Managing Noncognitive Behavioral Symptoms in Patients With Major Neurocognitive Disorders or Delirium

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Disclosures:

• Dr. Ellison reports no relevant conflicts of interest.

• Dr. Ellison will discuss and identify unapproved or investigational uses of products during this presentation.

• **Because no treatment is approved for NCBS and no approach works for everyone!**
Typical Current NCBS Problems

Mr. S is restrained in the ICU after assaulting a nurse.

Ms. J calls 911 from her bedroom: “Help me! This man here says he’s my husband”.

Mr. B hallucinates friendly children standing next to his bed.
Typical Current NCBS Problems

Mr. N fondles another ALF resident after entering her room at night, uninvited.

Ms. R bursts into tears frequently for no apparent reason.

Ms. D sits inactively before her TV. Is she depressed?
Typical Current NCBS Problems

Mr. M looks so depressed his family fears he’s a suicide risk.

Ms. K wanders around the house all night wishing she could sleep and worrying everyone else.
Agenda:

- Definitions
  - What are **Major Neurocognitive Disorders**?
  - What are **Noncognitive Behavioral Symptoms**?
- The case of Auguste D
- Assessment tips
- Nonpharmacologic management
- Somatic approaches:
  - What medications are used?
  - Evidence? Dangers? New trends?
- Applying these principles to **Delirium**
DSM 5 “Major Neurocognitive Disorder”

A. Evidence of significant cognitive decline in 1 or more cognitive domains based on
   1. Report ed symptoms
   2. Objective evidence

B. Cognitive deficits interfere with independence

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, HIV, Undetermined

The Importance of Behaviors Was Apparent Even in Alzheimer’s Index Patient

- Pathological jealousy
- Paranoid delusions
- Auditory hallucinations
- Screams for many hours in a horrible voice
- Agitated, non-cooperative
- Plaques and tangles on autopsy
Imporatnce of NCBS

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

\begin{itemize}
\end{itemize}
## 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><strong>Mood</strong></td>
<td>Especially Early</td>
<td>Frequent</td>
<td>Anxiety, Depression, Mania</td>
</tr>
<tr>
<td><strong>Thinking</strong></td>
<td>Early and Late</td>
<td>Frequent</td>
<td>Suicidal ideation, Delusions, Hallucinations</td>
</tr>
<tr>
<td><strong>Activity</strong></td>
<td>Early and Late</td>
<td>Frequent</td>
<td>Apathy, Agitation/Aggression, Wandering, Disordered eating behavior, Sexual inappropriate behavior, Sleep/activity cycle disruption</td>
</tr>
</tbody>
</table>
How Important Are Behaviors to Clinicians?

- Memory
- Attention
- Visuospatial
- Executive function
- Social cognition
- Language
- Behaviors
How Important Are Behaviors To Patients and Caregivers?
What Tools Do We Have Today For Treating Auguste D’s NCBS?

1) Methodical and adequate assessment and formulation
2) Nonpharmacologic approaches
3) Somatic approaches
   A) Cognitive enhancers
   B) Antipsychotics
   C) Antidepressants
   D) Anticonvulsants
   E) Additional AIDS (Applied In Desperate Situations)
Assessment Tips

Data Gathering:
- Course
- Onset
- Precipitants
- Context,
- Pre-existing conditions
- Prior interventions

Essential Rule-outs:
- Delirium
- Pain
- Constipation
- Sleep-disturbance
- Infection
- Metabolic (oxygen, glucose, lytes)
- Recreational drug intoxication/withdrawal
- TIA/CVA
- Communication barriers/Sensory deficits

Capacity to consent:
- Who is LAR if capacity is deficient?

Unmet psychosocial needs

Medications (adverse effects, DDI, anticholinergic burden)
Nonpharmacologic Interventions
DICE: A Systematic Nonpharmacologic Approach to NCBS

Describe → Investigate

Describe ← Evaluate

Evaluate → Create

Create ← Investigate

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, itching
  - 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

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?

