Updates on Parkinson’s Disease and Parkinson-Plus Syndromes

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Disclosures

None
Overview of the talk

1. Parkinson’s disease and related disorder as proteinopathy/proteopathy

2. DAT SPECT

3. What is new in treatment
Pathology: How does selective neurodegeneration happen???
Lewy Body: What is it?

- First described by French pathologist Friedrich Lewy over a century ago
- But its constituent was only identified in 1997
Lewy Body = alpha-synuclein plus other proteins (ubiquitin etc)

In 1997, mutation in the alpha-synuclein gene identified in families with PD.
(Polymeropoulos et al, Science, June 1996)

Lewy Body stained strongly against antibodies to alpha-synuclein
Subsequently, alpha-synuclein duplication, triplication also found to cause PD

Too much alpha-synuclein = PD??
Misfolded alpha-synuclein maybe toxic

- Alpha-synuclein is a neuronal cytosolic protein
- Concentrates in terminal synapse
- Natively exists as an unfolded monomer, or anchored to synaptic vesicles
- Function unknown: thought to regulate synaptic function; neurotransmitter release, synaptic plasticity
- Under pathological conditions; misfolds and aggregates; eventually into insoluble amorphous; oligomers or fibrillar amyloid-like assembles
Synucleopathy: PD, DLBD, MSA

Characterized by accumulation/aggregation of insoluble alpha-synuclein

PD
Lewy Body Disease
Multiple System Atrophy (glial Cytoplasmic Inclusion in oligodentrocytes, stains for alpha-synuclein)
Different strain of alpha synuclein leads to different disease

Cylinder (Sphagghetti) Type: PD

Ribbon (Linguine) Type: MSA
Native α-syn (random coil) → Misfolded proteins → Oligomers (β-pleated sheet) → Amyloid fibrils (β-pleated sheet)

Phagosomes and lysosomes → Proteasome → Peptides

- Oxidative stress
- Protein sequestration
- Disruption of axonal transport
- Synaptic dysfunction
- Inhibition of UPS
- Mitochondrial dysfunction

Lewy neurite → Lewy body

Transmission
Taupopathy

Neurodegenerative disorders involving abnormal tau protein isoforms in neurons/glial cells.

AD
FTD-17
PSP
CBD
AD
Amyloid plaque
Tufted Astrocytes
Astrocytic plaque
PSP
NFT
Globose NFT
Ballooned neuron
CBGD
Neuritic plaque
Coiled body (oligodendrocytes)
Picks
Pick Body
Oleuropein
Oleocanthal
Oleuropein aglycone
Hydroxytyrosol
Exebryl-1*
TR-2*
Methylene Blue*

NGase inhibitor*†
CHIP*
Hsp104*†
NMNAT*
YM-08†
Myricetin†
Trehalose*
Curcumin*
Resveratrol†
TOMA*

Geldanamycin
Withaferin A
PDIs
N-phenylamines†
Anthraquinones
ATPZ
Rhodanines†
PcTS
P-tau antigen
AT8 Ab
HJ9.3, HJ9.4 & HJ8.7 Abs

Natively unfolded monomer
Misfolded monomer
Oligomer
Fibrils/NFTs

Tubastatin
17-AAG†
Radicicol†

Degradation
Aggregation inhibition/refolding
Degradation & aggregation inhibition/refolding
Immunotherapy

*Lowers toxic tau oligomers
†Target not directly tested
Native protein ➔ Unfolding protein ➔ Protolibrils ➔ Fibrils ➔ Amyloid plaques

Soluble oligomers/amorphous aggregates
Common Theme in Neurodegenerative disease

Aggregation of intraneuronal or extracellular protein = Proteinopathy

But What causes relentless progression?
Staging of α-synuclein pathology by Braak et al.5

Dorsal nucleus of vagus, olfactory tubercle
Substantia Nigra
Neocortex

Rostral to Caudal fashion.

