Disease Modifying vs. Symptomatic Therapy

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Disclosures

• Funding
  – NIH
  – Parkinson Foundation
  – Abbott

• Conflicts
  – None
Overview

• Classes of therapies

• Symptomatic treatments disease-modifying?

• Studies for disease-modifying therapies
Two Main Types of Therapies

• Symptomatic

• Disease-modifying (neuroprotective)
Two Main Types of Therapies

• Knee pain analogy:

  – Symptomatic therapy: if you have knee pain from any cause, Tylenol or ibuprofen might help

  – Disease-modifying therapy: fixing the source of the knee pain (ACL repair, meniscal repair) stops worsening of pain
Symptomatic therapies

• Changing brain chemical levels
  – Dopamine replacement
  – Serotonin boosters
  – Acetylcholine boosters

• Changing brain network function
  – Deep brain stimulation
  – MRI-guided Focused Ultrasound
Why Replace dopamine?

Dopaminergic neuron loss in PD

Onset

Presymptomatic phase

Nonmotor

Sleep
Smell*
Mood
Constipation

Early nonmotor symptoms

Motor symptoms

Diagnosis

Motor

Tremor
Stiffness
Slowness
Imbalance

*Olfactory dysfunction may predate clinical PD by at least 4 years.

Why Replace dopamine?

Dopaminergic neuron loss in PD

- Onset
- Diagnosis
- Treatment

Presymptomatic phase
- Early nonmotor symptoms
- Motor symptoms

Brain Dopamine

Time (years)

Dopamine replacement: levodopa

- Earlier use of levodopa ≠ earlier dyskinesia and wearing-off
- Effect on disease course
Motor fluctuations / dyskinesias

Early Parkinson Disease

Later Parkinson Disease

http://people.virginia.edu/~rf3y/Elias/Motor_Fluctuations.html
Some of the risk depends on **how long you have had PD, not how long you take levodopa**

- **Black bars** = started levodopa soon after PD diagnosis
- **White bars** = started levodopa ~5-7 years after PD diagnosis
“Wasted” time with poor symptom control
**Time Until Wearing-Off and Dyskinesia**

- After 80 weeks
  - *No* difference in wearing-off
  - *No* difference in dyskinesia

*Delayed group started levodopa*

Verschuur et al. NEJM 380(4):315s
# Symptomatic Treatment: Motor

## Two main types

### Dopamine replacement

- Carbidopa/levodopa
  - Sinemet
  - Duopa
  - Rytary
  - Inbrija

- Dopamine agonists
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)
  - Apomorphine (Apokyn)
  - Rotigotine (Neupro)
  - Pergolide
  - Bromocriptine

### Other

- Amantadine

- Trihexyphenidyl (Artane)

- Dopamine extenders
  - Entacapone
  - Tolcapone
  - Opicapone
  - Selegiline
  - Rasagiline
  - Safinamide
**Dopamine Replacement**

**Blood**

- COMT inhibitors
- 3-OMD
- L-DOPA
- Carbidopa
- DA

**Blood-brain barrier**

- Blood
- Neuron

**Brain**

- AADC
- DOPAC
- MAO-B inhibitors
- 3-MT
- COMT inhibitor*
- Dopamine agonists
- Dopamine receptors

*L-DOPA = levodopa
3-OMD = 3-O-methyldopa
DA = dopamine

AADC = aromatic acid decarboxylase
DOPAC = dihydroxyphenylacetic acid
3-MT = 3-methoxytyramine

*Only tolcapone inhibits COMT in brain.
Symptomatic Treatment: Motor
Dopamine replacement

- **Levodopa**
  - Carbidopa reduces nausea: *Sin + emet IR*
  - Half-life ~ 1.5 hours
  - More effective in reducing motor symptoms
    - Ropinirole (class I)
    - Pramipexole (class I)
    - Pergolide (class I)
  - *Sinemet CR → does not delay motor complications compared to Sinemet IR*
Disease-Modifying Therapies
Two Main Types of Therapies

• Knee pain analogy:
  – **Symptomatic therapy**: if you have knee pain from any cause, Tylenol or ibuprofen might help
  – **Disease-modifying therapy**: fixing the source of the knee pain (ACL repair, meniscal repair) stops the cause of pain
Disease modification

Onset 

Presymptomatic phase 

Early nonmotor symptoms 

Motor symptoms 

Brain Dopamine 

Nonmotor 

Sleep 
Smell* 
Mood 
Constipation 

Motor 

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Stiffness 
Slowness 
Imbalance 

Time (years) 

*Olfactory dysfunction may predate clinical PD by at least 4 years.

