The Confusion of Old Age:
the relationship of dementia, depression, and agitation to executive dysfunction in the elderly

William B. Orr, Ph.D., M.D.
Orr Memory and Geriatric Behavioral Clinic,
Mendota Heights, MN
Med.Dir., Grace Geriatric Behavioral Unit, Regina Med. Ctr., Hastings, MN and Senior Behavioral Unit, Mille Lacs Med. Ctr., Onamia, MN
Assistant Professor of Psychiatry, University of Minnesota School of Medicine

Cognitive Enhancers

<table>
<thead>
<tr>
<th>Drug/Brand</th>
<th>Dosing</th>
<th>Minimum effective dose</th>
<th>Metabolism</th>
<th>Most Common S.E.s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>(5,10,23) pill, ODT</td>
<td>5 mg qd</td>
<td>renal</td>
<td>nausea, diarrhea, vivid dreams</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>(1.5,3,4,5.6) pill, liq, patch</td>
<td>3.0 mg bid</td>
<td>renal</td>
<td>nausea, diarrhea, anorexia</td>
</tr>
<tr>
<td>Galantamine</td>
<td>(8,16,24 SR) pill, non-SR liq</td>
<td>16 mg qd</td>
<td>renal</td>
<td>nausea, diarrhea, anorexia, agitation</td>
</tr>
<tr>
<td>Memantine</td>
<td>(5,10)</td>
<td></td>
<td>renal</td>
<td></td>
</tr>
</tbody>
</table>

Dosing
- 5 mg x 4 wk, then 10 mg x 3 mo, then 23 mg
- 1.5 bid & incr 1.5 bid q 4 wk
- Patch: 4.6 mg sw wk, 9.5 mg
- 8 mg x 4 wk, 16 mg x 4 wk, 24 mg q AM
- (Non-SR bid)*
- 5 mg x 7 da, then 5 mg bid, incr by 5 mg to 10 mg bid

Minimum effective dose
- 5 mg qd
- 3.0 mg bid
- 4.6 mg patch
- 16 mg qd
- ?

Metabolism
- renal
- renal
- renal
- renal

Most Common S.E.s
- nausea, diarrhea, vivid dreams
- nausea, diarrhea, anorexia
- nausea, diarrhea, anorexia
- dizziness, nausea, anorexia, agitation

* Restart at initial dose and re-titrate if patient stops medication

Normal Aging

MCI

Acetylcholine esterase inhibitor (AEI)

“Dementia”

AEI & Mementine Rx

Alzheimer’s w/o Rx
Assessment of Clinical Depression

- What the patient says. What is their “Mood?”
- How the patient appears. What is their “Affect?”
- The forgotten symptoms of clinical depression:
  - Decreased “Self Attitude”
  - Hopelessness, helplessness, guilt, burden to others
  - Suicidal thinking

Epidemiology of Depression in the Elderly

- Major depression less frequent in elderly than in young (prevalence 1%)
- 15-25% of elderly have “minor depressive disorder”
- Research criteria of “minor depression”: fewer symptoms (>2 but <5) and less impairment than MDD
- Minor depression assoc. w/ strokes, cancer, diabetes
- Associated risk factors for depression in elderly: social isolation, loss of spouse, decreased functioning, LTC placement

Differentiating the Symptoms

<table>
<thead>
<tr>
<th>Depression</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor concentration</td>
<td>STM retrieval deficit</td>
</tr>
<tr>
<td>Decreased self-attitude</td>
<td>Intact self-attitude</td>
</tr>
<tr>
<td>Problems coping w/ disability</td>
<td>Able to cope w/ disability</td>
</tr>
<tr>
<td>Irritability/pessimism</td>
<td>Content/apathy</td>
</tr>
<tr>
<td>Episodes of tearfulness</td>
<td>Episodes of confusion</td>
</tr>
<tr>
<td>Ruminations</td>
<td>Perseveration</td>
</tr>
</tbody>
</table>
Antidepressants in the Elderly

- **SSRIs**
  - sertraline, citalopram, escitalopram: least drug-drug interactions, diarrheoa and G.I. side effects
  - paroxetine: anticholinergic, sedating, many drug-drug interactions
  - fluoxetine (Prozac): long half-life, drug-drug interactions
- Often best tolerated in elderly
- All equally effective for depression and anxiety
- Usually begin at bedtime, but may increase dreaming

Potential Hazards of SSRIs in Elderly

- Bradycardia and cardiogenic syncope
  - Movement disorders
    - Loss of appetite
    - Night sweats
    - Apathy

