SPECT and PET Tracers for the Evaluation of the Dopaminergic System

John P. Seibyl, MD
Executive Director and Senior Scientist
Institute for Neurodegenerative Disorders, and Molecular NeuroImaging, LLC
New Haven, CT   USA

Disclosure: Dr. Seibyl has equity interest In Molecular NeuroImaging

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Parkinson’s disease

• Described in 1817 by Dr. James Parkinson while observing pedestrians walking outside his office in London

• Key Features:
  - Stiffness (rigidity)
  - Tremor
  - Slowed movements (bradykinesia)
  - Disturbed pattern of walking/ difficulty standing (postural instability)
  - Symptoms progress slowly over time
Natural History of PD

Preclinical

Symptomatic

Diagnosis

Dopamine Neurons

Motor ratings

Time
Is early and accurate diagnosis really necessary in PD?

• Initiate appropriate treatment/Avoid inappropriate potentially harmful therapy.

• Provide patient and family additional diagnostic certainty
  - Improved quality of life/reduce anxiety
  - Enable life-style planning

• Reduced unnecessary resource use - physicians, tests (MRI)

• Provide referral physician with a (rule-in) diagnosis to expedite referrals.
Is early and accurate diagnosis really necessary in PD?

- Does early therapy provide a long-term symptomatic advantage - early start studies
- Early treatment with disease modifying medications. - HOLY GRAIL
### Potential PD Disease Modifying Targets and Drugs

<table>
<thead>
<tr>
<th>Targets/pathways</th>
<th>Drugs/Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-oxidants</td>
<td>Co-Q10, dopamine agonists</td>
</tr>
<tr>
<td>Growth factors</td>
<td>GDNF, immunophilin ligands</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Propargylamines, dopamine agonists</td>
</tr>
<tr>
<td>Caspase-inhibitors</td>
<td>MLK inhibitors</td>
</tr>
<tr>
<td>Glutamatergic agents</td>
<td>Receptor modulators</td>
</tr>
<tr>
<td>Adenosine agent</td>
<td>A2A antagonists</td>
</tr>
<tr>
<td>Mitochondrial drugs</td>
<td>Co-Q10</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Non-steroidal anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td>Cell replacement - Stem Cell</td>
</tr>
<tr>
<td></td>
<td>Exercise</td>
</tr>
<tr>
<td></td>
<td>DBS</td>
</tr>
</tbody>
</table>
How Accurate is Clinical Diagnosis?

- 299/402 (74%) subjects dx as PD by PCP met criteria for Parkinsonism - Meara 1999
- 18/33 (55%) subjects dx as PS by PCP found to have PD by MDS - Kis 2002
- 20% of subjects with PD by MDS were not dx by PCP - Schrag 2002
- General neurologists - Approx 25% of dx incorrect compared to 6-12 month ‘gold standard’ diagnosis - Jennings 2004
- Movement disorder specialists - Approx 15% of dx incorrect compared to 6-12 month ‘gold standard’ diagnosis - Jennings 2004

Diagnoses most commonly mistaken for early PS include: ET, vascular PS, drug-induced PS, AD, aging, psychogenic PD
<table>
<thead>
<tr>
<th>Commercially Available CNS Imaging Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 F –FDG</td>
</tr>
<tr>
<td>99mTc- HMPAO</td>
</tr>
<tr>
<td>99mTc- ECD</td>
</tr>
<tr>
<td>123-I FP-CIT (Europe)</td>
</tr>
<tr>
<td>123-I iodoamphetamine (Japan)</td>
</tr>
<tr>
<td>123-I iomazenil (Japan)</td>
</tr>
</tbody>
</table>
Imaging in the brain: Molecular targets of radioligands.  

