Medical Management of Early PD
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Conflict of Interest Statement

No drug company pays me any money
Outline

◆ So, you diagnosed Parkinson disease
  ▪ Natural history of the disease
  ▪ When to start drug therapy?
  ▪ Which drug to use first for symptomatic treatment?
    ● Levodopa vs dopamine agonist vs MAOI
Natural History of Parkinson Disease

- **Before levodopa:** Death within 10 years
- **After levodopa:**
  - “Honeymoon” period (~ 5-7 years)
  - Motor (ON/OFF) fluctuations & dyskinesias:
    - Drug therapy effective initially
    - Surgical intervention by 10-15 years
      - Deep brain stimulation (DBS) therapy

#### Motor Response vs. Dyskinesia Timeline
- **Several days**
  - ON state
  - OFF state
- **Several hours**
  - Dyskinesia
- **5-7 yrs**
  - ON state
  - OFF state
- **>10 yrs**
  - ON state
  - OFF state
- **1-2 hour**
Nature History of Parkinson Disease

- Prominent gait impairment and autonomic symptoms by 20-25 years (Merola 2011)
- Behavioral changes before or with motor symptoms:
  - Sleep disorders
  - Depression
  - Anxiety
  - Hallucinations, paranoid delusions
- Dementia at anytime during the illness
  - When prominent or early: diffuse Lewy body disease
Symptoms of Parkinson Disease

- Motor Symptoms
- Sensory Symptoms
- Mental Symptoms:
  - Cognitive and psychiatric
- Autonomic Symptoms
Presenting Symptoms of Parkinson Disease

◆ Mood disorders: depression and lack of motivation
◆ Sleep disorders: “acting out dreams” and nightmares
◆ Early motor symptoms: Typically Unilateral
  ▪ Rest tremor: chin, arms or legs or “inner tremor”
  ▪ Bradykinesia: focal and generalized slowness
  ▪ Rigidity: “muscle stiffness or ache”
◆ Also: (usually no early postural instability)
  ▪ Facial masking with hypophonia: “does not smile anymore” or “looks unhappy all the time”
  ▪ Micrographia: “shrinking handwriting”
  ▪ Unilateral shoulder pain
  ▪ Decreased arm swing or leg drag
  ▪ Decreased fingers dexterity with/without action tremor
  ▪ Dystonia: toes curling
  ▪ Dystonic hand or arm posturing with stooped posture
When to Start
Symptomatic Therapy

- Impaired activities of daily living
- Decreased dominant hand dexterity
- Gait impairment or falls
- Pain (often due to rigidity)
- Socially embarrassing symptoms

Time of initiation of Rx depends on:
- Patient’s personal preference
- Caregivers’ personal preference
- Neurologist’s perception of risk vs benefit of treatment
How to Beat The Disease

Non-pharmacologic treatment:
- Social support
- “The right attitude”
- Physical therapy & exercise
- (A good doctor?)

Pharmacologic treatment:
- Choosing the right drug(s)
L-Tyrosine → L-Dopa → Dopamine

Tyrosine Hydroxylase (rate limiting step)

L-Aromatic amino acid decarboxylase

Dopamine re-uptake

DA re-uptake

Dopaminergic neuron

L-Dopa

Dopamine

D_2-R

D_1-R

COMT

Striatal medium spiny neuron

Astrocyte

DA

HVA

MAO-B

OR
Treatment of Motor Symptoms of PD

Dopamine Replacement:
- Levodopa with aromatic amino acid decarboxylase inhibitors (carbidopa or benserazide, in Sinemet/Stalevo or Madopar, respectively)
- Catecholamine-O-methyl transferase (COMT) inhibitors: tolcapone (Tasmar), entacapone (Comtan, in Stalevo)
- Dopamine agonists: bromocriptine (Parlodel), pramipexole (Sifrol, Mirapex), ropinirole (Requip), apomorphine (Apokyn), cabergoline (Dostinex), rotigotine patch (Neupro)

Dopamine Releaser: amantadine (Symmetrel, PK-Merz)

Mono-amine oxidase Type B inhibitors (MAOI):
- Selegiline (Eldepryl), rasagiline (Azilect)

