Treatment Options for Dementia and Related Behaviors

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No industry disclosures

Many of the discussions about medication for behavioral problems in dementia reference off-label use
Objectives

• Cultural influence is critical
• Discuss medications for treatment of dementia
• Discuss treatment for Behavioral and Psychological Symptoms of Dementia (BPSD)
• Consider benefits vs. risks of medications
Goals of Treatment

- Slow the progression of dementia
- Treat mood disturbance and behavior problems
  - Anxiety, agitation, depression
  - Psychosis
  - Disinhibition and aggression
- Decrease caregiver stress
- Delay nursing home placement
- Limit social and financial costs
- Improve quality of life for all who are impacted
- Ongoing research to prevent onset
Native Americans and Dementia

Maintaining an awareness of cultural norms is crucial in treating dementia especially in non-pharmacologic approaches.
Medication Overview

Dementia medications
  • Cholinesterase Inhibitors
  • Memantine (Namenda)

Manage behavioral and psychological symptoms of dementia:
  • Antidepressants—mood, anxiety, sleep
  • Anxiolytics
  • Mood stabilizers
  • Stimulants
  • Antipsychotics—use with caution
Cholinesterase Inhibitors (CEI)

• First-line treatment for mild to severe AD

• Premise since the 80’s:
  • Acetylcholine promotes memory and attention
  • Nerve cells producing acetylcholine are injured due to extracellular amyloid plaques and intracellular tangles.
  • CEI’s inhibit the enzyme cholinesterase from breaking down acetylcholine so it lasts longer
  • In some, it may slow decline or stabilize functioning and behavior for a period
  • Some people may find words more easily, repeat questions less often, become more engaged or manage self-care longer.
Cholinesterase Inhibitors

**Donepezil** *(Aricept)* - pill once daily (5, 10, 23mg)

**Rivastigmine** *(Exelon)* - capsule twice daily (1.5, 3, 4.5, 6 mg) or 24 hr patch (4.6, 9.5, 13.3 mg), liquid 2 mg/ml

**Galantamine** *(Razadyne)* – tablet twice daily (4, 8, 12 mg), Extended Release (ER) once daily (8, 16, 24mg), liquid 4 mg/ml

- Titrate up slowly; I start w/ ½ of a 5 mg Donepezil
- Most common potential side effects
  - GI problems (nausea, diarrhea, **weight loss**).
    - Give with breakfast for fewest GI side effects
  - Vivid dreams, disrupted sleep, **psychotic delusions**
  - Cardiac-bradycardia/syncope
  - Can lower seizure threshold (as can dementia)
  - Skin irritation with patch (rotate site and remove slowly)
  - Depression, irritability w/ prolonged use
- Evaluate for improvement or stabilization after 3-6 months re cognition, ADL fxn, and/or behavior and document well
Cholinesterase Inhibitors
How to choose?

- All are equally effective, how to choose?
  - Donepezil best tolerated of oral agents
  - Exelon patch good option if GI distress w/ orals
  - Mode of delivery and cost (independent phar?)
  - If impaired kidney or liver function, decrease Galantamine dose
  - Rivastigmine-low protein binding, fewer interaxns?
  - Special indications e.g., rivastigmine for Parkinson’s dementia, donepezil has indication for severe dementia, though all likely interchangeable
  - If changing due to side-effects, wait 48 hours

- There are no markers to determine response but higher cog fxn at start and good initial response may predict better long term response.
Summary: Cholinesterase Inhibitors

• Approved for treatment of mild to severe AD
• A trial is worthwhile for most, not for frail old-old
• May be of similar modest benefit in other dementias
  • Parkinson’s and Lewy body dementias involve loss of cholinergic and dopaminergic neurons
  • Vascular disease often mixed with AD (beware irritability)
• Frontotemporal dementias – may help (25% may also have AD pathology) or may increase agitation
• Mild Cognitive Impairment (MCI) no evidence of benefit
• Goal: temporary stabilization (not miracle drugs)
• Delay rate of decline in function for some
• May benefit behavior and reduce demands on caregivers
• Try before stronger meds if behavioral problems emerge
Memantine (Namenda)

- Mechanism of action: works as a surge protector
  - Regulates glutamate, a neurotransmitter involved in learning and the formation of memories
  - Blocks “excitotoxicity” which can cause nerve cell death
- May see improvement in attention, alertness, mood stabilization, and possibly memory, social engagement and functional ability. Esp. helpful with irritability, mood swings
- Approved for treatment of moderate to severe AD, possible benefit in other dementias
- Used in combination with cholinesterase inhibitors
- The dose is gradually increased over 4 week; available in extended release form for once daily dosing
- Most common possible side effects
  - confusion
  - drowsiness
  - headaches
  - dizziness
  - constipation
Memantine/Donepezil combo (Namzaric)

