PSP and CBD

Working Toward Disease-Modifying Therapies

Brad Boeve MD
Department of Neurology
Mayo Clinic
Rochester, Minnesota

Outline

• Observational studies - overview
  • Theoretical considerations
  • Importance of biomarkers

• Observational studies - protocols
  • Molecular Anatomic Imaging Analysis
  • ARTFL Protocol
  • 4RTNI2 Protocol
  • LEFFTDS Protocol

• Focus on tau

• Clinical trials

• Additional words of wisdom
PSP and CBD Research

Observational Studies - Overview

Theoretical considerations for experimental drug trials
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Theoretical considerations for experimental drug trials

Test or scan

Eval #1 Eval #2 Eval #3 Eval #4 Eval #5

Tx

Slowed progression with disease-modifying therapy

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Theoretical considerations for experimental drug trials

Test or scan

Eval #1 Eval #2 Eval #3 Eval #4 Eval #5

Tx

Halted progression with disease-modifying therapy
There is a critical need to study the natural history of PSP and CBD to prepare for future therapies → observational studies

- Clinical testing
- Neuropsychological testing
- MRI scans
- PET scans
- Blood samples
- CSF samples
- Neuropathologic examination
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Clinical Testing: PSP Rating Scale

Boxer et al, Lancet Neurol 2014

MRI

Kato et al, J Neurol Sci 2003

“hummingbird sign” in PSP
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MRI

Josephs et al, Mov Disord 2013

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FDG (glucose) PET

Zalewski et al, J Neurol 2014
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AV1451 (tau) PET

Rojas et al, Ann Clin Transl Neurol 2016

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Blood and CSF

Rojas et al, Ann Clin Transl Neurol 2016
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Importance of Observational Studies

Uncertainties:
- Variability across persons
- Variability over time within individual persons
- Which measures are best for trials?

Aims:
- Determine the best measures that track disease progression (maximize science, minimize time and cost)
- Determine the easiest measures to do the least number of times (minimize burden, time and cost)

Goal:
Prepare for trials which will identify 1 or more treatments that halt or slow disease progression as quickly, cheaply and easily as possible
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Importance of Observational Studies

If you, or a loved one, is participating in research:

THANK YOU FOR PARTICIPATING!

If you, or a loved one, desires to get involved in research:

THANK YOU FOR CONSIDERING!

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Observational Studies - Protocols
A Molecular Anatomic Imaging Analysis of tau in Progressive Supranuclear Palsy

- **Study leaders**: Drs. Keith Josephs and Jennifer Whitwell
- **Study coordinator**: Sarah Boland (507-293-4707)

This study will improve understanding of disease progression in PSP which is critically important for the development and testing of future treatments that will likely target tau

https://clinicaltrials.gov/show/NCT02605785

Advancement of Research in Frontotemporal Lobar Degeneration

- **Study leaders**: Drs. Adam Boxer and Howard Rosen
- **Study coordinator**: Reilly Dever 415-476-0670  Reilly.Dever@ucsf.edu

This study will improve understanding of disease progression in PSP and CBD (and other FTLD disorders) which is critically important for the development and testing of future treatments that will likely target tau

https://clinicaltrials.gov/show/NCT02365922
4 Repeat Tauopathy Neuroimaging Initiative – 2 (4RTNI2)

- **Study leader:** Dr. Adam Boxer
- **Study coordinators:**
  - Dan N Luong (415) 476-9578 Phi.Luong@ucsf.edu
  - Hilary Heuer, PhD (415) 476-6743 Hilary.Heuer@ucsf.edu

  - This study will improve understanding of disease progression in PSP and CBD which is critically important for the development and testing of future treatments that will likely target tau

  https://clinicaltrials.gov/show/NCT02966145

Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects

- **Study leaders:** Drs. Brad Boeve and Howard Rosen
- **Study coordinator:** Christina Dheel 507-293-5551 dheel.christina@mayo.edu

  - This study will improve understanding of biomarker and disease progression in familial FTD in those who have a mutation in MAPT (tau), progranulin or C9orf72.

  https://clinicaltrials.gov/show/NCT02372773
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Focus on Tau

? Tauopathy therapies
- microtubule stabilizers
- tau reducers
- tau kinase inhibitors
- tau aggregation inhibitors
- Hsp70/Hsp90 inhibitors

Dickey & Petrucelli, Expert Opin Ther Targets 2006
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Clinical Trials

https://www.psp.org/iwanttolearn/our-research/
## PSP and CBD Research

### Clinical Trials

There are a number of clinical trials being undertaken at any given time that may present opportunity for patient participation. CurePSP will endeavor to keep this list as up to date as possible.

