Common Misconceptions About Parkinson’s Disease

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Objectives

• Discuss the diagnostic approaches to Parkinson’s disease

• Address the influence of genetics on Parkinson’s disease risk

• Discuss the concept of delaying dopamine replacement therapy to avoid motor complications of therapy

• Discuss use and timing of advanced symptomatic therapies in Parkinson’s disease
Funding / Conflicts

• Funding
  – NIH / NINDS K23
  – NIH / NINDS R01 (Northwestern University)
  – Abbott / St. Jude (Site PI)
  – Parkinson Foundation

• Conflicts of Interest
  – None
Case #1

• 47 y/o mother of 2, 5 months of left hand tremor while watching TV
• More difficult shampooing hair
• Loss of smell sensation, dream enactment.

• Reason for consultation:
  – Do I have PD (my neurologist didn’t do a brain scan or labs so I don’t believe her)?
  – What can I do to stop it? I heard there is nothing that can be done to slow down the disease.
How do we diagnose Parkinson’s?

Patient:

“I don’t think my neurologist did a thorough evaluation. She did not even do an MRI of my brain. How could she know this is Parkinson’s disease?”
Parkinsonism

- Cardinal features
  - Bradykinesia (slow, small movement)
  - Rest Tremor
  - Rigidity

\[ \text{Required} \quad \text{Need 1} \]
Causes of parkinsonism:

- Parkinson's disease
  - Hereditary forms
  - Sporadic
- Multiple system atrophy (MSA)
- Diffuse Lewy body disease
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration
- Frontotemporal dementia with parkinsonism
- Pallidal degenerations
- Alzheimer disease
- Spinocerebellar ataxias (types 2,3,17)

- Huntington's disease
  - Juvenile presentation
  - Later in disease course
- Wilson disease
- Acquired hepatolenticular degeneration
- Parkinsonism Dementia Complex of Guam
- Neuroferritinopathy
- Basal Ganglia calcification
- Gaucher’s disease
- GM1 gangliosidosis
- Chediak-Higashi disease
- Chorea-acanthocytosis
How do we diagnose Parkinson’s?

### Diagnosis of Clinically Established PD requires:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria, and
3. No red flags

### Diagnosis of Clinically Probable PD requires:

1. Absence of absolute exclusion criteria
2. Presence of red flags counterbalanced by supportive criteria

If 1 red flag is present, there must also be at least 1 supportive criterion

If 2 red flags, at least 2 supportive criteria are needed

No more than 2 red flags are allowed for this category

### Supportive criteria

(Check box if criteria met)

- □ 1. Clear and dramatic beneficial response to dopaminergic therapy. During initial treatment, patient returned to normal or near-normal level of function. In the absence of clear documentation of initial response a dramatic response can be classified as:
  
  a) Marked improvement with dose increases or marked worsening with dose decreases. Mild changes do not qualify. Document this either objectively (>30% in UPDRS III with change in treatment), or subjectively (clearly-documented history of marked changes from a reliable patient or caregiver).
  
  b) Unequivocal and marked on/off fluctuations, which must have at some point included predictable end-of-dose wearing off.

- □ 2. Presence of levodopa-induced dyskinesia

- □ 3. Rest tremor of a limb, documented on clinical examination (in past, or on current examination)

- □ 4. The presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy

### Absolute exclusion criteria: The presence of any of these features rules out PD:

- 1. Unequivocal cerebellar abnormalities, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze-evoked nystagmus, macro square wave jerks, hypometric saccades)

- 2. Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades

- 3. Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 y of disease

- 4. Parkinsonian features restricted to the lower limbs for more than 3 y

- 5. Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism

- 6. Absence of observable response to high-dose levodopa despite at least moderate severity of disease

- 7. Unequivocal cortical sensory loss (ie, graph aesthesia, astereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia

- 8. Normal functional neuroimaging of the presynaptic dopaminergic system

- 9. Documentation of an alternative condition known to produce parkinsonism and plausibly connected to the patient’s symptoms, or, the expert evaluating physician, based on the full diagnostic assessment feels that an alternative syndrome is more likely than PD

