Advances in Management of Parkinson’s Disease and Essential Tremor

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Outline

• Parkinson’s (PD) updates
  – Diagnostic
    • SWI-MRI
    • DaTscan
  – Medication
    • Motor complications
      – Xadago
      – Gocovri
    • Non-motor symptoms
      – Nuplazid
      – Northera
    • Coming down the pipeline
      – Inhaled levodopa
      – Subcutaneous apomorphine patch/pump
      – Update on disease modifying therapies
  – Non-medications
    • PT, speech therapy
    • Exercise

• Essential tremor (ET)
  – Management options
  – Surgical options
Diagnosis of Parkinsonian syndrome

- Clinical exam
  - Motor scale (MDS-UPDRS)

- MRI brain
  - Typically normal in idiopathic PD, especially early
  - Recent data on high-resolution SWI to assess for loss of neuromelanin
  - Conventional Can be very useful when atypical parkinsonism is suspected
    - Vascular parkinsonism
    - Progressive supranuclear palsy (PSP)
    - Multiple system atrophy (MSA)

- DaTscan
  - I\(^{131}\) ioflupane brain SPECT
  - FDA approved for ET vs parkinsonian syndrome
  - Cannot differentiate between idiopathic PD vs atypical parkinsonism
Absent swallow tail sign on high-resolution 3T SWI-MRI in diagnosis of PD

Detection of nigroson 1 of the SNpc – in clinically well established patients
Sensitivity 100%, specificity 90%, PPV 50%, NPV 100%, accuracy 91%

Schwarz et al., 2014, PLoS One
A. Normal: “largely symmetrical; approximately equal bilat”. Two commas.

B. Abnormal 1: asymmetrical; almost normal or reduced putamen activity in one hemisphere and a more marked change on the other side w/ significantly lower or no uptake in the putamen. One comma, one circle.

C. Abnormal 2: included significantly reduced putamen bilat. Activity was confined to the caudate nuclei. Two circles.

D. Abnormal 3: virtually no uptake bilat. No circles.

Kupsch et al. 2011 BMJ
DaTscan accuracy

• Clinically established ET vs PD vs healthy control
  – 95% Sensitivity
  – 93% specificity for the consensus blinded read
  – Benamer et al. 2000 Movement Disorders

• Clinically unclear parkinsonian syndrome
  – Baseline DaTscan vs diagnosis after 3 years
  – 78% positive percent agreement
  – 97% negative percent agreement
  – Hauser et al. 2011 J Neuroimaging

• 3T SWI-MRI vs DaTscan: PD, PSP, MSA, healthy control, ET
  – 89% sensitivity
  – 84% specificity
  – 86% concordance with DaTscan with false positives and false negatives
  – Bae et al. 2016 Movement Disorders
Motor complications of PD

- **ON time** = feeling well, muscles are loose, movements are smooth
- **OFF time** = feeling stiff, rigid, stuck, frozen, slow, fatigued
- **DYSKINESIAS** = abnormal involuntary movements (does not include tremor)
- **Non-motor fluctuations**
- **Within 5 years of treatment with levodopa:**
  - 50% of patients experience dyskinesias, but only 20% find them troublesome
  - About 40% of patients experience troublesome on-off fluctuations
Safinamide (Xadago)

• FDA approved March 2017
• MAO-B inhibitor (similar to rasagiline (Azilect) or selegiline (Eldeprys), reducing metabolism of dopamine
• Phase III study 2017 JAMA Neurology
  – Patients with 1.5 hours of OFF who were taking levodopa
  – 50-100 mg once daily
  – Improved ON time by 1.4 hours (compared to 0.6 hours in placebo)
  – Dyskinesias in 15% vs 5% in placebo
Safinamide

• Other biochemical effects:
  – Blocks Sodium channels
  – Blocks Potassium channels
  – Reduces abnormal Glutamate release
    • In rats this controlled the neurodegenerative process
    • Has not been proven clinically useful in humans
• No evidence of use as monotherapy
• No head-to-head comparison vs other MAO-B inhibitors or vs COMT inhibitors for clinical data
  – More specific to MAO-B (vs A) compared to rasagiline and selegiline
• Some pts had transient confusion as a side effect
• Was also noted to have insomnia, dizziness, headache and nausea (similar to placebo)
• Not effective in reducing dyskinesias
• Is being studied to see if initiating safinamide early could prevent dyskinesia
• Drug interactions with SSRIs, SNRIs, and TCA’s
Extended-release amantadine for dyskinesia (Gocovri)

