UVM Project ECHO: Adult Complex Mental Health

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“Introduction” to ZOOM

• Please mute microphone when not speaking
• Please use camera as much as possible
• Test both audio & video before joining
• Communicate clearly during session:
  • Can use “raise hand” feature to comment
  • Use chat function for questions, comments or technical issues
RECORDING OF SESSION TO BEGIN
Series Objectives

Learning objectives for this ECHO series include the ability to:
• Enhance diagnostic skills in patients with complex mental health issues
• Incorporate new treatment strategies into management of common but challenging mental health disorders
• Improve the care that patients with mental health issues receive in the primary care setting
Session Agenda

- Welcome
- Objectives
- Didactic Presentation (30-35 min)
- Case presentation(s)
  - Clarifying questions
  - Participants – then faculty panel
- Discussion
- Recommendations
- Closing Announcements
  - Submission of new cases
  - Completion of evaluations
CMIE Disclosures

University of Vermont (UVM) Office of Continuing Medical and Interprofessional Education (CMIE) is approved as a provider of Continuing Medical Education (CME) by the ACCME. UVM designates this internet live activity for a maximum of 1.5 AMA PRA Category 1 Credits.

UVM CMIE is accredited by the American Nurses Credentialing Center (ANCC) to provide CE for the healthcare team. This program has been reviewed and is acceptable for up to 1.5 Nursing Contact Hours.

As a Jointly Accredited Organization, The Robert Larner College of Medicine at the University of Vermont is approved to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Organizations, not individual courses, are approved under this program. State and provincial regulatory boards have the final authority to determine whether an individual course may be accepted for continuing education credit. The University of Vermont maintains responsibility for this course. Social workers completing this course receive 1.5 continuing education credits.

This activity was planned by and for the healthcare team, and learners will receive 1.5 Interprofessional Continuing Education (IPCE) credit for learning and change.

Participants should claim only the credit commensurate with the extent of their participation in the activity.
CMIE Disclosures

**Interest Disclosures:** As an organization accredited by the ACCME to sponsor continuing medical education activities, UVMCMIE is required to disclose any real or apparent conflicts of interest (COI) that any speakers may have related to the content of their presentations.

**Meeting Disclaimer:** Regarding materials and information received during this educational event, the views, statements, and recommendations expressed during this activity represent those of the authors and speakers and do not necessarily represent the views of the University of Vermont.
Mental Health Disorders in Older Adults: Depression, Anxiety, Dementia... Oh My!

Jennifer M. Hall, DO
Assistant Professor of Psychiatry
May 11, 2022
Disclosures

With respect to the following presentation, there has been no relevant (direct or indirect) financial relationship between any for-profit company in the past 24 months which could be considered a conflict of interest.

I will be discussing the use of off-label medications.
Objectives

1. Discuss pharmacological strategies for treating depression in older adults including agent selection and strategies for switching or augmenting.

2. Review challenges of prescribing benzodiazepines for older adults with anxiety disorders.

3. Discuss appropriate prescribing practices for managing behavioral and psychological symptoms of dementia (BPSD) focus on antipsychotics.
Past Year Prevalence of Any Mental Illness Among U.S. Adults (2020)

Data Courtesy of SAMHSA

<table>
<thead>
<tr>
<th>Percent</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
<th>18–25</th>
<th>26–49</th>
<th>50+</th>
<th>Hispa...</th>
<th>White</th>
<th>Black...</th>
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<td>17.3</td>
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<td>35.8</td>
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</table>

Sex | Age | Race/Ethnicity

https://www.nimh.nih.gov/health/statistics
Barriers to Older Adults Seeking Treatment

- Tendency to “normalize” symptoms
- Stigma of mental health disorders
- Limited access to mental health providers/geriatric psychiatrists
- Unaware of available/effective treatments
Prescribing Challenges

• Overlapping symptoms can contribute to diagnostic uncertainty → use of validated rating scales
• Limited treatment algorithms to guide treatment decisions (CANMAT)
• Older adults are more susceptible to drug interactions
• Adverse Events/Side Effects
  • Pharmacokinetic changes with aging → further impacted by medical illness
  • Many medications have anticholinergic properties (Beers Criteria)
• Cost/insurance coverage
• Treatment Adherence Snafus
Common Prescribing Pitfalls

• Dosing blunders
  • Start low and go slow... but go!!!
• Not allowing appropriate time for medications response
• Making multiple medication changes at once
• Not asking specifically about side effects
• Continuing medications despite lack of efficacy/positive clinical response → polypharmacy
• Not keeping up with blood monitoring parameters
Depression in Older Adults
Past Year Prevalence of Major Depressive Episode Among U.S. Adults (2020)