• Once-daily capsule for patients currently taking both Memantine and Donepezil

  10 mg bid + 10 mg
  28 mg XR + 10 mg
  *14 mg XR + 10 mg
  *for renal impairment

• Capsules can be opened and sprinkled on food for swallowing or compliance issues

• HOWEVER, combining the two generics is far less costly
Evaluating Dementia Medications

- Monitor for side effects for several weeks
- Medication trial for 3-6 months
- Evaluate based on patient and caregiver report and cognitive re-testing
- Observe for improvement, slower rate of decline or relative stability (untreated, expect 3 point decline in MMSE/year)
- If stopping, taper off and observe for decline
- Consider resuming.
- Some may benefit even in late stage dementia
THE GREATEST CHALLENGES: MOOD AND BEHAVIORS

It is important to remember that behavior is a form of communication.
Common Behavioral Problems in *Mild to Moderate* Dementia

<table>
<thead>
<tr>
<th>Most frequent</th>
<th>Sometimes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Depression</td>
<td>• Apathy/indifference</td>
</tr>
<tr>
<td>• Irritability</td>
<td>• Mood swings</td>
</tr>
<tr>
<td>• Sleep disturbances</td>
<td>• Restlessness</td>
</tr>
<tr>
<td>• Agitation</td>
<td>• Delusions</td>
</tr>
<tr>
<td>• Anxiety</td>
<td>• Hallucinations</td>
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<tr>
<td></td>
<td>• Aggression</td>
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<td></td>
<td>• Disinhibition</td>
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<tr>
<td></td>
<td>• Catastrophic reactions to minor stresses</td>
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</tbody>
</table>
Common Behavioral Problems in Moderate to Severe Dementia

**Frequently**
- Sundowning
- Irritability
- Restlessness
- Agitation
- Sleep disturbance
- Aggression
- Wandering
- Disinhibition
- Delusions

**Sometimes**
- Mood swings
- Catastrophic reactions
- Hallucinations
- Depression
- Anxiety
Consider Other Causes of Mood and Behavior Disturbance

- Illness (UTI, constipation)
- Pain: consider routine Tylenol
- Medication—benzos and opiates worsen mood and can cause irritability
- Delirium—beware the tipping point
- Environment: altered routine, noisy, too isolated
- Psychosocial issues: depression, bored, or caregiver stress
- Sleep disturbance
Non-pharmalogic Approaches

• Seek triggers, don’t rush them
• Learn communication strategies—connect!
• Distractions-change subject, fold clothes, car ride
• Don’t correct the record—better to be kind than to be right
• Don’t ask them to do what they can’t do
• Learn local customs of Native Americans
• Music—people can sing when they can’t talk; Alive Inside movie will inspire you
Sleep Disturbances

Can worsen cognition and behavior.

- More frequent nightly awakening
- Daytime sleep increases
- Quality of sleep declines
- Circadian Rhythm Disorder
- Restless Leg Syndrome, Periodic Limb Movements of Sleep & REM Behavior Disorder (common in Lewy Body disorders)
- Sleep apnea—common in dementia
Treatment for Sleep Disturbance

• Improve sleep hygiene (limit caffeine, naps, tobacco, alcohol, and late night news)
• Bright light therapy, music, warm milk
• Treat sleep apnea, diabetes, restless legs, pain, mood)
• AVOID Benadryl and “PM” medications that contain diphenhydramine and functionally depletes acetylcholine
• Melatonin with bright light is good,
• Consider routine Tylenol, Trazodone
• Psychostimulants may help daytime sedation
Antidepressants

- Trialed for depressed mood, apathy, psychosis, sleep and appetite disturbance, inappropriate sexual behavior, and agitation in dementia. Well-tolerated.

**FIRST-LINE: SSRI’S:**
- Citalopram (5-10 mg/d, rarely 20-30) or Sertraline (25-100 mg) my 1st choices, Escitalopram okay (more side effects?) (less ideal: paroxetine, fluoxetine)
- May benefit behavior, attention/focus, obsessing
- Side effects of SSRIs: nausea, diarrhea, restlessness, insomnia or somnolence, low sodium, seizures, falls?, serotonin syndrome, apathy with higher doses
Antidepressants

Other potentially useful agents:

- Mirtazapine (Remeron) 7.5-15 mg qhs
- Venlafaxine (Effexor)
- Bupropion (Wellbutrin) may cause anxiety, incr seizure risk
- Methylphenidate (Ritalin) 5-10 mg at 8 am and noon after meals
- Trazodone (Desyrel) mostly used for behavior, anxiety, or agitation up to 300 mg/d

