Managing Noncognitive Behavioral Symptoms in Patients With Major Neurocognitive Disorders

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Disclosures:

- Dr. Ellison reports no relevant conflicts of interest.
- Dr. Ellison will discuss unapproved or investigational uses of products during this presentation.
Agenda:

- Definitions
  - What are *Major Neurocognitive Disorders*?
  - What are *Noncognitive Behavioral Symptoms*?
- Nonpharmacologic Management
- Medications:
  - How are they used?
  - How helpful are they?
  - What harm can they do?
Major Neurocognitive Disorder (MND): The New Name for Dementias

Acquired loss of one or more cognitive abilities sufficient to interfere with independence.
DSM 5 “Major Neurocognitive Disorder”

A. Evidence of significant cognitive decline in 1 or more cognitive domains based on
   1. Expressed concern, AND
   2. Substantial cognitive impairment (assessed quantitatively)

B. Cognitive deficits interfere with independence in everyday activities

C. Not Delirium

D. Not another mental disorder

*Specify: AD, FTLD, LBD, VD, TBI, SUD, HIV, prion, PD, HD, other, multiple, unspecified

Alzheimer’s Disease: The Most Prevalent MND

Other Major ND’s include: PD, NPH, Alcohol dementia, TBI, Undetermined

Some Other, Potentially Modifiable Medical Causes of Cognitive Impairment

- Substances
  - Recreational drugs
  - Toxins
  - Medications: Prescribed/Abused
- Depression
- Sleep Disorders
- Post-surgical (post-anesthesia) impairment

- Infectious Diseases
- Cardiopulmonary Disorders
- Nutritional/Metabolic Disorders
- Endocrine Disorders
- Autoimmune Disorders
- Neoplasms
The Physician’s Map of Dementia

- Memory
- Attention
- Visuospacial
- Executive function
- Social cognition
- Language

Behaviors
## Medications: Cognitive Enhancers
**Better for Cognitive Symptoms Than for NCBS**

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cholinesterase Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donepezil</td>
<td>Modest benefits in cognition, ADLs, Caregiver Burden, but questionable benefit for NCBS</td>
<td>Begin with 5 mg/d Increase to 10 mg/d (23 mg/d?)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td></td>
<td>Begin with 1.5 mg bid po Increase up to 6 mg bid po Or begin 4.6 mg patch and increase up to one 9.5 or 13.3 mg/patch per day</td>
</tr>
<tr>
<td>Galantamine ER</td>
<td></td>
<td>Begin with 8 mg ER q d Increase up to 24 ER q d</td>
</tr>
<tr>
<td><strong>NMDA Receptor Antagonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Namenda (memantine) or Namenda XR</td>
<td>Modest benefits in cognition, ADLs, Caregiver Burden, but questionable benefit for NCBS</td>
<td>Begin with 5 mg IR bid and increase to 10 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Begin with 7 mg q d and Increase to 28 mg q d</td>
</tr>
</tbody>
</table>
The Cholinesterase Inhibitors: Differentiating Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Donepezil (Aricept)</th>
<th>Rivastigmine (Exelon, Exelon Transdermal)</th>
<th>Galantamine and “ER” (Razadyne)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage strengths (mg)</td>
<td>5, 10, 23 mg +ODT*</td>
<td>1.5, 3, 4.5, 6 mg 4, 8, 12 mg ER: 8, 16, 24 mg</td>
<td></td>
</tr>
<tr>
<td>Oral solution</td>
<td>1 mg/mL</td>
<td>2 mg/mL</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>Transdermal</td>
<td>NA</td>
<td>4.6 mg/24 hr, 9.5 mg/24 hr 13.3 mg/24 hr</td>
<td>NA</td>
</tr>
<tr>
<td>T1/2 (hours)</td>
<td>73</td>
<td>5</td>
<td>6-8</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>96%</td>
<td>40%</td>
<td>18%</td>
</tr>
<tr>
<td>CYP450 substrate of</td>
<td>2D6/3A4</td>
<td>NA</td>
<td>2D6/3A4</td>
</tr>
<tr>
<td>Monthly cost – Brand/Generic</td>
<td>Can be high!</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ODT=orally disintegrating tablet.
### Memantine: Characteristics

<table>
<thead>
<tr>
<th>Available in oral tablets, oral solution, immediate and extended release</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting dose</strong></td>
</tr>
<tr>
<td><strong>Maximum recommended dose</strong></td>
</tr>
<tr>
<td><strong>T$_{1/2}$ (hours)</strong></td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
</tr>
<tr>
<td><strong>CYP450 substrate of</strong></td>
</tr>
<tr>
<td><strong>CYP450 inhibitor of</strong></td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
</tr>
</tbody>
</table>
How Helpful? / How Harmful?

