

Psychotropics and the Elderly

Caring for the Aging patient (and ourselves)

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Disclosure

- Board certified in Adult and Addiction Psychiatry
- Not Geriatric Psychiatry
- No financial arrangements related to the content of this activity

Objectives

- Weigh the risks of behavioral interventions vs medications in the management of neuropsychiatric symptoms in dementia
- Apply knowledge about different antidepressant classes for the safest treatment of elders
- Understand indications, risks, and benefits for electroconvulsive therapy
- Distinguish between delirium and neurocognitive disorders

Demographics

- Older patients are less likely to perceive a need for mental health care, seek such care, or receive it from mental health providers
- Elders received anti anxiety and antidepressants more than twice as often as 21-64 year olds in 1 large study
- Less likely to see a psychiatrist (6.32 vs 11.82/100 visits)
- Or to receive psychotherapy (4.34 vs 6.78/100 visits)

Reduced Reserve=Increased Side Effect Risk

- Brain mass falls 5% per decade after age 40
- Reduced dopamine, 5HT_{2A}, α and β adrenergic receptors
- Decreased cholinergic innervation:
- Increased sensitivity to RX

Safest Rule with Elders and Psychotropic Prescriptions:

- Start low, and go slow!

Mood Disorders and the Elderly

- Low prevalence in community samples
- HIGH prevalence in hospitals, long term care facilities Better prognosis in depression w females, extroverts, w sobriety, “absence of major life events and serious medical illness,” “self-efficacy,” normal cognition
- “Increased biological vulnerability” vs. resilience of age

Depression Treatment

- Cognitive Behavioral Therapy (CBT): “directive and time limited...effective for depressed elderly”
- Equal efficacy to antidepressants w mild, moderate depression
- “Long term benefit may be greater” than meds
- Elders may be more open to therapy than medications

Question One

- SSRIs are the safest choice of antidepressants for elders
- Drugs with anticholinergic side effects may worsen cognition, risk of vehicle crashes, death in elders
- SNRIs are best used after 1-2 failures of SSRIs due to safety concerns in elders
- ECT is more effective for treatment-resistant depression than antidepressants
- Questions 1-4 are true

Antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs)

- Preferred antidepressant choice for depression, especially w vascular disease
- “Lack of anticholinergic, orthostatic” side effects; “safety in overdose”
- Paroxetine most sedating, likely to cause weight gain, sexual side effects
- Fluoxetine most activating, longest half life
- Both have important potential drug interactions

SSRI Other FDA Indications

- Fluvoxamine: OCD, social anxiety
- Fluoxetine: OCD, bulimia, panic, PMDD; TX resistant depression and bipolar depression w olanzapine
- Paroxetine: OCD, panic, social anxiety, generalized anxiety (GAD), PTSD, vasomotor sx, PMDD
- Sertraline: OCD, panic, PTSD, PMDD, social anxiety
- Escitalopram: GAD
- Citalopram: depression

SSRI Side Effects

- Increase with age: activation, vivid dreams, headache, GI upset/diarrhea, hyponatremia, bradycardia
- Serotonin syndrome
- Prolonged QTC with escitalopram, citalopram, fluoxetine: citalopram max 20mg for ≥ 60 yo
- Do not clearly increase risk of falls, but may affect effect bone metabolism/fracture risk

SSRIs and Suicide

- “Large pharmacoepidemiological study” of people ≥ 66
- “A very large meta-analysis and controlled data” review by the “FDA indicated a substantial REDUCTION in the risk...in older patients” of suicidal ideation vs placebo—now reflected in black box warning

SSRI Side Effects

- Increase risk of “cerebral, gastrointestinal, or postsurgical bleeding”
- Synergistic action increases risk of bleeding with “NSAIDs, low-dose aspirin, or warfarin”

Serotonin and Bleeding Risk

- Platelets release serotonin w “vascular injury”
- Serotonin causes platelet activation, promotes “vasoconstriction and a conformational change in shape that enhances aggregation” of platelets
- Platelets release but cannot synthesize serotonin
- Serotonin reuptake inhibition by antidepressant prevents serotonin re-entry into platelets:
- “impaired” platelet activation=bleeding risk