**Multiple Ascending Dose Study of BMS-990168 in PSP Patients - recruitment completed**

This study will evaluate the safety and tolerability of multiple ascending intravenous infusions of BMS-990168, and assess the pharmacodynamics of BMS-990168 on cerebrospinal fluid (CSF) extracellular tau (tau) concentrations in patients with PSP.

[Read more here](https://www.psp.org/iwanttolearn/clinical-trials/)

**Safety, Tolerability, and Pharmacodynamics of C2H8-912 in Subjects With PSP**

To participate, call the Jane Call Center at 702-487-0333, and refer to this study by its identifier: NCT02494024, or follow this link to learn more.

**Extension Study of BMS-990168 in Patients With Progressive Supranuclear Palsy Who Participated in NCT02020153**

ClinicalTrials.gov Identifier: NCT02055103. This study is enrolling participants by invitation only.

**Safety Study of TPI-287 to Treat CBS and PSP (NCT-287-497)**

ClinicalTrials.gov Identifier: NCT02208902.

**A Molecular Anatomic Imaging Analysis of Tau in Progressive Supranuclear Palsy**

ClinicalTrials.gov Identifier: NCT01200705.

**Alzheimer’s Disease Trial with TPI-287**

This study is to determine the dose of TPI-287 that is safe and tolerable in people with mild to moderate AD, as well as to measure the properties and preliminary efficacy of TPI-287.

### Table 2: Planned or ongoing clinical trials involving tau therapeutics

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Disease</th>
<th>Phase</th>
<th>ClinicalTrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPK-275&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Mitochondrial activator</td>
<td>Alzheimer’s disease, corticobasal degeneration, PSP</td>
<td>1</td>
</tr>
<tr>
<td>AAR&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Tau kinase activator</td>
<td>Alzheimer’s disease</td>
<td>1</td>
</tr>
<tr>
<td>AC-35&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Tau aggregation inhibitor</td>
<td>Alzheimer’s disease</td>
<td>1</td>
</tr>
<tr>
<td>TPK&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Tau aggregation inhibitor</td>
<td>Alzheimer’s disease, behavioral-variant frontotemporal degeneration</td>
<td>3 (both negative)</td>
</tr>
<tr>
<td>Abi-8512 (C2H8&lt;sup&gt;4&lt;/sup&gt;-912&lt;sup&gt;5&lt;/sup&gt;)</td>
<td>Anti-Tau monoclonal antibody</td>
<td>PSP, Alzheimer’s disease</td>
<td>2</td>
</tr>
<tr>
<td>RMS-56418&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Anti-Tau monoclonal antibody</td>
<td>PSP</td>
<td>2</td>
</tr>
<tr>
<td>Salazosyn&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Inhibitor of tau acetylation</td>
<td>PSP, Alzheimer’s disease</td>
<td>1</td>
</tr>
<tr>
<td>Young plasma transfusions&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Rejuvenation</td>
<td>PSP, Alzheimer’s disease</td>
<td>1</td>
</tr>
<tr>
<td>Varyos&lt;sup&gt;9&lt;/sup&gt;</td>
<td>D-Glucosamine inhibitors</td>
<td>PSP</td>
<td>Animal studies</td>
</tr>
<tr>
<td>Trehalose oligosaccharide&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Reduce tau gene expression</td>
<td>Varyos</td>
<td>Animal studies</td>
</tr>
</tbody>
</table>

<sup>1</sup>Progressive supranuclear palsy

[Boxer et al, Lancet Neurol 2017](#)
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Clinical Trials

• Contact an MD or site to discuss details of the trial

• Procedures:
  – Note strict criteria for enrollment (age, overall health, medications, severity, etc.)
  – Must be prepared to commit to the entire trial
  – Written informed consent form provides all details
  – Screening visit is key
  – Duration usually 3 months to 2 years
  – Visits vary from every 2 to 12 weeks
  – Clinical testing, questionnaires, blood, EKG, MRI
  – CSF exam and/or PET scans (depending on the study)
  – Strong focus on safety

• Enormously important for scientific advancement

• May impact one's own symptoms or rate of progression

Additional Words of Wisdom
(from patients and families)
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- Non-medication approaches are as or more important than currently available medications
- Patients and care partners - stay mentally active, socially active, physically active
- Blame the illness and not the person who is facing the challenges
- Maintain a sense of humor
- Learn and practice mindfulness

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- Strive for optimizing one’s purpose in life despite the illness

MAN’S SEARCH FOR MEANING
VIKTOR E. FRANKL

• Strive for optimizing one’s purpose in life despite the illness
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- Thank you for your attention
- Thank you for participating, or considering to participate, in research
- Thank you for your involvement/participation with CurePSP
- Maintain the Fight!