- Both med classes: Modest benefits in multiple domains
- Cholinesterase inhibitors:
  - Common: GI symptoms, insomnia, vivid dreams, fatigue, increased urination, cramps
  - Uncommon: syncope, bradycardia, confusion, depression, agitation
  - Caution with liver/gastric disease, COPD, bradycardia, sick sinus, inadequate supervision
- Memantine
  - More common: headache, constipation
  - Uncommon: confusion
  - Agitation can occur early, but is infrequent
And Yet Other Aspects of MNDs Are As Important As Cognition

Cognition

Activities of Daily Living

Noncognitive Behaviors*

Caregiver Burden

*behaviors in demented individuals not attributable to other medical or psychiatric cause
The Caregiver’s Map of Dementia

BEHAVIORS

Memory
Importance of NCBS

- More than 90% of people with MND will experience NCBS
- NCBS are associated with significant morbidity, more rapid functional decline\(^1\),\(^2\)
- **No medication is FDA approved for NCBS**
- **There is no established standard for the management of NCBS**

Even Alzheimer’s Index Patient Showed Severe Behavioral Symptoms

The NCBS of Alzheimer’s index patient, Auguste D:

- Pathological jealousy
- Paranoid delusions
- Auditory hallucinations
- Screams for many hours in a horrible voice
- Agitated, noncooperative
# Common Noncognitive Behavioral Symptoms

<table>
<thead>
<tr>
<th>Changes in:</th>
<th>Timing</th>
<th>Frequency</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>Early</td>
<td>Frequent</td>
<td>Anxiety, Depression, Mania</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thinking</td>
<td>Early</td>
<td>Frequent</td>
<td>Suicidal ideation, Delusions, Hallucinations</td>
</tr>
<tr>
<td></td>
<td>Later</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>Early</td>
<td>Frequent</td>
<td>Apathy, Agitation/Aggression, Wandering</td>
</tr>
<tr>
<td></td>
<td>and Late</td>
<td></td>
<td>Disordered eating behavior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sexual inappropriate behavior, Sleep/activity cycle disruption</td>
</tr>
</tbody>
</table>
NCBS: Range and Peak Prevalence During AD Progression

Describe

- Caregiver *describes problematic behavior*
- Context (who, what, when and where)
- Social and physical environment
- Patient perspective
- Degree of distress to patient and caregiver

Investigate

- 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

Create

- 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

Behavioral Intervention Examples

- Caregiver education
- Prosthetic (habititative) environment
- Distraction and redirection
- Activity/exercise
- Simulated presence/Reminiscence
- Individualized music therapy
- Aromatherapy / massage

*Treatment must not exceed patient’s capacity to learn/remember*
Evaluate

- Has the intervention(s) been effective for the problem behavior?
- Have there been any unintended consequences or “side effects” from the intervention(s)?
- Which interventions did the caregiver implement?
- If the caregiver did not implement the interventions, why?
- What changes in the environment have been made?

Clinical Vignettes

- Psychosis
- Agitation/Aggression
- Apathy
- Depression
- Sexualized Inappropriate Behavior
- Sleep Disturbance

All vignettes are composite descriptions in order to protect individual identities.
Vignette 1: Psychosis

- Mr. A, 78 years old with Lewy Body Dementia, has appeared intermittently psychotic and at times his delusions precipitate agitated, aggressive, or wandering behavior. Symptoms threaten his continued residence at home, where his frail wife cares for him.

- In addition to behavioral interventions, what medication might be helpful?
## Medications: Atypical Antipsychotics

Modest Effects, Significant Drawbacks

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Usual Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychosis</strong></td>
<td><strong>Risperidone</strong></td>
<td>Modest benefit</td>
<td>Begin with 0.25 mg/d Increase up to 2 mg/d</td>
</tr>
<tr>
<td><strong>Agitation</strong></td>
<td><strong>Olanzapine</strong></td>
<td>Modest benefit</td>
<td>Begin with 2.5 mg/d Increase up to 15 mg/d</td>
</tr>
<tr>
<td><strong>Aggression</strong></td>
<td><strong>Quetiapine</strong></td>
<td>Questionable</td>
<td>Begin with 12.5 mg/d Increase up to 200 mg/d</td>
</tr>
<tr>
<td></td>
<td><strong>Aripiprazole</strong></td>
<td>Questionable</td>
<td>Begin with 2 mg/d Increase up to 10 mg/d</td>
</tr>
<tr>
<td></td>
<td><strong>Clozapine</strong></td>
<td>Questionable</td>
<td>Begin with 6.25 mg/d Increase up to 300 mg/d</td>
</tr>
</tbody>
</table>
CATIE-AD Results

