Debunking Ten Myths that May Sabotage Treatment of Parkinson’s Disease

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Background
What is Parkinson’s Disease?

• Neurodegenerative disorder
• Many of the symptoms are from degeneration of **substantia nigra**
  • Midbrain nucleus
  • Critical link with **striatum**
Substantia Nigra

Striatum
Neurons have wire-like connections: Axons
Critical link in brain movement circuit

**Substantia nigra projects to striatum**

- Signals by releasing **dopamine** (neurotransmitter)

- **In Parkinson’s disease**: Substantia nigra degenerates $\rightarrow$ Low brain dopamine levels
The majority of symptoms due to loss of brain dopamine
Dopamine is not the whole story but is crucial to effective treatment.

Braak staging: Very early and very late problems are not dopamine-based.
Progression of Lewy pathology

*Alpha-synuclein may be culpable protein*

### Braak PD stages

**Dementia**

**Levodopa Refractory Motor Symptoms**

(Stages 5-6)

**Levodopa-responsive motor signs**

(Stages 3-4)

**Smell loss**

(Stages 1-2)

**REM sleep disorder, dysautonomia**

(Stages 1-2)
1960’s Research: Restoration of brain dopamine

Dopamine by mouth or injection cannot cross the blood-brain barrier

Levodopa is precursor to dopamine

Levodopa \rightarrow \text{Dopamine} \quad \text{Dopa decarboxylase}

Mid 1970’s: Carbidopa added to prevent premature conversion of levodopa to dopamine (carbidopa / levodopa)
Most Potent Drug for Parkinson’s Disease

Carbidopa / levodopa

- Levodopa
- L-dopa
- Sinemet

(Rytary)
Other dopamine-active drugs

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

MAO-B inhibitors
- Selegiline,
- Rasagiline (Azilect)

Expert opinion, PD treatment:

Prof. S (Annals of Neurology 2008):
“we would advocate the initiation of either an MAO-B inhibitor or a dopamine agonist”

Prof. O (Neurology 2009):
“Initiate symptomatic therapy with an MAO-B inhibitor and/or a dopamine agonist”

Prof. S (Neurodegenerative Dis. 2010):
“treatment of PD should be started with rasagiline and/or with long-acting DA agonists”

But why???
Denigrating Carbidopa / levodopa

Ten myths unsupported by facts
Myth #1 Levodopa stops working after a few years

Never stops working

(except in parkinsonism-plus disorders, i.e., not PD)

• Over 10 to 20 years:
  1. Responses less dramatic
  2. Response fluctuates with each dose
     (“short-duration responses”)

*Reflects the natural history of PD*

• After 80, age-related factors superimpose
Myth #2 Almost everyone develops disabling dyskinesias on levodopa

• Wiggly movements of Michael J. Fox

• Are not painful

If painful, then dystonia, reflecting levodopa under-dosage
Tremor  ➔  Dyskinesias
Dyskinesias are age-related

Incidence after five years of levodopa*

<table>
<thead>
<tr>
<th>Age</th>
<th>% with dyskinesias</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 59 years</td>
<td>50%</td>
</tr>
<tr>
<td>60 - 69 years</td>
<td>26%</td>
</tr>
<tr>
<td>70 - 79 years</td>
<td>16%</td>
</tr>
<tr>
<td>80 - 89 years</td>
<td>14%</td>
</tr>
</tbody>
</table>

* Kumar et. al. 2004: Olmsted County, MN
Myth #3 Dyskinesias are worse than parkinsonism

Dyskinesias always resolve with reduction of levodopa doses

*Excessive levodopa effect*

Driven by each levodopa dose

Reflects the most recent dose of levodopa

Does NOT reflect the total daily dose
After 10 years of levodopa, 43% had dyskinesias sufficient to require medication adjustment.