Braak et al; Neurology 2005;64:1404-1410
Neuronal spread of alpha-synuclein

In 2008, pathology of patients receiving nigral transplants showed Lewy bodies in transplanted healthy cells; suggesting neuronal transmission of alpha-synuclein. Subsequently; growing body of evidence suggests that alpha-synuclein spreads between cells with a prion-like self propagation of pathogenic a-SYN aggregates.
Prion theory

Similarity:
abnormal misfolding, aggregation, spreading

Difference:
  Can be transmitted to different animals
  Nontoxic infectious mechanism: can self-propagate as oligomers

Best to call it “Prion-Like propagation” for now
DAT SCAN: differentiates ET vs parkinsonism but not PD vs parkinson-plus

SPECT scan
Dopamine transporter
Approved 2011
Differentiate normal/ET vs reduced dopamine uptake (PD, parkinsonian syndrome)
Subject to error in reading
DAT SCAN now available in Hawaii

Kuakini Nuclear Medicine will offer Prepped (SSKI), injected (Ioflupane I-123), wait 3-4 hours, then scan

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## Table: Concomitant Medications and DATscan

The data below are compiled from approved labeling and published literature to provide some assistance in deciding how to handle concomitant medications prior to administration of DaTscan for SPECT imaging.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maximum influence on DaTscan binding if not stopped</th>
<th>Half-life³</th>
<th>Time from last dose to minimum interference with DaTscan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram⁴</td>
<td>▲ binding 20%</td>
<td>24-48 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Escitalopram⁴</td>
<td>▲ binding 20%</td>
<td>27-32 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Sertraline²</td>
<td>▼ binding 20%</td>
<td>66 hours</td>
<td>3 days</td>
</tr>
<tr>
<td>Paroxetine⁴</td>
<td>▼ binding 10%</td>
<td>21 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>no data</td>
<td>30 hours</td>
<td>4 days</td>
</tr>
<tr>
<td>Benztropine²</td>
<td>▼ binding up to 70%</td>
<td>up to 24 hours</td>
<td>3 days</td>
</tr>
<tr>
<td>Bupropion²</td>
<td>▼ binding 20%</td>
<td>24 hours</td>
<td>48 hours</td>
</tr>
<tr>
<td>Buspirone</td>
<td>no data</td>
<td>3 hours</td>
<td>15 hours</td>
</tr>
<tr>
<td>Cocaine²</td>
<td>▼ binding 50%</td>
<td>2 hours</td>
<td>6 hours</td>
</tr>
<tr>
<td>Methamphetamine²</td>
<td>▼ binding 20%</td>
<td>5 hours</td>
<td>24 hours</td>
</tr>
<tr>
<td>Methylphenidate²</td>
<td>▼ binding ~20%</td>
<td>4 hours</td>
<td>20 hours</td>
</tr>
<tr>
<td>Selegiline²</td>
<td>no data</td>
<td>10 hours</td>
<td>48 hours</td>
</tr>
</tbody>
</table>

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* Inclusion of half-life of active metabolites.
Treatment
Parkinson’s Disease
Treatment Overview

- Neuroprotection: no definitive treatment available
  (?? Rasagiline)
  - Anti-alpha synuclein strategy

- Symptomatic
  - Pharmacological
  - Surgical (Deep Brain Stimulation), Gamma knife, MRI-guided Ultrasound,

- Non-motor management
  - Psychiatric/Sleep
  - Urinary/Bowel
  - Drooling, hypotension

- Restorative- experimental
  - Cell Transplantation
  - Gene therapy
Neuroprotection: Failed agents: not from lack of trying

- acamprosate, AIT-082, apomorphine, bromocriptine, carnitine, CEP1347, Clioquinol, Dimebon, Donepezil, EGCG (tea extract), KW-6002, gamma-hydroxybutyrate, levetiracetam, lipocortins, lipo-oxygenase inhibitors, lipoic acid, lithium, mithramycin, 7-nitroindazole, pergolide, phenelzine, phosphodiesterase inhibitors, polyADP-ribose polymerase inhibitors, Resveratol, Riluzole, Sulforaphanes, Taurine, Theophylline, Tocotrienol, Topiramate, Tranylcypromine, Uric acid, Zonisamide

Since then, list has grown; CoQ10, Creatine, Pioglitazone
What’s New in neuroprotective agents

- Isradipine (Ca Channel antagonist)
  - Neuroprotective property in animal model of PD
  - Phase II; safe, tolerable
  - Phase III underway (STEADY-PD III, Hawaii one of study sites: Dr. Webb Ross)

- Exenatide (BYETTA)
  - glucagon-like peptide agonist
  - Phase II underway

- Uric Acid
  - Inosine (urate precursor); safe, in phase II trial
  - Phase III recruiting

