What if it’s not Alzheimer’s?

Update on Lewy body dementia and frontotemporal dementia
Dementia: broad term for any acquired brain condition impairing mental function such that ADLs are impaired. Includes:

- Alzheimer’s disease
- Multi-infarct dementia (due to strokes)
- Lewy body dementia
- Frontotemporal dementia
- many others......
Outline for tonight

• Lewy body dementia
• Frontotemporal dementia
• Treatment
• Research
• Support programs
Outline for tonight

• Lewy body dementia  
  – PDD (Parkinson’s Disease Dementia)  
  – LBD (Lewy body dementia)

• Frontotemporal dementia  
  – Behavioral variants  
  – Language variants  
  – Genetic variants

• Treatment

• Research

• Support programs
Some definitions:

- Dementia = any acquired brain condition that interferes with the ability to think and to carry out routine daily functions
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Parkinson’s disease = A disease of movement With dementia occurring Years after diagnosis.

Amyloid plaques

Neurofibrillary tangles

Cerebral atrophy
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- Alzheimer’s disease = the most common cause of dementia, characterized by “plaques” and “tangles” in brain.

- Parkinson’s disease = A disease of movement with dementia occurring years after diagnosis.
Parkinson’s: Classical view:

- Tremor
- Rigidity
- Bradykinesia
- Gait disorder
Cognitive Function in PD
Classical View:

- ...a motor disease without a significant cognitive component:
- “by the absence of any injury to the senses and to the intellect, (we conclude) that the morbid state does not involve the encephalon.”
- ---James Parkinson, An Essay on the Shaking Palsy (1817)
Revised View:

• Cognitive impairment is a common feature of PD

• Cognitive impairment is a significant source of distress and disability
Prevalence of Cognitive Impairment in PD

• Dementia
  – 20% of PD have mild cognitive impairment (MCI) at time of PD diagnosis
  – 30-40% of all PD have dementia
  – Up to 80% by 15 years into disease
  – 4-6x greater than elderly without PD
What “domains” of mental function are affected in Parkinson’s?

- Attention*
- Memory
- Executive function*
- Visuospatial function*
- Language function
### Alzheimer’s vs Parkinson’s’s:

<table>
<thead>
<tr>
<th></th>
<th>Alzheimer’s</th>
<th>PD Dementia</th>
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<tbody>
<tr>
<td>Attention</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Memory</td>
<td>++++</td>
<td>++</td>
</tr>
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<td>++</td>
<td>++++</td>
</tr>
<tr>
<td>Language</td>
<td>++++</td>
<td>+</td>
</tr>
</tbody>
</table>
What causes cognitive decline in Parkinson’s?

• Many causes

• Changes in neurotransmitters are part of the problem---but it’s not the same neurotransmitters that cause the movement disorder
Motor Symptoms are Dopamine Responsive

Cut section of the midbrain where a portion of the substantia nigra is visible

Substantia nigra

Diminished substantia nigra as seen in Parkinson's disease
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Diminished substantia nigra as seen in Parkinson's disease.
Cognitive symptoms are due to impairment in a different neurotransmitter: acetylcholine:

Drugs to boost acetylcholine help in PD dementia: Rivastigmine for Dementia Associated with Parkinson’s Disease


541 Patients underwent randomization

362 Assigned to rivastigmine

- 99 Prematurely discontinued the study
  - 62 (17.1%) Had adverse events
  - 21 (5.8%) Withdrew consent
  - 4 (1.1%) Were lost to follow-up
  - 5 (1.4%) Had a protocol violation
  - 4 (1.1%) Died
  - 2 (0.6%) Had unsatisfactory therapeutic results
  - 1 (0.3%) Had abnormal test results

- 263 (72.7%) Completed treatment

179 Assigned to placebo

- 32 Prematurely discontinued the study
  - 14 (7.8%) Had adverse events
  - 2 (1.1%) Withdrew consent
  - 1 (0.6%) Was lost to follow-up
  - 2 (1.1%) Had a protocol violation
  - 7 (3.9%) Died
  - 4 (2.2%) Had unsatisfactory therapeutic results
  - 2 (1.1%) Had an "administrative problem"

- 147 (82.1%) Completed treatment
Rivastigmime for Dementia Associated with Parkinson’s Disease

Rivastigmine for Dementia Associated with Parkinson’s Disease


![Bar chart showing ADCS-CGIC Score at 24 Wk for Rivastigmine (n=329) and Placebo (n=165).](chart.png)
Conclusions:

- Parkinson’s dementia is distinct from Alzheimer’s
- Neurotransmitters involved in dementia are distinct from the ones involved in impaired movements.
What is “Lewy body dementia”?