Data Courtesy of SAMHSA

<table>
<thead>
<tr>
<th>Sex</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
<th>18-25</th>
<th>26-49</th>
<th>50+</th>
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<th>Black...</th>
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<td>10.5</td>
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<td>9.1</td>
<td>5.4</td>
<td>7.0</td>
<td>9.5</td>
<td>6.0</td>
<td>4.2</td>
<td>4.2</td>
<td>15.9</td>
</tr>
</tbody>
</table>

https://www.nimh.nih.gov/health/statistics
Common Presentations of Depression in Older Adults

- Depression without sadness (lonely, irritable, withdrawn)
- Anxiety (tension, unrest, fear)
- Vague/nonspecific concerns
  - Feeling generally unwell
  - Pain/headaches
  - Failure to thrive/weight loss
  - Fatigue/weakness/frailty
- Sleep disturbance
- Agitation
- Forgetfulness/decreased concentration
- Psychosis

Hageman et al. 2012
## Table 1: Comparison of Select Features of Depression and Dementia

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Depression</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood</td>
<td>Develop a persistently sad mood over a period of weeks</td>
<td>Usually normal but can become transiently unhappy in reaction to events</td>
</tr>
<tr>
<td>Sense of Guilt or Worthlessness</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Suicidal Thinking</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Anxiety/Agitation</td>
<td>• Can develop over weeks</td>
<td>• Seen as dementia progresses</td>
</tr>
<tr>
<td></td>
<td>• Often worse in the morning</td>
<td>• Often worse in latter part of the day (sundowning) and in unfamiliar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>surroundings</td>
</tr>
<tr>
<td>Cognition</td>
<td>• Problems with concentration and focus that develop over weeks</td>
<td>• Progressive, gradual decline in memory and other domains</td>
</tr>
<tr>
<td></td>
<td>• Indecisiveness and anxiety about making mistakes</td>
<td>• Concentration normal early on</td>
</tr>
<tr>
<td>Concern about Cognitive Deficits</td>
<td>• Seem to exaggerate severity</td>
<td>• Show little concern</td>
</tr>
<tr>
<td></td>
<td>• Preoccupied with deficits</td>
<td>• Minimizes and often denies</td>
</tr>
<tr>
<td>Interest in Hobbies and Other</td>
<td>Loss of interest in hobbies and formerly pleasurable activities over weeks</td>
<td>Gradual loss of interest and initiative over years</td>
</tr>
<tr>
<td>Pleasurable Activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Symptoms</td>
<td>• Changes in appetite over weeks — weight can be up or down</td>
<td>• Gradual loss of weight over years</td>
</tr>
<tr>
<td></td>
<td>• Over weeks can see either more or less sleep than usual</td>
<td>• Gradual disruption of normal sleep-wake cycles</td>
</tr>
<tr>
<td></td>
<td>• Frequent complaints of fatigue and, if depression is severe, can</td>
<td>• Often less active but rare to see psychomotor retardation</td>
</tr>
<tr>
<td></td>
<td>become “slowed down” (psychomotor retardation)</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Strategies for Depression

• Lifestyle Modification

• Psychotherapy
  • Cognitive Behavioral Therapy (CBT)
  • Intrapersonal Psychotherapy (IPT)
  • Behavior Activation
  • Brief Psychodynamic Psychotherapy
  • Supportive/problem solving Therapy

• Antidepressants
  • Selective serotonin reuptake Inhibitors (SSRIs)
  • Serotonin-noradrenergic reuptake inhibitors (SNRIs)
  • Tricyclic antidepressants (TCA)
  • Monoamine oxidase inhibitors (MAOIs)
  • Others: bupropion, mirtazapine, trazodone

• Neurostimulation (ECT/TMS)
<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Treatment</th>
<th>First Step (use one or more agents in sequence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Duloxetine**</td>
<td>Mirtazapine, sertraline, venlafaxine, vortioxetine**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Citalopram, desvenlafaxine, escitalopram</td>
</tr>
<tr>
<td>Level 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 3/4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Treatment</th>
<th>Second Step (if multiple first-step treatments are not effective or not indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Nortriptyline</td>
<td>Switch to: Fluoxetine, moclobemide, paroxetine, phenelzine, quetiapine, trazodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Or augment with: Aripiprazole, Methylphenidate, Lithium</td>
</tr>
<tr>
<td>Level 2</td>
<td></td>
<td>Bupropion</td>
</tr>
<tr>
<td>Level 3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Treatment</th>
<th>Third Step (if multiple first- and second-step treatments are not effective or not indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2</td>
<td>Amitriptyline, imipramine</td>
<td>Switch to: Bupropion</td>
</tr>
<tr>
<td></td>
<td>OR Combine SSRI or SNRI with:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR</td>
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</tbody>
</table>
Notable Antidepressant Side Effects

- **Hyponatremia/SIADH 0.1%-4%**
  - SSRIs, SNRIs, TCAs
  - General malaise, mental status changes, seizures
  - Higher risk on older adults secondary to decline in renal function

- **Increased bleeding risk**
  - SSRI/SNRIs
  - Easy bruising/GI bleeds/CVA
  - Impact on platelet aggregation & increase in gastric acid production, greatest risk when on ASA, NSAIDs, anticoagulation

