Pharmacologic and Non-pharmacologic Management of Dementia

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Objectives

• Participants will identify and utilize appropriate non-pharmacologic strategies for managing impaired cognition and other symptoms in demented patients
• Participants will implement select pharmacologic strategies for managing impaired cognition and other symptoms in demented patients
• Participants will address common palliative issues in patients with advance dementia
Dementia

• Definition: acquired, progressive syndrome affecting cognition
  – Memory
  – Language
  – Attention
  – Behavior

Dementia

• Disease course
  – Early, middle and late stages
  – Terminal illness
  – Average life expectancy of 4.5 years from diagnosis
    • Gender
    • Age
    • Behavior

Disease Trajectory

- Lung Cancer
- Organ Failure
- Dementia/Frailty

**Functional Disability or Severity of Illness**

**Time**

**1 in 8 older Americans has Alzheimer’s disease**
Dementia in Primary Care

- Multicenter RCT of dementia care in primary care vs in specialty setting
  - NO improvement in patient QOL
  - NO improvement in carer perception of burden

doi:10.1136/bmj.e3086

Jim

67 yo very active – a runner.
Expressed concerns re memory changes during annual review - ST memory concerns.
- nl exam
- nl neuro exam
- no evidence of depression
- nl lab evaluation (CBC, CMP, thyroid, B12, folate, ESR)
- nl MMSE
Jim

Follow-up 1 year later – MMSE abnormal (23/30), no change in symptoms per pt, taking supplements and thought they were working
- nl MRI
- patient refused additional w/u

Follow up months later – normal MMSE

One year later – symptoms clearly progressed, MMSE 23/30, now with some executive dysfunction as well.

Alzheimers Disease

• Impacts 5.4 million Americans
  – Most common reason for dementia
  – Woman more commonly effected than men

• Severity
  – Mild – some functional dependence
  – Moderate – dependent on others for some functions (unable to drive or bathe, or dress)
  – Severe – total dependence on caregivers
• Distinguish from other forms of dementia:
  – Vascular
  – Dementia with Lewy-Bodies
  – Fronto-temporal dementia
  – Mixed
  – Other reversible causes of dementia

• Jim may have had **Mild Cognitive Impairment** at first visit

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**Table 1 - Classification of the categories evaluated by the Clinical Dementia Rating.**

<table>
<thead>
<tr>
<th>Impairment level</th>
<th>None (0)</th>
<th>Questionable (0.5)</th>
<th>Mild (1)</th>
<th>Moderate (2)</th>
<th>Severe (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>No memory loss or slight inconsistent forgetfulness</td>
<td>Consistent forgetfulness, partial re-collection of events</td>
<td>Moderate memory loss; more marked for recent events; deficit interferes with daily activities</td>
<td>Severe memory loss; only highly learned material retained</td>
<td>Severe memory loss; only fragments remain</td>
</tr>
<tr>
<td>Orientation</td>
<td>Fully oriented</td>
<td>Fully oriented except with slight difficulties with time relationships</td>
<td>Moderate difficulty with time relationships, oriented in familiar areas</td>
<td>Severe difficulty with time relationships, almost always disoriented to place</td>
<td>Oriented to person only</td>
</tr>
<tr>
<td>Judgement &amp; Problem Solving</td>
<td>Solves everyday problems, such as financial affairs, judgement preserved</td>
<td>Slight difficulty in solving problems, similarities and differences</td>
<td>Moderate difficulty on handling problems, similarities and differences, social judgement maintained</td>
<td>Severely impaired in handling problems, similarities and differences; social judgement impaired</td>
<td>Unable to make judgements or solve problems</td>
</tr>
<tr>
<td>Community Affairs</td>
<td>Independent function in jobs, shopping, social groups</td>
<td>Slight impairment in these activities</td>
<td>Is not independent in these activities, appears normal to casual inspection</td>
<td>Is not independent outside home, appears well enough to be taken to events outside the home</td>
<td>Is not independent outside the home, appears to be too ill to be taken to events outside the home</td>
</tr>
<tr>
<td>Home and Hobbies</td>
<td>Daily life at home, hobbies and intellectual interests well maintained</td>
<td>Daily life at home, hobbies and intellectual interests slightly impaired</td>
<td>Slight impairment of tasks at home, more difficult choices, hobbies and interests are abandoned</td>
<td>Only simple choices are maintained, restricted interests, poorly maintained</td>
<td>No significant function at home</td>
</tr>
<tr>
<td>Personal Care</td>
<td>Fully capable of self-care</td>
<td>Fully capable of self-care</td>
<td>Needs assistance</td>
<td>Requires assistance in dressing and hygiene</td>
<td>Requires much help with personal care: frequent incontinence</td>
</tr>
</tbody>
</table>

*Source: Berglind et al.*
Cognitive Symptoms: non-pharmacologic

Cognitive Stimulation
Trained staff work with small group engaged in enjoyable conversations/interactions. Focus on active engagement, optimal learning environment, social stimulation.

