Management of Behavioral Disturbances in Dementia

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Disclosures

- Grant Support: VA HSR&D
Learning Objectives

• At the end of this presentation, you will be able to:
  – Recognize the behavioral disturbances that are most commonly associated with dementia
  – Be familiar with strategies to identify the cause of the behavioral disturbance
  – Identify behaviors that respond to nonpharmacological approaches
  – List several behavioral interventions for behavioral disturbances
Different Etiologies for Dementia

- Alzheimer’s
- Lewy Body
- Vascular
- Frontotemporal
- HIV-related
- Huntington’s
- Dementia pugilistica
- Corticobasilar degeneration
- Creutzfeldt-Jakob/Prion illnesses
Dementia of the Alzheimer Type

- Most common cause
- Currently affects 4 million people, will affect more than 14 million by 2050 (NIA)
- Patients are symptomatic on average for 8-10 years
- Progressive, irreversible, and degenerative
- Characteristic pathology
- Unknown etiology, although probably multifactorial.
Prevalence of Alzheimer’s Disease by Age

AGE

%
Pathophysiology: Neuritic Plaques

- Amyloid deposits mixed with parts of neurons, microglia and astrocytes
Pathophysiology: Neurofibrillary Tangles

- Tangles within neurons, mainly Tau protein
- Contribute to neuronal cell death
Dementia Results in Loss of Brain Activity & Function

PET Imaging

Normal Memory

Dementia

Small GW et al. Proc Natl Acad Sci USA. 2000;97:6037-6042
Progression of Alzheimer’s Disease

- Early diagnosis
- Mild-moderate
- Severe

- Cognitive symptoms
- Loss of IADL’s
- Behavioral problems
- Nursing home placement
- Death

Prevalence of Behavioral Disturbances in Dementia

- Psychosis: 40%
- Depression: 25%
- Non-psychotic "Agitation": 75%
- Threatening or Violent: 25%
- Anxiety: 40%

Cumulative Incidence of Psychosis of AD

N=329

% Psychosis

Years following diagnosis of AD

“Agitation”

- Excessive motor or verbal activity that is:
  - 1 of the following:
    - Disruptive
    - Unsafe
    - Distressing to the patient
  - Interferes with care and
  - Is not because of need
- Appears similar despite great variety of causes
- Need to identify cause, not focus only on symptoms
- When severe, may require urgent intervention

Cohen-Mansfield J. Int Psychogeriatr. 1996(Summer);8(2):233-245 (Review)
## Behavioral Disturbances

<table>
<thead>
<tr>
<th>Physical</th>
<th>Verbal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitting</td>
<td>Threats</td>
</tr>
<tr>
<td>Pacing</td>
<td>Accusations</td>
</tr>
<tr>
<td>Kicking</td>
<td>Name-calling</td>
</tr>
<tr>
<td>Biting</td>
<td>Obscenities</td>
</tr>
<tr>
<td>Pushing</td>
<td>Complaining</td>
</tr>
<tr>
<td>Spitting</td>
<td>Attention-seeking</td>
</tr>
<tr>
<td>Scratching</td>
<td>Screaming</td>
</tr>
</tbody>
</table>

Cohen-Mansfield J. Int Psychogeriatr. 1996(Summer);8(2):233-245. (Review)
When Behavioral Problems Become Problematic

- Interfere with health or well-being of the patient
- Threaten to overburden or endanger the caregiver
- Degrade the well-being of others with whom the patient resides
Attributes of Patient

- Cortical deficits
- Sensory impairment
- Unrecognized psychiatric or medical illness
- Protective or reflexive assault
- Unmet needs: pain, urinary/fecal urgency, incontinence, hunger, lack of stimulation, excessive stimulation
Attributes of Caregiver

- Lack of support
- Threshold for unusual/abnormal behavior
- Lack of information
- Misinterpretation of behavior as willful
- Depression
- Exhaustion (lack of respite)
- Abuse
Assessment of Behavioral Disturbances