D2/D3 (raclopride, others)

Vesicular transporter (VMAT2)

DOPA → dopamine

neuronal dopamine metabolism (fluorodopa)

dopamine transporter (β-CIT, others)

dopamine receptors

Adapted from Science 2000; 289: 409-411.
MZ co-twins

MZ co-twin
Asymptomatic at baseline

Control

MZ co-twin symptomatic 5 years later

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123-I β-CIT SPECT

Age-matched healthy control  Parkinson’s patient
123-I $\beta$-CIT

123-I altropane

99m-Tc TRODAT
Healthy control  
AVM and bradykinesia  
Hoehn-Yahr Stage 2 Parkinson’s disease
## Characteristics of SPECT Dopamine Transporter Radioligands

<table>
<thead>
<tr>
<th>SPECT Tracer</th>
<th>[(^{123}\text{I})](\beta)-CIT Dopascan</th>
<th>[(^{123}\text{I})]FP-CIT DATScan</th>
<th>99mTc-TRODAT StriataView</th>
<th>[(^{123}\text{I})]Altropane Altropane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to peak specific uptake</td>
<td>Protracted 8-18 h</td>
<td>Rapid 2-3 h</td>
<td>Rapid 2-3 h</td>
<td>Rapid 0.5-1 h</td>
</tr>
<tr>
<td>Washout phase</td>
<td>Prolonged</td>
<td>Prolonged</td>
<td>Intermediate</td>
<td>Rapid</td>
</tr>
<tr>
<td>DAT binding affinity</td>
<td>1.4 nM Ki</td>
<td>3.5 nM Ki</td>
<td>9.7 nm Ki</td>
<td>6.62 nM IC50</td>
</tr>
<tr>
<td>DAT:SERT selectivity</td>
<td>1.7:1</td>
<td>2.8:1</td>
<td>26:1</td>
<td>28:1</td>
</tr>
<tr>
<td>Target: background tissue ratio</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>
## Status of Commercial Development of PD imaging agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Prop name</th>
<th>Company</th>
<th>Region</th>
<th>Status</th>
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</thead>
<tbody>
<tr>
<td>123-I FP-CIT</td>
<td>DATScan</td>
<td>GEHC</td>
<td>EU</td>
<td>Marketed</td>
</tr>
<tr>
<td>123- I altropane</td>
<td>Altropane</td>
<td>Alseres</td>
<td>US</td>
<td>Phase 3</td>
</tr>
<tr>
<td>123- I β-CIT</td>
<td>DopaScan</td>
<td>Fuji RL</td>
<td>Japan</td>
<td>Phase 3</td>
</tr>
<tr>
<td>18-F AV 133</td>
<td>AV133</td>
<td>Avid</td>
<td>US, Australia</td>
<td>Phase 1-2</td>
</tr>
</tbody>
</table>
What characteristics of the imaging agent are important for PD evaluation?

- The pharmacokinetic properties of the radiopharmaceutical are important for determining how to use imaging in PD.

- Most DA presynaptic radiopharmaceuticals produce good quality images for visual read by the physician to identify reduced striatal uptake.

- If quantitation is necessary (PD progression studies)- it is more difficult to obtain a reliable and accurate measure of within an individual patient.
Potential applications of imaging biomarkers in PD

Clinical
• Diagnosis
• Identification of ‘at risk’ population for neuroprotective agents to delay or prevent the onset of symptoms

Research
• Early and accurate diagnosis- subject pool enrichment
• Monitor disease progression and assess disease-modifying treatments
Some Large Imaging Trials of PD Diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Tracer</th>
<th>Subjects</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson Study Group</td>
<td>123-I b-CIT</td>
<td>60 PD-ism, 14 ET, 22 HS</td>
<td>PDism vs HS &amp; ET sensitivity = .98, specificity = .83</td>
<td>Multicenter, core lab visual read, quantitative read .96 sens, .94</td>
</tr>
<tr>
<td>Neurology 2000 55:1540-1547</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The [123-I]FP-CIT Study Group</td>
<td>123-I FP-CIT</td>
<td>128 PD-ism, 27 ET, 35 HS</td>
<td>PDism sensitivity = .95, specificity = .93</td>
<td>Spec. Multicenter, core lab visual read</td>
</tr>
<tr>
<td>Movement Dis 2000 3:503-510</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwarz, Linke, Kerner, et al Arch Neurol 2000 2:205-8</td>
<td>123-I IPT</td>
<td>28 PD, 9 HS</td>
<td>Excellent discrimination between PD and HS</td>
<td>Only on PD subject overlapped with control</td>
</tr>
</tbody>
</table>

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Unsure about a Parkinsonian diagnosis??