Van Gerpen, 2006: Olmsted County, MN
After **10 years** of levodopa, only **12%** had dyskinesias that could not be controlled with medication adjustment.
Myth #4 Levodopa should be saved for later

i.e., don’t start it until doing badly

No evidence that the best responses can be saved

Any decline in the levodopa benefit is primarily related to duration of PD, not how long you have been treated
Myth #5 The levodopa dose should be limited

Makes no sense:

Carbidopa/levodopa is the most efficacious PD drug & has few side effects

(Optimize the dosage: Take what you need but not more)

Six-year levodopa trial (Poewe, 1986)

“Low-dose” vs “Maximum tolerated dose”

Low-dose group after 6 years: Poor control of parkinsonism
Myth #6 Carbidopa / levodopa should be taken with meals

- Levodopa is an amino acid
- Dietary proteins generate circulating amino acids
- Dietary amino acids compete with l-dopa at blood-brain barrier

Mealtime dosing common cause of poor response

Full effect if taken ≥ 1 hour before meals or ≥ 2 hours after the end of a meal
Myth #7: Controlled-release carbidopa / levodopa is preferred (Sinemet CR)

Facts about the CR formulation:

1. **Effect:** Only 60-90 minutes longer than regular carbidopa / levodopa
2. Not fully absorbed; slow kick-in and more erratic
3. Complex interactions with food
4. Not a mg-to-mg correspondence with regular carbidopa/levodopa

New combination of regular and sustained-release carbidopa/levodopa: Rytary capsules

- Expensive; not necessary for initial treatment
- Useful when levodopa responses less than 4 hours
Myth #8 The dopamine agonist drugs are nearly as effective as levodopa

Synthetic forms of dopamine

- Pramipexole (Mirapex)
- Ropinirole (Requip)
- Rotigotine (Neupro patch; $22 per patch)

- Not nearly as efficacious as levodopa
- Few can get by with these alone after 2-4 years

Unique side effects of pramipexole, ropinirole

- Pathological behaviors (gambling, sex, etc.)
- Sleepiness
- Swelling
- Hallucinations
Myth #9 Levodopa disrupts sleep

Facts:

Insomnia is common in PD

Cause: Insufficient levodopa or wearing-off

Treatment: Carbidopa/levodopa

Levodopa: Reduces inner restlessness & stiffness that prevents sleep

Adequate levodopa is best sleep aid for PD
Myth #10: 50% of people with Parkinson’s disease experience hallucinations (TV ad)

Hallucination Facts:
- Carbidopa/levodopa: Low risk
- Other PD drugs: High risk

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

MAO-B inhibitors:
- Selegiline
- Rasagiline (Azilect)

Other drugs:
- Bladder urgency meds
- Opioids (narcotics)

Recall expert opinions:
- Prof. S (Annals of Neurology 2008): “…we would advocate the initiation of either an MAO-B inhibitor or a dopamine agonist”
- Prof. O (Neurology 2009): “Initiate symptomatic therapy with an MAO-B inhibitor and/or a dopamine agonist”
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Surprising but indisputable facts

Carbidopa / levodopa: 40+ year old drug

- Most efficacious, by far
- Fewest side effects
- Cheapest
- Sufficient and adequate by itself in most cases
- Limited roles for adjunctive drugs
Starting Carbidopa / Levodopa
Mayo-Rochester strategy

25/100 regular

• Take on an **empty stomach**: 1 or more hours before and 2 or more hours after end of meals

• Start low (1 tablet 3 times daily) & increase weekly by ½ tablet all doses

• Continue up to 2 ½ tablets 3 times daily

• Settle on best dose or lowest of equipotent doses  Max is 3 tablets each dose (higher individual doses provide no further benefit)
**Myth #11 We have drugs that may slow PD progression**

Eleven controlled PD drug trials (> 100 patients)

No evidence for slowing PD progression, but…

<table>
<thead>
<tr>
<th>Clinical trial name</th>
<th>Drugs assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATATOP</td>
<td>Selegiline (MAO-B inhibitor); vitaminE</td>
</tr>
<tr>
<td>CALM-PD</td>
<td>Pramipexole (dopamine agonist)</td>
</tr>
<tr>
<td>REAL-PET</td>
<td>Ropinirole (dopamine agonist)</td>
</tr>
<tr>
<td>PRECEPT</td>
<td>CEP-1347 (inhibits programmed cell death: apoptosis)</td>
</tr>
<tr>
<td>TCH346</td>
<td>TCH346 (inhibits programmed cell death: apoptosis)</td>
</tr>
<tr>
<td>ADAGIO</td>
<td>Rasagiline (MAO-B inhibitor)</td>
</tr>
<tr>
<td>QE3</td>
<td>Coenzyme Q10 (mitochondrial co-factor)</td>
</tr>
<tr>
<td>MitoQ</td>
<td>Coenzyme Q10 analogue (lipid-soluble to increase brain concentrations)</td>
</tr>
<tr>
<td>FS-1</td>
<td>Creatine; minocycline (antibiotic)</td>
</tr>
<tr>
<td>FS-TOO</td>
<td>Coenzyme Q10; GPI-1485 (immunophilin, thought to have neurotrophic properties)</td>
</tr>
<tr>
<td>LS-1</td>
<td>Creatine</td>
</tr>
</tbody>
</table>
Evidence that regular vigorous exercise may slow Parkinson’s disease progression
Aerobic Exercise: Evidence for a Direct Brain Effect to Slow Parkinson Disease Progression


