The Reality of LBD: Hallucinations and Delusions and How to Manage Them

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Disclosures

- Board of Directors and Scientific Advisory Committee for LBDA
- Grants from NIH, AFTD, Florida Department of Health, and several private foundations
- Clinical trials for Axovant, Biogen, Novartis, Janssen, Genentech
Quickie Review of Things Associated With LBD

Movement Problems
• Bradykinesia
• Rigidity
• Postural instability with repeated falls
• Slow, shuffling gait
• Myoclonus
• Rare rest tremor but may have postural or action tremor

Cognitive Problems
• Visual tracking and attention
• Visual-spatial and perceptual
• Verbal and motor initiation
• Clock drawing and block design (construction)
• Timed attention tasks
• Executive tasks
Quickie Review of Things Associated With LBD

**Psychiatric/Behavioral Problems**
- Visual Hallucinations
- Hallucination in other modalities
- Delusions
- Depression
- Anxiety
- Apathy
- REM Sleep behavior disorder
- Cognitive fluctuations

**Autonomic/Constitutional Problems**
- Loss of Smell
- Constipation
- Urinary incontinence
- Drooling
- Runny nose
- Dizziness and lightheaded
- Abnormal sweating
- Sexual dysfunction
- Oily flaky skin
## Caregivers and LBD Symptoms

<table>
<thead>
<tr>
<th>First Symptom Presentation (%)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>43.8</td>
<td>38.4</td>
<td>41.4</td>
</tr>
<tr>
<td>Motor</td>
<td>15.6</td>
<td>14.4</td>
<td>14.2</td>
</tr>
<tr>
<td>Behavior</td>
<td>15.6</td>
<td>18.3</td>
<td>15.4</td>
</tr>
<tr>
<td>Language</td>
<td>0</td>
<td>4.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Personality</td>
<td>3.1</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Mood</td>
<td>3.1</td>
<td>5.3</td>
<td>6.8</td>
</tr>
<tr>
<td>Sleep</td>
<td>18.8</td>
<td>15.6</td>
<td>16.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Disturbing Symptom (%)</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive</td>
<td>50.0</td>
<td>29.4</td>
<td>29.6</td>
</tr>
<tr>
<td>Motor</td>
<td>15.6</td>
<td>17.2</td>
<td>24.1</td>
</tr>
<tr>
<td>Behavior</td>
<td>12.5</td>
<td>23.3</td>
<td>20.4</td>
</tr>
<tr>
<td>Language</td>
<td>12.5</td>
<td>7.3</td>
<td>12.3</td>
</tr>
<tr>
<td>Personality</td>
<td>9.4</td>
<td>5.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Mood</td>
<td>0</td>
<td>11.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Sleep</td>
<td>0</td>
<td>6.1</td>
<td>4.3</td>
</tr>
</tbody>
</table>
Neuropsychiatric Symptoms of Dementia (NPS)

• Also known as behavioral and psychiatric symptoms of dementia (BPSD)
• While cognitive impairment is the clinical hallmark of dementia, NPS often dominate both presentation and course
• Present in >90% of patients at some point
• Etiology is not well understood, but is likely multifactorial
Behavioral Symptoms Worsen as Cognition Declines

Dementia patients who display marked behavioral disturbances in a given time frame are more likely to display them again in the future.¹

Timeline of NPS in Dementia

Adapted from: Jost BC, Grossberg GT. J Am Geriatr Soc. 1996;44(9):1078-1081

- Agitative symptoms
- Depressive symptoms
- Psychotic symptoms
- Other symptoms

Months Before/After Diagnosis

Frequency, % of Patients
0 20 40 60 80 100
-40 -30 -20 -10 0 10 20 30

- Social Withdrawal
- Depression
- Suicidal Ideation
- Paranoia
- Accusatory
- Anxiety
- Mood Change
- Irritability
- Agitation
- Wandering
- Aggression
- Socially Unacceptable
- Hallucinations
- Sexually Inappropriate
- Accusatory
- Delusions
- Depression
- Anxiety
- Social Withdrawal
- Agitative symptoms
- Depressive symptoms
- Psychotic symptoms
- Other symptoms
RBD=rapid eye movement (REM) sleep behavior disorder. PLMD=periodic limb movement disorder.