• What is happening?
• What is in the environment?
• When does it happen?
• Where does it happen?
• Who is around?
• Why is it a problem?
Assessment of Behavioral Disturbances

Behavioral Disturbance

- Due to Medical Cause
- Neuropsychiatric Cause Responsive to Behavioral Interventions
- Neuropsychiatric Cause Responsive to Pharmacologic Management
Medical Causes Of Behavioral Disturbances

- Infections
- Impaction
- Medications
- Pain
- Metabolic disturbances
Neuropsychiatric Symptoms that respond to Non-pharmacologic Strategies

- Wandering
- Poor self-care
- Uncomplicated depression
- Fidgeting
- Nervousness
- Uncooperativeness
- Agitation without any danger to resident or others

OBRA: Guidance to Surveyors
Care resistance

- Task too difficult
- Task overwhelming
- Caregiver rushes
- Pain
- Inability to understand directions (too many, too fast, wrong language)
- Fear
Management of care resistance

- Divide task into small, successive steps
- Patience
- Flexibility: try later
- Treat pain
- State instructions, one at a time, simply
- Reassure, comfort, explain
- Distract with conversation
- Ask patient to assist
## Non-Pharmacologic Management of Behavioral Disturbances

<table>
<thead>
<tr>
<th>Techniques</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distraction</td>
</tr>
<tr>
<td>Tolerance</td>
</tr>
<tr>
<td>Speak slowly, low pitched voice</td>
</tr>
<tr>
<td>One-step commands</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Light Therapy</td>
</tr>
<tr>
<td>Music Therapy</td>
</tr>
<tr>
<td>Time orientation</td>
</tr>
<tr>
<td>Routine</td>
</tr>
<tr>
<td>Slow pace</td>
</tr>
<tr>
<td>Choice of clothes</td>
</tr>
</tbody>
</table>
Currently no drug is FDA-approved to treat the behavioral disturbances associated with the dementias.
# Placebo-Controlled Trials of Atypical Antipsychotics in Dementia

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Study</th>
<th>N</th>
<th>Dur (wk)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Katz et al</td>
<td>625</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>DeDeyn et al</td>
<td>344</td>
<td>13</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td></td>
<td>Brodaty et al</td>
<td>337</td>
<td>12</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Satterlee et al</td>
<td>238</td>
<td>8</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td>Street et al</td>
<td>206</td>
<td>6</td>
<td>Improved symptoms</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Tariot et al</td>
<td>294</td>
<td>12</td>
<td>Improved/no difference</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>DeDeyn et al</td>
<td>208</td>
<td>10</td>
<td>Improved/no difference</td>
</tr>
<tr>
<td>Drug</td>
<td>Initial (mg/Day)</td>
<td>Typical range (mg/Day)</td>
<td>OBRA Max (mg/Day)</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>12.5</td>
<td>25-50</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5</td>
<td>1-2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5</td>
<td>5-10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25</td>
<td>50-250</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2.5</td>
<td>5-15</td>
<td>?10</td>
<td></td>
</tr>
</tbody>
</table>
Risperidone for Dementia-Associated Behavioral Disturbances and Psychosis

- Alzheimer’s, vascular or mixed dementia patients (N=625)
- All with significant behavioral symptoms or psychosis
- 12-week trial in nursing home
- Randomly given placebo, 0.5 mg/day, 1 mg/day or 2 mg/day
- Primary outcome was changes on BEHAVE-AD or Cohen Mansfield Agitation Inventory
- Secondary behavioral measures included EPS monitoring

Katz et al. J Clin Psychiatry. 1999(Feb);60(2):107-115
Risperidone for Dementia-Associated Behavioral Disturbances and Psychosis

Aggressiveness Subscale—CMAI

Mean shift at endpoint

<table>
<thead>
<tr>
<th>Dose of Risperidone (mg/Day)</th>
<th>Placebo (N=161)</th>
<th>0.5 mg (N=146)</th>
<th>1 mg (N=148)</th>
<th>2 mg (N=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Improvement Over Baseline</td>
<td>0.91</td>
<td>1.34</td>
<td>1.74</td>
<td>2.43</td>
</tr>
</tbody>
</table>