- Multi-center, double-blind, randomized, placebo-controlled 36 week flexible dosing study in 421 AD outpatients with agitation and/or psychosis.
- Assessed effectiveness and safety of:
  - Olanzapine (5.5 mg/d)
  - Risperidone (1 mg/d)
  - Quetiapine (~50 mg/d)
  - Placebo

- Primary outcomes:
  - All-cause treatment discontinuation
  - CGIC responder rates

Schneider LS et al. NEJM 2006;355:1525-38.
Figure 2. Discontinuation of Treatment in Phase 1 According to Study Group.

Schneider LS et al. NEJM 2006;355:1525-38.
CATIE-AD: CONCLUSIONS

- All cause discontinuation: drugs = placebo
- EPS a common reason for drug discontinuation
- Olanzapine & risperidone equally effective in treating behavioral problems and superior to quetiapine and placebo, but only in patients who did not develop EPS
- “No large clinical benefit of treatment with atypical antipsychotic medications as compared with placebo”

Schneider LS et al. NEJM 2006;355:1525-38.
What Harm Can It Do?

- Somnolence, orthostatic hypotension, gait disturbance\(^1\)
- Extrapyramidal symptoms including tardive dyskinesia\(^1\)
- ADA warning for risk of diabetes with all atypical antipsychotics\(^2\)
- FDA warning of increased CVAEs and increased mortality in elderly patients with dementia\(^3,4\)

Class-Associated Severe AE And Mortality Concerns

- FDA Boxed Warning (April 11, 2005) notes “increased risk of death compared with placebo”

  In 17 PCTs, Deaths among 3611 drug treated patients were 4.5%, Deaths among 1766 placebo treated patients were 2.6% (OR = 1.6)

  Causes of death - Most were heart related (heart failure, sudden death) or infections (pneumonia)

  Studies included: aripiprazole (3), olanzapine (5), risperidone (7), quetiapine (2), ziprasidone (1), haloperidol (2); and warning was extended to clozapine and Symbyax (olanzapine/fluoxetine) and later to typical antipsychotics as well (based on additional case-controlled studies)

Antipsychotics: Clinical Recommendations

- Document use of behavioral and environmental interventions
- Document antipsychotic’s target symptoms
- Educate health care representative about benefits, risks
- Coordinate care with that of other involved clinicians
- Establish time frame for assessment of results
- Frequently assess (and document) benefits and AEs
- Use lowest doses necessary for the shortest time period
- **Evidence suggests typicals are as dangerous as the atypicals**

## Suggested Screening/Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>Quarterly</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/Family History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
AND...Discontinuation May Be An Option

Table 2. Differences in Change in Behavioral Symptoms Between Placebo (N = 36) and Neuroleptic (N = 46) Groups of Patients With Dementia Enrolled in a 3-Month Discontinuation Trial: Statistical Evaluation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD Change</th>
<th>z Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Neuroleptic</td>
<td></td>
</tr>
<tr>
<td>Behavioral factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI total score</td>
<td>−1.3 ± 9.4</td>
<td>0.2 ± 12.0</td>
<td>0.73</td>
</tr>
<tr>
<td>Agitation</td>
<td>−1.0 ± 5.1</td>
<td>−1.0 ± 5.3</td>
<td>0.14</td>
</tr>
<tr>
<td>Mood</td>
<td>−1.1 ± 7.7</td>
<td>−0.62 ± 8.1</td>
<td>0.19</td>
</tr>
<tr>
<td>Psychosis</td>
<td>−0.5 ± 3.2</td>
<td>−0.9 ± 3.5</td>
<td>0.83</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well-being</td>
<td>−0.18 ± 1.72</td>
<td>0.35 ± 2.41</td>
<td>0.77</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mann-Whitney U test.
Abbreviation: NPI = Neuropsychiatric Inventory.
# Medications: Typical Antipsychotics