Hallucinations

• Abnormal perception with a physical stimulus
• Simple or complex
  • Simple: brief and fragmentary
  • Complex: detailed
Simple Hallucinations in LBD

• Sense of presence
  • Sensation that someone is looking over your shoulder
  • Deceased relative, animal

• Passage
  • Seeing something pass sideways in the peripheral of vision
  • People, previously owned pet
  • Shadows

• Illusions
  • Misperception based on actual objects
  • Seeing a person when there is a coat on a hanger
  • Images emerging from wall paper
Complex Hallucinations in LBD

• Predominantly visual in nature
  • Occur early in the course of the disease
  • May not be frightening to patients
  • Typically of little people, children, or furry animals
  • May or may not have an auditory component
  • Complex in nature

• Auditory (hear)
• Olfactory (smell)
• Gustatory (taste)
• Tactile (feel)
Delusions

• False, fixed beliefs
• Maintained despite evidence to the contrary
• Several types in DLB
  • Misidentification
  • Paranoid
  • Phantom boarder
  • Abandonment
Common Delusions in LBD

- Capgras
  - Familiar people are thought to be identical or near-identical imposters
- Fregoli
  - Familiar people are thought to be disguised as strangers
- Othello
  - Jealousy – usually spousal infidelity
- Cotard
  - Belief that one does not actually exist or is dead
- Reduplicative paramnesia
  - A place simultaneously exist in two or more physical locations
- Mirrored self-identification
  - Not recognizing self in mirror
- Ekbom
  - Infestation by insects or parasites
- Diogenes
  - Self-neglect, domestic squalor
Capgras Syndrome and Lewy Bodies

• Capgras syndrome is characterized by the recurrent and transient belief that a person, usually someone closely related, has been replaced by an imposter.
  • The imposter usually has features that are very similar to those of the original person, although subtle physical differences are used to differentiate the original person from the imposter

• Examined case series of 55 consecutive LBD patients (11 with Capgras, 44 without)
## Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Capgras</th>
<th>No Capgras</th>
<th>p-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>77.1 (8.5)</td>
<td>74.7 (7.1)</td>
<td>.35</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.4 (3.9)</td>
<td>14.8 (3.3)</td>
<td>.16</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>63.6</td>
<td>63.6</td>
<td>1.0</td>
</tr>
<tr>
<td>% married</td>
<td>81.8</td>
<td>68.2</td>
<td>.52</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinsonism, %</td>
<td>90.9</td>
<td>88.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Visual hallucinations, %</td>
<td>100.0</td>
<td>61.4</td>
<td>.01</td>
</tr>
<tr>
<td>Cognitive fluctuations, %</td>
<td>65.6</td>
<td>40.9</td>
<td>.19</td>
</tr>
<tr>
<td>REM sleep disorder, %</td>
<td>72.7</td>
<td>47.7</td>
<td>.18</td>
</tr>
<tr>
<td><strong>Dementia Ratings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-mental state exam</td>
<td>19.7 (5.2)</td>
<td>19.3 (6.7)</td>
<td>.87</td>
</tr>
<tr>
<td>Clinical dementia rating</td>
<td>1.6 (0.7)</td>
<td>1.5 (0.8)</td>
<td>.64</td>
</tr>
<tr>
<td>CDR Sum of boxes</td>
<td>10.6 (3.6)</td>
<td>9.0 (4.5)</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Behavioral Ratings</strong>b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric inventory</td>
<td>15.7 (4.8)</td>
<td>11.6 (5.7)</td>
<td>.03</td>
</tr>
<tr>
<td>HADS-Depression, %</td>
<td>21.1</td>
<td>20.0</td>
<td>.61</td>
</tr>
<tr>
<td>HADS-Anxiety, %</td>
<td>31.8</td>
<td>8.3</td>
<td>.05</td>
</tr>
<tr>
<td><strong>Caregiver Ratings</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zarit Burden Inventory</td>
<td>26.2 (10.1)</td>
<td>19.3 (6.7)</td>
<td>.02</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>5.8 (5.8)</td>
<td>3.6 (3.8)</td>
<td>.21</td>
</tr>
</tbody>
</table>