- Myeloperoxidase Inhibitor AZD-3241
  - Myeloperoxidase is reactive oxygen generating enzyme expressed by microglia
  - Phase II safe
  - Phase II for Multiple System Atrophy as well
PD treatment may need to target alpha-synuclein

PREVENT neuronal transmission of alpha-synuclein!
anti-alpha synuclein strategy is already starting

prevent clumping
- NPT200-11 small molecule alpha synuclein stabilizer: phase I safe

Vaccine: Elicit antibody response against alpha-synuclein
- AFFITOPE (AFFiRis): Safe Phase I, Phase II planned

immunotherapy/antibody
- PRX 002: Phase II underway
- BIIB054: Phase I underway
Nilotinib (TASINA)

Approved for CML
Inhibits c-Ab1

c-Ab1 : inhibits normal parkin function

Encourage alpha-synuclein aggregation

Possibly impact dopamine signaling

Positive in small open label study (media hype)
Promising but recommend to await larger clinical trial
Glutathione

Oral: not great bioavailability

IV: not effective
not recommended
can cause liver toxicity

Nasal spray: Phase II study underway
Naltrexone (opiate antagonist)

Did not help PD motor symptoms/dyskinesia

Did not help impulse control disorder in PD

Medical Marijuanna

Tremor:
THC, CBD, probably infective
nabixinols; possibly ineffective

Dyskinesia:
CBD probably ineffective
Nicotine

Epidemiologically, smokers have less Parkinson’s disease

Study results are mixed; some positive, other negative

May have antidysskinesia effect

Bee Venom (acupuncture)

UPDRS score improved in small open label study

Apamine indicated to help in animal studies

? neuroprotective
? help inflammation
? enhance acupuncture
? botox like effect
## Ongoing disease modification trial in PSP and MSA

<table>
<thead>
<tr>
<th>Agent</th>
<th>Action mechanism</th>
<th>Disease</th>
<th>Phase</th>
<th>Clinicaltrial.gov identifier</th>
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</thead>
<tbody>
<tr>
<td>TPI-287</td>
<td>Microtubule stabilizer</td>
<td>AD, CBD, PSP</td>
<td>1</td>
<td>NCT01966666, NCT02133846</td>
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<tr>
<td>BMS-986168</td>
<td>Antitau monoclonal antibody</td>
<td>PSP</td>
<td>1</td>
<td>NCT02460094</td>
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<tr>
<td>C2N-8E12</td>
<td>Antitau monoclonal antibody</td>
<td>PSP</td>
<td>1</td>
<td>NCT02494024</td>
</tr>
<tr>
<td>Salsalate</td>
<td>Inhibiting tau acetylation</td>
<td>PSP</td>
<td>1</td>
<td>NCT02422485</td>
</tr>
<tr>
<td>Young plasma</td>
<td>Rejuvenation</td>
<td>PSP</td>
<td>1</td>
<td>NCT02460731</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Selective serotonin reuptake inhibitor</td>
<td>MSA</td>
<td>2</td>
<td>NCT01146548</td>
</tr>
<tr>
<td>Mesenchymal stem cells</td>
<td>Cell replacement</td>
<td>MSA</td>
<td>1</td>
<td>NCT02315027</td>
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<tr>
<td>EGCG</td>
<td>Inhibition of toxic a-synuclein oligomers formation</td>
<td>MSA</td>
<td>3</td>
<td>NCT02008721</td>
</tr>
<tr>
<td>AFFITOPE</td>
<td>Active immunization</td>
<td>MSA</td>
<td>1</td>
<td>NCT02270489</td>
</tr>
<tr>
<td>AZD3241</td>
<td>Inhibition of microglia</td>
<td>MSA</td>
<td>2</td>
<td>NCT02388295</td>
</tr>
</tbody>
</table>
Symptomatic treatment

Control motor symptoms
Discuss goals: preserve function, independence, as long as possible
QOL
Drug Classes for Symptomatic Treatment

- **L-DOPA**
  - Sinemet: Carbidopa/L-dopa regular (25/100, 10/100, 25/250), sustained CR(50/200), Parcopa (oral dissolving),
  - Stalevo: Sinemet plus entacapone
  - **Rytary** (combination short acting and long acting carb/L-dopa)