Anticholinergic drugs: trihexyphenidyl (Benzhexol, Artane), biperiden (Akineton), procyclidine (Kemadrin), benztropine (Cogentin), ethopropazine…
General Principles of Drug Therapy

- Start low
- Go slow
- Titrate symptoms
Levodopa

- Most powerful anti-parkinsonian drug
- Therapeutic range: 300 mg to >2000 mg per day
- Formulation:
  - Sinemet 10/100, 25/100, 25/250, CR 25/100, CR 50/200
  - Madopar 125, 250
  - Stalevo 25, 50, 75, 100, 125, 150, 200
  - Parcopa 10/100, 25/100, 25/250 (orally disintegrating)
  - Rytary 23.75/95, 36.25/145, 48.75/195, 61.25/245
  - Duodenal levodopa gel via Duodopa pump
- On-going studies:
  - Inhaled levodopa (CVT-301)
  - Transdermal levodopa ethyl ester (ND0611)
  - Sustained-release pro-drug of levodopa
- Adverse effects:
  - Nausea or constipation: Rx with high-dose of carbidopa (Lodosyn) 25-75 mg tid or domperidone (Motilium) 10-30 mg tid
  - Motor fluctuations/dyskinesia at ~ 5 years (earlier in young patients)
# Dopamine Agonists

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Total Daily Dose</th>
<th>Dosing Schedule</th>
<th>Tablets strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pramipexole</td>
<td>Sifrol</td>
<td>1.5-6 mg/day</td>
<td>tid/qid</td>
<td>0.18, 0.7, ER 0.375, 0.75, 1.5, 3 mg</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Requip(XL)</td>
<td>10-24 mg/day</td>
<td>tid/qid</td>
<td>0.25, 0.5, 1, 2, 4, 5 mg</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Parlodel</td>
<td>10-30 mg/day</td>
<td>tid/qid</td>
<td>2.5, 5 mg</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Dostinex</td>
<td>1-3 mg/day</td>
<td>qd</td>
<td>0.5 mg</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Neupro</td>
<td>2-16 mg/day</td>
<td>qd</td>
<td>2, 4, 6, 8 mg (patch)</td>
</tr>
</tbody>
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- **Removed from market:**
  - Pergolide (ergot-related tricuspid valve disease, retroperitoneal fibrosis)
Dopamine Agonists

- Relatively weak clinical effect but long-acting as compared to levodopa
- Mostly D2-receptor agonists
- Cause severe psychosis, confusion and sedation in elderly (especially above 70 years)
- May cause impulse control disturbances (gambling, hypersexuality, compulsive shopping, …)
  (Vilas, Parkinsonism Relat Disord 2012)
- Non-motor adverse effects (edema, daytime sedation, dizziness, hallucinations and nausea) were much more common with dopamine agonist than levodopa
  (Stowe, Cochrane Database Syst Rev 2008)
- PD MED Study: a large, open-label, pragmatic randomized trial showed a very small but persistent benefits for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy
  (PD Med Collaborative Group, Lancet 2014)
# Levodopa vs Dopamine Agonists

<table>
<thead>
<tr>
<th></th>
<th>Levodopa</th>
<th>Dopamine Agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Motor benefit</strong> (4 points difference on UPDRS)</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Motor fluctuations at 7 years</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Dyskinesia at 7 years</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Mental adverse effects</strong></td>
<td></td>
<td>&lt; 70 yrs: ++ &gt; 70 yrs: +++</td>
</tr>
<tr>
<td>- Hallucinations, delusions</td>
<td>+</td>
<td>increased with advanced disease</td>
</tr>
<tr>
<td>- Impulse control (hypersexuality, gambling, compulsive shopping)</td>
<td></td>
<td>increased with advanced disease and age of patient</td>
</tr>
<tr>
<td>- Daytime sedation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Orthostasis at 15 years of illness</strong></td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Monoamine Oxidase Inhibitors (MAOI)

MAO-Type B inhibitors:

- **Selegiline** (Eldepryl, Zelapar, Deprenyl)
  - 5 mg qam/bid, irreversible inhibitor
  - Adverse effects: insomnia (via amphetamine-like metabolite) and hallucinations