Consider a referral to the Query-PD study and participate in the development of a diagnostic tool for PD
Demographics/Baseline Data

Community Neurologists (n=37)
Patients enrolled (n=137)
Patients completing final clinical visit (n=131)

Age 62.3 yrs (range 30-92)
Gender 54% male, 46% female
Sx duration 2.1 yrs
Scan result
   60 (46%) positive scans
   71 (54%) negative scans
Sensitivity and Specificity: MDE 6-12 mo dx = ‘Gold Standard’

<table>
<thead>
<tr>
<th>Final Clinical Diagnosis</th>
<th>PS</th>
<th>No PS</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area under the curve</th>
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<tbody>
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<td>Visual Rater 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PS</td>
<td>47</td>
<td>3</td>
<td>0.7344</td>
<td>0.9268</td>
<td>0.8306</td>
</tr>
<tr>
<td>No PS</td>
<td>17</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Visual Rater 2</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>48</td>
<td>5</td>
<td>0.8727</td>
<td>0.9123</td>
<td>0.8925</td>
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<tr>
<td>No PS</td>
<td>7</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual Rater 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS</td>
<td>44</td>
<td>11</td>
<td>0.9362</td>
<td>0.8254</td>
<td>0.8808</td>
</tr>
<tr>
<td>No PS</td>
<td>3</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
What Presynaptic Dopaminergic Imaging Can and Cannot Do

Can distinguish PD and related disorders from ET, psychogenic, drug-induced, and possibly vascular parkinsonism.

Cannot readily distinguish idiopathic PD from multisystem atrophy or progressive supranuclear palsy.

Can distinguish AD from DLB (dementia with Lewy bodies).

Can show changes occurring in brain prior to manifestation of symptoms.
Potential applications of imaging biomarkers in PD

**Clinical**
- Diagnosis
- Identification of ‘at risk’ population for neuroprotective agents to delay or prevent the onset of symptoms

**Research**
- Early and accurate diagnosis- subject pool enrichment
- Monitor disease progression and assess disease-modifying treatments
Natural History of Parkinson’s Disease

Dopamine Neurons

Preclinical

Symptoms

Diagnosis

Motor ratings

Time
Challenges in Clinical Trials Assessing PD Modification

• Slowly progressing chronic disease- large sample sizes, long duration, no clear proof of concept
• Marked inter-subject variability
• Disease heterogeneity
• Outcomes may be confounded by medications- distinguish symptomatic effect
• Uncertain dose-response
• High cost of neuroprotection studies
Imaging Studies of PD progression

- PET and SPECT studies with have all consistently shown a 4-11% loss of striatal signal per year in early PD patients.
- Marked variability in the rate of change of the scan between individuals.
- Some reports of variability in a PD patient on the rate of change as a function of stage of the disease (faster loss early in the illness).
Some large clinical trials- each included an imaging study

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Duration</th>
<th>Imaging Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALM-PD</td>
<td>82</td>
<td>4 years</td>
<td>123-I β-CIT SPECT</td>
</tr>
<tr>
<td>REAL-PET</td>
<td>126</td>
<td>2 years</td>
<td>18-F Dopa PET</td>
</tr>
<tr>
<td>ELLDOPA</td>
<td>105</td>
<td>5 years</td>
<td>123-I β-CIT SPECT</td>
</tr>
<tr>
<td>PELMOPET</td>
<td>294</td>
<td>2 years</td>
<td>18-F Dopa PET</td>
</tr>
<tr>
<td>PRECEPT</td>
<td>799</td>
<td>2 years</td>
<td>123-I β-CIT SPECT</td>
</tr>
<tr>
<td>GPI-1485</td>
<td>212</td>
<td>2 years</td>
<td>123-I β-CIT SPECT</td>
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</table>
Problems in using Imaging Biomarkers in PD Therapeutic Studies