- **DA (agonists):**
  - Bromocriptine, pergolide (now off market, cardiac valve complication)
  - Pramipexole (mirapex ER), ropinirole (requip XL)
  - Rotigotine patch (withdrawn 08 crystallization, reapproved 2012)
  - Apokyn (IV)

- **MAO-B inhibitors:** Selegiline, Zydis selegiline (MLT) Rasagiline

- **COMT inhibitors** (entacapone, tolcapone)

- Amantadine, Anticholinergics
L-Dopa

Absorbed using amino acid transporter system (can interfere with protein)

Sinemet: Carbidopa/L-Dopa IR (25/100, 10/100, 25/250), Sustained CR(50/200)
Parcopa (ODT); not faster onset, help in dysphagia
Stalevo: Sinemet plus entacapone
Rytary (combination short acting and long acting carb/L-dopa)
DUOPA (carbidopa/L-Dopa gel) continuous jejunal pump
Inhaled L-dopa powder (CVT 301) phase III underway
Liquid L-Dopa SQ Delivery (ND0612L)
Late Motor Complication

- Narrowing of therapeutic window,
- Receptor supersensitivity
- Nonphysiological intermittent stimulation of dopamine receptors
Rytary

Each capsule contains both:
- Immediate-release beads.
- Extended-release beads.\(^2\)

Figure 9: Levodopa Plasma Concentrations Following a Single Oral Dose of RYTARY\(^\text{R}\) (carbidopa and levodopa) and the Individual Components Based on Separate Pharmacokinetic Studies\(^40\)

Based on RYTARY pharmacokinetic characteristics, the dosages of other carbidopa-levodopa products are not interchangeable with dosages of RYTARY. You cannot convert on a 1-to-1 basis.\(^26\)

Each capsule contains\(^{40,41}\):
- Total levodopa level
- Immediate-release beads
- Extended-release beads: Type 1
- Extended-release beads: Type 2
  - Tartaric acid (absorption enhancer) beads

Healthy volunteers

Levodopa Plasma Levels (ng/mL)

Time (hours)

Reference: 36. Data on file, MA-2016-2001-DOF, Impax Laboratories, Inc. (Data based on Studies IPX066-B05-07, IPX066-B06-02, IPX066-B07-03, and IPX066-B08-10).
Rytary dose adjustment

Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to RYTARY

<table>
<thead>
<tr>
<th>Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa</th>
<th>Recommended Starting Dosage of RYTARY</th>
<th>RYTARY Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg to 549 mg</td>
<td>855 mg</td>
<td>3 capsules RYTARY 23.75 mg / 95 mg taken TID³</td>
</tr>
<tr>
<td>550 mg to 749 mg</td>
<td>1140 mg</td>
<td>4 capsules RYTARY 23.75 mg / 95 mg taken TID</td>
</tr>
<tr>
<td>750 mg to 949 mg</td>
<td>1305 mg</td>
<td>3 capsules RYTARY 36.25 mg / 145 mg taken TID</td>
</tr>
<tr>
<td>950 mg to 1249 mg</td>
<td>1755 mg</td>
<td>3 capsules RYTARY 48.75 mg / 195 mg taken TID</td>
</tr>
<tr>
<td>Equal to or greater than 1250 mg</td>
<td>2340 mg or 2205 mg</td>
<td>4 capsules RYTARY 48.75 mg / 195 mg taken TID or 3 capsules RYTARY 61.25 mg / 245 mg taken TID</td>
</tr>
</tbody>
</table>

³ TID: three times a day

Table 4: RYTARY Dosing at the End of Study

<table>
<thead>
<tr>
<th>2X</th>
<th>3–5</th>
<th>76%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily dose of levodopa was approximately double that of IR CD-LD</td>
<td>3 to 5 divided doses were given per day</td>
<td>Patients required adjustment from starting dose; 60% titrated up and 16% titrated down</td>
</tr>
</tbody>
</table>
Continuous jejunal pump: DUOPA (carbidopa/L-dopa gel) approved 2015
Inhaled dopamine powder (CVT301)
Liquid L-Dopa SQ Delivery (ND0612L)

Small belt pump

Patch pump

Phase III study to start soon
Dopamine agonist

Ergot derivatives (Bromocriptine, pergolide, cabergoline)
- Now off market for concerns of cardiac valvular problem

Ropirinol (Requip, Requip XL)

Pramipexaloe (Mirapex, Mirapex ER)