*p ≤ 0.002 vs. placebo; **p ≤ 0.001 vs. placebo; CMAI = Cohen-Mansfield Agitation Inventory; Katz IR et al. J Clin Psychiatry. 1999;60:107-115
### Incidence of Cerebrovascular Adverse Events in elderly patients in placebo-controlled trial of risperidone

<table>
<thead>
<tr>
<th>Study</th>
<th>Risperidone</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS-5</td>
<td>9 (15/167)</td>
<td>2 (3/170)</td>
</tr>
<tr>
<td>INT-24</td>
<td>8 (9/115)</td>
<td>2 (2/114)</td>
</tr>
<tr>
<td>USA-63</td>
<td>1 (5/462)</td>
<td>1 (2/163)</td>
</tr>
<tr>
<td>BEL-14</td>
<td>0 (0/20)</td>
<td>0 (0/19)</td>
</tr>
<tr>
<td>TOTAL*</td>
<td>4 (29/764)</td>
<td>2 (7/466)</td>
</tr>
</tbody>
</table>

* 4-12 week trials; 4 deaths in risperidone group; 1 in placebo group

Wooltorten, CMAJ 2002
Olanzapine in the Treatment of Alzheimer’s Disease

Study Design

- N=206
- Washout and placebo lead-in (3-14 days)
- 6-week, double-blind acute treatment
  - Placebo: 36% improvement
  - Olanzapine 5 mg/day: 66% improvement
  - Olanzapine 10 mg/day: 57% improvement
  - Olanzapine 15 mg/day: 43% improvement
- 18-week open-label: 5-15 mg/day of Olanzapine (ongoing)

Street J et al. Arch Gen Psychiatry. 2000(Oct);57(10):968-976
Olanzapine in Dementia

Agitation/Aggression

Mean Change from Baseline (LOCF)

Placebo  5 mg  10 mg  15 mg

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>5 mg</th>
<th>10 mg</th>
<th>15 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.40</td>
<td>8.38</td>
<td>8.35</td>
<td></td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

NPI/NH = Neuropsychiatric Inventory-Nursing Home; *p<0.05 vs. placebo; LOCF = last observation carried forward; Street et al. Eur Neuropsychopharmacol. 1999;9(suppl 5)
# Olanzapine in Dementia

## Treatment-Emergent Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Pbo (N=47)</th>
<th>OLZ 5 mg (N=56)</th>
<th>OLZ 10 mg (N=50)</th>
<th>OLZ 15 mg (N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accidental injury</td>
<td>27.7</td>
<td>25.0</td>
<td>24.0</td>
<td>37.7</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6.4</td>
<td>25.0*</td>
<td>26.0*</td>
<td>35.8*</td>
</tr>
<tr>
<td>Pain</td>
<td>10.6</td>
<td>14.3</td>
<td>12.0</td>
<td>24.5*</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>14.9</td>
<td>8.9</td>
<td>12.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>6.4</td>
<td>3.6</td>
<td>12.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Fever</td>
<td>2.1</td>
<td>8.9</td>
<td>14.0</td>
<td>13.2</td>
</tr>
<tr>
<td>Agitation</td>
<td>8.5</td>
<td>8.9</td>
<td>12.0</td>
<td>11.3</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>2.1</td>
<td><strong>19.6</strong></td>
<td>14.0†</td>
<td>17.0</td>
</tr>
<tr>
<td>Falls</td>
<td></td>
<td>Reported within accidental injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPS</td>
<td></td>
<td>No differences from placebo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 vs. Pbo; **p<0.01 vs. Pbo; †Simpson-Angus Gait item from baseline: 5/9 patients no change; 3/9 patients improved; †p not significant vs. Pbo; Simpson-Angus Gait item from baseline: 6/7 patients no change; Street JS et al. Arch Gen Psychiatry. 2000;57(10):968-976
Open-Label Trial of Quetiapine in the Elderly