Serotonin and Bleeding Risk

- Risk is proportional to potency of serotonin reuptake inhibition
- Clomipramine, SSRIs block reuptake more potently than SNRIs (venlafaxine, duloxetine) or secondary tricyclic antidepressants (nortriptyline, desipramine)
- Additional risk if antidepressant (or other rx) inhibits metabolism of antiplatelet drugs like clopidogrel
- Sertraline may be safest SSRI, w no QTC prolongation and only weak enzyme inhibition

Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

- Venlafaxine, desvenlafaxine, duloxetine, levomilnacipran
- Similar serotonergic side effects (SE) to SSRIs AND
- Noradrenergic SE: HTN, orthostasis, urinary retention, arrhythmia, angle-closure glaucoma, “death in overdose”, constipation, dry mouth
- Hepatotoxicity risk w duloxetine

SNRIs continued

- Venlafaxine also approved for generalized anxiety, social anxiety, panic disorder
- Duloxetine for generalized anxiety
- Both are CYP 2D6 substrates, duloxetine also inhibits 2D6, is a substrate for CYP 1A2: drug interaction risk
- Controlled and other trials establish efficacy w elders
- BUT “should be reserved for those whose symptoms do not respond to one or two SSRIs” due to cardiac, tolerability issues

Vilazodone and Vortioxetine

- Serotonin reuptake inhibitors
- Vortioxetine also affects (by increasing or decreasing effect at) multiple serotonin receptors
- Vilazodone is a partial agonist of 5HT_{1A} receptor
- SE of both are similar to SSRIs, also angle-closure glaucoma
- Recommend waiting for more data in elders prior to use

Bupropion

- Also approved for seasonal affective disorder (XL) and tobacco cessation (SR)
- Norepinephrine dopamine reuptake inhibitor (NDRI)
- CYP2B6 substrate, strong inhibitor of CYP 2D6
- Lowers seizure threshold: risk is 0.1% at 300mg or lower, 0.4% at max dose
- Avoid w hx of bulimia, seizures, post-stroke, serious/multiple head injuries, other illnesses/RX that lower sz threshold

Bupropion continued

- Avoid with active substance use disorder (except tobacco) or very recent withdrawal that may increase seizure risk
- More activating than other antidepressants (energy, anxiety, insomnia)
- Hypertension risk

Tricyclic Antidepressants (TCAs)

- “Narrow therapeutic range,” lethal in overdose
- Orthostasis, anticholinergic SE (cognition, constipation...)
- Avoid tertiary TCAs: amitriptyline, doxepin, imipramine, clomipramine
- Secondary TCAs nortriptyline, desipramine have less anticholinergic, orthostatic risk
- Monitor drug levels and ECG in elders

Low-dose Tricyclics and Elders

- 3,434 people over 65 followed more than 7 years
- “Greater risk for dementia with over 3 years of”:
 - 10mg doxepin daily
 - 4mg chlorpheniramine
 - 5mg oxybutynin
- “10 year cumulative dose-response” increased risk of dementia and Alzheimer’s dementia ($p < .0001$)
- Effects may persist after cessation of drug

Monamine Oxidase Inhibitors (MAOIs)

- MAOIs: “fourth line” for depression
- “now rarely used in” elders
- Selegiline transdermal patch: dietary restrictions still necessary above 6mg (hypertensive crisis)
- “No geriatric data”
- Avoid with general anesthesia
- Contraindicated w serotonergic and many other RX

Electroconvulsive Therapy (ECT)

- “Continues to be the most effective form of treatment...for severe major depressive episode”
- “overall success rate...in those who have not responded to drug therapy is usually 80% or greater”
- More effective in those over 40 than under 40
- “may be more effective and have fewer side effects than antidepressants” in very old

Electroconvulsive Therapy (ECT)

- High relapse rate, better response w maintenance ECT and antidepressant than meds alone
- “Concentration, short-term memory, and learning” most frequent cognitive SE
- But ECT vs sham in 70 severely depressed elders w “widespread” pre ECT cognitive impairments found improvement post ECT on “most tests” of memory, concentration