Person-Centered Communication

- An alternative to fibbing, reminding, distracting, reorienting, arguing, or convincing
- Adopt the patient's perspective
  - What are they experiencing?
  - How does it look for their perspective?
- Embrace the patient's reality
  - Remember their experience is real to them
  - You can “join them” without accepting their point of view, yet still not contradict/argue
  - Acceptance communicates helpfulness

Feil N, de Klerk-Rubin V. The Validation Breakthrough: Simple Techniques for Communicating with People with Alzheimer's and Other Dementias / Edition 3
A More Overt Case of Autoprosopagnosia

Photo courtesy of David Olson MD PhD, McLean Hospital
Other Nonpharmacologic Aids

- Caregiver training – emphasizing use of routine preventively, acceptance of agitation, address underlying causes, distraction, not arguing, assuring safety then walking away, “me time”, use of family/services
- Environmental adaptation
- Tailored activity program
- Music – e.g. exposure to favorite music during personal care
- Aromatherapy – Melissa officinalis oil (lemon balm) massage or extract, Lavandula officinalis (lavender)
- Robot – improved communication, trend to help agitation
- Animal – shown to improve QoL
- Simulated presence – more research needed

Paro – Therapeutic Seal
Somatic Interventions
First, Evaluate Current Regimen

- Is treatment evidence-supported?
- Is medication matched with target symptom?
- Is dose appropriate? Has trial been adequate?
- Are there drug/drug interactions or adverse effects?
- Are there multiple drugs from same class?
- If there are multiple providers, are they communicating/coordinated?
- Is there excessive anticholinergic burden?

*Removing medication is sometimes more effective than adding medication*
### 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, questionable benefits for NCBS</td>
<td>Begin with 5 mg/d Increase to 10 mg/d (23 mg/d?)</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>ADLs, Caregiver Burden, questionable benefits for NCBS</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, possible mild benefit for NCBS</td>
<td>Begin with 5 mg IR bid and increase to 10 mg bid Begin with 7 mg q d and increase to 28 mg q d</td>
</tr>
</tbody>
</table>

Combination of cholinesterase inhibitor with memantine may be more beneficial for NCBS
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><strong>Dosage strengths (mg)</strong></td>
<td>5, 10, 23 mg +ODT*</td>
<td>1.5, 3, 4.5, 6 mg</td>
<td>4, 8, 12 mg ER: 8, 16, 24 mg</td>
</tr>
<tr>
<td><strong>Oral solution</strong></td>
<td>1 mg/mL</td>
<td>2 mg/mL</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td><strong>Transdermal</strong></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><strong>T&lt;sub&gt;1/2&lt;/sub&gt; (hours)</strong></td>
<td>73</td>
<td>5</td>
<td>6-8</td>
</tr>
<tr>
<td><strong>Plasma protein binding</strong></td>
<td>96%</td>
<td>40%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>CYP450 substrate of</strong></td>
<td>2D6/3A4</td>
<td>NA</td>
<td>2D6/3A4</td>
</tr>
<tr>
<td><strong>Monthly cost – Brand/Generic</strong></td>
<td>Can be high!</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ODT=orally disintegrating tablet.
# Memantine: Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Available in oral tablets, oral solution, immediate and extended release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>5 mg/d IR, 7 mg/d XR</td>
</tr>
<tr>
<td>Max recommended dose</td>
<td>10 mg bid IR, 28 mg/d XR</td>
</tr>
<tr>
<td>( T_{1/2} ) (hours)</td>
<td>60-80</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>45%</td>
</tr>
<tr>
<td>CYP450 substrate of</td>
<td>NA</td>
</tr>
<tr>
<td>CYP450 inhibitor of</td>
<td>NA</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal</td>
</tr>
<tr>
<td>Cost</td>
<td>Can be high, esp XR</td>
</tr>
</tbody>
</table>
What Harm Can It Do?