• Organic psychoses (degenerative disorders) N=132 (72%)
  – Alzheimer’s disease (AD) N=80 (43%)
  – Parkinson’s disease (PD) N=41 (22%)
  – Vascular disease (VD) N=11 (6%)

• Idiopathic psychoses N=52 (28%)
  – Schizophrenia N=32 (17%)
  – Delusional disorder N=8 (4%)
  – Bipolar disorder N=5 (30%)
  – Schizoaffective disorder N=6 (3%)
  – Major depressive disorder N=1 (1%)

Tariot PN, Salzman C, Young PP, Pultz J, Rak I. Clin Ther. 2000(Sept);22(8):1068-1084
Quetiapine in Elderly Psychotic Patients

Results from a 52-Week, Open-Label Study

Mean BPRS Total Score

Baseline 2 4 6 12 24 36 52

Trial Week

*p<0.0001 vs. baseline; Quetiapine median dose 138 mg/day
Tariot PN, Salzman C, Yeung PP, et al. Clin Ther. 2000(Sep);22(9):1068-1084
Open-Label Trial of Quetiapine in the Elderly: Dosing

Results of the 52-Week, Open-Label Quetiapine Trial

- Patients who completed trial
- Patients who withdrew

Study Day

Quetiapine Adverse Effects in Elderly Patients

- Somnolence 31%
  - Occurred early (day 7) and at low doses (50 mg)
- Accidental injury 24%
- Agitation 16%
- Dizziness 17%
- Postural hypotension 15%
- EPS 13%
  - Tremor 3%
  - Dyskinesia 3%
  - Abnormal gait 2%
  - Akathisia 3%
  - Other 2%
- Weight gain (>7%) occurred in 23%

Tariot PN, Salzman C, Young PP, Pultz J, Rak I. Clin Ther. 2000(Sept);22(8):1068-1084
Antipsychotic Use in Older Adults

Safety considerations

- Lower doses compared to schizophrenia
- Increased risk for adverse effects:
  - EPS/tardive dyskinesia (TD)
  - Orthostatic hypotension
  - Sedation
  - Anticholinergic effects
  - Diabetes
  - Falls

Managing Risk of Diabetes in Patients Taking an Atypical Antipsychotic

- Identify patient risk factors (FHx; gestational diabetes; obesity; sedentary lifestyle; diet)
- Consider baseline and follow-up plasma glucose screening in patients with known risk factors
- Patients who do gain weight will need to have triglycerides checked
- Consider starting with an atypical with lower incidence of hyperglycemia
FDA Alert

• Patients with dementia-related psychosis who are treated with atypical antipsychotics are at increased mortality risk (April 2005)

• Conventional antipsychotics are also associated with this elevated risk (June 2008)
DART-AD

- 165 patients with Alzheimer dementia who had taken antipsychotics for at least 3 months were randomized: 83 continuation; 82 placebo
- 24 month follow up

## DART-AD: Survival Probability

<table>
<thead>
<tr>
<th></th>
<th>Antipsychotics</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>70% N=45 (13)</td>
<td>77% N=49 (3)</td>
</tr>
<tr>
<td>24 months</td>
<td>46% N=20 (6)</td>
<td>71% N=29 (6)</td>
</tr>
<tr>
<td>36 months</td>
<td>30% N=9 (1)</td>
<td>59% N=19 (2)</td>
</tr>
</tbody>
</table>

CATIE-AD

• 36 week
• Atypical antipsychotics compared with placebo for behavioral disturbances in Alzheimer’s dementia
• Conclusion: The modest benefits of antipsychotics are insufficient to justify treatment with these agents due to the adverse risks

Summary

- Behavioral disturbances are quite prevalent among patients with various types of dementia.
- Behavioral Interventions are effective in managing many of these behavioral disturbances.
- Atypicals are modestly effective in the management of psychosis and agitation in the elderly.
- Benefits v. risks/adverse events must be weighed in decision to treat with medications as well as in selection of agent.