- **Anticholinergic Properties:**
  - Paroxetine & TCAs (Secondary Amines: Nortriptyline < Tertiary Amines: amitriptyline)
  - Falls, mucosal dryness (tooth decay), urinary retention, confusion

- **QTc prolongation: >450ms in men >470ms in women**
  - Citalopram (black boxed warning), Escitalopram, TCA (overdose)
  - Greater risk when combined with other QTc prolonging agents (antipsychotics, antiemetic, cholinesterase inhibitors)

- **Serotonin Syndrome:**
  - 40% of cases can occur with a single agent, but more often a concern when combing agents
  - Confusion, HTN, tachycardia, tachypnea, diaphoresis, hyperthermia, hyperreflexia/clonus
# Switching vs. Augmenting

<table>
<thead>
<tr>
<th>Consider Switching:</th>
<th>Consider Augmenting:</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is the first antidepressant trial</td>
<td>There have been at least 2 trials of antidepressants</td>
</tr>
<tr>
<td>Poorly tolerated side effects to first antidepressant</td>
<td>Initial antidepressant is well tolerated</td>
</tr>
<tr>
<td>No response to initial antidepressant ( (&lt; 25% \text{ improvement}) )</td>
<td>Partial response to initial antidepressant ( (\geq 25% \text{ improvement}) )</td>
</tr>
<tr>
<td>There is time to wait for response ( (\text{less functional impairment, less severity}) )</td>
<td>There are specific residual symptoms or side effects to the initial antidepressant that can be targeted</td>
</tr>
<tr>
<td>Patient prefers switching medications</td>
<td>There is less time to wait for response ( (\text{more severe case, more functional impairment}) )</td>
</tr>
<tr>
<td></td>
<td>Patient prefers to add on another medication</td>
</tr>
</tbody>
</table>

# Switching Treatments

<table>
<thead>
<tr>
<th>Medication Classes</th>
<th>Strategy for Switching</th>
</tr>
</thead>
</table>
| SSRI to SSRI                        | • Direct switch  
• Can consider a cross-taper if dose of concurrent SSRI is high  
• Consider short washout (7-10 days) when converting from fluoxetine due to long half-life                                                                 |
| SSRI or SNRI to SNRI (vice-versa)   | • Direct switch  
• Can consider a cross-taper if dose on concurrent SSRI or SNRI is high  
• May consider short washout (7-10 days) when converting from fluoxetine due to long half-life                                                                 |
| SSRI/SNRI to bupropion (vice-versa) | • Cross-taper  
• Direct switches not well tolerated as bupropion will not mitigate serotonin discontinuation syndrome  
• High doses of strong CYP 2D6 inhibitors (i.e., fluoxetine, paroxetine, bupropion) should be reduced to lower doses prior to starting. Avoid concomitant administration of high-dose bupropion and high-dose fluoxetine or paroxetine due to potential to lower seizure threshold. |
| Switches to and from mirtazapine, trazodone, nefazodone | • Cross-taper due to mechanistic differences  
• Be careful with CYP 3A4 interactions and nefazodone (antidepressant dependent)                                                                                                                                     |

Hirsch M, Birnbaum RJ. Switching antidepressant medications in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed January 2, 2022


## Switching Treatments

<table>
<thead>
<tr>
<th>Medication Classes</th>
<th>Strategy for Switching</th>
</tr>
</thead>
</table>
| **Switches to and from vortioxetine or vilazodone** | • Cross-taper  
• May consider short washout (4-7 days) when converting from vortioxetine due to long half-life |
| **Switches to and from TCAs** | • Cross-taper  
• TCAs are CYP 2D6 substrates and are subjective to plasma concentration increases when CYP 2D6 inhibitors are added. TCAs should be tapered to a low dose prior to initiation of any CYP 2D6 inhibiting antidepressant.  
• CYP 2D6 inhibiting antidepressants should be tapered to a low dose prior to initiating a TCA at the lowest possible dose. Consider a small-washout of fluoxetine (7-10 days) prior to starting a TCA due to the long-half life. |
| **Switches to and from MAOIs** | • Complete wash-out required prior to initiating an MAOI or switching from an MAOI  
• A complete wash-out (i.e., a total of 5 half-lives have passed for both the parent drug and active metabolites) is required prior to switching to an MAOI from a different monoaminergic drug  
• A two-week washout is required when switching from an MAOI to a different antidepressant |

Hirsch M, Birnbaum RJ. Switching antidepressant medications in adults. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed January 2, 2022  
Role of Antipsychotics in Late Life Depression

• Generally reserved for cases with limited or partial response to monotherapy or for patients with psychotic depression

• Factors for consideration:
  • Depression specifiers
  • Symptom severity
  • Treatment history
  • Medical comorbidities
  • Presence of neurocognitive disorder
  • Access to non-pharmacological treatment
  • Social supports and access to care
Aripiprazole Augmentation for MDD in Older Adults