- Capgras patients experienced more visual hallucinations, had higher self-reported anxiety, and had worse behavioral ratings.
- Capgras patients less likely to tolerate cholinesterase inhibitors.
- Capgras caregivers experienced more burden.
- Predictors of Capgras were visual hallucinations (OR 18.3) and anxiety (OR 2.9).

Thaipisutikul et al. Int Psychogeriatr 2013
Challenges in Neuropsychiatric Assessment

• Clinician challenges\textsuperscript{1,2}
  • Unfamiliar with appropriate diagnostic criteria
  • Limited time for visits
  • Differential diagnosis: symptoms can be overlapping between mild to moderate depression and dementia

• Patient issues\textsuperscript{3}
  • May not complain or may divert attention to more routine problems
  • May take offense at physician’s suggestions
  • Medical history may be unreliable: based on cognitively impaired patient and on family recollections

• Caregiver issues\textsuperscript{2,3}
  • Need help to recognize symptoms
  • May be overwhelmed due to stress

• Neuropsychiatric symptoms may have multiple etiologies\textsuperscript{4}
  • Primary: due to underlying disease and its neuropathology
  • Secondary: due to drug therapy or co-morbid conditions
    • Potential for drug-induced neuropsychiatric symptoms with current medications

# Diagnosing Behavioral Changes: NPI Questionnaire

<table>
<thead>
<tr>
<th>Category</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>Does the patient believe that others are stealing from him or her or planning to harm him or her in some way?</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Does the patient act as if he or she hears voices? Does he or she talk to people who are not there?</td>
</tr>
<tr>
<td>Agitation or aggression</td>
<td>Is the patient stubborn and resistive to help from others?</td>
</tr>
<tr>
<td>Depression or dysphoria</td>
<td>Does the patient act as if he or she is sad or in low spirits? Does he or she cry?</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Does the patient become upset when separated from you? Does he or she have any other signs of nervousness?</td>
</tr>
<tr>
<td>Elation or euphoria</td>
<td>Does the patient appear to feel too good or act excessively happy?</td>
</tr>
<tr>
<td>Apathy or indifference</td>
<td>Does the patient seem less interested in his or her usual activities and in the activities and plans of others?</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>Does the patient seem to act impulsively?</td>
</tr>
<tr>
<td>Irritability or lability</td>
<td>Is the patient impatient and cranky? Does he or she have difficulty coping with delays or waiting for planned activities?</td>
</tr>
<tr>
<td>Motor disturbance</td>
<td>Does the patient engage in repetitive activities?</td>
</tr>
<tr>
<td>Nighttime behaviors</td>
<td>Does the patient awaken you during the night, rise too early in the morning, or take excessive naps during the day?</td>
</tr>
<tr>
<td>Appetite and eating</td>
<td>Has the patient lost or gained weight or had a change in the food he or she likes?</td>
</tr>
</tbody>
</table>
# Neuropsychiatric Symptoms in Dementias