Give adequate time to trial 2-3 mos. then switch or augment
Depression vs Apathy

**APATHY**

- Blunted emotional response
- Socially withdrawn
- Decreased initiative

**OVERLAP**

- Decreased interest
- Psychomotor retardation
- Fatigue/hypersomnia

**DEPRESSION**

- Self-critical
- Hopeless
- Wishes for death
Anxiety

• Most antidepressants treat depression and anxiety
• Try Donepezil/Aricept if not yet trialed
• Trazodone (12.5-50 mg tid prn, up to 100 mg tid); may cause paradoxical agitation at higher doses.
• Buspirone (Buspar) 5-10 mg tid
• Benzodiazepines - avoid if possible due to worse memory, confusion, falls, sleep apnea, disinhibition/paradoxical agitation with regular use, seizures if abruptly stopped. Lorazepam best for limited period.
• Beta blockers may help; beware bradycardia
• Severe anxiety may require mood stabilizers, rarely antipsychotics if crippling
Mood Stabilizers

- Depakote: blood, liver abnormalities, decri hippocampus, gait abnormalities. Dose to benefit, not for therapeutic level though check one. 250-500 mg bid-tid
- Lamotrigine (Lamictal): risk of severe rash
- Gabapentin (Neurontin): sedating
- Carbamazepine (Tegretol): risk of blood abnormalities and may affect other meds
- Overall evidence lacking for efficacy but are effective for irritability or unrelenting mood swings (especially if life-long)
Psychosis and Agitation

Psychosis
- Delusions – Fixed false beliefs, irrational
  - Impostor, paranoia, stealing, infidelity
- Hallucinations: Visual, auditory mostly
  - Friendly or frightening; can change

Agitation: what are they trying to communicate
- Mild: moans, cries, argues, paces, wanders but can be redirected
- Severe: aggressive, endangering or disruptive behavior posing threat to self or others, screams, tries to leave, difficult feeding, throws objects, grabs, striking out

Dementia progression vs. medical, environmental or task-related
Antipsychotics in Dementia

• Use for psychosis if severely distressing or if safety is compromised.
  • **Trial a low dose for 3 months**
  • Best evidence is for Risperidone 0.25-1 mg bid, Olanzapine 2.5-5 mg bid (rarely higher)
  • Monitor for EPS (parkinsonism), increased blood sugar or cholesterol, weight gain, sedation, movement disorders (dyskinesias)

• Symptoms decrease but don’t fully remit

• Can worsen symptoms in Lewy Body Disease; Quetiapine (Seroquel) 25-100 mg bid or more

• Increased risk of infection, stroke, death
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

*In prescribing information for aripiprazole, olanzapine, risperidone, ziprasidone, and quetiapine.
Sexually Inappropriate Behaviors

• May occur in 15-25% of those with dementia.
• Are we interpreting them correctly?
• Re-direction when possible
• No clearly effective pharmacological approach but the following have been tried:
  • Antidepressants (SSRI’s)
  • Anxiolytics
  • Mood stabilizers
  • Antipsychotics
  • Hormonal agents-leuprolide, estrogens
  • Possibly Gabapentin, Pindolol, Cimetidine
Behavior and Medication

• The most successful interventions are directed at the specific symptom
• There is no single treatment that works for all patients or in all situations
• There is very little long term research to support particular medications for behavior problems in dementia
• All behavioral medications have potentially serious side-effects but not treating has risks too
• Starting doses should be low and treatment trials closely monitored with frequent attempts to wean psychotropic medications
• Realistic goal – reduce not eliminate symptoms
Resources

• [www.alzforum.com](http://www.alzforum.com) technical information
• [www.alznews.org](http://www.alznews.org) daily articles; not all science-based
• [www.alz.org](http://www.alz.org) Trial Match
• [www.clinicaltrials.gov](http://www.clinicaltrials.gov) Research trials

• Academic institution websites:
  • [www.adrc.mc.duke.edu](http://www.adrc.mc.duke.edu)
  • [www.alzresearch.org](http://www.alzresearch.org)
  • [www.mayoclinic.com](http://www.mayoclinic.com)

• **For families:** Alzheimer’s Reading Room
Summary

• Dementia meds are worth trying

• Behavioral symptoms are common
  • Rule out correctable causes
  • Use non-pharmacologic interventions first
  • Consider Tylenol first, then go from least to higher risk
  • Antidepressants, Trazodone, Mirtazapine, Buspar, Depakote, Risperidone
  • Use antipsychotics for severe, distressing psychosis; to withhold is cruel
  • Use low dose, short term, but taper slowly
  • Careful use of antipsychotics in Lewy Body Disease

• Exercise, eat well, brain games, social engagement, sleep

• Up-to-date med list is crucial
Ancient Wisdom

Aristotle claimed that the highest level of wisdom requires **phronesis**. Phronesis involves the ability to reflect upon and...discern the correct action when there is insufficient scientific evidence to determine the absolute truth.

*Adapted from John E. Morley, J Am Ger Soc 2011*
At the end of the day, our patients and their families need us to be a source of comfort on this challenging journey, and to offer compassionate care along the way....
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