Rotigotine patch (Neupro)
- unique in transdermal technology
- recalled in US because of crystallization, reapproved June 2012

Apomorphoine (Apokyn)
- Subcutaneous, short acting for rescue
- Thin-film under the tongue strip (like Listerine)
  currently under phase III trial (APL-130277)
COMT inhibitor

Entacapone  
Tolcapone  

**Opicapone (ONGENTYS):** once a day dosing  
Approved by European Commission July 2016  
2 phase III studies demonstrating reduce OFF time, and non-inferiority compared to entacapone
MAO-B inhibitors

- Selegiline,
- Zydis selegiline (MLT)
- Rasagiline

**Safinamide (XADAGO)**
- Multiple mechanism
  - Also blocks voltage dependent Na channel,
  - modulates Ca channel,
  - modulate glutamate release
- 50-100 mg daily
- Approved in Europe
- USA: under review by FDA
Other neurotransmitters

- Adenosine A2a receptor antagonists
  - Istradefylline: recent negative study
  - Tozadenant: found to reduce OFF time in Phase II trial
    - Phase III underway (TOZ-PD)

- Alpha 2-adrenergic alpha 2 Receptor Antagonist
  - Fipamezole (ODT) for dyskinesia, safe in phase II trial

- Glutamate (metabotropic glutamate 5R antagonist)
  - Animal model effective for dyskinesia
  - Maraglurant (AFQ056) negative phase II
  - Dipraglurant (ADX48621) being explored
Surgical Treatment

- Ablative
  - Thalamotomy, pallidotomy

- Electrical Stimulation (DBS)-high frequency, pulsatile, bipolar electrical stimulation
  - VIM thalamus (for tremor),
  - Gpi, STN

- Cell Transplant

- Gene Therapy (direct infusion of adeno-virus vector gene to BG)

- MR-guided ultrasound
DBS of STN/GPi
Not All symptoms respond to DBS

Responsive
- Motor symptoms responsive to L-dopa
- Tremor
- Rigidity
- Bradykinesia
- Dyskinesia
- Dystonia
- Motor fluctuations

Unresponsive
- Speech (may worsen)
- Cognition
- Gait and postural instability (if not responsive to L-dopa)
- Autonomic Symptoms
- Mood and Behavior (can improve or worsen)
When do we refer patients?

- **L-dopa responsive patients**, who cannot maintain the stable ON state from motor fluctuations and dyskinesias
  - UPDRS score of 30% difference between ON/OFF state
  - Surgery will help prolong patient's “BEST ON STATE” on meds
  - Will not provide antiparkinsonian benefits that are superior to what can be achieved by L-dopa.

- Medically refractory tremor
- Patients who cannot tolerate oral medication
- **IF** their biggest disability is from non-motor features, they are not good candidates
Before proceeding with DBS…

- **Ensure correct diagnosis!!**
  - If they have atypical parkinsonism, they will not respond to surgery.
  - If they never responded to L-dopa, they may have atypical parkinsonism

**Establish preserved cognitive function**
- Cognitive function can worse after surgery
- Patient with severe depression may not benefit from surgery

**Establish realistic expectation**
Future: DBS and biologics

“Hybrid” stereotactic surgery

A. DBS and biologic therapy delivered at the same surgical session with the same stereotactic platform

B. Diagram showing DBS electrode, gene or cell therapy, Globus pallidus, and Putamen.
MR-Guided Focused Ultrasound

FDA approved for Essential Tremor (VIM)

Does benefit PD tremor as well; but more study needed for other targets

pilot study for Dyskinesia
ExAblate Neuro

Real time MRI monitor
Precise monitoring of temperature rise
Feedback on localization with mid-temperature before final thermal necrosis
Head completely shaved
4 hours in scanner
Cell Based Therapy

- “Doc, when will stem cell cure Parkinson’s disease?”
- “Should I go to China to get stem cell?”
- (stem cell tourism)
Different methods of cell based therapy

- Fetal nigral cell
- Embryonic porcine dopaminergic cell
- Retinal pigmented epithelial cell
- Embryonic stem cell
- Autologous stem cell
  - i-PS cell (success in animal model)
  - Kyoto University in Japan, planning to test in PD patients 2018