• A dementia characterized by:
  – Parkinsonism
  – Hallucinations
  – Sensitivity to anti-psychotic medications
  – Fluctuations
  – Brain autopsy shows lewy bodies in the brain
What is “Lewy body dementia”?

• The “cognitive profile” looks like parkinson’s dementia
• Brain autopsy shows lewy bodies in the brain
How is Lewy body dementia different from Parkinson’s disease?

• In Parkinson’s disease, the dementia appears several years after diagnosis of movement problems.

• In Lewy body dementia, the movement problems and the dementia come on together.
How is Lewy body dementia different from Parkinson’s disease?

• Tremor is less common
• Slowness and stiffness are more symmetric
• Motor symptoms are less responsive to medication in lewy body dementia than in parkinson’s disease
How is Lewy body dementia different from Parkinson’s disease?

• In Parkinson’s disease, hallucinations are promoted by the drugs used to treat Parkinson’s disease.

• In Lewy body dementia, hallucinations appear without being triggered by any drugs.
What is “Lewy body dementia”?  

• “Sensitivity to antipsychotic medications” is part of Lewy body dementia.  
  – Patients can become “frozen” from low doses of these medications  

• Fluctuations in level of consciousness are also common in Lewy body dementia.
How is Lewy body dementia treated?

• Need to be careful with Parkinson’s medicines, because they will increase hallucinations.
• Need to be careful with medicine for hallucinations, because it worsens parkinsonian motor symptoms.
• Some patients do well with medicines that increase acetylcholine.
The ability to increase brain acetylcholine is limited:

• Because acetylcholine also works on the stomach and intestines

• Most of the drugs that boost acetylcholine in brain also boost it in GI tract and cause nausea, vomiting, loose stools, diarrhea

• If only there was a way to boost acetylcholine in the brain without affecting the gut....
About RVT-101

- RVT-101 works by blocking the 5HT6 receptor in the brain and raising levels of acetylcholine, a vital chemical in the brain that helps with cognition.

- RVT-101 has been studied in 13 clinical trials and administered in more than 1,250 people. It is currently in a global Phase 3 study in Alzheimer’s disease.
Research on Lewy body dementia

- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
  - 28 studies currently recruiting world-wide
  - 1 study recruiting in Oregon
A Study Evaluating RVT-101 in Subjects with Dementia with Lewy Bodies: The HEADWAY-DLB Study

*Study Design*

- A double-blind, randomized, placebo-controlled study in 240 individuals with a diagnosis of dementia with Lewy bodies
- Total participation in the study will be about 32 weeks, including the screening period
- Stable background therapy will be allowed
- Following completion of this study, individuals will be able to participate in an extension study where all participants will receive RVT-101
Key Inclusion Criteria

- Male or female individual with probable dementia with Lewy bodies
- Age 50 years to 85 years
- Individuals currently receiving therapy for dementia are also eligible for enrollment
- Mini Mental State Examination (MMSE) score of 14-26 inclusive at Screening and Baseline
- Must be able to comply with procedures for cognitive and other testing in the opinion of the investigator
- Must have a caregiver or care provider who is willing to report on his/her status throughout the study
For more information, please email or call:

Memory Health Center

(503) 228-CARE (2273)

www.MemoryHealthCenter.com
What can we do about hallucinations in Parkinson’s dementia and Lewy body dementia

• The medications usually used for hallucinations make parkinsonism worse.
• One exception is clozapine, but there are risks with that drug which require weekly blood tests to monitor.
• A new approach to hallucinations in this population is needed.
Pimavanserin for patients with Parkinson’s disease psychosis: a randomised, placebo-controlled phase 3 trial

Jeffrey Cummings, Stuart Isaacson, Roger Mills, Hilde Williams, Kathy Chi-Burris, Anne Corbett, Rohit Dhall, Clive Ballard

Lancet 2014; 383: 533-40

314 individuals screened beginning in August, 2010

199 randomly allocated treatment (randomisation completed by Aug 29, 2012)

115 excluded: 53 did not meet SAPS/NPI entry criteria, 14 declined to participate, 48 other reasons

94 assigned placebo
0 did not receive ≥1 dose

4 discontinued before post-baseline SAPS assessment
1 adverse event
1 withdrew consent
2 other

90 included in the full analysis set

87 completed study treatment

105 assigned pimavanserin 40 mg
1 did not receive ≥1 dose

9 discontinued before post-baseline SAPS assessment
6 adverse events
2 withdrew consent
1 other

95 included in the full analysis set

89 completed study treatment
Figure 2: Treatment effects on psychosis severity reduction in the 6 week study period in the full analysis set.
Figure 3: Treatment effects on SCOPA-sleep (night-time sleep and daytime wakefulness measures) and caregiver burden in the full analysis set.
<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=94)</th>
<th>Pimavanserin 40 mg (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6 (6%)</td>
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</tr>
<tr>
<td>Peripheral oedema</td>
<td>3 (3%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>11 (12%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Fall</td>
<td>8 (9%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>3 (3%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hallucination (including visual)</td>
<td>4 (4%)</td>
<td>7 (7%)</td>
</tr>
</tbody>
</table>

Data are n (%).