Electroconvulsive Therapy

- “ECT may lead to significant improvement in memory of cognitively impaired older adults w depression”
- 86% mood response in study of depressed elders w dementia
- 21% w worse cognition, 49% w improved memory
- Limiting drugs that worsen cognition during ECT reduces cognitive risk

Electroconvulsive Therapy

- Relative contraindications: CNS edema, space-occupying lesion, unstable C spine, recent MI
- Evaluate for C-spine compression fractures
- Cardiovascular SE highest concern: “premature ventricular contractions, ventricular arrhythmias, and transient...hypertension” during ECT
- Headaches, confusion, status epilepticus
- TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Question Two

- There is no consensus on the best medications for bipolar disorder in elders
- Long-term lithium use may reduce renal function
- Anticonvulsants can lower platelets, white blood count, raise liver enzymes
- Antipsychotics are generally not first line choices for maintenance
- Questions 1-4 are true

Mood Stabilizers for Bipolar Disorder

- “High-risk medications for” elders. “There is a paucity of controlled studies and an abundance of concerns regarding...potential toxicity, problematic side effects, and drug interactions”
- “Currently, no consensus exists as to which drug should be preferred as a first-line mood stabilizer in older individuals with bipolar disorder or secondary mania”

Lithium

- Anti-suicide properties, potentially neuroprotective
- Effective for tx, prevention of mania
- Impact on renal function ↑ w duration of use
- May alter thyroid, parathyroid function
- Increased risk toxicity w age (neuro, cardiac, renal)
- Concentration increased w thiazide diuretics, NSAIDs, ACE inhibitors, dehydration, CKD, hyponatremia
- Toxicity w ca channel blockers, carbamazepine, haloperidol, phenytoin, methyldopa

Valproate

- Divalproex is sodium valproate and valproic acid
- “Pharmacokinetics vary according to formulation”:
- Divalproex sodium, divalproex sodium ER, and valproic acid “are not interchangeable”
- Effective in mania, mixed mania, maintenance tx
- Increases concentration of, is decreased by, multiple anticonvulsants and other drugs

Valproate

- SE: “sedation, nausea, weight gain,” hair loss, tremor
- “up to half” of elders have reversible thrombocytopenia
- Rare liver failure, pancreatitis
- Rash, transient increase of liver enzymes, ammonia
- “increases in bone turnover and reduction of serum folate, with...elevations of homocysteine”
- AVOID use w dementia: neurotoxicity more common than placebo, and no more effective than placebo in 6 trials

Carbamazepine

- ER carbamazepine approved for mania, mixed mania
- “Common side effects” in elders “include sedation, nausea, dizziness, rash, ataxia, neutropenia, and hyponatremia”
- Drug interactions are “protean”, metabolized by CYP3A4, induces own metabolism and that of many other drugs
- Effective for NPS vs placebo in small study of dementia

Carbamazepine and Oxcarbazepine

- Carbamazepine: severe drug allergy, hepatitis aplastic anemia risk
- Pre-tx HLA-B*1502, HLA-A*3101 testing w Asian ancestry
- May cause AV block, lowers thyroid hormone
- Oxcarbazepine: “10-keto analogue of carbamazepine is a less potent”
CYP 3A4 enzyme inducer (fewer drug interactions)
- Not FDA approved, no mood studies in elders: “not recommended”

Lamotrigine

- FDA-approved for maintenance tx of bipolar disorder
- Increased by valproate, decreased by carbamazepine
- Few other drug interactions
- Weight neutral
- “Pooled geriatric data from 2 RPC trials support” efficacy in “preventing bipolar depression” in elders
- Severe rash risk 0.3%, may be lower w slower titration
- May reduce folate

Lamotrigine

- May cause sedation in elders, but can also trigger activation/mania/hypomania
- Rare risk aseptic meningitis
- Half-life 25 hours
- Binds to melanin (regular ophthalmologic fu)
- For ALL of these anticonvulsants, stop RX and go to ER for rash, fever, sore throat, flu sx, adenopathy, blisters