Abstract

No medications are proven to slow the progression of Parkinson disease (PD). Of special concern with longer-standing PD is cognitive decline, as well as motor symptoms unresponsive to dopamine replacement therapy. Not fully recognized is the substantial accumulating evidence that long-term aerobic exercise may attenuate PD progression. Randomized controlled trial proof will not be forthcoming due to many complicating methodological factors. However, extensive and diverse avenues of scientific investigation converge to argue that aerobic exercise and cardiovascular fitness directly influence cerebral mechanisms mediating PD progression. To objectively assess the evidence for a PD exercise benefit, a comprehensive PubMed literature search was conducted, with an unbiased focus on exercise influences on parkinsonism, cognition, brain structure, and brain function. This aggregate literature provides a compelling argument for regular aerobic-type exercise and cardiovascular fitness attenuating PD progression.
Note, not all exercise is exercise...
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 physical activity:
“Heavy leisure-time” (Saaksjarvi, 2014); “increased” (Yang, 2015); “high level” (Shih, 2016)
Will exercise reduce risks of Parkinson’s disease-Dementia?

Cortex (non-dopaminergic)

No PD clinical trials of exercise on dementia outcomes
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 of higher physical activity and later dementia (de Bruijn, 2013)

**Meta-analysis, exercise & later dementia-risk**

(Hamer & Chida, 2009)

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Exposure</th>
<th>Sample size</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Sumic et al. (2007) ♦</td>
<td>&gt; 4 h/week</td>
<td>27</td>
<td>0.91 (0.25–3.40)</td>
</tr>
<tr>
<td>1b Sumic et al. (2007) ♦</td>
<td>&gt; 4 h/week</td>
<td>39</td>
<td>0.12 (0.03–0.41)</td>
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<tr>
<td>2 Larson et al. (2006) ♦♀</td>
<td>× 3 times/week</td>
<td>1740</td>
<td>0.88 (0.48–0.96)</td>
</tr>
<tr>
<td>3 Wang et al. (2006) ♦♀</td>
<td>Highest quintile</td>
<td>5437</td>
<td>0.98 (0.95–1.01)</td>
</tr>
<tr>
<td>4 Ravio et al. (2005) ♦♀</td>
<td>× 2 times/week</td>
<td>1449</td>
<td>0.47 (0.25–0.90)</td>
</tr>
<tr>
<td>5 Podewils et al. (2005) ♦♀</td>
<td>× 2 times/week</td>
<td>3375</td>
<td>0.58 (0.41–0.83)</td>
</tr>
<tr>
<td>6 Abbott et al. (2004) ♦</td>
<td>&gt; 2 miles/day walking</td>
<td>2257</td>
<td>0.63 (0.43–0.93)</td>
</tr>
<tr>
<td>7 Verghese et al. (2003) ♦♀</td>
<td>Highest quintile</td>
<td>469</td>
<td>1.27 (0.78–2.06)</td>
</tr>
<tr>
<td>8 Wang et al. (2002) ♦♀</td>
<td>Daily physical activity</td>
<td>732</td>
<td>0.41 (0.13–1.31)</td>
</tr>
<tr>
<td>9a Laurin et al. (2001) ♦♀</td>
<td>× 3 times/week vigorous</td>
<td>1831</td>
<td>0.91 (0.45–1.83)</td>
</tr>
<tr>
<td>9b Laurin et al. (2001) ♦♀</td>
<td>× 3 times/week vigorous</td>
<td>2784</td>
<td>0.55 (0.25–1.21)</td>
</tr>
<tr>
<td>10a Ho et al. (2001) ♦♀</td>
<td>Any exercise</td>
<td>519</td>
<td>0.73 (0.53–1.01)</td>
</tr>
<tr>
<td>10b Ho et al. (2001) ♦♀</td>
<td>Any exercise</td>
<td>469</td>
<td>0.84 (0.71–0.99)</td>
</tr>
<tr>
<td>11 Fabrigoule et al. (1995) ♦♀</td>
<td>Any sports</td>
<td>2040</td>
<td>0.33 (0.10–1.04)</td>
</tr>
</tbody>
</table>