- Medication treatment could affect the imaging measure
- Some patients who meet diagnostic criteria for PD have normal scans (SWEDD)
- Imaging measures of disease progression do not correlate well with clinical measures of progression
- Quantitative imaging is difficult to do in multicenter settings over long time periods
Dopamine Transporter Brain Imaging to Assess the Effects of Pramipexole vs Levodopa on Parkinson Disease Progression

Parkinson Study Group

Parkinson disease (PD) is a slow but relentlessly progressive neurodegenerative disorder characterized clinically by bradykinesia, tremor, rigidity, and gait dysfunction. The clinical decline reflects ongoing nigrostriatal dopaminergic degeneration. Dopaminergic replacement therapy with the precursor levodopa or agonists that stimulate the dopamine receptor is effective in ameliorating many signs and symptoms of early PD. However, progressive neurodegeneration ultimately results in severe motor, mental, and functional disability.

Increasing evidence from laboratory and animal studies suggests that in addition to their symptomatic effects, levodopa and dopamine receptor agonists may either accelerate or slow the dopaminergic degeneration of PD. Recent data regarding the effects of levodopa have been controversial with in vitro data supporting both a potential toxic and protective effect on dopaminergic neurons. Studies have demonstrated that dopamine receptor agonists protect cultured dopaminergic neurons from potential levodopa toxicity and may exert direct antioxidant and receptor-mediated ant apoptotic effects. The putative neurotoxic or neuroprotective actions of levodopa or dopamine receptor agonists have provided the rationale for assessing the progression of dopaminergic neuronal degeneration in patients with PD after treatment with these drugs.

Context Pramipexole and levodopa are effective medications to treat motor symptoms of early Parkinson disease (PD). In vitro and animal studies suggest that pramipexole may protect and that levodopa may either protect or damage dopamine neurons. Neuroimaging offers the potential of an objective biomarker of dopaminergic neuron degeneration in PD patients.

Objective To compare rates of dopamine neuron degeneration after initial treatment with pramipexole or levodopa in early PD by means of dopamine transporter imaging using single-photon emission computed tomography (SPECT) with [123I]-carbonyl-2-bromo-4-iodophenyl-6-triethylammoniumpropylidene) (123I-CIT) labeled with iodine 123.

Design Substudy of a parallel-group, double-blind randomized clinical trial.

Setting and Patients Eighty-two patients with early PD who were recruited at 17 clinical sites in the United States and Canada and required dopaminergic therapy to treat emerging disability. Enrolled between November 1996 and August 1997.

Interventions Patients were randomly assigned to receive pramipexole, 0.5 mg 3 times per day with levodopa placebo (n = 62), or carbidopa/levodopa, 25/100 mg 3 times per day with pramipexole placebo (n = 40). For patients with residual disability, the dosage was escalated during the first 12 weeks, and subsequently, open-label levodopa could be added. After 34 months of follow-up, the dosage of study drug could be further modified.

Main Outcome Measures The primary outcome variable was the percent change from baseline in striatal [123I]-CIT uptake after 46 months. The percentage changes and absolute changes in striatal, putamen, and caudate [123I]-CIT uptake after 22 and 34 months were also assessed. Clinical severity of PD was assessed using the Unified Parkinson Disease Rating Scale (UPDRS) 12 hours off anti-PD medications.

Results Sequential SPECT imaging showed a decline in mean (SD) [123I]-CIT striatal uptake from baseline of 10.2% (9.8%) at 22 months, 19.3% (12.3%) at 34 months, and 20.7% (14.4%) at 46 months — approximately 9.2% per year. The mean (SD) percentage loss in striatal [123I]-CIT uptake from baseline was significantly reduced in the pramipexole group compared with the levodopa group (7.1% (9.0%) vs 13.5% (9.6%) at 22 months (P = .004); 10.9% (11.8%) vs 19.6% (12.4%) at 34 months (P = .009); and 14.0% (13.3%) vs 25.5% (14.1%) at 46 months (P = .01). The percentage loss from baseline in striatal [123I]-CIT uptake was correlated with the change from baseline in UPDRS at the 46-month evaluation (r = −0.40; P = .001).