Question Three

- Insomnia increases the risk for car crashes and falls
- Sedating medications increase the risk for car crashes, dementia, and death in elders
- Drugs most likely to contribute to dementia and death include low dose tricyclic antidepressants
- Questions 1-3 are true
- Questions 1-3 are false

Treating Insomnia

- Infirmary, isolation, sensory losses, boredom, napping, “dysfunctional beliefs about sleep” may disrupt sleep/wake cycle, good health, sleep habits
- Safest treatment by FAR is cognitive behavioral treatment: as or more effective as meds in some studies
- More enduring effect on sleep than meds

“Sedative Hypnotic Medication Use and the Risk of Motor Vehicle Crash”

- 409,171 adults in an “integrated health care plan” med use compared to crash records in WA state
- 5.8% received new sedative hypnotic rx
- Increased risk of crash with temazepam HR 1.27
- Trazadone HR 1.91, zolpidem HR 2.20 “equivalent to
- BAL 0.06-0.11%
- “3 fold increased risk premature mortality,” 4 fold in first year of treatment.

Anticholinergic Cognitive Burden Scale (ACB)

- Drugs are scored from 1-3 points based on anticholinergic impact. 2-3 points="definite" risk.
- "Each definite anticholinergic (sic-medication) may increase the risk of cognitive impairment by 46% over 6 years."
- For each 1 point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested...each 1 point increase in the ACB total score has been correlated with a 26% increase in the risk of death."

Delirium

- Disturbed attention (ability to sustain or shift focus)
- Develops quickly (hours to days)
- Disturbed cognition (memory, language, orientation, perception, visuospatial skills)
- Changes are due to medical factors, drug, toxin substance/withdrawal
- Changes are not from evolving neurocognitive disorder or coma

Delirium

- Missed 70% of the time
- Medications contribute "40% of the time":
- . Sedative hypnotics raised risk 3-12 times
- Narcotics increased risk 3 fold
- Anticholinergics increased risk 5-12 times : tricyclic antidepressants, antispasmodics, antihistamines, antimuscarinics, antipsychotics

Delirium Prevention also applies to Dementia Management

- Oxygenation, “fluid and electrolyte balance, pain management, reduction in psychoactive medications, bowel and bladder function, nutrition, early mobilization, prevention of postoperative complications, appropriate environmental stimuli, and treatment of delirium”
- Correcting sensory deficits

Delirium Management

- Medications for prevention or treatment:
“There is no convincing, reproducible evidence that any of these treatments are clearly effective for either prevention or treatment of delirium.”
- Example: Haloperidol reduced risk of delirium in 457 surgery patients without change in mortality, complications, or length of stay
- Olanzapine reduced delirium incidence, but worsened delirium severity, duration

Dementia/Major Neurocognitive Disorder

- Cognitive decline is “significant” in 1 or more of these: complex attention, executive function, learning and memory, language, perceptual-motor, social cognition
- Concern noted by patient, informant, or provider AND substantially affects cognitive performance, ADL’s
- Does not occur only during delirium, is not better explained by other disorders (e.g., depression)

Treatments for Major Neurocognitive Disorders

- “One of the most effective therapies for AD (Alzheimer’s dementia) is the aggressive management of associated vascular risk factors such as blood pressure...high cholesterol, diabetes, obesity and sedentary life style”
- Studies of anti-amyloid treatment, anti-tau therapy, dietary changes, exercise, cognitive stimulation, insulin, omega 3 fatty acids, naproxen, vitamins A, C, E are in progress

Medications for Memory

- Cholinesterase inhibitors: donepezil, rivastigmine, galantamine all approved for mild-moderate Alzheimer's dementia (AD)
- Donepezil, rivastigmine for mod-severe AD
- Rivastigmine for mild-mod dementia due to Parkinson's disease
- NMDA antagonist: memantine FDA approved for mod-severe AD
- AVOID these w VASCULAR DEMENTIA

Neuropsychiatric Symptoms (NPSs)

