PD ExpertBriefing:
Medical Therapies: What’s in the Parkinson's Pipeline?

Led By: Kapil D. Sethi, M.D., F.R.C.P.
Georgia Regents University, Augusta, GA

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Introduction & Welcome
by Robin Elliott
Executive Director
Parkinson’s Disease Foundation
Medical Therapies: What's in the Parkinson's Pipeline?

Kapil D. Sethi, M.D., F.R.C.P., F.A.A.N.
Professor of Neurology
Director, Movement Disorders Program
Medical College of Georgia at
Georgia Regents University
Augusta, Georgia
Senior Medical Expert, Merz Pharmaceuticals

Why Do We Need New Medications for Parkinson’s Disease?

• There is no drug/intervention that has been demonstrated conclusively to slow down the rate of clinical decline in Parkinson’s disease.

• The existing drugs that benefit motor symptoms have limitations:
  – levodopa results in motor complication
  – dopamine agonists have neuropsychiatric side effects
Why Do We Need New Medications for Parkinson’s Disease?

• The burden of nonmotor symptoms such as autonomic disturbances, cognitive problems and gait and balance issues is not adequately addressed by the currently available medications.

These Will Not Be There!

• Vitamin E (antioxidant)
• Coenzyme Q_{10}
• Minocycline (anti-inflammatory)
• CEP-1347 (JUNK inhibitor)
• Talampanel (AMPA receptor antagonist)
• GPI-1485 (immunophilin ligand)
• Istradefylline (A_{2A} antagonist)
• Riluzole (glutamate release inhibitor)
• Sarizotan (5HT_{1A} receptor agonist and weak D_{2} antagonist)
• Tesofensine (triple uptake inhibitor)
• TCH-346 (anti-apoptotic)
• Pardoprunox (a partial agonist at dopamine D_{2} and D_{3} receptors)
• Perampanel (AMPA receptor antagonist)
Medications in Development

• There are currently over 100 new therapies under development for Parkinson’s disease (PD). These include drugs aimed at
  – Disease modification/neuroprotection
  – Symptomatic management
    • Motor symptoms
    • Nonmotor symptoms

Neuroprotection vs Slowing the Clinical Progression

• Neuroprotection, or disease modification, in PD can be defined as an intervention that protects or rescues vulnerable neurons and thereby slows, stops, or reverses disease progression

• Slowing the clinical progression refers to reducing the rate of worsening of clinical signs and symptoms without alluding to the underlying mechanism
**Barriers to Developing Neuroprotective Therapies in PD**

- Lack of a clear understanding about the biological processes leading to cell death in PD
- Lack of a faithful animal model
- Inadequate translational research
- Heterogeneity in people with PD
- Lack of means to determine the proper dose to study neuroprotection
- Lack of a biomarker leading to reliance on clinical measures that may be influenced by the therapy itself

**Some Currently Ongoing Neuroprotective Therapy Trials**

- National Institutes of Health (NIH) neuroprotective studies
  - Creatine (ongoing Phase II/III study-NET PD)
  - FS-ZONE (pioglitazone)
- Pilot studies
  - Isradipine (dihydropyridine Ca^{2+} channel blocker)
  - Inosine (antioxidant, elevates urate levels)
Pioglitazone

- FS-ZONE Phase 2 NET-PD
- Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-G) also known as glitazone receptor and to a lesser extent PPAR-alpha
- This leads to anti-inflammatory and anti-apoptotic effects

Another Approach to Neuroprotection

- Substantia nigra pars compacta (SNC) neurons are autonomous pacemakers
- Pacemaking properties are unique for SNC and not present in ventral tegmental area (VTA) neurons
- Pacemaker affinity changes from Na\(^+\) to Ca\(^{++}\) with aging
- Ca\(^{++}\) dependence can be reversed back to Na\(^+\) with CaV1.3 Ca\(^{++}\) channel blockers

Systemic delivery of isradipine was neuroprotective in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine 6-OHDA models of PD in mice.
Other Drugs

• High serum urate levels predict slower decline of function in people with PD.

• Inosine is being studied in 90 people with early PD to assess its safety and its ability to raise CSF urate levels.