### Red flags

- □ 1. Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset

- □ 2. A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment

- □ 3. Early bulbar dysfunction: severe dysphonia or dysarthria (speech unintelligible most of the time) or severe dysphagia (requiring soft food, NG tube, or gastrostomy feeding) within first 5 y

- □ 4. Inspiratory respiratory dysfunction: either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs

- □ 5. Severe autonomic failure in the first 5 y of disease. This can include:
  
  a) Orthostatic hypotension—orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, in the absence of dehydration, medication, or other diseases that could plausibly explain autonomic dysfunction, or

  b) Severe urinary retention or urinary incontinence in the first 5 y of disease (excluding long-standing or small amount of urine incontinence in women), that is not simply functional incontinence. In men, urinary retention must not be attributable to prostate disease, and must be associated with erectile dysfunction

- □ 6. Recurrent (<1 y) falls because of impaired balance within 3 y of onset

- □ 7. Disproportionate saccadic (dystonic) or contractures of hand or feet within the first 10 y

- □ 8. Absence of any of the common-nominator features of disease despite 5 y disease duration. These include sleep dysfunction (sleep-maintenance insomnia, excessive daytime conmennce, symptoms of REM sleep behavior disorder), autonomic dysfunction (constipation, daytime urinary urgency, sympathetic orthostasis, hypotension, or psychopathic dysautonomia (depression, anxiety, or hallucinations)

- □ 9. Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyporeflexia (excluding mild reflex asymmetry and isolated extensor plantar responses)

- □ 10. Bilateral asymmetric parkinsonism. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination

Albanese et al. Movement disorders. 2015
How do we diagnose Parkinson’s?

• Physical exam:
  – Bradykinesia plus
  – At least one of:
    • Stiffness
    or
    • Resting tremor

• Supportive criteria
  – Levodopa response
  – Levodopa-induced dyskinesia
  – Rest tremor
  – Olfactory loss or sympathetic denervation on MIBG

• “Red flags” → signs/symptoms of other diseases

• You do not need labs or an MRI to diagnose Parkinson’s, only to rule-out other things.
How do we diagnose Parkinson’s?

Patient:

“I heard there is nothing that can be done to slow down the disease!”
Treatment Overview

- **Disease-modifying / Neuroprotective** – slowing the disease
  - Oral medications
  - Non-pharmaceutical

- **Symptomatic treatment**
  - Oral medications
  - Surgical – medication infusion
  - Surgery – ablation / stimulation
  - Surgery – gene therapy
General Principals: Should you get treated?

Neurologist care in Parkinson disease
A utilization, outcomes, and survival study

Figure
Survival of Medicare beneficiaries with incident Parkinson disease stratified by treating physician specialty, adjusted for race, age, sex, comorbidity index, and socioeconomic deprivation

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*Physicians in the following specialties: internal medicine, family practice, or geriatric medicine.
Parkinson’s “neuroprotection”:

- **Neuroprotection** = reversing the underlying process that kills dopaminergic cells
  - Football analogy: running back too slow → trade for a faster RB, train current running RB

- **Disease modifying** = slowing progression of the disease even if you do not directly affect this process
  - Football analogy: running back too slow → recruit better offensive line
**Parkinson’s “neuroprotection”**