Antidepressants in the Elderly

- **SNRIs**
  - Venlafaxine (Effexor, Pristiq): dizziness, hypertension
  - Duloxetine (Cymbalta): indications for MDD, GAD, diabetic peripheral neuropathy, fibromyalgia, musculoskeletal pain, (in Europe: urinary incontinence), possible liver problems
- Concerns Both SSRIs and SNRIs: Hyponatremia, platelet dysfunction, osteoporosis, serotonergic syndrome
- Bupropion (Wellbutrin): stimulating, might improve Parkinson’s, possible hallucinations, seizures
- Mirtazapine (Remeron): stimulates appetite and promotes sleep in low doses
Useful Non-Antidepressants

- Anti-Anxiety Medications
  - Benzodiazepines (e.g. Valium, Lorazepam, Xanax)
  - Buspar
- Sleep Medications
  - Trazodone, zolpidem, zaleplon, eszopiclone
- "Psychotropics"
  - Quetiapine, olanzapine, risperidone, ziprasidone, aripiprazole
- Mood Stabilizers
  - Valproate (Depakote), lamotrigine, lithium

Other Treatments for Clinical Depression

- Psychotherapy
  - Cognitive-Behavioral (CBT), Supportive, Individual, Insight-oriented
- Hormones
  - Thyroid, Androgens, Estrogen
- Light Therapy
  - "Seasonal Affective Disorder"
- Stimulants
- ECT/rTMS

Consider Risk Factors in the Differential Diagnosis

Alzheimer's Disease
- Age
- Family hx (early onset)
- Apolipoprotein E4
- Diabetes
- Lesser: TBI, depression
  - Protective factors?
  - Higher education
  - Apolipoprotein E2
  - Statins, antioxidants, ginko biloba, estrogen?

Depression in Elderly
- History of depression/anxiety
- Loss of autonomy/mobility
- Loss of spouse/child
- Sensory impairment
- Onset active medical problems:
  - MI, COPD, RA, cancer, hypothyroid, Parkinson's renal impairment, stroke
  - Chronic pain

Protective factors?
- Higher education
- Apolipoprotein E2
- Statins, antioxidants, ginko biloba, estrogen?
“Vascular” Depression

- **Evidence/Risks:**
  - High rate depression in HTN, DM, CAD
  - High rate of post-stroke depression
  - Late-onset depression associated with silent CVA and MRI subcortical white matter hyperintensities

- **Associated Symptoms:**
  - More cognitive impairment and disability
  - Deficits in verbal fluency and naming
  - More retardation, less agitation
  - Less guilt
  - More lack of insight


Loss of Executive Function

- **The most important symptom to caregivers**
- Loss of ability to plan, organize, and initiate
- Loss of decision making
- Personality change
  - Apathy: “bump on a log” syndrome
  - Agitation: keeps trying to make decisions

- Can’t see the big picture any more

Apathy in Dementia

- One of the most common neuropsychiatric sx
  - AD 37% (Starkstein et al., 2001)
  - Vascular and mixed 27% (Lyketsos et al., 2000)
  - Parkinson’s (Starkstein et al., 2003)

- Associated w/ increased disability (Zawacki et al., 2002)
- Increased caregiver burden (Norton et al., 2001)
- Related to Executive Dysfunction
Depression  
Apathy  
Dementia

**Executive Dysfunction associated with depression and dementia:** (i.e., problems with organizing, planning, & initiation)

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### Treatments for Apathy

- **Psychostimulants**
  - Methylphenidate: short-acting, begin 5mg in AM, then add 5 mg at noon, max approx 30-40 mg per 24 hrs
  - Watch for loss of appetite, irritability, hypertension, sleep disturbance
  - Others: modafanil (100-400 mg), pemoline (37.5-75 mg), dextroamphetamine (5-20 mg)
  - If works, but wears off or produces side effects, change to long-acting (e.g. Ritalin SR, Aderall, Concerta)

- **Dopamine Agonists**
  - Amantadine: 100 mg bid to tid
  - Bromocriptine: 2.5-20 mg per day
  - Pergolide: 1-5 mg per day
  - Levodopa/carbidopa: 25/100 tid – 25/250 qid
  - Selegiline: 5-10 mg per day
  - Bupropion: 75 to 450 mg per day
  - Cognitive enhancers
    - Acetylcholine esterase inhibitors: donepezil, rivastigmine, galantamine
    - Memantine (Namenda)
    - Atomoxetine (Strattera)
Assessment of Executive Functioning

