Spring 2013 Geriatric Health Lecture Series on Alzheimer’s Disease and Related Issues

Bipolar Disorder in the Elderly

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Learning Objectives

By the end of this lecture, you should be able to:

- Describe the criteria for diagnosis of bipolar disorder and differential diagnosis.
- Discuss the longitudinal course of bipolar disorder and its unique aspects in the elderly.
- List the major pharmacologic treatment options for mania and for bipolar depression.

A non-508-compliant streaming video of this lecture and related self-test is available on the NWGEC website (Bipolar Online Lecture, http://nwgec.org/educational-opportunities/lectures/online-videos/bipolar-disorder).

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Bipolar Disorder in the Elderly

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May 21, 2013

Overview

• Context and Epidemiology
• Diagnosis and Subtypes
• Association with Dementia
• Treatment
• Summary
Significance and Context

• Bipolar disorder w/significant disability

• Elders: treatment complex
  – Medical comorbidity
  – Increased risk for adverse drug side-effects

• Few studies in elderly
  – Most guidelines based on mixed-age studies

Epidemiology

• Lifetime prevalence 4%
• Equal prevalence males and females
• Less common in the elderly
• Geriatric Bipolar Disorder
  – 0.1-1.0% Community
  – 10% in hospitals, Long term care
  » RC Kessler et al, Arch Gen Psych 2005
  » J Unutzer et al, Psychiatr Serv 1998
  » RN Hirshfiek J Clin Psych 2003
  » A Vasudev Maturitas 2010
Bipolar Disorder Prevalence

Kessler et al., Arch Gen Psych 2005 62(6) 593

I'm having some troubles at work and in my marriage.

Sounds like you're bipolar!

Support your loved one.
Definition of Bipolar Disorder

- Mood disorder with alternating mood states of depression or mania
- Depression: criteria for Major Depression
- Mania: at least 4-7 days
- Mixed state: both depressed and manic
  – depressed, SI, energized, agitated

Bipolar-Depressed State

- Depressed mood, fatigue, guilt
- Sleep and appetite increased
- More episodes of depression than mania
- Earlier onset than unipolar depression
- Severe: psychotic or catatonic
Bipolar-Manic State

- Mood: Expansive, euphoric, irritable
- Other symptoms: require 3-4
  - Energized
  - Decreased sleep
  - Talkative, Racing thoughts, distractible
  - Grandiose,
  - Increased activities
  - Impulsive with money, sexual, travel

Psychotic if severe—religious delusions, grandiose delusions, paranoia

Bipolar Types

- Bipolar I
  - Severe mania and depression
- Bipolar II
  - Mild mania, Hypomania and depression
- Rapid cycling: >=4 episodes/yr
- Late onset: Onset age >= 50
Clues that Suggest Bipolar Disorder

• Early age onset of depression
• Family history of bipolar disorder
• More functional impairment, less well
• Refractory, repeated depression with ↑ sleep, appetite, fatigue, SAD
• Switch to mania with antidepressants

» Muzina 2007

Bipolar subtype by onset

• Late onset (>50 yrs old)
  – Often presents with mania
  – ↑ neurologic illness, white matter lesions
  – Risk for stroke and dementia

• Early onset (<50 yrs)
  – Stronger family history of bipolar disorder
  – More substance use 40% young ~ 15% elders

A. Vasudev Maturitas, 2010
Case: Early onset bipolar disorder

• Dr M retired professional, now disabled
• Alcohol dependence for many years
• Noncompliant with medication for first 30 yrs
• Numerous episodes of mania and depression
• Refractory mania with persistent psychosis and dementia
• Homeless, hoped to be institutionalized

Case: Late onset bipolar disorder

• Ms M was a retired teacher 66 yo woman
• History of depression, anxiety, no mania
• Developed pressured speech, numerous projects, insomnia, increased spending
• Refused treatment
• Committed as gravely disabled-released
• Travelled to Southwest
• Incarcerated and recommitted
Medical Causes of Manic States

Focal: Right side CNS lesion
Frontotemporal Dementia
Seizures: temporal lobe
Neurosyphillis, HIV encephalopathy
Multiple sclerosis
Hyperthyroid
Pheochromocytoma
Lupus

Medications that may cause Mania

Steroids
Cholinesterase Inhibitor
Bronchodilators, theophyline
Amphetamines, cocaine
Dopamine agonists, L-DOPA
Stimulants, Caffeine, Pseudophed
Antidepressants
Case

- Mr A was 61 yo man
- Admitted for chemotherapy for brain CA
- Received high dose steroids
- Increased irritability, pressured speech, insomnia, paranoia, grandiosity
- Threatened staff and AMA discharge
- Responded to DC of steroids and rx with antipsychotics

Medical Illness in Elderly with Bipolar Disorder

- Average 3-4 medical conditions
- Diabetes II (33%), Respiratory, Cardiovascular
- Cognitive disorders 4-19%