- Placebo-controlled antipsychotic augmentation trial for MDD in older adults
- Active treatment: aripiprazole augmentation
  - Target dose: 10 mg/day (Max: 15 mg/day)
- Higher remission rates with aripiprazole augmentation
  - OR: 2.0 (95% CI: 1.1-3.7, p=0.03)
  - NNT: 6.6 (95% CI: 3.5-81.8)
- Extrapyramidal symptoms (EPS) were more common with aripiprazole
  - Akathisia occurred in 26.7% of patients vs. 12.2% on placebo

STOP-PD Clinical Trial

- Meyers et al. 12 week RCT of Combination Antipsychotic/Antidepressant Treatment versus Antipsychotic Monotherapy for MDD w/Psychotic Features

Olanzapine/Sertraline vs. Olanzapine/Placebo in Psychotic Depression

- Remission Rates
  - Olanzapine/Sertraline 14.3/169 mg (n=129) [n=81/completed]
  - Olanzapine 14.7 mg (n=130) [n=61/completed]

Approximately 55% of patients were older than 60 years of age in the trial.
Combination therapy was comparably superior in both younger and older adults.
Antipsychotic Monotherapy for MDD in Older Adults?

- 11-wk (9-wk randomized; 2-wk posttreatment phase), DB, placebo-controlled trial

**Quetiapine XR Monotherapy in the Treatment of Depression in Older Adults**

**Response**
- Placebo (n=171): 30.40%
- Quetiapine XR 50-300 mg/day (n=164): 64%

**Remission**
- Placebo (n=171): 17%
- Quetiapine XR 50-300 mg/day (n=164): 45.10%

***p<0.001 vs. placebo

Other Combinations/Augmenting Steps

• Although antidepressant combinations are frequently used in practice, there is not substantial evidence to consistently recommend their use in older adults
  • Similar for liothyronine, limited data; data primarily supports use as adjunct to tricyclic antidepressant

• Lithium is effective, but can be challenging to use
  • Overall response rate is 42% (95% CI, 21%-65%)

• Lamotrigine and buspirone lack data in general populations as an augmenting strategy

<table>
<thead>
<tr>
<th>Second Step (if multiple first-step treatments are not effective or not indicated)</th>
<th>Treatment</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Or augment with:</td>
<td></td>
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</tr>
<tr>
<td>Aripiprazole</td>
<td></td>
<td>Level 1</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td></td>
<td>Level 2</td>
</tr>
<tr>
<td>Lithium</td>
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<td>Level 3</td>
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Anxiety Disorders in Older Adults

Data from National Comorbidity Survey Replication (NCS–R)

<table>
<thead>
<tr>
<th>Sex</th>
<th>Overall</th>
<th>Female</th>
<th>Male</th>
<th>18–29</th>
<th>30–44</th>
<th>45–59</th>
<th>60+</th>
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<tbody>
<tr>
<td>Age</td>
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<td>19.1</td>
<td>23.4</td>
<td>14.3</td>
<td>22.3</td>
<td>22.7</td>
<td>20.6</td>
<td>9.0</td>
</tr>
</tbody>
</table>

https://www.nimh.nih.gov/health/statistics
Anxiety Disorders in Older Adults

• More common than depressive disorders
• Heterogeneous group of disorders
  • Core feature: excessive worry or fear leading to functional impairment
• Symptoms tend to be chronic and may wax and wane over time
• High rates of comorbidity (psychiatric/medical illnesses)
  ~ 51.8 % of older adults with MDD meet criteria for an anxiety disorder and 36.7% of patients with anxiety disorders meet criteria for MDD
  ~ substance use disorders
  ~ cardiovascular/neurocognitive/COPD
• Risk factors: female, living alone, death of partner/stressful life events, decline in health (subjective/objective)
Clinical Presentation of Anxiety Disorders in Older Adults

• Likely to have mixed symptoms
• High rates of sleep disturbance
• High rates of somatic symptoms/general worries about health
• Older adults and providers often misattribute symptoms to medical condition
• Higher rates of healthcare utilization
Treatment Strategies for Anxiety Disorders

- Lifestyle Modification
- Psychotherapy
  - Cognitive Behavioral Therapy (CBT)
  - Intrapersonal Psychotherapy (IPT)
  - Behavior Activation
  - Brief Psychodynamic Psychotherapy
  - Supportive/problem solving Therapy
- Antidepressants
  - Selective serotonin reuptake Inhibitors (SSRIs)
  - Serotonin-noradrenergic reuptake inhibitors (SNRIs)
  - Tricyclic antidepressants (TCA)
  - Others: buspirone, pregabalin, mirtazapine
- Benzodiazepines (short term)
Benzodiazepines

- Most frequently prescribed class of medications for patients >65
- Not indicated for long term use → older adults are most likely to be prescribed benzodiazepines for years/decades