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Usual Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>Haloperidol (PO or IM)</td>
<td>No better than atypicals –EPS including TD, sedation, weight, anticholinergic, hypotension; Less metabolic syndrome; no less mortality</td>
<td>0.5 to 2 mg/d can be used for acute sedation</td>
</tr>
<tr>
<td>Agitation</td>
<td>Perphenazine</td>
<td></td>
<td>Not recommended</td>
</tr>
<tr>
<td>Aggression</td>
<td>Trifluoperazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medicolegal Considerations

- A patient with decisional capacity can consent to antipsychotic treatment.
- With GUARDIANSHIP:
  - Patient or guardian cannot give consent
  - Court order (Rogers Guardianship) is required
- With an ACTIVATED HEALTH CARE PROXY:
  - Patient can assent if HCP agrees
  - Patient’s refusal may imply valid wish to revoke HCP, requiring Rogers Guardianship.
- Massachusetts State Budget amendment, 2014, increases restriction of antipsychotics in LTCFs:
...(b) The department shall establish a schedule of psychotropic medications that shall not be administered to a resident by a facility without informed written consent. (c) Prior to administering psychotropic medication listed on the schedule created under subsection (b), a facility shall obtain the informed written consent of the resident, the resident's health care proxy or the resident's guardian. Informed written consent shall be obtained on a form approved by the department, which shall include, at a minimum, the following information: (i) the purpose for administering the listed psychotropic drug; (ii) the prescribed dosage; and (iii) any known effect or side effect of the psychotropic medication. The written consent form shall be kept in the resident's medical record.
Vignette 2: Agitation/Aggression

- The children of a 90 year old woman with moderate to severe AD ask for help. Mother’s nursing home says behavior is intolerable. She aggressively resists personal care – including changing of her Depends. She injured herself during a fall when she tried to bite her caregiver. She wanders anxiously day and night, seeking an exit. She is intrusive and frightening to other residents.

- Besides behavioral interventions, what medications might be of help?
Agitation

“Inappropriate verbal, vocal or motor activity that is not judged by an outside observer to be an obvious outcome of the needs or confusion of the individual.”

–Jiska Cohen-Mansfield, Ph.D.

- Aggression and psychosis are often comorbid
- Aggression is a safety issue in Long Term Care Facilities
  - 5% of nursing home residents are physically aggressive each year
  - 60-94% of these are cognitively impaired
  - More than 1000 of MA’s 110,000 nursing home residents are attacked by other residents each year

---

Memantine for Agitation

- Pooled analysis, three 6-month RCTs in moderately severe to severe AD subjects with agitation/aggression or psychosis showed:
  - 60% with NPI agitation/aggression, delusions, or hallucinations at baseline
  - More Memantine NPI responders at 12 and 24 weeks
  - More Memantine agitation/aggression responders
  - NNT for NPI at 24 weeks = 7, few adv. Event failures

- Possible synergistic benefit in combination with donepezil (cognition, ADLs, agitation, lability, eating behavior)

## Medications: Antidepressants
### A Safer Alternative for Agitation?

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Usual Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Citalopram</td>
<td>As good as antipsychotics – modestly beneficial¹-³</td>
<td>5 mg/d up to 20 mg/d, but higher doses are discouraged by FDA in elderly</td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosis</td>
<td>Escitalopram</td>
<td>Not tested in treatment of agitation, aggression, psychosis in dementia but</td>
<td>5 mg/d up to 20 mg/d</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Sertraline</td>
<td>may have value as alternatives</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Fluoxetine</td>
<td></td>
<td>25 mg/d up to 200 mg/d</td>
</tr>
<tr>
<td>Apathy</td>
<td>Paroxetine</td>
<td></td>
<td>Not well defined</td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- SRIs
  - QTc prolongation (citalopram)
  - Agitation, Insomnia
  - Hyponatremia
  - Loss of appetite
  - Sedation
  - EPS
  - Bruising/bleeding
  - Syncope
# Medications: Anticonvulsants