<table>
<thead>
<tr>
<th>NPI Item</th>
<th>AD</th>
<th>PDD</th>
<th>DLB</th>
<th>VaD</th>
<th>FTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>—</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>—</td>
<td>●●●●</td>
<td>●●●</td>
<td>●●●</td>
<td>—</td>
</tr>
<tr>
<td>Agitation</td>
<td>●●●</td>
<td>●●</td>
<td>●●●●</td>
<td>●●●</td>
<td>●●●</td>
</tr>
<tr>
<td>Depression</td>
<td>●●●</td>
<td>●●●●</td>
<td>●●●●</td>
<td>●●●</td>
<td>●●●</td>
</tr>
<tr>
<td>Anxiety</td>
<td>●●●●</td>
<td>●●●●</td>
<td>●●●●</td>
<td>●●●</td>
<td>●</td>
</tr>
<tr>
<td>Apathy</td>
<td>●●●●</td>
<td>●●●●</td>
<td>●●●●</td>
<td>●●●</td>
<td>●●●●</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>—</td>
<td>—</td>
<td>●</td>
<td>●</td>
<td>●●●●</td>
</tr>
<tr>
<td>Irritability</td>
<td>●●</td>
<td>●</td>
<td>●●</td>
<td>●</td>
<td>●●●</td>
</tr>
<tr>
<td>Sleep</td>
<td>●</td>
<td>●</td>
<td>●●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

— 0-14% ● 15-29% ●● 30-44% ●●● 45-59% ●●●● ≥60%

NPI=Neuropsychiatric Inventory. PDD=Parkinson’s disease dementia. DLB=dementia with Lewy bodies. VaD=vascular dementia. FTD=frontotemporal dementia. Karantzoulis and Galvin, 2013
Healthy Aging Brain Care Monitor (HABC-M)

- Assess the emergence and severity of dementia-related symptoms, promote effective decision-making, drive individualized interventions, and monitor response to therapy
- To meet this need, we created and validated the Healthy Aging Brain Care Monitor (HABC-M) to capture, quantify, and monitor cognitive, functional, and behavioral symptoms, and quality of life of FCGs
  - Higher scores represent greater impairment
  - Takes 5-6 minutes to complete
- The internal consistency of the caregiver-rated HABC-M is high (0.73 – 0.92)
- Sufficient dispersion to assess and monitor symptom severity

Monahan et al, Clin Interv Aging 2012
HABC-M is a copyright instrument: Boustani, Callahan, and Galvin, 2011
<table>
<thead>
<tr>
<th>Over the past two weeks, how often did your loved one have problems with: (Use ✓ to indicate your answer.)</th>
<th>Not at all (0-1 day)</th>
<th>Several Days (2-6 days)</th>
<th>More than half the days (7-11 days)</th>
<th>Almost daily (12-14 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judgment or decision-making</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Repeating the same things over and over such as questions or stories</td>
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</tr>
<tr>
<td>Forgetting the correct month or year</td>
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</tr>
<tr>
<td>Handling complicated financial affairs such as balancing checkbook, income taxes &amp; paying bills</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Remembering appointments</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Thinking or memory</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Learning how to use a tool, appliance, or gadget</td>
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</tr>
<tr>
<td>Planning, preparing, or serving meals</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Taking medications in the right dose at the right time</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Walking or physical ambulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bathing</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Shopping for personal items like groceries</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Housework or household chores</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Leaving her/him alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her/his safety</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Her/his quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falling or tripping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Less interest or pleasure in doing things, hobbies or activities</th>
<th>Feeling down, depressed, or hopeless</th>
<th>Feeling anxious, nervous, tense, fearful or panic</th>
<th>Believing others are stealing from them or planning to harm them</th>
<th>Hearing voices, seeing things or talking to people who are not there</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over the past two weeks, how often did you have problems with: (Use ✓ to indicate your answer.)</td>
<td>Not at all (0-1 day)</td>
<td>Several Days (2-6 days)</td>
<td>More than half the days (7-11 days)</td>
<td>Almost daily (12-14 days)</td>
</tr>
<tr>
<td>Your quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Your financial future</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Your mental health</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Your physical health</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Place Sticker Here**