Growth Factors

• GDNF and BDNF are important for neuronal survival and recovery from injury

• While the open-label studies of direct infusion of GDNF into striatum were positive, the double-blind (AMGEN) study was negative

• AAV-Neurturin employs a vector to transfer the gene that makes Neurturin directly into brain cells most affected by PD

• One double-blind study negative, but nigral and putamen targeting with higher dose under study
Oral Agent PYM 50028-Cogane

Oral Agent to Enhance NGF

- Cogane (PYM50028) is an oral non-peptide compound that crosses BBB and induces nerve growth factors (NGF) in dopaminergic and nondopaminergic neurons
- Results in over 40% improvement in parkinsonism in the MPTP primate model
- Unfortunately the Phase II trial failed to meet the endpoints
Future Targets

- Agents to inhibit hyperphosphorylation of alpha-synuclein
- Agents to inhibit alpha synuclein transfer from one cell to the other
- Novel kinase inhibitors for targeted populations such as LRRK2 related PD

Cocktail Therapy – Future of PD

- Multiple pathways involved leading to cell death
- All people with PD are not the same
- In other fields like cancer, and tuberculosis success achieved with strategic combinations of drugs acting on different pathways
Management of PD Motor Disability

A Little History
Reserpine Monkey Model
Levodopa remains the most potent medication for symptomatic control of Parkinson’s

Improving delivery of current drugs or creating novel formulations of existing medications
Levodopa Therapy – Future

• Long-acting levodopa – Rytary- IPX066 (IMPAX)
  – Clinical trials in de novo and advanced PD
  – Two Phase III studies, APEX-PD and more recent ADVANCE-PD, study show superiority over conventional levodopa

• Another drug XP21279 is a slow release formulation of levodopa that is absorbed throughout the small intestine and the early results are encouraging

Levodopa Therapy-The Future

• Levodopa Patch preparation abandoned by Neuroderm Israel due to skin irritation

• In the future Highly concentrated subcutaneous pumps and programmable patches may be developed

• Intrajejunal infusion of levodopa (DUODOPA)
Novel Formulations of Existing Medications

1. Carbidopa patch (ND0611) under development. Seems to reduce peripheral side effects of levodopa and improve pharmacokinetics hopefully resulting in more “on” time.

2. Long acting amantadine for dyskinesia being developed by ADAMAS pharmaceuticals.

3. Some ongoing discussions about developing a COMT patch.

4. A COMT inhibitor that is as potent as tolcapone (Tasmar) but without liver concerns.

Optimization of Dopamine Agonist Delivery

• Long-acting dopamine agonist
  – Ropinirole XL
  – Pramipexole ER
  – Rotigotine patch – is back again!
  – Lisuride patch in development

• Dopamine agonist continuous delivery
  – Apomorphine pump Subcutaneous¹
  – Lisuride pump Subcutaneous²

Management of PD Motor Complications - New Formulations of Existing Therapies

Continuous drug administration a competition to deep brain stimulation (DBS) surgery?

• DUODOPA
  – Intrajejunal levodopa gel delivery\textsuperscript{1,2}
  – Double-blind and open-label US studies show clear benefit

• Subcutaneous apomorphine infusion
  – Not yet studied in the United States
  – The problems of skin irritation and nodules has to be tackled and it will enhance utility

\textsuperscript{2} Devos, D; French DUODOPA Study Group. Mov Disord. 2009;24(7):993-1000.

MAO-B Inhibitors - Safinamide

• A selective, reversible MAO-B inhibitor 1000 times more selective for B than A with no tyramine effect.

• Voltage-dependent sodium and N-type calcium channel blocker, and inhibits glutamate release.

• May protect against seizures and may improve cognition.

• Development process has been long and frustrating!

Medications with Novel Mechanisms

• \( A_{2A} \) antagonists (GABA\(_A\) inhibition of globus pallidus)-caffeine is one of them!
  – Istradefylline-is coming back
    • Positive results in Phase 3 trials\(^1\)
    • Food and Drug Administration (FDA) did not grant approval in March 2008
  – Other \( A_{2A} \) antagonists in development: preladenent, SYN115


Medications with Novel Mechanisms

• Serotonin receptor partial agonists
  – Target dyskinesia – Sarizotan 5HT\(_{1A}\) agonist failed
  – Alpha adrenergic antagonists – fipamazole

• Nicotine receptor agonists
  – Strong epidemiological data re smoking\(^2\)
  – Clinical trials so far negative\(^3,4\)