Supported by Only Limited Evidence

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Specific Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Carbamazepine</td>
<td>Modest benefit&lt;sup&gt;1,2&lt;/sup&gt;, limited data base</td>
<td>Start 100 mg/d, increase up to 300 mg/d</td>
</tr>
<tr>
<td>Aggression</td>
<td>Divalproex</td>
<td>Poor evidential support for use except possibly in secondary mania</td>
<td>Typical range used is 500 to 1250 mg/d (blood level 50 to 100 mcg/ml)</td>
</tr>
<tr>
<td>Mania</td>
<td>Lamotrigine</td>
<td>Lacking evidence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topiramate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- Carbamazepine: SJS, arrhythmia, syncope, hepatotoxicity, agranulocytosis, thrombocytopenia, drug interactions, hyponatremia, nausea, constipation
- Divalproex: somnolence, thrombocytopenia, weight gain, tremor, hepatotoxicity, pancreatitis (rare), drug interactions
- Gabapentin: dizziness, sedation, ataxia, nausea, agitation, diarrhea, constipation, weight gain, SJS, renal failure, depression
## Medications: Others

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Use</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prazosin</strong>¹</td>
<td>Agitation</td>
<td>Small positive evidence base</td>
<td>1 mg/d, can increase up to 6 mg/d</td>
</tr>
<tr>
<td><strong>Dronabinol</strong>²</td>
<td></td>
<td>Small positive evidence base</td>
<td>2.5 mg/d Can increase to 10 mg/d</td>
</tr>
<tr>
<td><strong>Paracetamol</strong>³</td>
<td></td>
<td>One positive RTC</td>
<td></td>
</tr>
<tr>
<td><strong>Opioids</strong>⁴</td>
<td>Support for use based on hypothesized presence of pain (comfort care level)</td>
<td></td>
<td>Long-acting oxycodone 10 mg q 12 h or long-acting morphine 20 mg q d</td>
</tr>
<tr>
<td><strong>Cyproterone</strong>⁵</td>
<td>Sexualized behavior, aggression</td>
<td>Small supportive evidence base (not first line)</td>
<td>50 mg bid</td>
</tr>
<tr>
<td><strong>ECT</strong>⁶</td>
<td></td>
<td>Small positive evidence base</td>
<td></td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- Prazosin: Headache, drowsiness, tiredness, weakness, blurred vision, nausea, vomiting, diarrhea, constipation
- Dronabinol: drowsiness, dizziness, hypotension, hallucinations, dysphoria, headaches, palpitations
- Cyproterone: fatigue, dizziness, headache, nausea, flushing, leg pain, palpitations, chest pain, and others
- ECT: risk of anesthesia, temporary increase in confusion and memory difficulty
## Medications: Anxiolytics
Rarely Helpful / Significant Risks

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Specific Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Lorazepam</td>
<td>Sometimes useful for acute agitation¹</td>
<td>0.5 to 1 mg po or IM</td>
</tr>
<tr>
<td>Aggression</td>
<td>Clonazepam</td>
<td>Possible modest benefit for some patients with significant potential adverse effects²</td>
<td>0.5 mg hs to 0.5 mg bid, but generally not recommended</td>
</tr>
<tr>
<td></td>
<td>Alprazolam</td>
<td>Some support but problematic in practice³</td>
<td>0.25 to 0.5 mg qd to bid, but generally not recommended</td>
</tr>
<tr>
<td></td>
<td>Buspirone</td>
<td>Inconsistent support for use, but adverse effects are minimal⁴,⁵</td>
<td>15 to 90 mg/d in divided doses</td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- Benzodiazepines are controversial because of:
  - Sedation
  - Falls/fractures
  - Disinhibition/worse agitation
  - Impaired cognition
  - Dependance/tolerance/withdrawal
  - Minimal efficacy data

- Buspirone: mild side effects
  - Headache, nausea, rarely may increase agitation
Vignette 3: Apathy

- The husband of an 84 year old woman with moderate AD complains that his wife must be depressed. She no longer manages household chores or seems interested in doing anything. She was formerly an enthusiastic companion, but now seems content to watch TV and neglect other activities.

- What might help?
Definition of Apathy

- Loss of initiative and motivation
- Decreased social engagement
- Emotional indifference
- Often associated with:
  - Limited insight
  - Low interest
  - Blunted emotional response
  - Poor persistence
  - Impaired ADLs
- In AD: up to 92% of severely impaired

Distinguishing Apathy from Depression

- Diminished interest
- Psychomotor retardation
- Fatigue/hypersomnia
- Lack of insight

OVERLAP
- Diminished interest
- Psychomotor retardation
- Fatigue/hypersomnia
- Lack of insight

DEPRESSION
- Dysphoria
- Suicidal ideation
- Self-criticism
- Guilt feelings
- Pessimism
- Hopelessness

- APATHY
- Poor persistence
- Low social engagement
- Diminished initiation
- Blunted emotional response