Monahan et al, Clin Interv Aging 2012

Cognitive Subscale
Functional Subscale
Behavioral and Mood Subscale
Caregiver Stress Subscale
Total Score
<table>
<thead>
<tr>
<th>Clinical Diagnosis</th>
<th>HABC-Domains</th>
<th>Controls (n=17)</th>
<th>MCI (n=62)</th>
<th>Dementia (n=80)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cognitive</td>
<td>2.9 (3.8)</td>
<td>5.4 (4.4)</td>
<td>10.2 (5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>3.0 (3.4)</td>
<td>4.1 (4.4)</td>
<td>8.1 (8.7)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Behavioral</td>
<td>4.8 (6.6)</td>
<td>5.6 (5.0)</td>
<td>9.3 (6.8)</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>Total HABC-M Scores</td>
<td>10.6 (11.9)</td>
<td>15.1 (11.6)</td>
<td>27.5 (18.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severity of Cognitive Impairment</td>
<td>MMSE 24+ (n=76)</td>
<td>MMSE 18-23 (n=53)</td>
<td>MMSE 10-17 (n=30)</td>
<td>MMSE 0-9 (n=10)</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>Cognitive</td>
<td>5.3 (4.7)</td>
<td>8.1 (4.9)</td>
<td>11.5 (5.3)</td>
<td>14.3 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Functional</td>
<td>4.3 (5.0)</td>
<td>5.0 (5.1)</td>
<td>10.9 (10.2)</td>
<td>15.8 (11.5)</td>
</tr>
<tr>
<td></td>
<td>Behavioral</td>
<td>5.9 (5.6)</td>
<td>7.3 (5.8)</td>
<td>10.1 (6.9)</td>
<td>13.8 (9.0)</td>
</tr>
<tr>
<td></td>
<td>Total HABC-M Scores</td>
<td>15.5 (13.4)</td>
<td>20.3 (12.0)</td>
<td>32.5 (20.0)</td>
<td>43.9 (22.1)</td>
</tr>
</tbody>
</table>

- The HABC-M shows responsiveness to change and can differentiate between patients who improve, decline or remain stable.
- The largest effect sizes for the change scores were for the Behavioral domain, with a moderate improvement in the NPI Improved group (0.53) and moderate decline in the NPI Declined group (-0.43).
Neuropsychology

**Noise-Pareidolia**
- There are two types of images:
  - An array of ink blots with a facial image (Scene)
  - An array of ink blots with no facial image (Noise)
- Responses are recorded
  - Is there a face: Yes or No
  - Point to where the face is
- The scores are based on the number of:
  - Correct answers: “Yes” when there is a face or “No” when there is no face
  - Pareidolia: “Yes” when there is no face or “Yes” when there is a face but points to wrong spot
  - Missed responses: “No” when there is a face
- Short Form: 20 Items (13 Foils, 7 Faces)
- Each panel 30 seconds (10 minutes max)

### Differentiation between DLB and AD

<table>
<thead>
<tr>
<th></th>
<th>Scene Test</th>
<th>Noise Test</th>
<th>Pareidolia Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>0.92</td>
<td>0.60</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>0.58</td>
<td><strong>0.92</strong></td>
<td>0.92</td>
</tr>
<tr>
<td><strong>ROC AUC</strong></td>
<td>0.86</td>
<td>0.82</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Cut-Off Score</strong></td>
<td>1/2</td>
<td>2/3</td>
<td>4/5</td>
</tr>
<tr>
<td>#</td>
<td>Stimulus</td>
<td>Select Response</td>
<td>#</td>
</tr>
<tr>
<td>----</td>
<td>----------</td>
<td>-------------------------</td>
<td>----</td>
</tr>
<tr>
<td>1</td>
<td>Face</td>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>Noise</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Noise</td>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>Face</td>
<td>Yes</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Noise</td>
<td>Yes</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Noise</td>
<td>Yes</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>Noise</td>
<td>Yes</td>
<td>17</td>
</tr>
<tr>
<td>8</td>
<td>Face</td>
<td>Yes</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>Noise</td>
<td>Yes</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>Face</td>
<td>Yes</td>
<td>20</td>
</tr>
</tbody>
</table>

Correct Face responses _____/7  Number of Yes responses to face stimuli that point to the correct location
Correct Noise responses ____/13 Number of No responses to noise stimuli without face images
Total Correct _____/20  Correct Yes face responses + Correct No noise responses
Noise (Pareidolia) responses ____/13 Number of Yes responses to noise stimuli (points to a face where there is no face)
Key Elements to Approach NPS

• Accurate characterization and contextualization
• Examine underlying causes
• Devise treatment plan
• Avoid “knee-jerk” use of psychotropic medications
• Behavioral and environmental modifications should be tried first with 3 exceptions
  • Suicide risk
  • Psychosis causing harm or potential to cause harm
  • Aggression causing risk
• Assess intervention effectiveness
Does This Symptom Need to Be Treated?