- There is no “gold standard” test.
  - e.g. Clock drawing, WCST, Trails B, etc
- Deficits variable across patients
  - Related to pt’s baseline I.Q., intellectual style, and education
- Detection of deficit dependent on situation
  - High complexity tasks more likely to unmask deficits
  - Very difficult to assess in office/bedside
- Must make use of collateral information

Agitation is an interaction of factors:

Patient  Caregiver

Behavior

Environment

Assessment must include evaluation of all each of these factors

Top Questions to ask Caller from Nursing Home

- How well do you know this patient?
- What is the patient doing right now?
- Is the patient on a dementia unit?
- What do you mean by “agitation?”
  - Specific behaviors, how often, what times of day, correlations with environment?
- How many “prns” have they received and what was the response?
Non-Pharmacological Management of Agitation

- Assess the caregiver/caller:
  - How familiar are you with patient?
  - What is the patient doing right now?
  - What are their needs/goals, are they realistic?
- Assess the environment:
  - Home, Senior Care, ALF, NH, Dementia Unit
  - Number of caregivers, different approaches
  - What happens at night
  - Level of chaos, noise, changes
- Educate caregiver
  - What to expect
  - Adapt/change approach to pt
  - Support, rest, respite
  - Contact Alzheimer’s Association
  - Need to take over making decisions
- Modify Environment
  - Avoid changes
  - Day Program
  - Consider placement options
- “Taking care of someone with Alzheimer’s is more than a one person job – period!”

Caregiver’s Mantra

- Patience
- Distraction
- Flexibility
- Creativity
- Humor
- Therapeutic “White Lies”

Pharmacological Management of Agitation in Dementia:

- Cornerstone of Treatment: Atypical Antipsychotics
- Avoid using benzodiazepines
- Start low and go slow – may take weeks to get full effect.
- Learn to use a couple of antipsychotics and how to “niche” them.
- Cannot use for convenience of cares, only when behavior of patient threatens safety or prevents delivery of necessary cares.
- Consider them for short-term use (i.e. reassess)
### CATIE-AD Results

<table>
<thead>
<tr>
<th></th>
<th>Mean dose @ endpoint</th>
<th>Median time to discontin.</th>
<th>Extra pyramid. Sxs</th>
<th>Increased Confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>5.5 mg/d</td>
<td>22.1 wks</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>56.5 mg/d</td>
<td>9.1 wks</td>
<td>2%</td>
<td>No diff</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1 mg/d</td>
<td>26.7 wks</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0 wks</td>
<td>1%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

Schneider et al., NEJM 2006; 355: 1525-38

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### What does the CATIE-AD Trial Tell Us?

- Dr. Schneider: “trial should guide clinical practice, not radically alter it”
- Use only after behavioral/environmental techniques fail
- Re-evaluate often, consider taper 3-8 months
- Atypicals still much lower side effects than the older antipsychotics
- Poor evidence for effectiveness other drug classes and they have side effects as well (e.g. benzos.)

www.lynnwaltz.com/samples/cp_ad.pdf

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### Other Studies: Antipsychotics in dementia

  - Consensus of 50 experts in geriatric care
  - Recommend first line treatment of agitated dementia with delusions is antipsychotics, consider adding a mood stabilizer
- Franco et al., J Am Dir Assoc. 2006 7(3): 201-2.
  - Review of 29 db blind controlled trials
  - Modest benefit of atypicals, minimal side effects at low doses, but increased risk of stroke
  - Results of CATIE-AD may not be generalized to more severe cases in NH
  - Routine evaluations necessary, attempt taper 3-8 months
  - Insufficient evidence any psychotropics other than antipsychotics represent effective or safer choices for agitation in dementia.
Risk vs Benefit of Antipsychotics in Elderly

- 2005 FDA required same black box warning on all antipsychotic medications for off-label use for treatment of dementia related behavioral disorders in elderly:
  - Based on pooled analysis of 17 studies, >5,000 pts.
  - 1.6-1.7 fold increased risk of mortality due to CVA infection or cardiac problems.
- AAGP comment on FDA Advisory:
  - "In the face of even more limited data for alternative pharmacotherapy, AAGP does not believe that the use of atypical antipsychotic medications for treatment of psychiatric symptoms in dementia should be suspended on the basis of the FDA advisory. Clinicians might first consider nonpharmacological methods and should carefully assess and reassess the individual benefit of using any medication to treat non-cognitive behavioral symptoms against the potential risks."
  
  www.aagponline.org/prof/antipsychstat_0705.asp

Atypical Antipsychotic “Niches”

- **Risperidone (Risperidal)**
  - Starting doses 0.5 mg. Max 1.5-2.0 mg per 24 hrs.
  - Very reliable for acute, severe agitation in delirium and prominent delusions or hallucinations
  - Avoid long-term use or use in ambulatory patients because of EPS and TD concerns
  - Available in oral liquid