Conclusions Patients initially treated with pramipexole demonstrated a reduction in loss of striatal [123I]-CIT uptake, a marker of dopamine neuron degeneration, compared with those initially treated with levodopa, during a 46-month period. These imaging data highlight the need to further compare imaging and clinical end points of PD progression in long-term studies.

JAMA 2002;287:1651-1661 www.jama.com

Members of the Parkinson Study Group and Financial Disclosures are listed at the end of this article.

Corresponding Author and Reprints: Kenneth M. Mark, MD, The Institute for Neurodegenerative Disorders, 60 Temple St, Suite B, New Haven, CT 06510 (e-mail: kmike@idd.org).
### CALM-PD CIT Study Design

<table>
<thead>
<tr>
<th></th>
<th>Screen</th>
<th>Baseline Scan</th>
<th>Month 22 Scan</th>
<th>Month 34 Scan</th>
<th>Month 46 Scan</th>
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</thead>
<tbody>
<tr>
<td>CALM-CIT</td>
<td>82</td>
<td>10 week Scan</td>
<td>78</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>CALM-PD</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Study Drug**

*Either* dopamine agonist or Levo dopa
Percentage Change in Striatal $\beta$-CIT Uptake from Baseline by Treatment

- **Levodopa**
  - Scan Interval (mo): 0, 10, 20, 30, 40, 50
  - % Change from Baseline: 0, -10, -20, -30
  - Numbers in parentheses: 39, 35, 33

- **Pramipexole**
  - Scan Interval (mo): 0, 10, 20, 30, 40, 50
  - % Change from Baseline: 0, -10, -20, -30
  - Numbers in parentheses: 36, 32

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REAL-PET
Left and right putamen averaged % change in Ki

Relative difference: 35%  
95% CI (0.65, 13.06)  
p = 0.022

% Change in $^{18}$F-dopa uptake

Ropinirole (68)  -13
L-dopa (58)    -20

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Percentage Change in Putamen β-CIT and F-Dopa Uptake by Treatment

Scan Interval (mo)

% Change from Baseline

CALM-PD CIT
- Pramipexole
- Levodopa

REAL PET
- Ropinirole
- Levodopa

Levodopa

Pramipexole
Imaging Assessment of PD Progression - CALM-CIT/REAL-PET

Reduction in percentage loss of $\beta$-CIT/F-Dopa from baseline in pramipexole/ropinirole vs levodopa group

Caveats: No Placebo group

Uncertain short-term study drug effects on imaging outcomes

Modest correlation of imaging and clinical outcomes
Controversies in using imaging biomarkers in PD Therapeutic Studies

• Medication treatment could affect the imaging measure

• Imaging measures of disease progression do not correlate well with clinical measures of progression

• Some patients who meet diagnostic criteria for PD have normal scans (SWEDD)
Does Drug Treatment Affect Imaging?
INSPECT and AMADEUS Studies

Two studies to assess the short-term effects of dopamine Agonists and levodopa on imaging outcomes
- with adequate sample size

Early PD subjects (n=150)
- imaged at baseline
- randomized to dopamine agonists, l-dopa, no treatment for 12 weeks, imaged
- withdrawn from med for 8 weeks, imaged

Compare scan at baseline to 12 weeks
INSPECT Study Design

Three Treatment Groups- No treatment, L-dopa (600 mg), Pramipexole (3 mg)
Baseline Demographic Data

Enrolled=112
Completed 2 scans=103
Completed 3 scans=80

<table>
<thead>
<tr>
<th></th>
<th>no rx n=36</th>
<th>pramipexole n=38</th>
<th>l-dopa n=38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>64.3</td>
<td>65.3</td>
<td>65.3</td>
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<tr>
<td>Gender (% male)</td>
<td>67%</td>
<td>68%</td>
<td>53%</td>
</tr>
<tr>
<td>Duration of Diagnosis (yrs)</td>
<td>0.82 yrs</td>
<td>1.27</td>
<td>0.85</td>
</tr>
<tr>
<td>Total UPDRS</td>
<td>27.7</td>
<td>31.5</td>
<td>29.8</td>
</tr>
<tr>
<td>Motor UPDRS</td>
<td>18.9</td>
<td>22</td>
<td>20.3</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>1.7</td>
<td>1.9</td>
<td>1.9</td>
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<tr>
<td>Striatal [123I]b-CIT Uptake</td>
<td>3.6</td>
<td>3.5</td>
<td>3.9</td>
</tr>
</tbody>
</table>
Pramipexole