**TABLE 3. Summary of all of the previous clinical trials evaluating putative neuroprotective therapy for PD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Study design</th>
<th>Parallel arms (PA) versus placebo (P)</th>
<th>Washout period</th>
<th>Primary outcome(s)</th>
<th>Result</th>
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<tr>
<td>Selegiline</td>
<td>MAO-B inhibition; anti-apoptotic; antioxidant; other</td>
<td>PA</td>
<td>P</td>
<td>+ (Syneper 2 months)²¹</td>
<td>Need for symptomatic treatment; change in UPDRS³⁰</td>
<td>Positive²,²¹</td>
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<td>Rasagline</td>
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<td>DS</td>
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<td>Change in UPDRS</td>
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<td>THC-346</td>
<td>Anti-apoptotic; no MAO-B inhibition effects</td>
<td>PA</td>
<td>P</td>
<td></td>
<td>Need for symptomatic treatment</td>
<td></td>
</tr>
<tr>
<td>Pemipexole</td>
<td>Dopamine agonist, ant apoptotic</td>
<td>DS</td>
<td>P</td>
<td></td>
<td>Change in UPDRS</td>
<td>Negative³⁰</td>
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<tr>
<td>Pemipexole</td>
<td>Dopamine agonist, ant apoptotic</td>
<td>PA</td>
<td>A</td>
<td></td>
<td>Surrogate imaging marker</td>
<td></td>
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<tr>
<td>Ropinirole</td>
<td>Dopamine agonist, ant apoptotic</td>
<td>PA</td>
<td>A</td>
<td></td>
<td>Less change in striatal 5-CIT with pemipexane versus levodopa²³</td>
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<tr>
<td>Levodopa</td>
<td>Dopamine precursor; trophic</td>
<td>PA</td>
<td>P</td>
<td>+ (2 weeks; smaller subgroup had 4 weeks)</td>
<td>Change in UPDRS; surrogate imaging in subgroup</td>
<td>Positive for UPDRS; greater change in striatal 5-CIT with levodopa versus placebo²²</td>
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<td>Tacithanol</td>
<td>Antioxidant</td>
<td>PA</td>
<td>P</td>
<td></td>
<td>Need for symptomatic treatment</td>
<td>Negative³⁰</td>
</tr>
</tbody>
</table>

Lang et al., Mov Dis, 2013
# Parkinson’s “neuroprotection”

## Table 3: Summary of all of the previous clinical trials evaluating putative neuroprotective therapy for PD

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<th>Result</th>
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<td>CoQ10</td>
<td>Bioenergetic; antioxidant</td>
<td>PA</td>
<td>P</td>
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<td>Change in UPDRS</td>
<td>Positive&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FS</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Nontuit&lt;sup&gt;24&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Nontuit&lt;sup&gt;24&lt;/sup&gt;</td>
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<td>Mitoquinone</td>
<td>Bioenergetic; antioxidant</td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Negative&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td>Creatine</td>
<td>Bioenergetic</td>
<td>FS</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Nontuit&lt;sup&gt;26&lt;/sup&gt;</td>
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<tr>
<td>CEP-1347</td>
<td>Apoptotic; mixed lineage kinase inhibitor</td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Need for symptomatic treatment</td>
<td>Nontuit&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunophilin</td>
<td>Antiapoptotic;</td>
<td>FS</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Nontuit&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>? trophic</td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Negative&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>GDNF</td>
<td>Trophic</td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Negative&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Palireno</td>
<td>Trophic</td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Surrogate imaging marker</td>
<td>Negative&lt;sup&gt;32&lt;/sup&gt;</td>
</tr>
<tr>
<td>GM1 ganglioside</td>
<td>Stimulates recovery of damaged DA neurons (16 weeks); open-label 5 y</td>
<td>PA short term</td>
<td>NA</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Practically defined</td>
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<tr>
<td>Rituximab</td>
<td>Glutamate antagonist</td>
<td>PA</td>
<td>P</td>
<td>—</td>
<td>Need for symptomatic treatment</td>
<td>Negative&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Anti-inflammatory</td>
<td>FS</td>
<td>P</td>
<td>—</td>
<td>Change in UPDRS</td>
<td>Nontuit&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Parkinson’s “neuroprotection”: Current Trials

• **Isradapine** – phase III trial just closed, awaiting results

• **Antibodies** against α-synuclein – phase IIb

• **Nilotinib** – phase IIb/III enrolling

• **GLP-1 agonists**
  – **Exenatide** – phase III start-up
  – **NYL-01** – phase I
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

Parkinson’s disease-modifying: Exercise

• But what kind of exercise? (Shulman et al., JAMA Neurol, 2013)
  