Total 23 168 0.72 (0.60–0.86)

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

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

RR = 0.72; p < 0.001
Baltimore Longitudinal Study of Aging
Baseline fitness (VO_{2max}) & trajectories of cognitive decline

Worse fitness predicted accelerated cognitive decline (Wendell, 2014)
Brain volumes & exercise
(normal adults)
MRI hippocampal volumes (Non-demented seniors)

Treadmill (peak-VO₂) controlled for age, gender, education (also better spatial memory) (Erickson, 2009)

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

Replications:
Hippocampal volumes: 2-year controlled, prospective exercise (Rosano, 2016)
Fitness correlated with hippocampal (McAuley, 2011) & right entorhinal cortex volumes (Whiteman, 2015)
Cortical volume (MRI) in the general population: Greater with exercise

Fitness (cross sectional studies)
- **Physically-fit** seniors: Less cortical age-related volume loss (5 studies) (Gordon 2008; Colcombe 2003; Weinstein 2012; Vidoni 2012; Tseng 2013)
- Framingham study (N=1094): Poor fitness at age 40 significantly associated with smaller total cerebral brain volume 20 years later (but no association with cognition) (Spartano, 2016)

Prospective studies Exercise vs sedentary (6 months):
- Increased cortical volumes (Colcombe 2006; Ruscheweyh 2009); one negative study (Mortimer 2012)
- Low or medium intensity exercise: Increased local cortical volume & memory scores (Ruscheweyh, 2011)

Reported physical activity associated with greater:
- Gray and white matter volumes (Gow, 2012)
- Selected cortical volumes (but not white matter) (Bugg, 2011)

Walking-distances correlated with cortical volumes 9 years later (and reduced risk, cognitive impairment) (Erickson, 2010)
Exercise in animal models of parkinsonism

Rats, mice: Running wheels, treadmills
Exercise liberates neurotrophic factors in brain (mice, rats)

**BDNF** (brain-derived neurotrophic factor) 27 studies

**GDNF** (glial-derived neurotrophic factor) 3 studies
(Cohen, 2003; Tajiri, 2010; Lau, 2011)

**Insulin-like growth factor I** (interacts with BDNF) (Ding, 2006)
Exercise elevates in normal humans (Schwartz 1996)
Exercise neuroplasticity (rats, mice)

Elevated brain expression / enhancement:

• Neuroplasticity-related transcription factors (CREB, intra-cellular kinases) (5 studies) (Shen, 2001; Gomez-Pinella, 2008; Berchtold, 2010; Aguiar, 2011; Lee, 2012)

• Neurogenesis (14 studies) (Trejo, 2001; Fabel, 2003; Farmer, 2004; 2005; Eadie, 2005; Okamoto, 2012; Mustroph, 2012; Bechara, 2013; Li, 2013; Cho, 2013; Sung, 2015; Uysal, 2015; Vivar, 2015; Kodali, 2016)

• Synaptic plasticity genes (Stranahan, 2010)

• Synaptic proteins (7 studies) (synapsin I, synaptophysin) (Vaynman 2004; 2006; Bayod 2011; Lin 2012; Toy 2014; Brockett 2015; Shin 2016)

• Dendrite length, complexity, spines (5 studies) (Eadie, 2005; Redila, 2006; Lin, 2012; Brockett, 2015; Shin 2016)

• Long term potentiation (Farmer 2004; O’Callaghan 2007; VanPraag 1999)
Levodopa FDA-approved in 1969 (carbidopa / levodopa approved 1975)

Marked improvement in longevity time-locked to this new drug, levodopada

(7 studies documented)

Most plausible explanation: Reversed sedentary lifestyle
2 simple rules for Parkinson’s disease treatment

1. Optimize carbidopa/levodopa

2. Engage in regular aerobic-type exercise
DBS

Effective for:
- Fluctuations
- Dyskinesias

Ineffective for symptoms that do not respond to levodopa (except tremor)
Question and Answer Session
Background Reading