- FDA approved August 2017
  - NMDA antagonist
  - Mildly anticholinergic
  - Dopamine releasing
- Positive phase III:
  - 30% reduction in dyskinesia compared to placebo
  - Increased ON time without dyskinesia 2.4 hours
  - Reduced OFF time 1 hour
  - Approx 20% stopped due to AE’s (vs 7% in placebo)
- Same side effects as regular amantadine other than insomnia
  - visual hallucinations, dry mouth, dizziness, peripheral edema, falls, constipation, nausea, anxiety, decreased appetite, livedo reticularis, auditory hallucinations and orthostatic hypotension
Opicapone (Ongentys)

- Available in Europe
- In pipeline for FDA approval
- Long-acting (once daily)
- COMT inhibitor similar to currently available entacapone (Comtan)
- Reduces metabolism of levodopa, making levodopa last longer
- 2015 Phase III study
- 2-hour reduction in OFF time vs 0.9 hours for placebo
- 2014 study compared opicapone to entacapone
  - Opicapone once daily significantly improved duration of levodopa action compared to 3 times daily entacapone
  - No urinary discoloration or diarrhea (seen in entacapone)
  - May have higher risk of dyskinesia (16%) compared to entacapone (8%)
Non-oral levodopa treatment

Table 1: Existing and “in development” levodopa-based treatment strategies

From: Non-oral dopaminergic therapies for Parkinson’s disease: current treatments and the future

<table>
<thead>
<tr>
<th>Route</th>
<th>Agent</th>
<th>Clinical positioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>Levodopa belt pump</td>
<td>In development (phase 2 CT)</td>
</tr>
<tr>
<td>Subcutaneous/transdermal</td>
<td>Levodopa patch–pump</td>
<td>In development (phase 2 CT)</td>
</tr>
<tr>
<td>Intrajejunal infusion</td>
<td>Levodopa-carbidopa gel</td>
<td>In clinical use</td>
</tr>
<tr>
<td></td>
<td>TriGel</td>
<td>In development (phase 1 CT)</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Levodopa powder (CVT-301)</td>
<td>In development (phase 3 CT)</td>
</tr>
</tbody>
</table>

Abbreviation: CT, Clinical trial; TriGel, levodopa carbidopa entacapone (liquid form).
Duopa (levodopa intestinal gel infusion)

- Reduces OFF time ~ 4 hours (vs 2 hours in placebo)
- Improves ON time w/o dyskinesia ~ 4 hours (vs 2.2 hours in placebo)
- No reduction in dyskinesia
- 16-hour administration via a cartridge into a PEJ tube
- Same benefit as levodopa, but a smoother concentration over the course of the day
- Complications include tube malfunction, ileus, pulled tube, neuropathy, usually only in the first 2 weeks
- FDA approved 2015
- Used in Europe since 2004 (Duodopa)
- Consideration for those who are not candidates for DBS and/or refuse brain surgery
Inhaled levodopa (CVT-301)

- Inhalable levodopa (CVT-301, Acorda)
- The lung has good absorption for levodopa – higher peak compared to oral
- Rapid and predictable onset, lasting 4 hours
- Pure levodopa so pts still have to take oral carbidopa
- Doses 35 mg and 50 mg
- Pulmonary safety study ongoing
Inhaled levodopa (CVT-301)

- Phase III trial results presented
- 271 PD pts without chronic lung disease
- CVT-301 84 mg vs placebo up to five times daily
- Improvement in motor function compared to placebo at 30 minutes
- No lung safety issues noted
- Adverse effects: Mild cough or URI
- No increase in dyskinesias
Subcutaneous levodopa

- ND0612, Neuroderm
- Patch form of carbidopa/levodopa
- Phase II trial (open label)
- Met primary and secondary endpoints of pharmacokinetics
Subcutaneous apomorphine

- Pen / Pump similar to an insulin pump
- Highly selective dopamine agonist
- Phase III TOLEDO trial: 106 patients, 12 weeks, OFF time reduction 2.5 hours (vs 0.5 hours with placebo)
- Reduced dyskinesias
- Risk of new ICD ~ 19% in an observational study
- Typically patients can reduce but not stop levodopa
5HT1a agonists for dyskinesia