  – low-intensity $\rightarrow$ most increase in walking distance and pace
  
  – high-intensity $\rightarrow$ most increase in cardiovascular performance
  
  – Stretching / resistance $\rightarrow$ most increase in muscle strength
Parkinson’s disease-modifying: 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:
  – http://clinicaltrials.gov/
  – https://foxtrialfinder.michaeljfox.org/
Case #2

• 67 y/o M with 14 years of PD, now with complications of medical therapy and early cognitive impairment

• Family history: maternal uncle with PD

• Reason for consultation:
  – No one in my family has PD so it has to be due to something in my environment, right?
“Cause” of Parkinson’s disease

• **Genetics** – complex genetic disorder

• **Environment**
  – Pesticides like paraquat, rotenone, 2,4-D (Pouchieu et al. Int J Epidem 2017)
    • Gloves reduce risk of PD in farmers
    • Higher prevalence in rural areas
    • Milk consumption associated with risk
  – Saturated fats (Kamel et al. Park Rel Dis. 2014)
  – Ozone and fine particulate matter (FM2.5)
Genetics of Parkinson’s disease

- Genomes of 13,700 PD patients and 95,282 controls compared
- 44 genes found to influence PD risk
- Risk is cumulative with the more genes you have

Nalls et al. Nat Genet. 2014 Sep;46(9):989-93
Genetics of Parkinson’s disease

Genetics of Parkinson’s disease

• What I tell patients:
  – Yes in 10% of cases
  – 90% of cases – some increased risk if in your family, but not high risk
Case #3

- 62 y/o F with PD for 5.5 years. Becoming disabled from hobbies and work by tremor
- Breakthrough tremor despite pramipexole 1.5 mg TID + amantadine 100 mg TID

- Reason for consultation:
  - My neurologist recommended carbidopa/levodopa, are there any alternatives?
  - Me: Why?
I heard that you should hold off for starting levodopa until you are very disabled because you can only use it for about 5 years before you develop dyskinesia and other problems.

Misconception
Treatment Overview

- Disease-modifying – slowing the disease
  - Oral medications
  - Non-pharmaceutical
- Experimental / future therapies
- Symptomatic treatment
  - Oral medications
  - Surgical – medication infusion
  - Surgery – ablation / stimulation
  - Surgery – gene therapy
Goal of Dopamine Replacement Therapy

- Reduce motor (movement) symptoms
  - Slow movement (bradykinesia)
  - Stiffness (rigidity)
  - Tremor
  - Some types of gait impairment

- Does not alter underlying disease course

- Exception → less early disability reduces later disability
Why dopamine replacement is needed

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

Symptomatic Treatment: Motor

Two main types

Dopamine replacement

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

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

Other

- Amantadine / Gocovri

- Trihexyphenidyl (Artane)

- Dopamine extenders
  - Entacapone
  - Opicapone
  - Tolcapone
  - Selegiline
  - Rasagiline
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)
Motor fluctuations

Early Parkinson Disease

Later Parkinson Disease

http://people.virginia.edu/~rf3y/Elias/Motor_Fluctuations.html
Symptomatic Treatment: **Motor**

**Dopamine replacement**

- **Dopaminergic neuron loss in PD**
- **Nonmotor**
  - Sleep
  - Olfactory*
  - Mood
  - Autonomic system

- **Motor**

---

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

Motor fluctuations

Early Parkinson Disease

Later Parkinson Disease

Does using levodopa earlier in the course of disease cause you to get levodopa-induced dyskinesia earlier?

Does using levodopa earlier in the course of disease cause you to have “wearing-off” earlier than if you delay treatment?

http://people.virginia.edu/~rf3y/Elias/Motor_Fluctuations.html
When do levodopa-induced dyskinesias occur?

Some of the risk depends on **how long** you have had PD not **how long** you take levodopa.