- Risks Associated with Benzodiazepines
  - Falls/fracture
  - Sedation
  - MVA
  - Cognitive impairment/Delirium
  - Paradoxical reactions
  - Pneumonia
  - Tolerance/dependency
  - Overdose
  - Structural sleep changes
A Time and Place for Benzodiazepines

• Acute management of panic attacks/panic disorder
• Temporary bridge until another treatment takes effect (psychotherapy/SSRI/SNRI)
• Acute management of alcohol withdrawal/delirium tremens

….. Set the stage for prescribing with clear expectations and discussion of risks/benefits
Guidelines for tapering off benzos when used for insomnia not anxiety disorders → not specific to older adults
  • Decrease the benzodiazepine dose by 25% every 2 weeks
  • May need to the slow taper (12.5% by every 2 weeks) towards the end

Easiest to taper medications with long half lives/wide dose ranges → less interdose withdrawal

Set realistic expectations with tapers including strategies to target rebound anxiety

If complete discontinuation is not feasible- dose/harm reduction is still a win in my book
Neurocognitive Disorders with Behavioral and Psychological Symptoms of Dementia (BPSD)
Behavioral and Psychological Symptoms of Dementia (BPSD)

• Heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors that are unsafe, disruptive, and impair the care of the individual

• ~90% of individuals with dementia experience at least one BPSD at some point during the course of their illness (Lyketsos et al 2011)

<table>
<thead>
<tr>
<th>Neuropsychiatric Symptom</th>
<th>Anytime During Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delusions</td>
<td>50</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>28</td>
</tr>
<tr>
<td>Agitation/Aggression</td>
<td>63</td>
</tr>
<tr>
<td>Depression</td>
<td>54</td>
</tr>
<tr>
<td>Anxiety</td>
<td>50</td>
</tr>
<tr>
<td>Apathy</td>
<td>76</td>
</tr>
<tr>
<td>Irritability</td>
<td>63</td>
</tr>
<tr>
<td>Euphoria</td>
<td>17</td>
</tr>
<tr>
<td>Aberrant motor symptoms</td>
<td>65</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>54</td>
</tr>
</tbody>
</table>

Craig et al 2005
Impact of BPSD

• Accounts for 30% of caregiving costs in community-dwelling persons with dementia (*Beeri et al 2002*)
• Earlier nursing home placement
• Increased morbidity & mortality
• Longer hospital admissions
• Decreased quality of life for persons with dementia and their caregivers
• Caregiver burnout, depression, and reduced employment/income
Appropriate prescribing practices for management of BPSD

• No FDA approved medications
• ALWAYS implement non-pharmacological interventions first and NEVER STOP
• Match target symptoms with most appropriate medication class
• Consider psychotropic medications when....
  • Behavioral, environmental, and medical interventions are not sufficient to manage BPSD
  • Major depression +/- suicidal ideation
  • Psychosis causing harm/serious potential for harm
  • Aggression with risk to self/others

Kales et al 2015
Antipsychotics

- Most widely studied class of medication for management of BPSD but only modest effect: 0.13-0.16  (Kales et al 2015)

- **Two Classes:**
  - Typical: haloperidol
  - Atypical: risperidone, olanzapine, aripiprazole, quetiapine

- **Side Effect Profile**
  - Somnolence
  - Gait disturbance/falls
  - Cognitive worsening
  - Stroke
  - QTc prolongation
  - Metabolic syndrome (weight gain, dyslipidemia, diabetes)
  - Movement disorders (parkinsonism, dystonia, tardive dyskinesia)

**FDA Black Boxed Warning (2005):** increased risk of mortality (1.6-1.7x) for persons with dementia
Typical Antipsychotics

• No Clear evidence regarding efficacy of typical antipsychotics on BPSD (Sink et al 2005)
  • Early reports of modest effect (0.18) for thioridazine and haloperidol (Schneider et al 1990) but not sustained
  • Small sample sizes/short treatment duration (12 weeks)

• Lonergan et al 2002: haloperidol vs placebo
  • Aggression not agitation was significantly improved 1.2-3.5mg/day (-0.31, range -0.49 to -0.13)
  • Haloperidol recipients 2x more likely to have significant side effects (EPS/somnolence) resulting in high dropout rate
  • Modest effect may not be worth the risk (Sink et al 2005)
FIGURE 1. Efficacy Outcomes by Individual Comparisons: Aripiprazole, Olanzapine, Quetiapine, and Risperidone Compared With Placebo (weighted mean differences).