• Buspirone
  – Phase III trial to start soon
• Sarizotan
  – Phase II/III ongoing
• Eltoprazine: 5HT1A/B agonist
  – Proof of concept study
  – double blind, placebo controlled, dose finding: some efficacy at 7.5 mg
• Dipraglurant: mGluR5
  – phase IIa study: mAIMS positive results
When to consider DBS

- Good initial response to levodopa
- On-off fluctuations (improves ON by 5 hours (vs 0 in best medical therapy group); reduces OFF by 2.4 hours (vs 0 in BMT group)
- Dyskinesias (reduces by 70%)
- Disabling tremor (reduces by 60-70%)
- Absence of dementia/severe depression
- PD > 4 years and motor fluctuation x 4 months
- MRI normal for age
- Good medical health
- Realistic expectations
Non-motor symptoms

- Autonomic symptoms
  - Constipation
  - Delayed gastric emptying
  - Orthostatic hypotension
  - Urinary dysfunction
  - Sexual dysfunction
  - Diaphoresis

- Cognitive symptoms
  - Memory issues
  - Executive function trouble
  - Processing speed
  - Personality change

- Psychiatric symptoms
  - Depression
  - Anxiety
  - Apathy
  - Hallucinations / Delusions
  - Impulse control disorders (ICD)

- Sleep issues
  - Insomnia
  - Fatigue
  - REM sleep behavior disorder
Droxidopa (Northera) for orthostatic hypotension in PD/MSA

- Metabolized into norepinephrine
- Improve symptoms of OH by 2 points on a 0-10 scale (vs 1.5 in placebo)
- 100 mg 3 times per day x 1 week then titrate
- Most end up on 400-600 mg 3 times per day
- Stop midodrine with use of droxidopa
- Less supine hypertension than with midodrine
- Side effects: HA, dizziness, fatigue, which resolve with time and are not dose-dependent

![Mean change in OHSA Item 1 score by week (n=147)\(^1\,2\,\alpha,\beta\)](chart)

Supine SBP in Study 306\(^1\)

<table>
<thead>
<tr>
<th>Study 306</th>
<th>During 1- to 2-week titration Phase (% of patients)</th>
<th>At end of 8-week treatment Phase (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORTHERA (n=114)</td>
<td>Placebo (n=108)</td>
</tr>
<tr>
<td>Supine SBP &gt;200 mm Hg</td>
<td>2.6%</td>
<td>0%</td>
</tr>
<tr>
<td>Supine SBP &gt;180 mm Hg</td>
<td>2.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Supine SBP &gt;160 mm Hg</td>
<td>16.7%</td>
<td>19.4%</td>
</tr>
<tr>
<td></td>
<td>NORTHERA (n=86)</td>
<td>Placebo (n=93)</td>
</tr>
<tr>
<td>Supine SBP &gt;200 mm Hg</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Supine SBP &gt;180 mm Hg</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Supine SBP &gt;160 mm Hg</td>
<td>2.6%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
Nuplazid (pimavanserin) for Parkinson’s disease psychosis

• Novel anti-psychotic, not anti-dopaminergic
• Selective 5HT2A inverse agonist
• FDA approved April 2016
• No anticholinergic or histaminergic effect
• Improved SAPS-PD score (0 to 45) by ~ 6 points compared to ~ 3 points on placebo
• Side effects include nausea, constipation, edema, gait issues, confusion
Updates in disease modification

• Clearing alpha-synuclein
  – cAbl inhibitors e.g., nilotinib
    • Also regulates Parkin gene activity
    • Preclinical data and a small phase I study
    • Phase II studies recruiting
  – Affitope: vaccine to clear alpha-synuclein
    • Phase Ib study safe/tolerable
  – NPT088: human fusion protein
    • Phase I study

• Antioxidants
  – IV and intranasal glutathione showed no symptomatic benefit in well-done trials
  – Inosine increases uric acid
    • Phase III recruiting

• Calcium channel blocker
  – Phase III trial ongoing

• Nortriptyline
  – In vitro reduces alpha-synuclein clumping
  – Reduced levels of alpha-synuclein in rats
  – Delayed time to need levodopa in epidemiological studies
  – Collier et al., 2017 Neurobiology of disease
Updates in disease modification