Treatment of Apathy in Dementia

- Behavioral treatments
  - Maintain meaningful activities
  - Encourage preexisting interests
  - Structured music and art therapy program better than “free activities”
  - Schedule pleasant activities at energy nadirs

Treatment of Apathy in Dementia

- Potential pharmacologic treatments
  - Consider
    - Cholinesterase inhibitors +
    - Memantine +/−
    - **Methylphenidate** ++
    - **Antidepressants: Bupropion +, SSRIs +/−**
    - Antipsychotics -, Anticonvulsants -
- Avoid overmedication
- Take drug interactions into account

### Medications: Stimulants
Can Increase Agitation / Can Help Apathy

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Specific Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>Methylphenidate</td>
<td>Modest benefit in apathy</td>
<td>5 mg/d up to 10 mg bid with monitoring</td>
</tr>
<tr>
<td>Depression</td>
<td>Amphetamine</td>
<td>Evidence is lacking</td>
<td>Not recommended</td>
</tr>
<tr>
<td></td>
<td>Modafinil</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Medications: Antidepressants

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Usual Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>Bupropion</td>
<td>May benefit apathy</td>
<td>Start at 75 mg/d Increase in usual adult dose range with caution</td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- **Stimulants**
  - Agitation
  - Insomnia
  - Psychosis
  - Anxiety
  - Elevated BP

- **Bupropion**
  - Seizure, agitation, anxiety, insomnia, loss of appetite,
  - Elevated HR, BP
A woman expresses alarm at her 87 year old husband’s suicidal comments: “I’m a husk. I shouldn’t be alive”. Her husband has probable Vascular Dementia. She wants to know how to help him feel better and optimize enjoyment of his life despite his cognitive impairment.

What might help?
Depression in Alzheimer’s Disease

- Prevalence of clinically significant depression in AD: 30-50% (half or more is minor)
- Rate in Vascular Dementia may be higher
- Not solely determined by
  - awareness of dementia
  - severity of cognitive impairment
- Proposed mechanisms
  - Noradrenergic cell loss in locus ceruleus
  - Serotonergic cell loss in dorsal raphe nuclei

Provisional Criteria: Depression in AD

3 or more of following in 2 week period
- Depressed mood
- Decreased positive affect/pleasure in usual activities/contacts
- Social isolation or withdrawal
- Disruption in appetite
- Disruption in sleep
- Psychomotor changes
- Irritability
- Fatigue/loss of energy
- Worthlessness, hopelessness, guilt
- Thoughts of death, SI or behavior

• Meets criteria for DAT
• Distress or disruption
• Not delirium, drug, medication, or better accounted for by other conditions

Also Note “Masked” Depression in Demented Patients

- Likelihood that depression is present is increased in the presence of:
  - Delusions\(^1\)
  - Verbal/physical aggressive behaviors\(^2\)
  - Suicidal or self-destructive behaviors
  - Disruptive vocalizations\(^3\)
  - Weight loss\(^4\)

Figure 2.
CSDD medians* at each visit by treatment group. Error bars represent the range between the first and third quartiles.

Treatment of Depression in Dementia

- Non-Pharmacologic: Address dependency fears, self-esteem; Avoid frustration; Schedule pleasant events, including Music Therapy and other interventions.
- Antidepressant trials: Inconsistent conclusions
  - Positive: moclobemide, clomipramine, citalopram, sertraline
  - Negative: imipramine, fluoxetine, venlafaxine, sertraline, mirtazapine
  - ECT effective in retrospective study
  - Little support for antidepressant effect of stimulants
  - No evidence supporting the use of cognitive enhancers or antipsychotics in treating depressive symptoms

## Medications: Antidepressants

### Depression in AD Response Less Certain

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Usual Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Citalopram</td>
<td>As good as antipsychotics – modestly beneficial¹⁻³</td>
<td>5 mg/d up to 20 mg/d, but higher doses are discouraged by FDA in elderly</td>
</tr>
<tr>
<td>Agitation</td>
<td>Escitalopram</td>
<td>May be similar to escitalopram</td>
<td>5 mg/d up to 20 mg/d</td>
</tr>
<tr>
<td>Aggression</td>
<td>Sertraline</td>
<td>Not better than placebo for depression</td>
<td>25 mg/d up to 200 mg/d</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Fluoxetine</td>
<td>Evidence lacking</td>
<td>Not well defined</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Paroxetine</td>
<td>Evidence lacking</td>
<td>Not well defined</td>
</tr>
<tr>
<td>Apathy</td>
<td>Bupropion</td>
<td>May benefit apathy</td>
<td>Start at 75 mg/d Increase in usual adult dose range with caution</td>
</tr>
</tbody>
</table>

Antidepressants for Depressed, Demented Patients: What’s A Clinician To Do?