- **Olanzapine (Zyprexa)**
  - Starting and usual dose range 2.5-10 mg per 24 hrs.
  - Useful for delirium going on for days/weeks and for patients with prominent mood d/o symptoms (e.g. appear "manic").
  - Possibly useful for elderly patients who need to gain weight
  - May have a somewhat higher risk of TyII DM in patients
  - Zydis is oral rapidly dissolving form

Atypical Antipsychotic “Niches”

- **Quetiapine (Seroquel)**
  - Usual dosing 25 mg, bid-tid, 50-75 at bedtime
  - Mildly sedating, but do not use as a “sleeper”
  - Useful for content dementia patients who become agitated during cares (e.g. bathes)
  - Easy to titrate, use instead of benzodiazepines in NH
  - Essentially no EPS or TD
    - Makes it extremely useful in LBD, Parkinson’s, other patients with movement disorders
  - Very little anticholinergic side effects
  - Possible orthostatics, especially if > 200 mg per 24 hr
Atypical Antipsychotic “Niches”

- **Aripiprazole (Abilify)**
  - Starting doses 5-10 mg, usual dose range 10-30 mg (?)
  - Two controlled trials in elderly, though 1-2 weeks to work
  - Generally well-tolerated and “non-sedating”
  - May be useful for chronic stabilization and mood lability

- **Ziprasidone (Geodon)**
  - Target doses 40-60 mg bid, very well tolerated
  - Often takes several days to see effect in dementia
  - 20 mg IM very useful in elderly
  - Monitor Q-T interval changes in those at risk

Atypical Antipsychotics in the Elderly

<table>
<thead>
<tr>
<th></th>
<th>EPS</th>
<th>TD</th>
<th>Anti Ach</th>
<th>Sedation</th>
<th>Orthostasis</th>
<th>QT pro</th>
<th>Rx Mania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>+++</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Mood Stabilizers in Dementia

- **Depakote**
  - Lonergan et al., Cochrane Database Syst Review, 2004; (2): CD 003945
    - Narrowed to only 3 placebo-controlled trials
    - Too little data to do meta-analyses (e.g. Tariot 2001, 54% drop out)
    - Doses 480-2000 mg/d
    - Conclusion: questionable effectiveness vs SSRI
  - Meinhold et al., Drugs Aging 2005; 22(7): 615-26
    - Support use of depakote alone or w/ atypical
  - Forester et al., Am. J. Pharmecoother. 2007; 5(3): 209-17
    - 15 pts, inpt, NH, ALF
    - Especially effective on physical aggression and irritability, less on verbal agitation; side effects: gait instability
    - Mono Rx: 914 mg/d; w/ antipsychotics 656 mg/d
Mood Stabilizers in Dementia cont’d

- **Depakote**
  - Starting dose: 125 bid to tid, gradually titrate to 750 to 1000 mg/d, blood level 35-65
  - Sedation, ataxia, slurred speech, edema, tremor
- **Neurontin**
  - Starting dose: 50-100 tid, gradually titrate to 300 tid; sedation, ataxia, dizziness
  - Useful for agitation with anxiety/restlessness, pain
    - Sommer et al., Expert Opin Durg 2007, 6(2): 133-45
- **Oxcarbazapine, tegretol, lithium**
  - Many side effects, less data except for tegretol

“Accelerators” for DAT

- **Postmenopausal loss of estrogen in women**
  - Mixed results from trials on prevention of DAT. Some evidence might delay onset, but very difficult to test. Estrogen Rx of DAT not recommended.
- **Inflammatory response**
  - Ibuprofen and indomethacin lower risk of developing AD, but too many risks. NSAIDs not recommended for treatment of DAT.
- **Oxidative free radicals**
  - Might be option, but doses above 400 IU should be avoided.
- **Brain vascular disease**
  - May have direct effect on development of AD.
- **High cholesterol**
  - Use of statins may reduce risk of AD, not indicated for AD.
- **Glutamate excitotoxicity**
  - Memantine attenuation of NMDA receptors may be neuroprotective.

Can Alzheimer’s be Prevented?

- **Mental activity**
  - High verbal I.Q., mental exercise
- **Handling of stress**
  - Decrease cortisol, changing hormone balances
  - Loss of neurons in hippocampus
- **Diet**
  - High fiber, low fat
  - APOE 4 and cholesterol, steroid metabolism
- **Healthy Aging (when does it begin?)**
  - Lifestyle, exercise, minimize stress, treat depression/anxiety