications for PD clinicians. 1) Ongoing vigorous exercise and physical fitness should be highly encouraged. 2) PD physical therapy programs should include structured, graduated fitness instruction and guidance for deconditioned patients with PD. 3) Levodopa and other forms of dopamine replenishment therapy should be utilized to achieve the maximum capability and motivation for patients to maintain fitness.

Ahlskog, J.E. Neurology® 2011;77:288-294

PubMed search extended to Jan. 3, 2016:
“exercise” & “Parkinson’s disease” (1525 titles)
“exercise” & “cognition” (4270 titles)
Evidence that vigorous exercise has a direct favorable effect on brain integrity

1. Animal studies (rats, mice)
Exercise facilitates **neuroplasticity**

Elevated brain expression/enhancement (*rats, mice*)


- **GDNF** (Cohen, 2003; Tajiri, 2010; Lau, 2011)

- **Insulin-like growth factor I** (interacts with BDNF) (Ding, 2006)

- **Neuroplasticity-related transcription factors** (*CREB, intra-cellular kinases*) (Shen, 2001; Gomez-Pinella, 2008; Berchtold, 2010; Aguiar, 2011; Lee, 2012)

- **Synaptic plasticity genes** (*Stranahan, 2010*) & synaptic proteins (*synapsin I, synaptophysin*) (Vaynman, 2004; 2006; Bayod, 2011; Lin, 2012, Toy, 2014)
Exercise & neuroplasticity

Induced or enhanced in brain (rats, mice):


Long Term Potentiation (Farmer, 2004; O’Callaghan, 2007; VanPraag, 1999)

Dendrite length, complexity, spines (Eadie, 2005; Redila, 2006; Lin, 2012; Brockett, 2015)
2. Human exercise investigations

Selected studies representative of this literature
Parkinson’s disease: Serum BDNF elevates with exercise (Zoladz, 2014)

Parkinson’s disease patients (N=12): Moderate intensity cycling, 3 one-hr sessions weekly for 8 weeks

Early morning BDNF

BDNF crosses the BBB

P = 0.034
Prospective studies: midlife, regular exercise reduces PD-risk years later (Xu, 2010)

Meta-analysis
P-values:
Men = 0.0002
Women = 0.02
Both < 0.0001

Reduced risk of later PD with:
“Heavy leisure-time physical activity” (Saaksjarvi, 2014)
Greater general physical activity (Yang, 2015)
Most feared Parkinson’s disease outcome:

Dementia *

(Especially reflects PD duration & age)

* But no prospective studies of exercise on later dementia-risk in PD
Meta-analysis: Prospective studies of exercise on later dementia-risk, normal adults

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Exposure</th>
<th>Sample size</th>
<th>Hazard ratio (95% CI)</th>
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<tbody>
<tr>
<td>Sumic et al. (2007)</td>
<td>&gt; 4 h/week</td>
<td>27</td>
<td>0.91 (0.25–3.40)</td>
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<td>&gt; 4 h/week</td>
<td>39</td>
<td>0.12 (0.03–0.41)</td>
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<td>Larson et al. (2006)</td>
<td>x 3 times/week</td>
<td>1740</td>
<td>0.68 (0.48–0.96)</td>
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<td>Wang et al. (2006)</td>
<td>Highest quintile</td>
<td>5437</td>
<td>0.98 (0.95–1.01)</td>
</tr>
<tr>
<td>Rativo et al. (2005)</td>
<td>x 2 times/week</td>
<td>1449</td>
<td>0.47 (0.25–0.90)</td>
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<tr>
<td>Pedewils et al. (2005)</td>
<td>x 2 times/week</td>
<td>3375</td>
<td>0.58 (0.41–0.83)</td>
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<tr>
<td>Abbott et al. (2004)</td>
<td>&gt; 2 miles/day walking</td>
<td>2257</td>
<td>0.63 (0.43–0.93)</td>
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<tr>
<td>Verghese et al. (2003)</td>
<td>Highest quintile</td>
<td>469</td>
<td>1.27 (0.78–2.06)</td>
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<tr>
<td>Wang et al. (2002)</td>
<td>Daily physical activity</td>
<td>732</td>
<td>0.41 (0.13–1.31)</td>
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<td>Laurin et al. (2001)</td>
<td>x 3 times/week vigorous</td>
<td>1831</td>
<td>0.91 (0.45–1.83)</td>
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<td>x 3 times/week vigorous</td>
<td>2784</td>
<td>0.55 (0.25–1.21)</td>
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<td>Ho et al. (2001)</td>
<td>Any exercise</td>
<td>519</td>
<td>0.73 (0.53–1.01)</td>
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<td>0.84 (0.71–0.99)</td>
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<td>Fabrigoule et al. (1995)</td>
<td>Any sports</td>
<td>2040</td>
<td>0.33 (0.10–1.04)</td>
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Total: 23168

Test for heterogeneity: \( \chi^2(13) = 46.66, p < 0.001 \)

Test for overall effect: \( \chi^2(1) = 12.57, p < 0.001 \)

Reduced later risk; RR = 0.72; p < 0.001

More recent: Total & more intense physical activity reduced later dementia-risk (Buchman, 2012); physical activity reduced dementia-risk among those with leukoaraiosis (Verdelho, 2012); non-significant association between higher physical activity and later dementia (de Bruijn, 2013); highest levels of leisure activities (resulting in sweating and breathlessness) had lower dementia risk (Tolppanen, 2015)
Hippocampi: Fundamental to memory
MRI hippocampal volumes (Non-demented seniors)

Treadmill (peak-VO$_2$) controlled for age, gender, education (also better spatial memory) (Erickson, 2009)

One year (3d/wk):
Aerobic exercise vs Control (stretching & toning) (Erickson, 2011)

Fitness correlated with hippocampal (McAuley, 2011) & right entorhinal cortex volumes (Whiteman, 2015)
Baltimore Longitudinal Study of Aging

Baseline fitness ($VO_{2\text{max}}$) & trajectories of cognitive decline

Worse fitness predicted accelerated cognitive decline
(Wendell, 2014)
Parkinson’s disease longevity
Drugs to slow PD progression?

RCT’s with N > 100

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No clinical-trial proof of a neuroprotective effect with any drug

But...
Parkinson’s disease longevity

Longevity substantially increased, time-locked to the advent of levodopa in 1969:

7 independent studies (see Ahlskog, 2004)

Modern era longevity, Olmsted County MN:

Elbaz, 2003: 3 years short of actuarial predictions
Savica, 2016: Similar to controls

Interpretation:

• Unlikely: Levodopa directly influences the cause of PD.
• More likely: Related to mobilization from the sedentary effects of PD
2 simple rules for Parkinson’s disease treatment

1. Optimize carbidopa/levodopa
2. Engage in regular aerobic exercise

Novel consideration: Primary care physicians manage routine PD
Questions