- Improves
  - cognition
  - QOL
  - mood
  - social interactions


Alzheimers Potential Pharmacologic Treatment Mechanisms

- Cholinergic
  - Degeneration of cholinergic projections
  - Loss of cholinergic cell bodies

- Inflammatory
  - Antioxidants have shown no benefit

- Glutamate excitotoxicity
Cognitive Symptoms: pharmacologic

- Mild to moderate – acetylcholinesterase inhibitors may slow symptom progression
  - donepezil, galantamine, rivastigmine
  - Slightly improve cognitive function over 6-12 months
  - Clinical significance uncertain
  - Stop if no improvement 6-8 weeks
  - Side effects vary and are dose dependent


1) Acetyl CoA and Choline join
2) Acetylcholine is formed
3) Acetylcholine is packaged up to leave the axon
4) Acetylcholine leaves the neuron and heads to cross the synapse
5) Acetylcholine reaches the other side of the synapse and binds to the receptor causing the message to be sent
6) After the message is sent, Acetylcholinesterase is released into the synapse
7) Acetylcholinesterase breaks down Acetylcholine, inactivating it
Acetylcholinesterase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Donepezil (aricept)</th>
<th>Galantamine (razadyne)</th>
<th>Rivastigmine (exlon)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Side effects</strong></td>
<td>GI 5-24% HA 2-14% Insomnia 0-14% Agitation 3-13% Dizziness 10%</td>
<td>GI 24% HA 8-11% Dizziness 1-10% Arrhythmia 4-12.5% Confusion 11%</td>
<td>GI - 6-39% Dizziness 2-21% Arrhythmia 0-19% Wt loss 3-26% Anorexia 3-17%</td>
</tr>
<tr>
<td><strong>Common dose</strong></td>
<td>10 mg/d po</td>
<td>8 mg bid po; 16 mg LA/d po</td>
<td>6 mg bid po 9.5 mg/d transdermal</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cognitive Symptoms: pharmacologic

- **Moderate to severe – memantine**
  - 20 mg/d over 6 months slightly improves cognition and ability to do adl’s
  - Statistical difference in mild to moderate disease but not likely clinical significance
  - Small reduction in agitation (NNT 17)
  - Studies adding memantine to acetylcholinesterase inhibitors are mixed. Any improvement is very small.
  - Well tolerated
Glutamate Excitotoxicity

JIM

• Had mild disease
  – Anxious re starting treatment, using many supplements
  – Began 5 mg donepezil - with mild “side effects” reduced to 2.5 mg for a week then 5 again.
  – Spouse and pt felt sxs improved at 5 mg
  – Increased to 10 mg with stable symptoms
  – Family encouraged him to go to specialist
    • Eventually went and begun on memantine
At Diagnosis

- Offer to discuss dx with pt and caregiver
- Evaluate for depression
- Offer written information
  - Signs, sx
  - Course, prognosis
  - Treatment
  - Support services
  - Sources of financial and legal advice/advocacy
  - Medico-legal issues – AD’s (MDPOA), driving

Dementia and Behavioral Disturbances
Dementia and Pain

- Pain in patients with dementia is:
  - Common
  - Under-recognized
  - Under-treated


Evidence of Under-treatment of Pain in Dementia

- Hip Fracture - inpatient
  - Demented patients 1/3rd amount of morphine equivalents
  - Not dosed around the clock
- Nursing Home Residents
  - Documentation of pain and analgesic use decreased as cognitive impairment increased
- Community
  - 20% decreased chance of analgesics for daily pain.
Assessment for Pain

• Pain expression may differ with dementia
• Combine
  – patient report
  – caregiver report
  – direct observation

Self-Report / Caregiver Assessment

• “how much pain do you have now?”
• Pain scales
  – Verbal Rating Scale
  – Faces Pain Scale
  – Horizontal Visual Analog Scale (difficult to comprehend in AD)*
• The same scale should be used on repeat assessments

Observational assessment

- Especially monitor facial grimacing
- Other pain-related behaviors
  - guarding
  - rubbing