GForce-PD initiative
Cell based therapy has been a disappointment thus far

Fetal nigral cell transplantation:
- 2 large NIH sponsored double blinded placebo controlled (sham surgery) study failed to show clinical benefit (2001, 2003)
- severe off-medication dyskinesia occurred
- Postmortem showed Lewy Bodies in the transplanted cell (the transplanted cell developed PD years later)

Intrathecal Application of Autologous Bone Marrow Cell: negative.
First stem cell trial in human

Human parthenogenetic stem cell derived neuroal stem cells ISC-hpNSC (NCT02452723)
Open label phase I
12 patients
Royal Melbourne Hospital in Australia
Oct 2016: safety study published
ISC-hpNSC cell line safe
Stem cell may not be a cure

- Stem cell would not be superior to previous cell based methods that failed.
- Current cell based therapy targets dopamine replacement therapy
  - does not address nondopaminergic features
- There may be a host factor, in developing PD
Gene Therapy
Gene Therapy: Efficacy disappointing

<table>
<thead>
<tr>
<th>Treatment (approach)</th>
<th>Trial design</th>
<th>Year began</th>
<th>Subject # dosed</th>
<th>Highest total dose (vg)</th>
<th>Target(s)</th>
<th>Largest volume (µl)/site</th>
<th>Safety results</th>
<th>Efficacy outcomes</th>
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<tbody>
<tr>
<td>AAV2/GAD</td>
<td>Ph1-uncontrolled&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2003</td>
<td>12</td>
<td>1 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Subthal Nuc (unilat)</td>
<td>50</td>
<td>Acceptable</td>
<td>Advanced to Ph2</td>
</tr>
<tr>
<td></td>
<td>Ph2-double-blind&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2008</td>
<td>22/16&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Subthal Nuc (Bilat)</td>
<td>35</td>
<td>Acceptable</td>
<td>Mixed results; program suspended</td>
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<tr>
<td>AAV2/ AADC</td>
<td>Ph1-uncontrolled&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2004</td>
<td>10</td>
<td>0.3 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Putamen (Bilat)</td>
<td>50</td>
<td>Acceptable</td>
<td>Program suspended; revised Ph1 recently announced</td>
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<tr>
<td>AAV2/ AADC</td>
<td>Ph1-uncontrolled&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2007</td>
<td>6</td>
<td>0.3 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Putamen (Bilat)</td>
<td>50</td>
<td>Acceptable</td>
<td>No further testing; revised Ph1 recently announced by USA group</td>
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<tr>
<td>AAV2/ NRTN</td>
<td>Ph1-uncontrolled&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2005</td>
<td>12</td>
<td>0.54 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Putamen (Bilat)</td>
<td>5(10)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>Acceptable</td>
<td>Advanced to Ph2</td>
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<tr>
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<td>Ph2A-double-blind&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2006</td>
<td>38</td>
<td>0.54 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Putamen (Bilat)</td>
<td>5(10)&lt;sup&gt;**&lt;/sup&gt;</td>
<td>Acceptable</td>
<td>Mixed results; revised Ph1 designed</td>
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<tr>
<td></td>
<td>Ph1-uncontrolled&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2009</td>
<td>6</td>
<td>2.4 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Put + SN (Bilat)</td>
<td>50</td>
<td>Acceptable</td>
<td>Advanced to Ph2</td>
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<td>Ph2B-double-blind&lt;sup&gt;h&lt;/sup&gt;</td>
<td>2010</td>
<td>24</td>
<td>2.4 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Put + SN (Bilat)</td>
<td>50</td>
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<td>Program suspended</td>
</tr>
<tr>
<td></td>
<td>Ph1/2-uncontrolled&lt;sup&gt;i&lt;/sup&gt;</td>
<td>2008</td>
<td>15</td>
<td>Lentivirus dosing is not comparable to that of AAV&lt;sup&gt;**&lt;/sup&gt;</td>
<td>Putamen (Bilat)</td>
<td>50</td>
<td>Acceptable</td>
<td>Program suspended; additional work to optimize vector ongoing</td>
</tr>
<tr>
<td>LENTI/ AADC-TH-CH1</td>
<td></td>
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</tr>
<tr>
<td>AAV2/ GDNF</td>
<td>Ph1-uncontrolled&lt;sup&gt;k&lt;/sup&gt;</td>
<td>2013</td>
<td>Ongoing</td>
<td>0.7 x 10&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Putamen (Bilat)</td>
<td>150</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Synopsis</td>
<td>Total of seven phase 1 and three phase 2 trials</td>
<td>2003–2013</td>
<td>&gt;139</td>
<td>Tested up to 1 x 10&lt;sup&gt;12&lt;/sup&gt; vg AAV</td>
<td>Targets have included subthalamic nucleus, putamen and SN</td>
<td>50 µl (most common); 150 µl (largest)</td>
<td>No safety issues or serious side effects noted</td>
<td>Efficacy outcomes generally disappointing</td>
</tr>
</tbody>
</table>