- **Rasagiline** (Azilect)
  - 0.5 or 1 mg qd
  - No amphetamine-like metabolite but questionable cheese effect
  - NO neuroprotective effect

- **New drug**
  - lazabemide (reversible inhibitor)
Dopamine Releasers & Glutamate Antagonists

- **Amantadine (Symmetrel, PK-MERZ) 100 mg bid-tid**
  - Enhances dopamine release
  - Observed motor benefit is modest and short-lived ~ 6 months before needing to add another drug
  - May cause myoclonus or hallucinations/delusions, especially in the elderly
  - Anti-dyskinetic activity at high dose (400 mg/day) via NMDA-receptor antagonism (?)
Available Treatment of Early PD

- Levodopa 100 mg tid:
  - “quick fix”

- Dopamine agonists:
  - “slow fix”
  - avoid in elderly >70 years

- Selegiline/rasagiline:
  - mild benefit for few months
  - avoid in elderly
  - Not neuroprotective

- Amantadine
  - mild benefit for ~6 months
  - avoid in elderly

- Anticholinergic drugs
  - may benefit levodopa-resistant rest tremor
  - avoid in elderly and young patients
Is Levodopa Toxic?

Basis for the hypothesis of levodopa toxicity

- Potential for levodopa metabolism to induce reactive oxygen species (free radicals that injure cells)
- Evidence showing that the substantia nigra is in a state of oxidative stress in PD
- In vitro studies showing toxic effects of levodopa on cultured neurons
- Neuroimaging studies appear to support the hypothesis of levodopa toxicity

This lead to:

- Erroneous interpretation that levodopa-induced motor complications is due to toxicity (neuronal injury) rather than due to adverse pharmacological effect (excess stimulation of dopaminergic pathways)
- Levodopa-sparing approach: Increase use of expensive dopamine agonists to avoid using levodopa in early disease
**Fundamental Flaws of in vitro Levodopa-Induced Toxicity Studies**

- Most *in vitro* studies found that levodopa is toxic for cultured dopaminergic neurons at concentrations above 50 μM, while peak plasma concentrations of levodopa in patients with PD was ~ 10-20 μM
  
  (Mytilineou 1993; Mena 1993; Han 1996; Ling 1996)

- *In vitro* dopaminergic neurons cultures lacked antioxidants, for instance:
  
  - Vitamin C was almost undetectable in the cultures
  - Vitamin C at concentrations of 200 μM provides almost complete protection from levodopa toxicity *in vitro*
  - the concentration of vitamin C in human CSF is ~130 μM and is even higher in the brain extracellular fluid

  (Kalir 1991; Pardo 1993; Mena 1993; Riederer 1989; Tallaksen 1992)
**Fundamental Flaws of in vitro Levodopa-Induced Toxicity Studies**

- **Most in vitro studies used systems lacking glial cells**
  - Glial cells or factors produced by glial cells protect cultured dopaminergic neurons from levodopa toxicity
  - In the presence of glial cells, levodopa can elicit a **neurotrophic effect** manifesting as increased cell survival and enhanced neurite outgrowth
    
    (Langeveld 1995; Desagher 1996; Mena 1997; Mytilineou 1993; Mena 1993; Mena 1998)

- **Most in vitro systems consist of cultured embryonic cells, which could be particularly susceptible to drug toxicity**
  - Dopaminergic neurons obtained from post-natal rats mesencephalon:
    - Are resistant to levodopa toxicity
    - Levodopa has a **neurotrophic effect** on these cells

(Murer 1999)
No Levodopa-Induced Toxicity in in vivo Animal Studies

Absence of neurotoxicity of chronic L-DOPA in 6-hydroxydopamine-lesioned rats

Gustavo Dziewczapolski, Gustavo Murer, Yves Agid, Oscar S. Gershanik and Rita Raisman-Vozari

![Brain sections with images showing moderate and severe neurotoxicity in untreated and treated conditions with L-DOPA.](Image)
Chronic Levodopa Is Not Toxic for Remaining Dopamine Neurons, but Instead Promotes Their Recovery, in Rats with Moderate Nigrostriatal Lesions

M. Gustavo Murer, MD, PhD,* Gustavo Dziewczapolski, PhD,† Liliana B. Menalled, MS,† M. Carmen Garcia, MS,† Yves Agid, MD, PhD,* Oscar Gerhanik, MD,† and Rita Raisman-Vozari, PhD*

Ann Neurol 1998;43:561–575
No Levodopa-Induced Toxicity in Humans, Possible Neurotrophic Effects!