SV Lala J Geriatr Psych Neruol 2012 25:20
Mood Episodes Increase Risk for Dementia

- Severe mood episodes and dementia risk
- All hospitalizations 1970-1999 in Denmark
- Approx 23,000 pts, ~4000 bipolar pts
- 60-68% female, ages 52-58
- Mania: 6% increase dementia/episode
- Depression: 13% increase dementia/episode

Tsai, Am J Geriatr Psych 2009

Cognition and Bipolar Disorder

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bipolar Disorder (N = 59), N (%)</th>
<th>Comparison Group (N = 59), N (%)</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal education-adjusted MMSE scores</td>
<td>19 (32.2)</td>
<td>2 (3.4)</td>
<td>16.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medical comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>26 (44.1)</td>
<td>41 (69.5)</td>
<td>7.50</td>
<td>0.006</td>
</tr>
<tr>
<td>Previous diagnosis or awareness of hypertension</td>
<td>14 (23.7)</td>
<td>30 (50.9)</td>
<td>7.26</td>
<td>0.007</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>16 (27.1)</td>
<td>8 (13.6)</td>
<td>2.50</td>
<td>0.113</td>
</tr>
<tr>
<td>Atopic diseases</td>
<td>12 (20.3)</td>
<td>2 (3.4)</td>
<td>5.79</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Tsai, Am J Gerait Psych 2009
Dementia and Lithium

- Does lithium affect cognitive function
- Bipolar ds, mean duration>25 years
- 60+, current euthymic and treated
- Prevalent Alzheimer’s 13%
- Lithium compared to other treatment
- Mean lithium treatment 6 yrs

Alzheimers Disease and Lithium Treatment

Nunes et al, BJp 2007; 190:359
Lithium Associated with Decreased Risk of Dementia

- 10 yrs of data Danish medical registry 1995-2005
- Hospital dx bipolar disorder
- Approximately 5000 pts, age 52, 60% female
- Lithium-50% Mood stabilizers-37%

Kessing et al, Bipolar ds 2010 12:87

<table>
<thead>
<tr>
<th>Number of prescriptions</th>
<th>Lithium RR (95% CI)</th>
<th>Anticonvulsants RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2-4</td>
<td>0.46 (0.21–1.01)</td>
<td>1.49 (0.53–4.19)</td>
</tr>
<tr>
<td>5-9</td>
<td>0.38 (0.16–0.86)</td>
<td>1.81 (0.66–5.01)</td>
</tr>
<tr>
<td>10-19</td>
<td>0.39 (0.19–0.81)</td>
<td>2.24 (0.86–5.81)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>0.44 (0.23–0.85)</td>
<td>1.05 (0.38–2.93)</td>
</tr>
</tbody>
</table>

Lithium Neuroprotective Effects

BS Diniz 2013, Neuropsych Dx and Treatment
General Treatment Issues

• Collaborative Model
• Educate-compliance
  – More episodes $\rightarrow$ severe, refractory disorder
• Monitor: early signs of relapse/communicate
• Regular schedule
  – Insomnia $\rightarrow$ mania
• Collateral information from family
  – (SI, substance, function)

Treatment of Bipolar Disorder

- Mania
- Depression
- Maintenance
Treatment of Bipolar Mania

- Lithium
- Valproic acid
- Atypical antipsychotic

Treatment of Mania in the Elderly

- Valproic acid
  - Less neurotoxicity
  - Mixed episode, rapid cycling
- Consider lithium if prior use of it
- Atypical antipsychotic: if psychotic
  - Or need rapid response
- Neurologic illness: worse response
- Ensure Sleep
Lithium

• Indications: Mania or depression
• Benefits: Decr Suicide
• Side-effects:
  – GI, diarrhea, tremor, EPS acne, bradycardia
  – Renal and thyroid

Lithium Clearance

• Renally excreted
• Increased Lithium/Toxicity levels with:
  – NSAIDS
  – Diuretics: HCTZ
  – ACE inhibitors
  – Low sodium diet
  – Age: increased brain/sera levels
Lithium Toxicity

- NARROW therapeutic index

- Symptoms of toxicity:
  - slurred speech, ataxia, tremor, diarrhea, delirium

**Toxicity may occur at therapeutic levels**
- Levels young 1.0-1.5
- Levels Elderly 0.4-0.8

Valproic Acid

- Indications: Mania
- More effective than Lithium for mixed mania and rapid cycling
- Side-effects: sedation, ↑weight, hair loss, liver, intention tremor, ↓plts ↑ammonia
- Less discontinuation than lithium
Valproic Acid Use in the Elderly

- Well tolerated in elderly
- No controlled studies for mania in elderly
- Extrapolated from mixed age studies
- Mania: start 250 BID
- Mania with dementia:
  - 125 BID, increase slowly by 125 qd