• Diabetes drug exenatide
  – GLP-1 receptor agonist
  – Increase incretin effect
  – Stimulate the release of insulin
  – RCT, N = 62
  – Once weekly vs placebo for 48 weeks, washout x 12 weeks
  – Improved MDS-UDPRS by 1 point compared to worsened UPDRS by 2 points in placebo group
  – Side effects injection site reactions and GI symptoms
  – Does not affect blood sugar levels in non-diabetic patients
  – Athauda et al., 2017 Lancet

• Beta-agonists
  – Alpha-synuclein gene expression (SNCA) correlates with disease
  – Beta-2-agonists modulate epigenetic marks at the SNCA gene
  – Epidemiological studies suggest salbutamol associated with lower risk of PD
  – Propranolol associated with higher risk of PD (but often used for ET which can be misdiagnosis
  – Mittal et al., 2017 Science
Therapy advances for PT

- Ongoing evidence for power of PT, OT, speech therapy, physical activity, dance, exercise, well-being programs
- Speech therapy program:
  - SpeechVive

The SpeechVive device detects your speech
Background sounds play in your ear when you speak
The sounds trigger a reflex, causing you to speak louder & more clearly
Technology / Wearable Sensors

• Improve clinical data re:
  – Tremor control
  – Dyskinesias
  – ON vs OFF time
  – Freezing
  – Near falls
  – Medication consistency

• Improve research data especially for subtle aspects of gait in pre-symptomatic gene carriers or RBD patients
  – Could result in shorter study times

• Improve assessment of function, rather than capacity
  – What the patient actually does vs what they can do in the clinic

• A big step for personalization of care
Exercise and PD

Benefits of Exercise
- Improved gait and balance / reduced freezing of gait / reduced risk of falls
- Improved flexibility / reduced rigidity / reduced risk of contractures
- Improved endurance / energy
- Improved ability to complete activities of daily living / improved sense of well-being / improved quality of life
- Improved working memory and decision making
- Improved attention and concentration
- Improved mood / reduced depression and anxiety
- Improved quality of sleep

Direct Effects of Exercise
- More efficient use of dopamine by brain cells (neurons) (making medications more effective)
- Growth of blood vessels, improving blood flow
- Helps neurons make new connections (synapses) by releasing brain growth factors
- Improves neuroplasticity (teaching the brain a new pattern of thinking / functioning)
- Improves cardiovascular health / improves brain metabolism
- Supports the functioning of the immune system / reduces inflammation
Exercise and PD

Corcos et al., 2013
Mov Disorders
Essential Tremor (ET)

• Slowly progressive condition causing tremor, usually in bilateral hands, head or voice
• Much more common than PD, affects up to 8 million Americans
• Used to be called benign essential tremor to distinguish from PD
• Can be associated with significant disability, limiting writing, dressing, eating, drinking
Essential Tremor (ET) Management

- **Medications**
  - Propranolol up to 240 mg daily
  - Primidone up to 250 mg daily
  - Benzodiazepines (e.g., clonazepam)
  - Gabapentin
  - Topiramate

- **Injection**
  - Botulinum toxin injection for hand and head tremor

- **Non-medication treatment**
  - Use of travel mugs / straws
  - Zubits (magnetic shoelaces)
### Advanced Management of ET: comparing options

<table>
<thead>
<tr>
<th></th>
<th>Reversible</th>
<th>Laterality</th>
<th>Adjustable over time</th>
<th>Surgery and implant</th>
<th>Battery replacement needed</th>
<th>Frame for surgery</th>
<th>Time to completion</th>
<th>Time to recovery</th>
<th>Time for effect</th>
<th>Hair shaving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Brain Stimulation (DBS)</td>
<td>Yes</td>
<td>Bilateral</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Optional</td>
<td>5 hours (+1 hour battery)</td>
<td>Weeks</td>
<td>Immediate</td>
<td>Partial</td>
</tr>
<tr>
<td>Focused Ultrasound (FUS)</td>
<td>No</td>
<td>Unilateral</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>4 hours</td>
<td>Fast (Days)</td>
<td>Immediate</td>
<td>Full</td>
</tr>
<tr>
<td>Radiosurgery</td>
<td>No</td>
<td>Unilateral</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>1 hour</td>
<td>Fast</td>
<td>Delayed (months)</td>
<td>No</td>
</tr>
</tbody>
</table>