Adenosine A\textsubscript{2A} Receptors

- Changes in relative activities of direct (underactive) and indirect (overactive) pathways in PD
- Levodopa corrects changes in the direct pathway (D1 excitation) but not indirect (continued elevation of enkephalin mRNA), which relates to D2 inhibition – resulting in dyskinesias
- Mismatch of direct and indirect pathways
- Stimulation of A\textsubscript{2A} reduces D2 receptor affinity
- Antagonist will increase dopamine affinity to D2 receptors, hence inhibiting the indirect pathway
- Co-administration of A\textsubscript{2A} antagonist and apomorphine prevents dyskinesia

Preladenant – SCH 420814

- Phase I and II studies most recently doses used were 1, 2, 5, and 10 mg twice daily
- Doses well tolerated with LD; improved motor function (UPDRS) and improved “on” time
- Most frequent side effects dizziness and headache
- BP increases noted but diminished with continued therapy
- Asymptomatic liver enzyme (ALT) elevation on or after week 4; 25% with high doses (>25 mg/day) and a third 3x the ULN (cholestasis) NOT in the 10 mg twice daily group
• AFQ056 (Novartis) a metabotropic glutamate receptor 5 (mGluR5) antagonist, has recently showed positive results in a proof-of-concept trial in PD-LID

• Psychosis still an issue with mGluR5 antagonists

Dipragluran
• MGluR 5 antagonist found to have positive results in a Phase II study in people with Levodopa-induced dyskinesias
• Named as one of the Top 10 “Neuroscience Projects to Watch” by I don’t know who!
• Phase III studies are planned
Fipamezole (FJORD) Study

• Primary study
  – No significant change in levodopa-induced dyskinesias (LIDs) rating for the combined US and Indian study groups

• Secondary analysis
  – US subset (65% of the total study population)
  – Strong evidence of FIP efficacy against LID
  – Highest dose of FIP tested (90 mg, three times daily) may be useful to treat LID in advanced PD
    • Without making the PD worse

• Indian study subset
  – Lack of antidysskinetic efficacy unexplained!! I have an idea!


Treating Nonmotor Problems

• PD Psychosis including hallucination affects a large number of patients.

• Currently atypical antipsychotics such as Seroquel and Clozaril are used to treat PDP but these have limitations.

• Pimvanserin-A 5 HT2A antagonist and inverse agonist is being studied in Phase III studies

• So far results are encouraging.
Agonists, Antagonists and Inverse Agonists

Treating Nonmotor Manifestations

Lubiprostone studied in PD constipation – small DB study positive Ondo 2012
**Constipation Secondary to Puborectalis Syndrome**

Treatment: use an Indian toilet!

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**Treating Orthostatic Hypotension**

- Droxidopa (3-4 l-threo-DOPS) is norepinephrine precursor

\[
\text{DDCI} \\
\text{Droxidopa} \rightarrow \text{Norepinephrine}
\]

- Clinically it appears that carbidopa will not impair its action and the drug will be useful for hypotension due to multiple etiologies
Pharmacogenetics

- It has been known since the 1950s that a certain number of people lack butylcholinesterase and can have a severe reaction with succinylcholine.
- In the 1950s, a number of African American soldiers receiving antimalarial drugs developed hemolysis due to G6 PD deficiency.
- In the field of PD, this field is in its infancy.

Should Sergey Brin be on CEP-1347??
Hope Yogi Berra was wrong when he said, “The Future Ain't What It Used To Be.”
Questions & Answers

Resources from PDF

Fact Sheets
- Understanding PD Medications
- Medication Log

Parkinson's Disease Resource List
- 750 Resources

Online
- PD ExpertBriefing: Complementary Approaches to PD
- Online Course: Parkinson's Advocates in Research
Upcoming *PD Expert Briefings*

**Improving Communication in Parkinson’s: One Voice, Many Listeners**
Tuesday, June 4, 1:00 PM – 2:00 PM ET
*Angela Roberts-South, M.A., C.C.C.-S.L.P., C.A.S.L.P.O.(Reg.), Ph.D. Candidate, Western University, Ontario, Canada*

**Sex and Parkinson’s**
Tuesday, September 10, 1:00 PM - 2:00 PM ET
*Gila Bronner, M.P.H., M.S.W., C.S.T.*
*Sexual Medicine Center, Sheba Medical Center, Israel*

Please complete our SURVEY.

Your responses help us to improve the work that we do.

Thank you.