L dopa

No Treatment

N=28

N=28

N=24
<table>
<thead>
<tr>
<th></th>
<th>Prami Scan 1 to 2</th>
<th>Prami Scan 2 to 3</th>
<th>Prami Scan 1 to 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>-3.3%</td>
<td>1.0%</td>
<td>-2.8%</td>
</tr>
<tr>
<td><strong>Stdev</strong></td>
<td>8.8</td>
<td>10.8</td>
<td>9.5</td>
</tr>
<tr>
<td><strong>L-dopa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Scan 1 to 2</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Mean</strong></td>
<td>2.1%</td>
<td>-0.8%</td>
<td>0.8%</td>
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<tr>
<td><strong>Stdev</strong></td>
<td>11.3</td>
<td>9.9</td>
<td>10.5</td>
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<tr>
<td><strong>No Rx</strong></td>
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</tr>
<tr>
<td><strong>Scan 1 to 2</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Mean</strong></td>
<td>-0.26%</td>
<td>2.1%</td>
<td>1.3%</td>
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<tr>
<td><strong>Stdev</strong></td>
<td>9.6</td>
<td>8.3</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Significant within-group differences

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Controversies in using imaging biomarkers in PD Therapeutic Studies

- Medication treatment could affect the imaging measure
- Imaging measures of disease progression do not correlate well with clinical measures of progression
- Some patients who meet diagnostic criteria for PD have normal scans (SWEDD)
Scans without evidence of deficit (SWEDD)

Scans < 75% Age adjusted Healthy subjects

Baseline PRECEPT - % Age expected Putamen [123I] β-CIT uptake

DAT Deficit n=708

SWEDD n=91

Subject Number

% of age expected Putamen [123I] β-CIT uptake
SWEDD- Some Explanations

• Subjects do not have PD

• Subjects with PD may not have DAT or F-dopa deficit

• Subjects may demonstrate reduction of DAT only after disease progresses - imaging not sensitive
## SWEDD (Scans Without Evidence of Dopaminergic Deficit) in PD Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage –PD</th>
<th>Dur DX at Baseline (mo)</th>
<th>% SWEDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elldopa-CIT</td>
<td>Denovo</td>
<td>6</td>
<td>21/142 (14%)</td>
</tr>
<tr>
<td>PRECEPT</td>
<td>Denovo</td>
<td>10</td>
<td>91/799 (11%)</td>
</tr>
<tr>
<td>REAL-PET</td>
<td>Denovo</td>
<td>9</td>
<td>21/186 (11%)</td>
</tr>
<tr>
<td>Calm-CIT</td>
<td>Start of DA Rx</td>
<td>18</td>
<td>3/82 (4%)</td>
</tr>
<tr>
<td>NIL-A -CIT</td>
<td>Treated Stable responder</td>
<td>23</td>
<td>3/212 (1.4%)</td>
</tr>
</tbody>
</table>
### SWEDD in PD Trials

#### Follow-up

<table>
<thead>
<tr>
<th>Number of SWEDD</th>
<th>CALM-PD CIT</th>
<th>ELLDOPA CIT</th>
<th>Real-PET</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>3</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>22 months</td>
<td>3/3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 months</td>
<td>19/19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 months</td>
<td>17/17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 months</td>
<td>12/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 months</td>
<td>10/10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 months</td>
<td></td>
<td></td>
<td>19/19</td>
</tr>
</tbody>
</table>
PRECEPT Methods

- **Research Participants**: early PD not receiving or requiring dopaminergic (DA) treatment (n=806) were enrolled at 65 PSG research sites in the US and Canada