- Both med classes: Modest benefits in multiple domains
- Cholinesterase inhibitors can delay onset of NCBS, but:
  - Common: GI symptoms, insomnia, vivid dreams, fatigue, increased urination, cramps
  - Uncommon: syncope, bradycardia, confusion, depression, agitation, GI bleed
  - Caution with liver/gastric disease, COPD, bradycardia, sick sinus, inadequate supervision
- Memantine can mildly reduce agitation for some, but:
  - More common: headache, constipation
  - Uncommon: confusion
  - Agitation can occur early, but is infrequent
### 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>Psychosis</td>
<td>Aripiprazole</td>
<td>May have modest benefit for agitation/psychosis</td>
<td>Begin with 2 mg/d</td>
</tr>
<tr>
<td>Agitation</td>
<td>Risperidone (approved in Europe, not US)</td>
<td></td>
<td>Increase as high as 10 mg/d</td>
</tr>
<tr>
<td>Aggression</td>
<td>Quetiapine Questionable</td>
<td></td>
<td>Begin with 0.25 mg/d</td>
</tr>
<tr>
<td></td>
<td>Olanzapine Questionable</td>
<td></td>
<td>Increase as high as 2 mg/d</td>
</tr>
<tr>
<td></td>
<td>Brexpiprazole Investigational</td>
<td></td>
<td>0.5-2 mg/d in testing</td>
</tr>
<tr>
<td></td>
<td>Clozapine Inadequate data</td>
<td></td>
<td>Begin with 6.25 mg/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>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.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>SMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>0.30 (0.05, 0.55)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.19 (0.00, 0.38)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.19 (0.07, 0.31)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.19 (0.07, 0.31)</td>
</tr>
</tbody>
</table>

Aripiprazole effect size 0.30 for 2.5-10 mg/d
Olanzapine effect size 0.19 for 1-15 mg dose range
Quetiapine effect size 0.05 for 25-600 mg dose range
Risperidone effect size 0.22 for 0.5-2.5 mg dose range

What Additional Harm Can It Do?

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

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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)

APA New Guideline on Antipsychotics in Dementia - 2016

- Try nonpharmacologic interventions, use resources such as Alzheimer’s Association website (www.alz.org)
- Antipsychotics when agitation and/or psychosis “is severe, dangerous, and/or causing significant distress to the patient”
- Haloperidol is not a first line choice.
- Best evidence: modest support - risperidone for psychosis/agitation, olanzapine/aripiprazole for agitation.
- Monitor treatment response with an assessment tool - NPI (Neuropsychiatric inventory) is one option.
- Try a taper after 4 months, except with comorbid psychotic disorder or past failed attempts.
- Note: other pharmacologic options not reviewed in this guideline

Antipsychotics: Clinical Recommendations

- **Documentation:**
  - Behavioral and environmental interventions
  - Antipsychotic’s target symptoms
  - Education/Consent process

- Coordinate care with that of other involved clinicians
- Establish time frame for assessment of results
- Re-assess (and document) benefits and AEs
- Lowest doses necessary, shortest appropriate time
- **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></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></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

ADA, APA, AACE, NAASO Diabetes Care 2004;27:596-601
## 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><strong>Psychosis</strong></td>
<td>Haloperidol (PO or IM)</td>
<td>Not safer or 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><strong>Agitation</strong></td>
<td>Perphenazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aggression</strong></td>
<td>Trifluoperazine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AND…Discontinuation May Be Safe

- In a 3 month trial, discontinuation of antipsychotics in a stabilized group of patients with dementia and NCBS was not associated with significant behavioral changes.\(^1\)
- If tapering after adequate response, check monthly for 4 months.\(^2\)
- However, recurrence of symptoms may be increased after discontinuation.
  - In Antipsychotic Discontinuation in AD Trial, risperidone responders showed 2-4 fold risk of symptom reemergence at 16-32 weeks after discontinuation.\(^3\)
  - Auditory hallucinations or severe baseline irritability/lability were at high risk for recurrence after discontinuation.\(^4\)
- Without providing nonpharmacologic interventions, discontinuation of antipsychotics in care homes was associated with detrimental outcomes.\(^5\)

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## 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>Not worse than antipsychotics – modestly beneficial¹-⁴</td>
<td>5 mg/d up to 20 mg/d. FDA recommends max dose of 20 mg/d due to QTc prolongation risk</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 may have value as alternatives</td>
<td>5 mg/d up to 20 mg/d (may share QTc risk)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Sertraline</td>
<td></td>
<td>25 mg/d up to 200 mg/d</td>
</tr>
<tr>
<td>Depression</td>
<td>Fluoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apathy</td>
<td>Paroxetine</td>
<td></td>
<td>Not well defined</td>
</tr>
<tr>
<td>Maybe less useful</td>
<td>Vortioxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>for nighttime/sleep</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>behavior issues</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What Harm Can They Do?