Disease modification

Presymptomatic phase

Onset Diagnosis

Early nonmotor symptoms

Motor symptoms

Nonmotor

Motor

*Olfactory dysfunction may predate clinical PD by at least 4 years.

Disease modification

“Neuroprotection”

“Disease modification”

Onset

Presymptomatic phase

Diagnosis

Early nonmotor symptoms

Motor symptoms

Time (years)

*Olfactory dysfunction may predate clinical PD by at least 4 years.

Neuroprotection: slowing loss of brain cells and their connections

• Examples:
  – Remove effect of α-synuclein
  – Make brain cells more resilient
  – Reduce inflammation around brain cells
Overview

• Classes of therapies

• Symptomatic treatments disease-modifying?

• Studies for disease-modifying therapies
Does levodopa also modify disease course?

No

[Graph showing comparison between Delayed-start group and Early-start group with trend lines and error bars for UPDRS Total Score over Weeks since Randomization. The trend line for the Early-start group is consistently lower than that of the Delayed-start group with a notable decrease in score over time, indicating potential modification of disease course.]
Does levodopa also modify disease course?

Verschuur et al. NEJM 380(4):315s
Does levodopa modify disease course?

Yes

Before modern PD care:
- Levodopa
- Agonists
- MAO-B
- DBS
- Modern antidepressants

Minimal disability

Severe disability

Years since diagnosis

Hoehn and Yahr Stage

5 years

48 years

Hoehn & Yahr, 1967

QII, 2011
Parkinson’s disease-modifying: Exercise

• Neuroprotective vs. disease-modifying?
  
  – **Animals**
    • Exercise stimulates GDNF release (Cohen et al. J Neurochem 2003;85:299-305.)
  
  – **Humans**
    • Increases urate, assoc. with slower progression
    • Total physical activity associated with PD risk

Disease-modification: Exercise

• But what kind of exercise? (Shulman et al., JAMA Neurol, 2013)

  – low-intensity → most increase in walking distance and pace
  – high-intensity → most increase in cardiovascular performance
  – Stretching / resistance → most increase in muscle strength
Disease-modification: Exercise

- How intense should exercise be? (Shenkman, JAMA Neurol, 2017)

  - 3-point difference in UPDRS after 6 months
    - (average disease progression = ~3 points per year)
  - AE’s
    - 9 in high intensity exercise group (N=45)
    - 0 in usual care (N=40)
Parkinson’s “neuroprotection”: Research

- Ask a Parkinson’s researcher

- Web resources:
  - [https://foxtrialfinder.michaeljfox.org/](https://foxtrialfinder.michaeljfox.org/)
Questions?

• Need advice?
• PFNCA (parkinsonfoundation.org/)
• National Parkinson Foundation (NPF.org)
• Michael J. Fox Foundation (MJFF.org)
• Call 410-502-0133 ask for Chelsea
  – Advice on referrals
  – Direct you to a local support group
  – Other questions

The Johns Hopkins
Parkinson’s Disease and
Movement Disorders
Center Team!
But what about “stem cells”?!
“Stem Cell” Therapy

- Fetal ventral mesencephalon cells
- Embryonic stem cells
- Induced pluripotent stem cells
- Induced neurons

“Stem Cell” Therapy

- Fetal ventral mesencephalon cells
- Embryonic stem cells
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Why only *symptomatic and not a “cure”*?

Lewy bodies in grafted cells!

Li et al. PNAS. 2016 11:6544
“Stem Cell” Therapy

- Fetal ventral mesencephalon cells
- Embryonic stem cells
- Induced pluripotent stem cells
- Induced neurons

From another person and requires immunosuppression

From you but has your same Parkinson disease risk genes
“Stem Cell” Therapy

- Fetal ventral mesencephalon cells
  - 2 randomized trials -> no benefit (Freed et al. NEJM 2001; Olanow et al. Ann Neurol 2003)
  - New trial (TRANSNEURO) publication expected 2020
    - Cambridge, UK: NCT01898390
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