- Differential diagnosis
- Assess severity and “masked” depression
- Consider psychosocial interventions
- Choose a medication and target symptoms
- Monitor improvement and adverse effects
- Modify approach based on outcome
- Consider discontinuation
Vignette 5: Sexual Inappropriate Behavior

- A 78 year old man with moderate FTLD is in danger of being rejected from his Assisted Living Facility. He makes inappropriate sexual comments to staff, touches other residents, and masturbates in public areas.

- What might help?
Inappropriate Sexual Behaviors

- Prevalence: 7 - 25% of demented patients
- More frequent in:
  - Males
  - Long term care settings
  - Greater cognitive impairment severity
- Consequences:
  - Embarrassment
  - Confinement/isolation
  - Disruption of structured living environments
  - Trauma
  - STDs
  - Liability and regulatory issues for care setting
Nonpharmacologic Caregiver Interventions

Psychoeducation for caregivers
- Supportive counseling of spouse
- Reframe sexual expression as drive for closeness/ comfort/ reassurance
- Clarification of misinterpreted social cues

Staff attitudes
- Rigid attitudes may mistake acceptable sexual expression for inappropriate behavior
- Suitable sex education program for staff may improve patient care
Nonpharmacologic Patient Interventions

- Don’t ignore, but avoid confrontation
- Explanation to extent possible
- Distraction and redirection
- Environmental modifications
  - Single rooms for patients
  - Avoid inappropriate external cues like overstimulating television or radio programs.
  - Modified clothing, e.g. trousers that open in the back or lack zippers
  - Provide adequate social activity, keep hands busy
Pharmacologic Treatments

- No double-blind placebo controlled trials.
- Minimal studies of antipsychotics, anticonvulsants
- Use medications only when other methods fail and in combination with non-pharmacologic treatments.
  - Reduce or discontinue medications that can contribute to these behaviors.
  - Avoid potentially disinhibiting bzd’s
  - Start low and go slow with therapeutic medication
<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Dose</th>
<th>N</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>20 mg/d</td>
<td>1</td>
<td>GI sx, asthenia, sweating, tremors, dizziness, anxiety, headache, sedation</td>
</tr>
<tr>
<td>Citalopram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomipramine</td>
<td>150-200 mg/d</td>
<td>2</td>
<td>Sedation, GI sx, weight changes, anxiety, tremors, sweating</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 mg/d</td>
<td>1</td>
<td>Sedation, orthostatic hypotension, headache, dizziness, constipation</td>
</tr>
<tr>
<td>Trazodone</td>
<td>150-500 mg/d</td>
<td>4</td>
<td>Sedation, orthostatic hypotension, dizziness, headache, GI sx, priapism</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg tid</td>
<td>1</td>
<td>Somnolence, fatigue, dizziness, ataxia, peripheral edema, depression, weight gain, tremor</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>600-1600 mg/d</td>
<td>1</td>
<td>GI disturbance, confusion, LFT increases, rash, blood dyscrasias</td>
</tr>
<tr>
<td>Pindolol</td>
<td>40 mg/d</td>
<td>1</td>
<td>Bradycardia, CHF, hypotension, lightheadedness, depression, nausea, vomiting</td>
</tr>
</tbody>
</table>

# Medications for Treatment of Inappropriate Sexual Behavior in Dementia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Typical Dose</th>
<th>N</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics Cholinesterase inhibitors or memantine</td>
<td></td>
<td></td>
<td>Not shown efficacious for this symptom</td>
</tr>
<tr>
<td>MPA</td>
<td>100-300 mg/d IM q 2 wk</td>
<td>6</td>
<td>Weight changes, abdominal pain, dizziness, nausea, depression, insomnia, pelvic/breast pain, edema</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>1 mg/d</td>
<td>1</td>
<td>As above</td>
</tr>
<tr>
<td>Estrogen</td>
<td>0.625 mg/d</td>
<td>39</td>
<td>As above</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>7.5 mg/month IM</td>
<td>1</td>
<td>As above</td>
</tr>
</tbody>
</table>

Vignette 6: Sleep Disturbance

- An 86 year old man has been caring for his 84 year old wife with moderate to severe AD. Her insomnia is increasing, and she wanders around the house at night. He fears she’ll fall or wander out of the house.