- **Design**: double-blind, placebo-controlled, parallel-group, randomized assignment to 1 of 4 treatment groups (CEP-1347 at 10 mg bid, 25 mg bid, 50 mg bid, or placebo bid) and follow up for at least 24 months

- **Imaging**: Baseline and post randomization DAT imaging (22 months) with 123-I β-CIT
PRECEPT Study Recruitment Sites - Movement Disorder Specialists

Neurology Recruitment Sites Sending Patients to IND New Haven

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Primary Clinical Endpoint
Time to Disability Requiring Dopaminergic Treatment

% Reaching Endpoint

Months

- Placebo
- CEP-1347 10mg bid
- CEP-1347 25mg bid
- CEP-1347 50mg bid
Scans without evidence of deficit (SWEDD)

Scans < 75%

Age adjusted

Healthy subjects

**Baseline PRECEPT** -

% Age expected Putamen

[123I] β-CIT uptake

DAT Deficit n=708

SWEDD n=91
### 123-1 β-CIT Uptake % Change from baseline with 22 month Scan

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>700</td>
<td>Mean: -7.67%, SD: 12.21%</td>
</tr>
<tr>
<td><strong>DAT Deficit</strong></td>
<td>634</td>
<td>Mean: -8.63%, SD: 11.93%</td>
</tr>
<tr>
<td><strong>SWEDD</strong></td>
<td>66</td>
<td>Mean: 1.49%, SD: 11.07%</td>
</tr>
<tr>
<td>P Value</td>
<td></td>
<td>SWEDD vs DAT deficit: 8.1344E-11</td>
</tr>
</tbody>
</table>
**PRECEPT Study**
CEP-1347 in 797 de novo PD subjects studied over 22 months:
Diagnostic Confidence Assessed at End of Study

<table>
<thead>
<tr>
<th>Diagnostic Confidence</th>
<th>Non-SWEDD N (%)</th>
<th>SWEDD N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%-100%</td>
<td>640 (92.6%)</td>
<td>51 (7.4%)</td>
</tr>
<tr>
<td>50%-89%</td>
<td>41 (60.3%)</td>
<td>27 (39.7%)</td>
</tr>
<tr>
<td>10%-49%</td>
<td>9 (34.6%)</td>
<td>17 (65.4%)</td>
</tr>
<tr>
<td>0%-9%</td>
<td>3 (25.0%)</td>
<td>9 (75.0%)</td>
</tr>
</tbody>
</table>
What we know about imaging in PD clinical trials of potential disease-modifying drugs

De novo trials create diagnostic challenges- A proportion of subjects enrolled may not have the disease studied! Mounting evidence suggests a role for imaging as a possible enrollment criteria

Large PD studies of common dopaminergic treatments do not effect quantitative measures of DAT, but…… long-term effects of putative neuroprotective drugs might alter DAT imaging in ways unrelated to mechanisms of “protection”. Study designs must take this into consideration.

Imaging measures and clinical measures may not correlate
Imaging Biomarkers in Drugs Development in AD: How does the PD Experience Inform AD Studies?

Ongoing Phase 3 trials evaluating amyloid-beta “busting” strategies

- volumetric MRI
- FDG PET
- amyloid imaging (11C PIB, 18F AV45)

Questions lurking in these trials:

1) What will be the relationship between changes in imaging biomarkers and clinical measures?
2) Are acute drugs effects a potential source of confound in the quantitative imaging?
3) What is the meaning of abnormal scans in “normal” subjects?
Future Roles of Imaging in Clinical Nuclear Medicine Practice: Is This Coming to Your Nuclear Medicine Clinic?

• Early and accurate diagnosis in patients with minimal symptoms

• Early and accurate diagnosis in patients at risk for movement disorders- use of imaging coupled with high sensitivity screening tools

• Monitoring progression to assess the impact of neuroprotective drugs in an individual patient
2nd International Symposium on Neuroimaging in PD and Related Disorders
Chatham, Massachusetts, USA
October 21-22, 2008

Supported by The Movement Disorder Society
For more information please contact: info@NeuroimagingSymposium.com