- SRIs
  - QTc prolongation (citalopram, escitalopram)
  - Agitation, Insomnia, nightmares, sedation
  - Hyponatremia
  - Loss of appetite, increased appetite
  - Bruising/bleeding
  - EPS, apathy
  - Syncope
## Medications: Anticonvulsants

Support is limited and inconsistent

<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(^1,2), 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 It 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
Additional “AIDS”

(Applied In Desperate Situations)
## Medications:
**Quinidine/Dextromethorphan (Nuedexta)**

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Specific Agent</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
</table>
| Pseudobulbar Affect     | Dextromethorphan 10 mg \((\text{NMDA receptor antagonist and sigma-1 agonist})\), Quinidine 20 mg \((\text{for 2D6 inhibition})\) | FDA indication: PBA Tested in :ALS, MS  
In Alzheimer’s, one RCT \((n=220)\) showed reduced NPI agitation/agression but not total NPI improvement, rated by caregiver. Clinician rating showed significant change in agitation though not in quality of life, no sedation or cognitive AE. | 1 cap/d x 7  
Then 1 q 12 h  
Periodically reassess the clinical need |
| Agitation in AD         | Watch for deuterated formulation\(^2\)                                         |                                                                                                                                                                                                              |                                                    |

---

What Harm Can This Do?

- Diarrhea
- Vomiting
- Flatulence
- Dizziness
- Cough
- Weakness
- Edema
- LFT (GGT) elevation
- CYP2D6 inhibitor
- QTC prolongation
# Medications: Cannabinoids

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Use</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dronabinol</strong>¹,²</td>
<td><strong>Agitation, Aggression,</strong></td>
<td>AChE inhibition, reduced amyloid aggregation</td>
<td>2.5 mg/d  Can increase to 10 mg/d</td>
</tr>
<tr>
<td></td>
<td><strong>Resistance to care</strong></td>
<td>Small positive evidence base (several trials)</td>
<td></td>
</tr>
<tr>
<td><strong>Nabilone</strong>²,³</td>
<td><strong>0.5 mg in the evening,</strong></td>
<td>1 case report</td>
<td>0.5 mg in the evening, then increased to 0.5 mg bid</td>
</tr>
<tr>
<td></td>
<td><strong>then increased to 0.5 mg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td><strong>Marijuana</strong></td>
<td>Agitation in AD is a “qualifying condition” (no trials; only anecdotes)²</td>
<td>Unclear – anecdotes describe use of various products including oil extract</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What Harm Can This Do?

- Drowsiness
- Dizziness
- Hypotension
- Hallucinations
- Dysphoria
- Headaches
- Palpitations
# Medications: Stimulants

<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: Stimulating Antidepressant

<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
  - Anorexia
  - Elevated HR, BP

- **Bupropion**
  - Seizure, agitation, anxiety, insomnia, loss of appetite,
  - Elevated HR, BP
## Medications: Miscellaneous

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Use</th>
<th>Evidence Says</th>
<th>Suggested Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin(^1)</td>
<td>Agitation</td>
<td>Small positive evidence base</td>
<td>1 mg/d, can increase up to 6 mg/d; no significant BP AE.</td>
</tr>
<tr>
<td>Paracetamol(^2)</td>
<td></td>
<td>One positive RTC</td>
<td></td>
</tr>
<tr>
<td>Opioids(^3)</td>
<td></td>
<td>Support for use based on hypothesized presence of pain (comfort care level)</td>
<td>Long-acting oxycodone 10 mg q12 h or long-acting morphine 20 mg q d</td>
</tr>
<tr>
<td>Cyproterone(^4)</td>
<td></td>
<td>Small supportive evidence base (not first line)</td>
<td>50 mg bid</td>
</tr>
<tr>
<td>ECT(^5)</td>
<td></td>
<td>Small positive evidence base</td>
<td></td>
</tr>
<tr>
<td>Scyllo-Inositol(^6)</td>
<td></td>
<td>Investigational</td>
<td>100 mg bidx4 wk, then 250 mg/bid</td>
</tr>
</tbody>
</table>