AAV, adeno-associated virus; SN, substantia nigra.
<sup>a</sup>Kapli et al. 15. 1<sup>LeWitt et al. 2011</sup>. 1<sup>Christine et al. 22</sup>. 1<sup>Muramatsu et al. 28</sup>. 1<sup>Marks et al. 60</sup>. 1<sup>Marks et al. 38</sup>. 1<sup>Bartus et al. 39</sup>. 1<sup>Bartus et al. 37</sup>. 1<sup>Palfi et al. 31</sup>. 1<sup>Lonser 39</sup>.
<sup>*</sup>Twenty-two subjects were dosed but six were eliminated from efficacy analysis due to mistargeting of cannula. **Two 5 µl volumes infused via single needle tract –4 mrn apart. * Described as a Phase 1/2 trial, this open label (uncontrolled) study does not differ substantially from many dose-escalation Phase 1 safety studies that include secondary efficacy endpoints; thus, the distinction appears to be more a semantic preference than a reflection of a substantial difference in study design. ** A five-fold dose range was tested involving 3 dose levels (1.9x10<sup>7</sup> transducing units (TU); 4.0x10<sup>7</sup> TU; 1.0x10<sup>8</sup> TU).
Non-Motor Symptoms

Dysarthria/Dysphagia
- Lee-Silverman
- Swallow evaluation

Sialorrhea
- Anticholinergics (side effects may limit use)
  botulinum toxin A and B to salivary glands (double blinded study demonstrated reduced drooling and reduced disability)

Urinary Problem
- Peripherally acting anticholinergics

Sexual Dysfunction
- Eliminate agents that can aggravate sexual dysfunction (beta-blockers, TCAs, SSRI)
- Consider Pharmacological, urological approach
Non-Motor Symptoms

**Orthostatic hypotension**
- Nonpharmacological management, including education
- Reduce/eliminate agent that can aggravate orthostatic hypotension (dopamine agents, antihypertensive)
- Fludrocortisone, Midodrine
- DDAVP
- **Droxidopa (Northera)**: approved 02/2014

**Constipation**
- Nonpharmacological
- Smooth Move Tea
- Rancho’s receipt
- Stool softeners, polyethylene glycol (double dose, triple dose)
- MOM, laxatives, enema
- Mosapride (5HT4 agonist, partial 5HT3 antagonist)
- Amitiza (Lubiprostone)
- Linzess (Linaclotide)
Droxidopa (Northera)

Prodrug of norepinephrine
Cross BBB
100 mg TID, up to 600 mg TID
Side effect:
  Supine hypertension
  Dizziness
  Headache
Sleep disorder

- Excessive Daytime sleepiness:
  - Modafinil; promising in open-label, but not in controlled studies

- REM sleep disorder
  - May lead to alpha-synucleinopathy, including PD, Lewy Body dementia, and MSA
  - Low dose clonazepam 0.25 mg-0.5 mg

- Restless Leg Syndrome
  - Dopamine agonist (Augmentation)
  - gabapentin, clonazepam, opiates
Neuropsychiatric problems

- Dementia/Hallucination
  - Rivastigmine FDA approved for PD dementia
  - Reduce/Eliminate parkinsonian meds
    - cognitive benefit, vs worsening of parkinsonian features needs to be balanced
  - Clozapine (weekly CBC), Quetapine (Seroquel)
  - other atypical antipsychotics can worsen mobility
  - Pimavanserin (5HT2A R inverse agonist), approved

- Depression
  - SSRI, TCA, dopamine agonist

- Anxiety
Pimavanserin (Nuplazid)

Inverse agonist to serotonin 5-HT$_{2A}$ R
No affinity to dopamine R
17 mg 2 cap qhs
Phase III study: improvement in psychosis scale (SAPS-PD)
Onset of action 2-4 weeks
Prolong QTc
Side effect: edema, confusion