Pain Assessment in Advanced Dementia (PAINAD) Scale

<table>
<thead>
<tr>
<th>Items*</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathing independent of vocalization</td>
<td>Normal</td>
<td>Occasional labored breathing.</td>
<td>Noisy labored breathing.</td>
<td>Long period of hyperventilation. Cheyne-Stokes respirations</td>
</tr>
<tr>
<td>Negative vocalization</td>
<td>None</td>
<td>Occasional moan or groan. Low-level speech with a negative or disapproving quality.</td>
<td>Repeated troubled calling out. Loud moaning or groaning. Crying.</td>
<td></td>
</tr>
<tr>
<td>Consolability</td>
<td>No need to console</td>
<td>Distracted or reassured by voice or touch.</td>
<td>Unable to console, distract or reassure.</td>
<td></td>
</tr>
</tbody>
</table>

Total score range from 0 to 10 (based on a scale of 0 to 2 for five items), with a higher score indicating more severe pain (0="no pain" to 10="severe pain").
Behavioral Symptom Prevalence in Dementia

• Apathy (41-91%)
• Agitation (10-60%)
• Anxiety (15-66%)
• Irritability (20-42%)
• Depression (25-90%)
• Restlessness (6-65%)
• Disinhibition (36-61%)
• Delusions (0-22%)
• Hallucinations (0-10%)

Agitation, dysphoria, and apathy are more common as the cognitive impairment worsens

Lloyd et al. J. Geriatric Psychiatry Neuro 8:4:213-216, 1995

Lets see

• http://www.youtube.com/watch?v=76jW-xBIJI0
The Origin of Symptoms

Environment

Neurobiology

Neuropsychiatric Symptoms

Process

Comfort

Initial Approach: History

• Behavior Related
  – What is the behavior?
  – When did it begin?
  – How often does it occur?
  – Are there any triggers or patterns?
  – Is there an agenda to the behavior?

• Does the patient have any symptoms?
  – Constipation or impaction
  – Infection
  – Dehydration
  – Pain
  – Discomfort
  – Delirium
  – Injury

• Any recent medication changes? adverse drug reactions
• What comfort measures have been tried?

AGS and AAGP Consensus Statement on Improving the Quality of Mental Health Care in US Nursing Homes. JAGS 2003; 51:1287-1298
Understanding the Origin of Symptoms

<table>
<thead>
<tr>
<th>Environment</th>
<th>Process</th>
<th>Comfort</th>
<th>Neurobiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>unfamiliar</td>
<td>no dignity</td>
<td>pain</td>
<td>over-reactive</td>
</tr>
<tr>
<td>complex</td>
<td>no choices</td>
<td>wet</td>
<td>under-reactive</td>
</tr>
<tr>
<td>frustrating</td>
<td>no role</td>
<td>cold</td>
<td>misperception</td>
</tr>
<tr>
<td>disorienting</td>
<td>no intimacy</td>
<td>warm</td>
<td>misinterpret</td>
</tr>
<tr>
<td>noisy</td>
<td>hurried</td>
<td>hungry</td>
<td>affectively-dysregulated</td>
</tr>
<tr>
<td>busy</td>
<td>harried</td>
<td>impacted</td>
<td>amnestic</td>
</tr>
<tr>
<td>boring</td>
<td>can’t hear</td>
<td>reflux</td>
<td></td>
</tr>
<tr>
<td>intrusive</td>
<td>can’t see</td>
<td>tired</td>
<td></td>
</tr>
<tr>
<td>strangers</td>
<td>can’t understand</td>
<td>anxious</td>
<td></td>
</tr>
</tbody>
</table>


Comfort:
The Geriatric Psychiatry Systems Review “MOMS AND DADS”

<table>
<thead>
<tr>
<th>MOMS</th>
<th>AND</th>
<th>DADS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility</td>
<td>Aches</td>
<td>Depression</td>
</tr>
<tr>
<td>Output</td>
<td>Neuro</td>
<td>Appetite</td>
</tr>
<tr>
<td>Memory</td>
<td>Delirium/Delusions</td>
<td>Dermis</td>
</tr>
<tr>
<td>Senses</td>
<td></td>
<td>Sleep</td>
</tr>
</tbody>
</table>
Non-Pharmacologic Behavior Management

• Controlling stimulus
  – Identify and remove potential triggers
  – Positively reinforce protective behaviors
  – Redirect/reorient