• As a general rule, most behaviors do not need medications

• If a medication is used, then the lowest possible dose for the shortest period of time is the best route

• In order to “trigger” use of a medication, one of the following questions must be answered “YES”
  • Does the behavior interfere with patient care in a meaningful way
  • Does the behavior interfere with patient safety
  • Does the behavior interfere with someone else’s safety

• If “NO” is the answer to all three, medications should **NOT** be used
“Real-World” Management

• In many settings, NPS treated with antipsychotic medications
• No FDA-approved therapy for NPS
• All use is off-label
  • Antipsychotics
  • Antidepressants
  • Mood stabilizers
  • Benzodiazepines
  • Cholinesterase inhibitors
  • Memantine

Kales et al, Am J Psych 2007
Non-Pharmacologic Management

• Goals
  • Create a routine
  • Provide stability
  • Avoid distractions
• Suggestions to achieve goals
  • Provide a predictable and prompted routine
  • Maintain familiar possessions and clothes
  • Explain in simple language
  • Simply tasks
  • Provide a safe environment
  • Use calendars, clocks, labels, and color coding
  • Reduce stimulation and crowds
  • Reduce clutter, noise and excess glare
  • Consider an adult day program

Techniques and Methods

• Remove trigger, distract/redirect
• Caregiver education and support
• Adult day programs
• Psychotherapy techniques
  • Memory retraining
• Stimulation-oriented treatment
  • Music
  • Art
  • Recreational or social therapies
  • Exercise
  • Dance
  • Boxing
• Montessori-based activities
  • Memory BINGO
  • Group sorting
The DICE Approach

Describe
- Caregiver describes problematic behavior
  - Context (who, what, when and where)
  - Social and physical environment
  - Patient perspective
  - Degree of distress to patient and caregiver
- Provider investigates possible causes of problem behavior
  - Patient
    - Medication side effects
    - Pain
    - Functional limitations
    - Medical conditions
    - Psychiatric comorbidity
    - Severity of cognitive impairment, executive dysfunction
    - Poor sleep hygiene
    - Sensory changes
    - Fear, sense of loss of control, boredom
  - Caregiver effects/expectations
  - Social and physical environment
  - Cultural factors
  - Provider, caregiver and team collaborate to create and implement treatment plan
    - Respond to physical problems
    - Strategize behavioral interventions
      - Providing caregiver education and support
      - Enhancing communication with the patient
      - Creating meaningful activities for the patient
      - Simplifying tasks
      - Ensuring the environment is safe
      - Increasing or decreasing stimulation in the environment
- Provider evaluates whether “CREATE” interventions have been implemented by caregiver and are safe and effective

Evaluate

Investigate

Create

Consideration of Psychotropic Use (Acuity/Safety)
Management of Dementia-Related Behavior: A Practical Approach

- Define target symptoms and severity
- Environmental factors addressed
- Medical illness revisited
- Establish psychiatric diagnosis
- Non-pharmacological management
- Targeted pharmacotherapy (if needed)
- Initiate low and go slow
- Assess outcomes and re-evaluate