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>N</th>
<th>Drug Mean (SD)</th>
<th>Placebo Mean (SD)</th>
<th>WMD (fixed) 95% CI</th>
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</thead>
<tbody>
<tr>
<td>01 Aripiprazole BPRS Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN-138 004</td>
<td>339</td>
<td>-6.83 (11.05)</td>
<td>112</td>
<td>-4.17 (10.79)</td>
</tr>
<tr>
<td>CN-138 005</td>
<td>123</td>
<td>-7.73 (10.32)</td>
<td>117</td>
<td>-5.14 (10.49)</td>
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<tr>
<td>CN-138 006</td>
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<td>-8.83 (12.30)</td>
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<td>-6.20 (12.28)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>562</td>
<td></td>
<td>324</td>
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<tr>
<td>Test for heterogeneity: CH² = 0.12, df = 2 (P = 0.94), I² = 0'</td>
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<tr>
<td>Test for overall effect: Z = 3.14 (P = 0.00)</td>
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<tr>
<td>02 Aripiprazole NPI Total</td>
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</tr>
<tr>
<td>CN-138 004</td>
<td>357</td>
<td>-18.07 (19.64)</td>
<td>117</td>
<td>-12.95 (19.79)</td>
</tr>
<tr>
<td>CN-138 005</td>
<td>126</td>
<td>-16.43 (21.95)</td>
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<td>-10.01 (22.00)</td>
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<tr>
<td>CN-138 006</td>
<td>103</td>
<td>-11.20 (23.65)</td>
<td>100</td>
<td>-9.71 (21.50)</td>
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<td>Test for heterogeneity: CH² = 1.56, df = 2 (P = 0.46), I² = 0'</td>
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<td>03 Aripiprazole GMI Total</td>
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<tr>
<td>CN-138 004</td>
<td>347</td>
<td>-10.67 (15.09)</td>
<td>115</td>
<td>-6.60 (13.12)</td>
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<tr>
<td>CN-138 005</td>
<td>129</td>
<td>-10.25 (16.74)</td>
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<td>-6.16 (16.72)</td>
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<td>CN-138 006</td>
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<td>-9.09 (15.60)</td>
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<td>Subtotal (95% CI)</td>
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<tr>
<td>Test for heterogeneity: CH² = 0.00, df = 1 (P = 0.08), I² = 0'</td>
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<tr>
<td>Test for overall effect: Z = 3.14 (P = 0.00)</td>
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<tr>
<td>04 Olanzapine BPRS Total</td>
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</tr>
<tr>
<td>HGEU</td>
<td>116</td>
<td>-5.97 (9.90)</td>
<td>33</td>
<td>-1.10 (11.10)</td>
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<tr>
<td>HGGU</td>
<td>182</td>
<td>-3.50 (10.40)</td>
<td>84</td>
<td>-3.70 (9.30)</td>
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<tr>
<td>HQIV</td>
<td>470</td>
<td>-7.63 (9.35)</td>
<td>125</td>
<td>-6.90 (11.90)</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>769</td>
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<td>242</td>
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<td>Test for heterogeneity: CH² = 2.04, df = 2 (P = 0.32), I² = 32.0</td>
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<td>Test for overall effect: Z = 1.17 (P = 0.2)</td>
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<td>05 Olanzapine NPI Total</td>
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<tr>
<td>HGEU</td>
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<td>-14.25 (24.40)</td>
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<td>-10.40 (27.50)</td>
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<td>HGGU</td>
<td>193</td>
<td>-18.80 (22.80)</td>
<td>91</td>
<td>-12.30 (22.00)</td>
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<tr>
<td>HQIV</td>
<td>513</td>
<td>-16.10 (18.90)</td>
<td>139</td>
<td>-13.70 (20.30)</td>
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<td>Subtotal (95% CI)</td>
<td>861</td>
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<td>265</td>
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<td>Test for heterogeneity: CH² = 0.06, df = 2 (P = 0.62), I² = 0'</td>
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<td>Test for overall effect: Z = 2.20 (P = 0.03)</td>
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</tbody>
</table>

Note: The image includes graphical representations of the data with error bars indicating the weighted mean differences (WMD) and 95% confidence intervals (CI) for each comparison.
<table>
<thead>
<tr>
<th>Study</th>
<th>Measure</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Test for heterogeneity</th>
<th>Test for overall effect</th>
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<tbody>
<tr>
<td>06 Quetiapine</td>
<td>BPRS Total</td>
<td>124</td>
<td>-9.06 (11.07)</td>
<td>not applicable</td>
<td>Z = 1.74 (P = 0.06)</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>124</td>
<td>-6.74 (9.88)</td>
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<tr>
<td>07 Quetiapine</td>
<td>PANSS EC</td>
<td>241</td>
<td>-5.40 (7.35)</td>
<td>not applicable</td>
<td>Z = 1.67 (P = 0.10)</td>
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<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>241</td>
<td>-4.20 (7.23)</td>
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<tr>
<td>08 Quetiapine</td>
<td>CMAI Total</td>
<td>27</td>
<td>-4.00 (15.40)</td>
<td>not applicable</td>
<td>Z = 0.50 (P = 0.61)</td>
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<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>27</td>
<td>-6.20 (17.63)</td>
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<tr>
<td>09 Risperidone</td>
<td>Behav AD</td>
<td>149</td>
<td>-6.80 (9.77)</td>
<td>Ch²= 11.20, df = 3 (P = 0.01), I² = 73.2%</td>
<td>Z = 3.35 (P = 0.0001)</td>
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<tr>
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<td>Total</td>
<td>152</td>
<td>-2.30 (9.86)</td>
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<td>Subtotal (95% CI)</td>
<td>921</td>
<td>-4.20 (7.61)</td>
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<td>10 Risperidone</td>
<td>CMAI Total</td>
<td>149</td>
<td>-7.80 (12.21)</td>
<td>Ch²= 1.60, df = 2 (P = 0.43), I² = 0%</td>
<td>Z = 4.83 (P &lt; 0.0000)</td>
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<tr>
<td></td>
<td>Total</td>
<td>152</td>
<td>-3.10 (11.84)</td>
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<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>427</td>
<td>-1.60 (6.65)</td>
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<tr>
<td>11 Risperidone</td>
<td>BPRS Total</td>
<td>193</td>
<td>-3.10 (9.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>193</td>
<td>-3.70 (9.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Risperidone</td>
<td>NPI Total</td>
<td>190</td>
<td>-9.70 (19.50)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>190</td>
<td>-12.30 (22.00)</td>
<td></td>
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</tr>
</tbody>
</table>