What Harm Can These 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
<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 agitation(^1)</td>
<td>0.5 to 1 mg po or IM</td>
</tr>
<tr>
<td>Aggression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clonazepam</td>
<td>Possible modest benefit for some patients with significant potential adverse effects(^2)</td>
<td>0.5 mg hs to 0.5 mg bid, but generally not recommended</td>
</tr>
<tr>
<td></td>
<td>Alprazolam</td>
<td>Limited support, problematic in practice(^3)</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 minimal(^4,5)</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
- Dependence/tolerance/withdrawal
- Minimal efficacy data

Buspirone: mild side effects

- Headache, nausea, rarely may increase agitation
<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, with some support for insomnia/agitation(^1,2)</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 inpatients(^3), limited case reports in demented patients(^4)</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+insomnia(^5)</td>
<td></td>
</tr>
</tbody>
</table>

Not recommended: Diphenhydramine and other antihistamines, melatonin; ramelteon has been used to prevent/treat delirium.

What Harm Can This Do?

- Trazodone: sedation, hypotension, priapism
- Zolpidem:
  - Sedation
  - Falls/fractures
  - Disinhibition/worse agitation
  - Impaired cognition
  - Dependance/tolerance/withdrawal
  - “Sleep driving”
# Medications: Pimavanserin (Nuplazid)

<table>
<thead>
<tr>
<th>Syndromes</th>
<th>Specific Agent</th>
<th>Evidence Says</th>
<th>Recommended use</th>
</tr>
</thead>
</table>
| Hallucinations and delusions associated with PD Psychosis | **Pimavanserin** | 5HT2A selective inverse agonist  
PDP: 1 RTC showed benefit in treating hallucinations, delusions, and persecutory delusions without impaired motor function, sedation, hypotension. FDA indicated for this use.  
AD: Recent RTC in AD showed acute benefit for treating psychotic symptoms in high-baseline subjects²  
LBD? | 34 mg/d as two 17 mg tablets taken once daily without titration (one 17 mg tablet if taken with strong CYP3A4 inhibitor) |

What Harm Can This Do?

- In 1 published RTC, pimavanserin side effects resembled those of placebo.
- Most common (≥10%): somnolence, edema, increase in BUN vs placebo, subjects: hallucinations, dizziness, fall, headache, confusional state, hypotension.
- QTc prolongation.
- CYP3A4 substrate (reduce dose with CYP3A4 inhibitor).
Therapeutic Humility: Some Symptoms Unlikely to Respond to Medications

- Poor attention
- Rejection of care
- Unfriendliness
- Assaultiveness
- Repetitive questions / statements
- Shadowing
- Wandering

Kales et al 2014
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.
Applying These Principles to Delirium?

- **Definition of Delirium:**
  - A. Disturbance in attention and awareness
  - B. Developed over short period of time, fluctuating severity
  - C. Additional cognitive symptom present (memory, orientation, language, visuospatial, perception)
  - D. Not better explained by another psychiatric condition
  - E. Evidence of physiologic etiology or etiologies

Adapted from DSM 5, APA 2013.
How Important is Delirium?

- 25-60% incidence in acute med/surg settings
- Up to 87% incidence in ICU
- Many cases are missed or misdiagnosed as depression, psychosis, or dementia
- Delirium increases length/cost of hospital stay.

The Confusion Assessment Method (CAM): Standard Screen for Delirium

1) Acute onset and fluctuating course
2) Inattention
3) Disorganized Thinking
4) Altered Level of Consciousness

1 AND 2 necessary; and either 3 OR 4

Causes of Agitation in Delirium

- **Predisposing Factors:**
  - Cognitive impairment
  - Sleep deprivation
  - Immobility
  - Visual/Hearing impairment
  - Dehydration
  - Withdrawal
  - Pain

- **Precipitants**
  - Impaired oxygenation
  - Infection
  - Inflammation
  - Medications
  - Lytes/metabolic disturbances
Goals of Treatment

- Early screening and intervention can prevent some cases, improve treatment of others
- Find reversible factors
- Maintain adequate behavioral control
- Use medications sparingly/judiciously
Nonpharmacologic Interventions