Table 3: Treatment-emergent adverse events group in all participants who received ≥1 dose of study drug (occurring in ≥5% in either treatment)
Conclusions:

• New strategies for increasing acetylcholine in the brain may permit more effective treatment of Lewy body dementia.
• A new strategy for treating hallucinations in the setting of Parkinson’s disease may eventually be applied to Lewy body dementia.
Future directions for Lewy body dementia:

• Aimed at underlying pathology: Lewy bodies, the chief component of which is alpha synuclein:
Spread of “Lewy bodies” to thinking centers of the brain:
Experimental therapies targeting synuclein include:

• “small molecule” (ie, a pill)
• Immunotherapy (ie, antibodies, delivered by injection)
• Gene therapy
Support for Lewy body dementia:

• Alzheimer’s Association
  – www.alz.org
  – 1-800-272-3900

• Lewy Body Dementia Association
  – www.lbda.org
  – 800-359-9767
Frontotemporal dementia:

• Behavioral variant
• Language variant
Behavioral variant: disinhibited:

• 52 year old man:
  – Trouble learning new tasks at work
  – Gradual onset of disinhibited statements “there is no filter”
  – Over-spends, over-tips
  – Eats impulsively: Stuff mouth full without swallowing, episodes of choking
  – Acts impulsively: eg, jumped in white water with dog while out hiking
Behavioral variant: disinhibited:

• 52 year old man:
  – Mmse =29/30
  – EXIT-25 =14/50
  – Normal neuro exam
  – Bilateral frontotemporal atrophy on MRI scan
MRI in FTD:
Language variant:
Primary progressive aphasia (PPA)

- 53 year old woman referred for declining language function
- Worked as a traveling motel clerk until one year prior to evaluation.
- Telephone calls to husband and sister became “flat” about 1.5-2 years prior to eval.
- Laid off from work one year prior to eval.
Language variant-PPA

• She was referred to a local neurologist, who found normal EEG, normal MRI, and thought neurodegenerative disease unlikely.

• Social security examiner thought she was depressed and recommended ECT.

• Psychiatrist thought her language was impaired, doubted depression as the primary diagnosis, and referred her to another neurologist

• Chief complaint was difficulty with expressive language
Mental status exam

- mmse = 21/30
  - Orientation = 6/10
  - Attention = 2/5 ("DLORY")
  - Repetition = 0/1
  - obvious trouble with word-finding during spontaneous speech, to the point where even simple sentences were rarely fluent
labs

- Neuro exam: normal
- Brain MRI—normal
Brain autopsy

• Frontotemporal dementia confirmed in both instances

• Note:
  – Younger than Alzheimer’s patients
  – Memory is relatively preserved
  – Behavior or language are markedly impaired
  – With time, impairment generalizes and function declines
Brain autopsy

• Some variants of frontotemporal dementia, defined by brain autopsy:
  – Pick’s disease
  – FTDP-17
  – Progressive supranuclear palsy
  – Corticobasal degeneration
Genetics:

- FTDP-17 (rare)
- Progranulin (rare)
- C9ORF72: fairly common in familial FTD, also seen in “sporadic” cases
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- FTDP-17 (rare)
- Progranulin (rare)
- C9ORF72: fairly common in familial FTD, also seen in “sporadic” cases

- The genetics does not predict the particular symptoms
Treatment of FTD

- SSRI’s are recommended by most experts
- Otherwise symptomatic treatment on a case-by-case basis
Research on FTD

• [www.clinicaltrial.gov](http://www.clinicaltrial.gov)
  – 45 studies worldwide
  – none in Oregon
  – 7 in California, none are treatments
Support for FTD

• Association for Frontotemporal Dementia
  – www.theaftd.org
  – 866-507-7222

• Cure PSP
  – www.psp.org
  – 800-457-4777

• Alzheimer’s Association
conclusions

• Lewy body dementia and frontotemporal dementia are distinct from Alzheimer’s disease
• Ongoing research is under way to develop disease-modifying treatments.
• In the meantime, treatment is tailored to symptoms.
• Support for caregivers is available through a number of non-profit groups.
Thank you for your attention...
Questions?