No levodopa for ~5-7 years after diagnosis

Levodopa started within 1-2 years of diagnosis

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Alshkog et al. Movement Disorders. 2001. 16(3):448-458
Symptomatic Treatment: Motor
Levodopa-induced dyskinesias

Much of the dyskinesia risk depends on how long you have had PD

Symptomatic Treatment: Motor
Levodopa-induced dyskinesias

“The present study provides evidence that motor fluctuations and dyskinesias are not associated with the duration of exposure to levodopa therapy, but rather to disease progression itself.…

Therefore, there is no reason to delay the initiation of adequate levodopa therapy in patients with Parkinson’s disease. In contrast with past drug trials, recent experimental studies suggest that the best therapeutic option to delay the molecular changes in gene expression, synaptic morphology and abnormal corticostriatal connectivity associated with dyskinesias may be early initiation of levodopa treatment (Marin et al., 2009)”

Cilia et al. The modern pre-levodopa era of Parkinson’s disease: insights into motor complications from sub-Saharan Africa. Brain 2014. e-pub
Case #3

• 57 y/o F with PD for 7 years
• Levodopa wears-off after 2.5 hours
• Has bothersome dyskinesia when levodopa is working
• Treatments
  – Entacapone worsened dyskinesia
  – Pramipexole and ropinirole caused sedation at work
  – Trihexyphenidyl caused cognitive impairment

• Reason for consultation:
  – My neurologist recommended that I consider Deep Brain Stimulation (DBS) or levodopa infusion therapy (Duopa). I’ve heard Deep Brain Stimulation (DBS) is for when you are only “really advanced”, and I don’t feel that bad. Should I consider it?
Oral Management of motor complications

“Wearing-off” and dyskinesia

- Smaller doses of dopamine replacement, more frequently

- Extenders
  - COMT inhibitors: entacapone (Stelevo), opicapone, tolcapone
  - MAO-B Inhibitors: rasagiline, selegiline

- Adjunctive therapy:
  - dopamine agonist: pramipexole, ropinirole, rotigotine
  - Rescue therapy: Apokyn injection, Apokyn ODT, Inbrija
  - Amantadine, anticholinergics (trihexyphenidyl)
Advanced treatment of “motor complications”

- Deep brain stimulation
- More continuous levodopa
  - Duopa
Deep Brain Stimulation

- **Goals:**
  - Reduce motor fluctuations
  - Medication-refractory tremor
DBS: Mechanism

- How does it work?
  - Problematic brain arrhythmia
  - Stimulation “disrupts” arrhythmia
DBS: Efficacy

• Does it help?

Limousin et al., NEJM, 1998
DBS: Efficacy

• Does it help?

Limousin et al., NEJM, 1998
Surgical symptomatic treatment: Motor

Deep Brain Stimulation

**Current Medications:**

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<th>0900</th>
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* booster dose of 1/2 Sinemet IR 25/100

15 doses / day

**Patient's Medication List:**

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<th>Medicine/Time</th>
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<td>3.0</td>
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<td>Azilect (1 MG)</td>
<td>1.0</td>
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<tr>
<td>Mirapex (1 MG)</td>
<td>1.0</td>
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<tr>
<td>Sinemet (25/100 MG)</td>
<td>-</td>
<td></td>
<td>1.0</td>
<td>1.0</td>
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</tbody>
</table>

7 doses / day
DBS: Effect Duration

- How long does it work?

UPDRS Motor Score Off medications

Adapted from Castrioto et al., Mov Dis, 2012
DBS: Device

- **What is it?**
  - Implantable Pulse Generator (**IPG**) → battery and computer
  - **Lead extenders** → under skin from IPG to brain leads
  - **Brain leads** → go from under skin through skull into deep brain target
DBS: Programming
DBS: Candidate selection

- Who is a good candidate?
  - Idiopathic Parkinson disease
  - Symptoms that respond to levodopa but:
    - **Fluctuations** (wearing-off)
      And/or
    - **Dyskinesias**
  - Little or no cognitive impairment (dementia)
  - Healthy surgical candidate
DBS: Candidate selection

• Who is NOT a good candidate?
  – Dementia or severe cognitive impairment
  – Major psychiatric issues
  – Substantial medical problems

• Factors making it less likely to succeed
  – Mainly gait symptoms, no levodopa response
  – Little or no levodopa response
  – Poor social support or ability to return for programming
DBS: Timing