• Managing environment
  – Keep routines and minimize change

• Caregiver interaction
  – Model appropriate responses and affect

• Other measures
  • Music, Light exercise (eg. Walking), Massage, Pet therapy

Potential Pharmacologic Strategies

• Formulate diagnostic hypotheses
• Target appropriate symptoms
• Determine outcome goals
• Prescribe for target symptoms
• Review outcomes
• Consider augmentation
• Consider taper and discontinuation
Strategic Prescribing For Symptoms

Mood Stabilizer
- Irritability
- Impulsivity
- Hyperactivity
- Physical aggression

Antidepressant
- Anxiety
- Dysphoria
- Agitation or verbal aggression

Antipsychotic
- Delusions
- Hallucinations

Analgesic
- Restless
- Calling out
- Grimacing
- Combative w care

AChl/ memantine:
- Apathy
- Hallucinations
- Misperceptions
- Confusion
- Inattention

Agitation & Aggressiveness

• r/o pain and physical discomfort
• r/o modifiable environmental factor
• r/o delirium
• Consider co-morbid depression, mania or psychotic syndrome

Modified from Dr. Singer, Luxenberg and Eckstrom
Efficacy of treating pain to reduce behavioral disturbances

- Design: cluster randomized controlled trial
- Setting: 18 nursing homes in Norway
- Participants: 352 residents with moderate to severe dementia and clinically significant behavioral disturbances
- Outcomes: agitation, aggression, pain, ADLs, cognition

BMJ. 2011 Jul 15;343

Cohen-Mansfield agitation inventory scores
Were they just sedated?

- Most received only acetaminophen (69%)
- Unchanged:
  - Activities of daily living
  - Cognition based on MMSE scores

Antipsychotics and Dementia

What is known:
- No medication class is FDA approved for dementia-related psychosis or agitation
- Drug response rates in clinical trials for these symptoms are modest
- More clinical trial data for antipsychotics exist than for any other class of psychotropic
- Antipsychotics increase risk of mortality by 1-2% over placebo in clinical trials over 8-12 weeks, in addition to side effects
- Mortality risk for typicals and atypicals is similar
- Placebo response rates in these trials are high (30-40%) indicating spontaneous symptom resolution or non-pharmacologic factors may give impression of drug response

What is unknown:
- Co-morbid factors that affect risk for AP mortality
- Comparative safety and efficacy of alternate treatments

American College of Neuropsychopharmacology White Paper on Use of Antipsychotic Drugs in Dementia Jeste D et al. Neuropsychopharmacology 2007
Examples of Prescribing for Agitation or Aggression

- risperidone 0.25-0.5 mg bid
- olanzapine 2.5-10 mg qhs
- quetiapine 12.5-150 mg in divided doses
- aripiprazole 5-10 mg qd
- ziprasidone 20-80 mg bid
- Augmentation
  - SSRI
  - + sodium valproate 125 mg-500 mg bid
  - + trazodone 25-150 mg or Ambien 5 mg qhs?
  - + trazodone or lorazepam prn?
  - + AChEI or memantine

Advanced Dementia

- Acute illness in dementia is a poor prognostic sign:
  - > 50% six month mortality for pneumonia or hip fx
  - 25% six month mortality for unplanned admission

- Symptoms are common in advanced dementia: pain, eating problems, dyspnea, agitation, pressure ulcers
Specific Palliative Issues in Advanced Dementia

• Feeding
  – No evidence that enteral feeding improves survival, morbidity, nutrition, pressure ulcers

• Treating infection
  – Mixed evidence for improved survival
  – Uncertain impact on discomfort

• Caregiver needs

CONCLUSIONS

• Alzheimers dementia is a significant health problem that is growing in importance
• Acetylcholinesterase inhibitors may slow the rate of cognitive impairment for patients with mild to moderate Alzheimers dementia
• Memantine may improve global functioning for patients with moderate to severe Alzheimers dementia
• Cognitive Stimulation may improve cognitive and other symptoms for patients with dementia

Sampson E. British Medical Bulletin
2010; 1–16. DOI:10.1093/bmb/ldq024
CONCLUSIONS

• A careful history and consideration of likely triggers may help direct treatment for problematic behaviors associated with dementia
• Pain evaluation and management is usually the first choice for agitated behaviors in demented patients
• Palliative issues should be addressed in all patients with dementia and readdressed as illness severity progresses

Self-Help and Practical Guides

• “How to” nursing care
• Long-term legal planning guides
• Advice on how to structure basic daily care: activities of daily living
• Laws and structures for protection from harm and abuse