Schneider et al 2006

**Quetiapine**
- Mean [CI]: -2.32 [-4.93, 0.29]

**Risperidone**
- Mean [CI]: -1.40 [-3.14, 0.34]
Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE-AD)

Largest trial evaluating atypical antipsychotic use for treatment of psychosis, agitation or aggression in persons with dementia

- 421 community dwelling persons with AD followed for 36 weeks
- Randomized to risperidone, olanzapine, quetiapine, or placebo

Outcomes

1. Time to discontinuation (any reason) → no statistical difference

2. Time to discontinuation due to lack of efficacy → favor olanzapine (OR 0.51, 0.35 to 0.74; p > 0.001) and risperidone (OR 0.61, 0.41 to 0.89; p = 0.01)

3. Time to discontinuation due to adverse events → favor quetiapine (HR 3.58, 1.44 to 8.91; p = 0.006) and placebo

Schneider et al 2006
Most Recent Meta-Analysis of Atypical Antipsychotics for Treatment of BPSD (Tampi et al 2016)

- **Yury et al 2007 (7 RCTs)** overall mean effect size for atypical antipsychotics on BPSD 0.43 in comparison to placebo 0.26
- **Katz et al 2007 (4 RCTs)** risperidone in patients with AD/mixed dementia
  - improvement on behave AD (psychosis subscale (0.87 for Risperdal vs 0.57 placebo
- **Maher et al 2011 (18RCTs)**: aripiprazole, olanzapine, risperidone overall effect size (0.12-.20) with no significant effect for quetiapine
  - Higher doses of aripiprazole (10mg/day) and risperidone (2mg/day) may be more effective for BPSD
- **Cheug et al 2011 (5RCTs)**: improvement on NPI and CGI for quetiapine vs placebo
- **Ma et al 2014 (16RCTs)**: improvement on several rating scales (BPRS, NPI, CGI) in comparison to placebo
- **Wang et al 2015 (6RCTs)**: improvement with olanzapine and aripiprazole on NPI
- **Tran et al 2015 (23 RCTs)**: improvement in NPI only for aripiprazole and improvement in BEHAVE AD only for risperidone
- **Stinton et al 2015**: improvement on NPI in patient with DLB for olanzapine but not quetiapine
Antipsychotics: Lewy Body Dementia (DLB) & Parkinson Disease Dementia (PDD)

• High prevalence of BPSD and psychosis
• High risk for worsening motor symptoms with high potency antipsychotics (D2)
• First line treatment: donepezil/rivastigmine for reducing BPSD in PD & DLB \( (Rolinski \ et \ al \ 2012)\)
• If an antipsychotic is necessary...
  • Quetiapine: doses of 100-200mg/day are generally needed to see an antipsychotic effect
  • Clozapine: requires registration with a national database and routine blood monitoring due to risk for agranulocytosis
  • Primvanserin: FDA approved PD psychosis in 2016 with no D2 receptor activity
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose (daily)</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2.5 - 10 mg</td>
<td>Cerebrovascular events, death, extrapyramidal symptoms, falls, metabolic syndrome, neuroleptic malignant syndrome, QTc prolongation, sedation, sexual dysfunction</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5 - 10 mg</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.25 - 2 mg</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25 - 200 mg</td>
<td></td>
</tr>
</tbody>
</table>
1. Assess for type, frequency, severity, pattern and timing of BPSD
2. Assess for pain and other potentially modifiable factors that may influence treatment choice
3. Use a quantitative measure to assess response to treatment
4. Document treatment plan that includes person centered non-pharmacological & pharmacological interventions as indicated
5. Only use nonemergency antipsychotic medications for treatment of agitation or psychosis when symptoms are severe, dangerous, or cause significant distress
6. Review clinical response to non-pharmacological interventions prior nonemergency use of antipsychotic medications
7. Before nonemergency antipsychotic medications are used potential risks/benefits must be assessed by the clinician and discussed with the patient, family, or surrogate decision maker
8. If risk/benefit assessment favors use of an antipsychotic medications, low dose should be initiated and titrated up to the minimum effective dose
APA Practice Guidelines (Reus et al 2016)

9. If clinically significant side effects occur, potential benefits/risks should be reviewed by the clinician to determine if tapering/discontinuing medication is indicated.