Non-Pharmacologic Interventions for Behavior Clusters

<table>
<thead>
<tr>
<th><strong>“Negative” Symptoms</strong></th>
<th><strong>“Positive” Symptoms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive Resistance</td>
<td>Agitation, Aggression</td>
</tr>
<tr>
<td>Vocalizations, Screaming</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Wandering</td>
<td>Delusions</td>
</tr>
<tr>
<td>Purposeless Hyperactivity</td>
<td>Misidentifications</td>
</tr>
<tr>
<td>Apathy</td>
<td>Disinhibition</td>
</tr>
<tr>
<td>Social Isolation. Withdrawal</td>
<td>Depression, Anxiety</td>
</tr>
<tr>
<td><strong>Non-pharmacologic Interventions</strong></td>
<td><strong>Pharmacologic Interventions</strong></td>
</tr>
<tr>
<td>Behavioral Management Techniques (distraction,</td>
<td>Antipsychotic (Classic and Atypical)</td>
</tr>
<tr>
<td>redirection, relaxation)</td>
<td></td>
</tr>
<tr>
<td>Cognitive/emotion-oriented approaches (reminiscence therapy, validation therapy, stimulated presence therapy)</td>
<td>Cholinesterase Inhibitors</td>
</tr>
<tr>
<td>Sensory Stimulation Interventions (acupuncture, aromatherapy, light therapy, massage/touch therapy, music therapy)</td>
<td>Memantine</td>
</tr>
<tr>
<td>Psychoeducational approaches for caregivers</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>Montessori-based activities (Memory BINGO, Group sorting)</td>
<td>Anticonvulsants</td>
</tr>
<tr>
<td>Adult day programs</td>
<td>Benzodiazepines</td>
</tr>
</tbody>
</table>

Yusapov and Galvin, 2014
Treatment of Psychosis

• Avoid “Classic” neuroleptic medications such as haloperidol
  • Increased risk of side effects
    • Enhanced parkinsonism
    • Neuroleptic malignant syndrome (potentially fatal)

• Clozapine
  • RCT in PD psychosis demonstrated efficacy
  • Many side effects
  • Not commonly used
  • Can worsen motor function

• Quetiapine
  • Limited actual RCT evidence but anecdotal experience suggest effectively
  • Less side effects than Clozapine
  • Can worsen motor function
  • Can worsen autonomic symptoms

• Pimavanserin
Pimavanserin

Psychosis Scores

Caregiver Burden

Global Severity

Global Ratings

Nighttime sleep

Daytime wakefulness

RVT-101 in Dementia with Lewy Bodies (DLB)

- Significant unmet need: no drugs approved in the U.S. or EU
  - Aricept was approved in Japan for the treatment of DLB in 2014

- Cholinergic deficits are a prominent feature of DLB
  - Cholinergic neurotransmission is more dysfunctional in DLB than Alzheimer’s disease

- Increasing acetylcholine improves cognition and function in DLB
  - RVT-101 promotes the release of acetylcholine

- $5HT_{2A}$ activity is a driver of visual hallucinations
  - RVT-101 inhibits the activity of the $5HT_{2A}$ receptor

- Initiated 24-week Phase 2b study in 2016, study now closed to enrollment

Single successful study could serve as basis for approval of RVT-101 in DLB when combined with Alzheimer’s filing
Nelotanserin in Lewy Body Dementia

Highly selective and potent 5HT₂A inhibitor

- 5HT₂A is a proven target in the treatment of visual hallucinations
- 792 human subjects treated to date with nelotanserin in seven clinical trials
- Well-tolerated with a low incidence of adverse affects

Potential best-in-class compound

- Highly selective and potent only against 5HT₂A
- Minimal cross-reactivity with other 5HT, Dopamine, or Histamine receptors
- No evidence of QTc prolongation (cardiac side affect)
- Once-daily, oral dosing

Two phase 2 studies initiated in 2016

- Visual hallucinations in Lewy Body Dementia patients
- REM Behavior Disorder (RBD) in DLB patients
Summary

• Hallucinations and Delusions are common in LBD
• New emergent symptoms require a medical evaluation
• Not all behaviors require medication
• Non-pharmacological approaches should be first line
• If starting a medication, know all there is to know about that medication
• Start at lowest dose, increase doses slowly, constantly re-evaluate
• New medications are being tested that specifically target hallucinations in LBD
Contact

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