

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 interactions?
 - 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

Most frequent

- Depression
- Irritability
- Sleep disturbances
- Agitation
- Anxiety

Sometimes

- Apathy/indifference
- Mood swings
- Restlessness
- Delusions
- Hallucinations
- Aggression
- Disinhibition
- Catastrophic reactions to minor stresses

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-pharmacologic 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

- Tried 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, decr 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

Black Box Warning

Black Box Warning*

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 technical information
- www.alznews.org daily articles; not all science- based
- www.alz.org Trial Match
- www.clinicaltrials.gov Research trials
- Academic institution websites:
 - www.adrc.mc.duke.edu
 - www.alzresearch.org
 - 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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