- 1. Affect and Motivation changes are present in 50% of dementias (depression, apathy)
- 2. Psychosis (hallucinations, delusions)
- 3. Change in drives (appetite, sex, sleep)
- 4. Disinhibition (aggression, sex, wandering, verbal):
- “executive dysfunction syndrome”

Neuropsychiatric Symptoms (NPS) and Antidepressants/Mood Stabilizers

- Citalopram reduced agitation, but at 30mg (20mg or less recommended for age ≥ 65 and poor metabolizers due to QTC prolongation risk)
- Sertraline improved depression, but not agitation
- Trazadone did not improve NPS in a placebo controlled trial
- Carbamazepine improved agitation and aggression at 300mg-400mg in 2 studies, but may lower sodium and WBC, WILL lower concentration of drugs that are metabolized by CYP4503A4 (many!)
- Valproic acid studies had high rates of side effects, dropouts, same mortality risk as risperidone in one study

Neuropsychiatric Symptoms and Memory Medications

- Most studies of anticholinesterases in Alzheimer's disease did not improve NPS's; 3 showed "modest" efficacy
- Best evidence is for rivastigmine w Lewy Body sx of apathy, anxiety, delusions, and hallucinations (but may worsen sleep sx)
- PDBPC study of memantine w "moderate to severe Alzheimer's dementia " was negative for agitation
- But a "pooled retrospective analysis of three" memantine studies suggested "efficacy and tolerability" for "agitation, aggression", or psychosis over 3-6 months in moderate-severe Alzheimer's disease

Melatonin

- May be reduced in Alzheimer's dementia
- “Highly effective in the treatment of REM behavioral disorder and should be considered as a potential first-line treatment option given the lack of potential adverse affects”
- Data is from small sample size studies
- Not regulated by FDA

Psychosis in Dementia

- 20% incidence in first year of Alzheimer's dementia
- 50% at year two, 51% at year 4
- 41% prevalence overall
- More frequent w faster cognitive decline, may improve in late illness
- Delusions of theft, persecution, belief that those around them are not who they say they are

Question Four

- Antipsychotics treat hallucinations and delusions
- Antipsychotics are appropriate for primary psychotic and bipolar disorders
- Antipsychotics increase mortality in dementia
- Questions 1-3 are true
- Questions 1-3 are false

Neuropsychiatric Symptoms and Antipsychotics

- "Psychotropics are unlikely to affect poor self-care or refusal of care, memory problems, inattention, unfriendliness, repetitive verbalizations or questioning, shadowing, or wandering"
- "Be mindful that select isolated disturbances are unlikely to respond to to medications"

Antipsychotics for Neuropsychiatric Symptoms

- None are FDA-approved for this
- Antipsychotics may help reduce psychosis and agitation, but "one patient will die for every 9-25 people who are treated with an atypical antipsychotic"
- Typical antipsychotics had higher mortality risk vs atypicals in 4 studies; two studies found an equal risk
- 33,604 patient study by the VA found highest risk of side effects w haldol, then risperidone, olanzapine, valproic acid

Antipsychotics

- Effective for late onset schizophrenia
- "Long –term use is justified "with schizophrenia, "bipolar disorder, and possibly major depressive disorder with" psychosis
- Otherwise, use only after failure of behavioral strategies or non antipsychotic medication interventions
- Use at lowest effective dose for shortest possible time, attempt dose reductions after a period of stabilization unless prior attempts to lower dose worsened sx
- Atypicals are more likely than typicals to raise glucose, lipids, risk of pancreatitis, cerebrovascular events, fractures, venous thromboembolism

Antipsychotics

- Typical antipsychotics are more likely than atypicals to cause/worsen tardive dyskinesia (TD), Parkinsonian symptoms: use w EXTREME caution w Parkinson's and Lewy Body diseases
- All antipsychotics increase risk of neuroleptic malignant syndrome (very rare with clozapine)
- May cause, worsen restless leg syndrome
- 2004 FDA meta-analysis of "17 Placebo-controlled trials of" atypicals found 4.5% risk mortality vs 2.6% in placebo: BLACK BOX WARNING
- Black box warning added to typicals in 2008