- Frequent reorientation
- Appropriate level of sensory stimulus
- Consistent caregivers/Family available
- Correct sensory impairment (hearing aids, glasses)
- Quiet environment at night
- Avoid Restraints
- *Encourage ambulation/optimal activity*
Approaches to Medication In Agitated/Delirious Patients

- Avoid sedatives (e.g. benzodiazepines\(^1\), trazodone), anticholinergics, antihistamines, excessive pain medications
- Low dose antipsychotic medications
  - Risperidone 0.25-0.5 po bid prn (be aware of potential CVA risk increase)
  - Quetiapine 25 mg po bid prn
  - Haloperidol 0.25-0.5 po bid/IM, or as IV drip < 40 mg/d, when QTc<440, K+ is wnl, (for delirium, not for dementia)
- PRNs have a useful role in treating delirium

---
\(^1\) Pandharipande P et al. Anesthesiology 2006;104:21-6 (re risk of lorazepam in ICU).
Ramelteon for Delirium Prevention

- Ramelteon, an hypnotic with higher M1/M2 affinity than melatonin, has been used for:
  - Prevention of delirium in ICU and medical patients – N=67 prospective study.¹
  - Treatment of delirium in 10 consecutive open-label patients.²
  - Resolution of “sundowning” in an n=1 case report.³

Key Points

- NCBS are debilitating and dangerous – they require assessment/management.
- In assessment, consider context, comorbidity, and evaluate medications!
- Antipsychotic use is phasing out in favor of:
  - Non-pharmacologic interventions
  - SSRI antidepressants
  - Several other medications can be tried prior to antipsychotic use.
- To protect patient’s rights, capacity and informed consent must be considered.
Next Best Steps

- Inquire about NCBS.
- Adopt an organized approach to assessment to rule out treatable conditions.
- Consider use of non-pharmacologic approaches before medications.
- Reserve antipsychotic use until after failure of other approaches.
- Avoid use of non-evidence-based meds (anticonvulsants, benzodiazepines).
- An SSRI trial may make specialist consultation less urgent/necessary.
- Some areas where specialists (geriatric psychiatry, neurology) can help include diagnosis/treatment of rapidly progressive dementia, diagnostic clarification, management of treatment-resistant symptoms.
For Discussion
Mr. S is restrained in the ICU after assaulting a nurse. How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
Mrs. J calls 911 from her bedroom: “Help me escape. This man says he’s my husband. I want to go home!” How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
Mr. B hallucinates a friendly child next to his bed. How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
Mr. N enters another resident’s room at the Assisted Living Memory Unit at night, gets into her bed, and fondles her. How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
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
## Medications for Treatment of Inappropriate Sexual Behavior in Dementia Anecdotally Supported – Use With Caution

<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>Not shown efficacious for this symptom</td>
<td></td>
<td></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>

Mrs. R bursts into tears for no apparent reason. How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
Pseudobulbar Affect

- A neurological disorder secondary to disinhibition of emotional control
- Uncontrollable, unpredictable episodes of laughing or crying unrelated to person’s actual emotions
- Common in MS (10%), ALS, AD; embarrassing, leads to social withdrawal
- NOT depression
- Nonpharmacologic: distraction, breathing/relaxation, open acknowledgment
- Pharmacologic: SSRI, quinidine/dextromethorphan
Ms. D sits inactively before his TV. Is he depressed? How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
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 Depression¹

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

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

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

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

Mr. M looks depressed. His family fears he’s a suicide risk. How can we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
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

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\(^4\)

---

Mrs. K wanders around the house all night wishing she could sleep and worrying everyone else. How do we help?
Discussion points:

- What is the history of this symptom?
- Could it have been foreseen and prevented?
- What’s the differential diagnosis?
- What nonpharmacologic interventions could be used?
- What medications would be appropriate?
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:
  - Day-night disturbances, sun-downing
  - Awakenings – increased and extended. Up to 40% of time in bed can be awake. Insomnia common in AD.
  - Sleepiness and napping are common. EDS in LBD/PDD.
  - 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
Conclusions

- Neurocognitive disorders include symptoms that are:
  - Cognitive
  - Noncognitive
- Nonpharmacologic tools are tried first
- Pharmacologic tools can supplement nonpharmacologic approaches with caution.
QUESTIONS AND DISCUSSION