- What might help?
Sleep Disturbances In AD

- Sleep disturbances affect majority of Alzheimer’s disease patients
  - Half of outpatients, more with severe dementia
  - Sleep disorder can worsen cognitive and behavioral functioning

- Typical sleep disturbances:
  - Awakenings – increased and extended
  - Decreased SWS and REM
  - Up to 40% of time in bed can be awake
  - Sleepiness and napping is common in day
  - Day-night disturbances, sun-downing
  - RLS and nightmares in FTD, LBD, PDD
  - RBD in FTD, AD, VaD

Multifactorial Etiology Of Sleep Disturbances

- Neurodegenerative disorder effects on circadian rhythm
- Medication effects
- Environmental conditions including boredom with daytime napping
- Comorbid disorder
  - Medical illness including pain
  - Sleep disorder
  - Mood or anxiety disorder

Behavioral Treatment Of Sleep Disturbances

- Differential diagnosis required
- Caregiver education re hygiene
- Attention to sleeping environment
- Therapeutic use of activity schedule:
  - Target activities during nap time
  - Schedule pleasant, engaging events
- Efficacy of bright light therapy not clear

Pharmacotherapy of Sleep Disturbances

- Lack of long-term trials
- Cholinesterase inhibitors can affect sleep adversely.
- Antipsychotics may worsen circadian rest-activity disturbances.
- Antidepressants: Consider trazodone, avoid anticholinergic drugs
- Anticonvulsants: further study needed
- Benzodiazepines’ side effects create potential hazard; avoid short-term agents especially
- Zolpidem 10 mg hs improved duration of sleep\(^1\) and decreased nighttime wandering\(^2\) but can be hazardous.

2. Shelton and Hocking Ann Pharmacother. 1997;31:319-227
<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Specific Agents</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>Trazodone</td>
<td>Mixed, but not consistent support for insomnia/agitation¹,²</td>
<td>25 to 250 mg/d, use divided doses in higher range</td>
</tr>
<tr>
<td></td>
<td>Zolpidem</td>
<td>Possible benefit claimed in elderly psychiatric inpatients³, limited case reports in demented patients⁴</td>
<td>5 to 10 mg at hs (lower doses now recommended)</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>Anecdotal support in AD with depression+insomnia⁵</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not recommended: Diphenhydramine and other antihistamines, melatonin, ramelteon</td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- Trazodone: sedation, hypotension, priapism
- Zolpidem:
  - Sedation
  - Falls/fractures
  - Disinhibition/worse agitation
  - Impaired cognition
  - Dependence/tolerance/withdrawal
  - “sleep driving”
Complying With Institutional Psychotropic Monitoring Guidelines
CMS’ State Operations Manual Guides Nursing Home Surveys

- Citation for use of “Unnecessary Drugs” (F-329), includes:
  - Excessive dose, includes duplicate therapy
  - For excessive duration
  - Without adequate monitoring
  - Without adequate indications for use
  - In presence of adverse consequences—dose should be decreased or discontinued
  - Any combination of the reasons above
F329 - Unnecessary Meds

- Antipsychotics
  - ...not indicated for wandering, poor self care, restlessness, impaired memory, fidgeting, nervousness, uncooperativeness, verbal expressions, insomnia, mild anxiety, inattention or indifference to surroundings, behaviors that do not represent a danger to others
  - [only for] Danger to self or others, symptoms due to mania or psychosis, acute emergencies of 7 days or less.
Residents who use antipsychotic drugs receive gradual dose reductions (GDR), and behavioral interventions, unless clinically contraindicated, in an effort to discontinue these drugs:

- Within 1st year after admission on antipsychotic or after initiation
- GDR in 2 separate quarters, with at least one month between attempts
- After 1st year, GDR annually
- GDR is clinically contraindicated if:
  MD documents clinical rationale for use and worsening after GDR attempts (2 in last year or 1 within facility) – or specific approved diagnosis.
Summary: What Is “Best Practice” for Treatment of NCBS in AD?

- Behavioral analysis and nonpharmacologic treatment when possible
- Consider full range of medications
- Choose medication based on symptoms, side effects, drug interactions, patient factors.
- Monitor response and adverse effects, aiming for lowest effective dose and shortest duration needed.
- Comply with regulatory guidelines for use.
Useful References