- EARLYSTIM trial → 4 years or more of PD, early motor complications
  - Quality of life better with DBS than medical therapy
  - Largest improvements in ADL function, emotional well-being, and stigma

Schupach et al. NEJM 2013;368:610-22
DBS: Timing

- **EARLYSTIM trial**
  - Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Neurostimulation (N=124)</th>
<th>Medical Therapy (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events</td>
<td>123 (54.8%)</td>
<td>128 (44.1%)</td>
</tr>
<tr>
<td>Death, all by suicide</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
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<tr>
<td>Life-threatening event</td>
<td>14 (9.7%)</td>
<td>17 (7.1%)</td>
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<tr>
<td>Event related to medication or stimulation</td>
<td>24 (19.4%)</td>
<td>52 (29.9%)</td>
</tr>
<tr>
<td>Worsening of mobility†</td>
<td>5 (4.0%)</td>
<td>13 (8.7%)</td>
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<tr>
<td>Motor fluctuations</td>
<td>0 (0.0%)</td>
<td>7 (5.5%)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1 (0.8%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Psychosis or hallucinations</td>
<td>0 (0.0%)</td>
<td>8 (6.4%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0 (0.0%)</td>
<td>3 (2.4%)</td>
</tr>
<tr>
<td>Impulse control disorder</td>
<td>1 (0.8%)</td>
<td>5 (3.9%)</td>
</tr>
<tr>
<td>Depression</td>
<td>6 (4.8%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>2 (1.6%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Cardiac disorder</td>
<td>0 (0.0%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Injury</td>
<td>3 (2.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Respiratory or thoracic disorder</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>Other</td>
<td>4 (3.2%)</td>
<td>7 (5.3%)</td>
</tr>
<tr>
<td>Event related to surgery or device</td>
<td>26 (21.7%)</td>
<td>—</td>
</tr>
<tr>
<td>Impaired wound healing</td>
<td>4 (3.2%)</td>
<td>—</td>
</tr>
<tr>
<td>Intracerebral abscess or edema</td>
<td>2 (1.6%)</td>
<td>—</td>
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<tr>
<td>Dislocation of device§</td>
<td>5 (4.0%)</td>
<td>—</td>
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<tr>
<td>Reoperation necessary§</td>
<td>4 (3.2%)</td>
<td>—</td>
</tr>
<tr>
<td>Other</td>
<td>11 (8.8%)</td>
<td>—</td>
</tr>
<tr>
<td>Event related to Parkinson’s disease</td>
<td>57 (31.5%)</td>
<td>58 (24.4%)</td>
</tr>
</tbody>
</table>

Balance benefit against risks

Schupach et al. NEJM 2013;368:610-22
Carbidopa/levodopa enteral suspension (Duopa)
Carbidopa/levodopa enteral suspension (Duopa)

- Long-term outcomes at 52 weeks: Benefits

Fernandez et al. Movement Disorders. 2018; 33(6):928-936
Carbidopa/levodopa enteral suspension (Duopa)

- Long-term outcomes at 52 weeks: Adverse Events

Fernandez et al. Movement Disorders. 2018; 33(6):928-936
Questions?

- Need advice?
- Parkinson Foundation of the NCA (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

Thanks
Extra Slides
Parkinson’s “neuroprotection”: Rasagiline (Azilect)

- **1 mg a day**: patients who had taken it retained a lower movement score after the placebo group had started.

- **2 mg a day**: both groups ended up having *the same* movement score.

- **Consider**
  - FDA did not approve for “neuroprotection”
  - Is improvement of 2 UPDRS points important to patients
  - $$ Cost $$

Olanow et al., NEJM, 2009
MRI-guided Focused Ultrasound

- Just FDA-approved for essential tremor
- NOT approved for PD
MRgFUS Pallidotomy in PD

- 1 patient
- 320 mm$^3$ ablated
- Bilateral PD
- UPDRS part III “off”
  - Baseline 31
  - 1 week -> 12
  - 1 month -> 12
  - 3 months -> 13
  - 6 months -> 14

Young Cheol Na et al. Neurology 2015;85:549-551