Parkinson Study Group, *NEJM* 2004

361 patients

- Placebo: n=70
- 150 mg: n=78
- 300 mg: n=82
- 600 mg: n=81
Neuroprotection Study Design: Wash-out Design

Figure 2  Possible outcomes of the wash-out study design

A Symptomatic only
B ‘Disease-modification’ only
C Inconclusive

Rascol O, Neurology, 2009
More Reliable Neuroprotection

Study Design: Delayed-Start Design

Rascol O, Neurology, 2009
Delayed-Start Rasagiline Study: ADAGIO

- **N = 1176 patients**
- **Inconclusive study:**
  - 1 mg/day may be neuroprotective, with 1.7 points difference on UPDRS
  - 2 mg/day NOT neuroprotective
$^{123}\text{Beta-CIT Single Photon Emission Tomography (SPECT) in PD}$
**ELLDOPA Study Beta-CIT SPECT**

- Assumption: # of striatal dopamine transporter measured by SPECT correlates with # of striatal dopaminergic terminals and, therefore, correlates with motor outcome

- 116 patients Beta-CIT SPECT imaging:
  - 19 had no dopaminergic deficits at baseline SPECT
  - The 600 mg levodopa/day group had:
    - The best UPDRS motor scores 2 weeks after levodopa withdrawal
    - PARADOXICALLY, the greatest loss of striatal β-CIT uptake
    - Presumably therefore meaning the greatest loss of nigrostriatal dopaminergic neurons

- Clinical outcome measures discordant with imaging measures
  - β-CIT SPECT is a poor surrogate endpoint
  - Why: Modulation of binding sites by levodopa? Wrong assumptions?

- **Conclusion:** One cannot use Beta-CIT SPECT for measurement of progression of illness in treated PD patients
For More Details About

Neuroimaging Biomarkers for Parkinson Disease: Facts and Fantasy

Joel S. Perlmutter, MD¹ and Scott A. Norris, MD²

In this grand rounds, we focus on development, validation, and application of neuroimaging biomarkers for Parkinson disease (PD). We cover whether such biomarkers can be used to identify presymptomatic individuals (probably yes), provide a measure of PD severity (in a limited fashion, but frequently done poorly), investigate pathophysiology of parkinsonian disorders (yes, if done carefully), play a role in differential diagnosis of parkinsonism (not well), and investigate pathology underlying cognitive impairment (yes, in conjunction with postmortem data). Along the way, we clarify several issues about definitions of biomarkers and surrogate endpoints. The goal of this lecture is to provide a basis for interpreting current literature and newly proposed clinical tools in PD. In the end, one should be able to critically distinguish fact from fantasy.

ANN NEUROL 2014;76:769–783
Onset of Motor Fluctuations/Dyskinesia is Dependent on Disease Duration, NOT on Duration and Dose of Levodopa Rx

Conclusion: There is NO point in delaying levodopa treatment!
MY Bottom Line: Treatment of Early PD

- In young patients < 60 years
  - Low dose levodopa 100-200 mg tid (for a quick fix) to prevent early dyskinesia, then add dopamine agonist

- In older patients 60 to 70 years
  - Levodopa 100 to 250 mg tid
  - Once patient needs > 250 mg qid or develops motor fluctuations/dyskinesia, consider adding dopamine agonist

- In elderly > 70 years:
  - Levodopa 100 to 250 mg tid
  - No dopamine agonists

- May be rasagiline 1 mg/day (not selegiline)
  - Not neuroprotective

- Not amantadine, Not anticholinergic drugs

- Golden Rule: Use the lowest effective dose of any drug