10. If there is no clinically significant response after 4 weeks of an adequate dose antipsychotic medications should be tapered/discontinued.

11. If there has been a positive response initiate discussion about possible taper, review goals, patient preferences, observed response, side effects, potential risks, and past experiences with antipsychotic medications including past tapers.

12. If there has been an adequate response, attempt to taper/discontinue antipsychotic medications within 4 months is recommended unless there was a recurrence of significant symptoms with previous taper.

13. If antipsychotic medication is tapered, monthly reassessment of symptoms is recommended during taper and for 4 months after medication is discontinuation to identify signs of recurrence.

14. In the absence of delirium, if nonemergency antipsychotic medication is indicated, haloperidol should not be the first line agent.

15. In patients with dementia with psychosis or agitation, long acting injectable should not be utilized unless indicated fora chronic co-occurring psychotic disorder.
Thank you!
RECORDING OF SESSION TO END
CASES

**DO NOT INCLUDE:**
- Names
- Address
- DOB
- Phone/Fax #
- Email address
- Social Security #
- Medical Record #

The discussion and materials included in this conference are confidential and privileged pursuant to 26VSA Section 1441-1443. This material is intended for use in improving patient care. It is privileged and strictly confidential and is to be used only for the evaluation and improvement of patient care.
**SESSIONS ARE ON WEDNESDAYS FROM 12:00PM TO 1:30PM**

<table>
<thead>
<tr>
<th>Dates</th>
<th>Session</th>
<th>Didactic Topics (in addition to case review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 19</td>
<td>TeleECHO Session 1</td>
<td><strong>Attention Deficit Disorder – Diagnosis</strong> (Sara Pawlowski, MD)</td>
</tr>
<tr>
<td>Feb 2</td>
<td>TeleECHO Session 2</td>
<td><strong>Attention Deficit Disorder – Management</strong> (Sara Pawlowski, MD)</td>
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<tr>
<td>Feb 16</td>
<td>TeleECHO Session 3</td>
<td><strong>Resistant Depression</strong> (Evan Eyler, MD)</td>
</tr>
<tr>
<td>Mar 2</td>
<td>TeleECHO Session 4</td>
<td><strong>Management of Sleep Disruption (including menopause) and Impact on Mental Health</strong> (Jess Oehlke, MD)</td>
</tr>
<tr>
<td>Mar 16</td>
<td>TeleECHO Session 5</td>
<td><strong>Role of Electroconvulsive Therapy</strong> (Evan Eyler, MD)</td>
</tr>
<tr>
<td>Mar 30</td>
<td>TeleECHO Session 6</td>
<td><strong>Mental Health in Patients with Substance Use Disorders</strong> (Speaker TBD)</td>
</tr>
<tr>
<td>Apr 13</td>
<td>TeleECHO Session 7</td>
<td><strong>Eating Disorders</strong> (Kathy Mariani, MD)</td>
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<tr>
<td>Apr 27</td>
<td>TeleECHO Session 8</td>
<td><strong>Chronic Pain and Mood Disorders</strong> (Mark Pasanen, MD)</td>
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<tr>
<td>May 11</td>
<td>TeleECHO Session 9</td>
<td><strong>Mental Health in the Elderly</strong> (Jennifer Hall, DO)</td>
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<tr>
<td>May 25</td>
<td>TeleECHO Session 10</td>
<td><strong>Bipolar Disease – Diagnosis</strong> (Suzanne Kennedy, MD)</td>
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<tr>
<td>June 8</td>
<td>TeleECHO Session 11</td>
<td><strong>Bipolar Disease – Management</strong> (Suzanne Kennedy, MD)</td>
</tr>
<tr>
<td>June 22</td>
<td>TeleECHO Session 12</td>
<td><strong>Resistant Anxiety</strong> (Jessica O’Neil, DO)</td>
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</table>
CONCLUSIONS

• Slides are posted at [www.vtahec.org](http://www.vtahec.org)
• Volunteers to present cases (this is key to the Project ECHO model)
  • Please submit cases to [Mark.Pasanen@uvm.edu](mailto:Mark.Pasanen@uvm.edu)
• Please complete evaluation survey after each session
• Once your completed evaluation is submitted, CE information will be emailed.
• Please contact us with any questions, concerns, or suggestions:
  • [Mark. Pasanen@uvm.edu](mailto:Mark. Pasanen@uvm.edu)
  • [Elizabeth.Cote@uvm.edu](mailto:Elizabeth.Cote@uvm.edu)