Valproic Acid Metabolism

- Metabolism: hepatic
- Clearance in the elderly by 40%
- Valproic acid drug interactions
  - ↓ dilantin levels
  - ↑ lamotrigine levels
- Adjust level to therapeutic response,
- In mania level ~ 65-90 (same as young)
Caution: Valproic Acid

- Encephalopathy, ammonia levels
- Free serum valporait
- Protein binding
- Asa, warfarin, dig, dilantin

Adverse Events with Lithium and Divalproex in Elderly NH Patients

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Lithium Carbonate (n = 28)</th>
<th>Divalproex Sodium (n = 44)</th>
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</thead>
<tbody>
<tr>
<td>Toxicity and/or dehydration*</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>MICU hospitalizations</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Leukocytosis*</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Hepatotoxicity†</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total occurrences</td>
<td>32</td>
<td>10</td>
</tr>
</tbody>
</table>

MICU = medical intensive care unit.
*As evidenced by an increased serum level over therapeutic levels (lithium, 0.6 to 1.2 mEq/L; divalproex, 50 to 120 µg/mL) and/or clinical signs or symptoms.
†Indicated by abnormal values on serum test results.

Conney Am J Managed Care 1999, 197
Case Lithium toxicity

- Mr. G treated with lithium
- Rxed ibuprofen after dental procedure
- Developed N&V, tremor, diarrhea
- Presented to ED and discharged
- Presented to another ED next day
- Severe lithium toxicity
- Residual
  - Extended hospitalization and rehab
  - Dysphagia, ataxia, memory loss
Atypical Antipsychotics

- FDA approved for mania
  - Olanzapine (zyprexa)
  - Risperidone (Risperidol)
  - Aripiprazole (Abilify)
  - Quetiapine (Seroquel)
  - Ziprasidone (Geodon)

- Europe: first line for mania, US mood stabilizers first line

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<thead>
<tr>
<th></th>
<th>Benefits</th>
<th>Adverse</th>
<th>Dose mg</th>
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<tbody>
<tr>
<td>Quetiapine</td>
<td>Least EPS, Sedating</td>
<td>Postural BP</td>
<td>12.5-200</td>
</tr>
<tr>
<td>(Seroquel)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>More potent, ~Metabolic</td>
<td>EPS, Postural BP</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>(Risperidol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Low EPS, Low Postural BP</td>
<td>Metabolic, Weight</td>
<td>5-10</td>
</tr>
<tr>
<td>(Zyprexa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Low sedation, Low metabolic</td>
<td>Akathisia, Anxiety</td>
<td>10-15</td>
</tr>
<tr>
<td>(Abilify)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Low sedation, Low metabolic</td>
<td>Qtc 20 msec</td>
<td>20 BID</td>
</tr>
<tr>
<td>(Geodon)</td>
<td></td>
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</table>
Antipsychotics and Mortality

• ↑Mortality and stroke in dementia pts
  • FDA advisory 2005
• Review 17 placebo studies with atypicals
  – Mortality:HR 1.6, absolute risk 1-2%
  – CVA, absolute risk 1%
• Recent studies: Increased mortality risk with typical antipsychotics

Treatment of Bipolar Depression

- Lithium
- Lamotrigine
- Atypical Antipsychotic
- Antidepressant
Bipolar depression and antidepressants

• Depression is more common, refractory

• Mood stabilizers: if severe symptoms
  – Lamotrigine: slow titration upward
  – Lithium: hx of lithium rx, suicide prevention

• Antipsychotics: olanzapine, quetiapine

• Antidepressants → switch but risk less in elderly

Lamotrigine

• Indications: Bipolar depression
• Side effects: headache, nausea, rash,
• Lamotrigine: Start 25 mg increase slowly
  – (12.5 mg q/wk)
  – Target dose in Elderly 75-200 mg qd
  – COMPLIANT PT OR TOO RISKY
• Stevens Johnson syndrome
  – 1% of patients: ↑ high and rapid dose
  – Halve dose if given with valproic acid
**Maintenance Treatment**

- Continue mood-stabilizers indefinitely
- Decrease relapse and severity
- Prevent depression: Lamictal and Lithium
- Prevent mania: Lithium and Valproic acid
- Combination rx if needed
- Taper after stable for 6-12 months
Treatment Summary

• Bipolar depression
  – Lamictal or lithium
  – Lamictal or lithium or VPA + antidepressant
  – If hypomania → stop antidepressant

• Mania in elderly, r/o neurologic disease
  – Valproic acid—better tolerated in elderly
  – Lithium—prior lithium and normal renal function
  – Antipsychotic— if psychotic symptoms, rapid rx

Resources for Education and Support

• An Unquiet Mind, by Kay Jamison, PhD

• Depression and Bipolar Support Alliance
  www.dbsalliance.org

• NAMI: National Alliance for Mental Illness
  www.nami.org
Conclusions

• Bipolar ds less common in elderly
• Late onset associated with neurologic illness
• Bipolar disorder associated with dementia
• Recommend chronic treatment- need to consider phase of illness