“Considerations Specific to Antipsychotics” in Long Term Care Facilities

- <http://www.nhqualitycampaign.org> has “Hand in hand” video for “nursing assistant training” and more (caregiver reference)
- “Gradual Dose Reduction” (GDR) required with use for NPS in dementia “in two separate quarters (with at least one month between attempts), unless clinically contraindicated. After the first year, a GDR must be attempted annually, unless clinically contraindicated”
- Contraindications to GDR: “target sx returned or worsened” after GDR
- “Physician has documented clinical rationale” for why GDR would be harmful

Antipsychotics and Neuropsychiatric Symptoms: Risperidone

- "First choice among antipsychotics" for dementia w agitation/psychosis
- Randomized trials with haloperidol, olanzapine, promazine
- Sx may worsen w cessation of Rx
- RCT: may improve OR worsen delirium
- Atypical Antipsychotic most likely to raise prolactin
- Less likely to worsen cognition than olanzapine
- Very likely to cause or worsen parkinsonian sx w Parkinson's and Lewy Body disease

Olanzapine

- Not recommended as first line tx of "older patients at special risk for anticholinergic or metabolic adverse effects"
- May improve OR prolong, worsen delirium
- Most recent review of data from 2006-2011 found small but statistically significant benefit for NPS behavioral sx in dementia
- Highest risk except for clozapine for diabetes, weight gain
- Sedation, constipation, cognitive side effects

Quetiapine

- Studies in "older patients with behavioral and psychological sx" are "inconclusive"
- Lowest risk except for clozapine for Parkinsonian sx , tardive dyskinesia (especially w Parkinson's disease, Lewy Body dementia), but no efficacy in 2 double-blind studies
- Lipid, glucose, weight increases are similar to risperidone
- Hypotension, sedation
- High response rate in study of 338 elders w major depression

Clozapine

- "Drug of choice" for psychotic disorders resistant to other antipsychotics, hx of neuroleptic malignant syndrome, tardive dyskinesia
- Best data in Parkinson's disease for drug-induced psychosis (use low doses)
- Weekly CBC for 6 months, Q 2 weeks 6 months, then monthly due to bone marrow suppression risk
- Greatest risk among antipsychotics of diabetes, weight gain, hyperlipemia, sedation, seizures, ileus, hypotension
- Myocarditis (most likely early in treatment)

Aripiprazole

- Antipsychotic w lowest metabolic risk (but risk remains, especially for triglycerides)
- Partial dopamine 2 receptor agonist: low risk of Parkinsonian sx
- Low risk sedation, hypotension, cognitive sx
- Higher risk of akathisia (restlessness) that may look like and be described as anxiety
- Efficacy noted in RCT, meta analysis, and 5 year data review for elders w NPS of dementia

Ziprasidone

- Most likely atypical (second among all antipsychotics) to prolong QTC interval (3 small studies of IM use in elders found no CV or ECG effect)
- "In the absence of systematic geriatric studies...should be used w caution"
- Lower risk of sedation, weight gain, diabetes than all atypicals except aripiprazole
- No muscarinic (sedation, constipation) side effects
- Taken w food to enhance absorption

Thank you!

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Alive Inside: A Story of Music and Memory

Trazadone

- Lower doses (25-50mg) are sedating, but have sedative, hypotensive side effects
- Doses over 150mg are antidepressant
- Low risk of weight gain or sexual side effects
- At higher doses, similar side effects to SSRI's
- Arrhythmia, angle-closure glaucoma
- Rare risk priapism

Mirtazapine

- 5HT_{2A}, histamine antagonism (sedating effect)
- 5HT_{2c} antagonism (weight gain)
- alpha₂ antagonism potently boosts norepinephrine, serotonin release (antidepressant, activating)
- 5HT₃ antagonism reduces nausea/vomiting/diarrhea
- 7.5-45mg for depression
- Rare marrow suppression, warnings about torsades de pointes, angle-closure glaucoma, hypersensitivity reactions