Bipolar Disorders in Late Life

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Self-Assessment Question 1

As reported by Himmelhoch et al in 1980, comorbid conditions associated with poorer acute response to lithium in bipolar elders included which of the following:

a) Personality disorder

b) Substance abuse

c) Dementia

d) b and c

Self-Assessment Question 2

In elderly patients, factors that modify concentration/dose ratios of lithium include which of the following:

a) Treatment with thiazide diuretics
b) Treatment with nonsteroidal anti-inflammatory agents
c) Renal insufficiency
d) all of the above

Self-Assessment Question 3

Findings of a randomized controlled trial of valproate treatment of manic symptoms in dementia (Tariot et al, 2001) included which of the following:

a) Greater effect on psychotic symptoms with twice daily dosing
b) Side effects at low dose/concentration
c) Positive association between psychosis and response
d) a and c

Self-Assessment Question 4

A post-hoc analysis (Sajatovic et al, 2005) of findings from randomized, placebo controlled trials of continuation-maintenance treatment in bipolar patients aged 55 years and older found evidence of efficacy for which of the following:

a) nortriptyline

b) haloperidol

c) lamotrigine or lithium

d) carbamazepine

Self-Assessment Question 5

Which of the following does NOT characterize the long term outcome of elderly bipolar patients?

a) Preserved cognition

b) High mortality

c) Substantial utilization of services

d) Recurrent episodes

Outline

- Diagnosis, assessment
- Psychopathology
- Epidemiology
- Course
- Etiology and pathophysiology
- Pharmacotherapy and other treatment
- Main Points
- Suggested Readings
- Questions

Major Points

- Bipolar states in the elderly are heterogeneous and require careful differential diagnosis.
- Medical assessment is essential.
- Cognitive impairment is a frequent concomitant of bipolar disorders in the elderly.
- Evidence related to pharmacotherapy is limited.
- Some data are available to support use of: lithium, valproate/divalproex, or atypical antipsychotics for mania; lithium, lamotrigine, or some antidepressants for bipolar depression.

Differential Diagnosis of Mania in Elders

- The differential diagnosis is broad and includes:
  - bipolar manic and mixed states
  - schizoaffective disorder- bipolar type
  - schizophrenia
  - dementia
  - delirium
  - substance intoxication, and
  - mood disorder due to general medical conditions or induced by substances (e.g., medications)
- Lack of detection and misdiagnosis may be more likely in some settings --e.g., long term care homes

Geriatric Bipolar Disorder

- Bipolar Disorder
  - Early age at onset (recurrent bipolar disorder)
  - Late age at onset
    - new mania and new depressive episodes
    - new mania in recurrent major depression
    - family history often negative for bipolar disorder
- Mood disorder related to general medical conditions or substances including medications
  - family history often negative for bipolar disorder
  - commonly has late age at onset

Some Medical Causes of Mania: Disorders/Substances

- **Neurologic**
  - Dementia
  - Head injury
  - CNS tumor
  - Multiple sclerosis
  - Stroke
  - Epilepsy
  - Wilson's disease
- **Sleep apnea**
- **Vitamin B12 deficiency**
- **Endocrine**
  - Hypo- or hyperthyroidism
  - Hypercortisolemia
- **Infectious**
  - HIV
  - Syphilis
  - Lyme disease
  - Viral encephalitis
- **Toxic**
  - Medications (corticosteroids, amphetamines, and other sympathomimetics, L-DOPA)
  - Other substances

Adapted from Forester et al 2004

Heterogeneity in Bipolar Elders

Bipolar elders present with a broad range of age-associated factors that add to heterogeneity:

- clinical features
- prior illness course
- treatment history
- physical and psychiatric co-morbidity
- functional impairment
- psychosocial stressors
- outcomes

Assessment

- Psychiatric, medical/neurological, treatment history;
- Mental status examination;
- Physical/neurological examination;
- Clinical laboratory tests include TSH, folates, B12 EKG
- Neuroimaging when indicated --e.g., neurological signs/symptoms, abrupt late onset, presentation different from prior episodes

Manic Psychopathology

- Geriatric mania is qualitatively similar to mania in younger patients
- Hyperactivity, aggression, insomnia, and self-neglect pose risks to self and others
- Delusions, hallucinations can be present
- Lack of insight can be a challenge for management
- Some evidence for negative association between age and overall severity of mania
- Elders may cycle into depression more often

Broadhead & Jacoby 1990; Young et al 2007; Oostervink et al 2009

Cognitive Impairment

- Frequent in elders with mania
- Can be quantified by instruments such as Folstein Mini-Mental State (MMSE) or Mattis Dementia Rating Scale (DRS)
- Typically includes deficits in executive function, attention, memory, and processing speed
- Can improve with treatment
- Deficits may persist despite remission
- Mania in context of dementia is poorly characterized

Savard et al 1980; Lyketsos et al 1995; Wylie et al 1999; Bearden et al 2001; Gildengers et al 2004

Mood Rating Scales

- Used in research studies
- May aid clinical management
- Utility of self-report not clear in elders

- Depression (e.g., Hamilton; Montgomery Asberg
- Mania (e.g. Young; Blackburn; Bech-Rafaelsen)

Utilization of Services

In bipolar elders:

- High utilization
- Greater than in unipolar depression

Bartels et al 1997; Sajatovic et al 1997

Comorbid Substance Use

In a retrospective study:

- Frequently comorbid in elderly manic patients
- Associated with poor outcome of lithium treatment

Rate may be lower than in younger patients

Himmelhoch et al 1980; Cassidy et al 2001

Epidemiology of Late-Life Bipolar Disorder

- 5-19% among geropsychiatric admissions
- Low community prevalence (ECA study)
- Age of reported first manic episode in elderly patients is late on average, i.e., 6th decade
- Late-onset manic patients may be more likely to be male

Shulman & Post 1980; Glasser & Rabins 1984; Eagles & Whalley 1985

Behavioral Disability

- Common feature of early-life bipolar disorder
- Little studied in bipolar elders
- Associated with cognitive impairment

Bartels et al 2000; Gildengers et al 2007; Depp et al 2006

Etiology and Pathophysiology

- Abnormalities of brain morphology --e.g., signal hyperintensities-- are prevalent in elderly bipolar patients.
- In some but not all studies, late onset bipolar elders differ from those with early onset:
  - Lower rate of familial mood disorder
  - Higher rate of vascular risk factors
  - More co-morbid neurological and physical disorders
  - Greater abnormality on structural neuroimaging
  - More cognitive impairment

Steffens & Krishnan 1998; Wylie et al 1998; Cassidy & Carroll 2000

Mania in Neurological Disorders

- Mania can accompany stroke or other focal brain diseases, especially in right orbitofrontal and basotemporal areas

- Mania can occur in other neurological disorders
  - Huntington's disease
  - Multiple sclerosis
  - Dementia

Starkstein et al 1991; Shulman 1997

Psychosocial Factors

- Bipolar elders report lack of social support
- Bipolar elders residing in nursing home lack spouses
- Bipolar elders generate high caregiver burden
- Stressful life events precede mania in some bipolar elders

Bartels et al 1997; Beyer et al 2000

Course

- Depressive episodes can precede manic episodes by a decade
- High rate of relapse/recurrence, especially in those with neurological abnormality
- Excess non-suicide mortality on follow-up
- Excess emergent dementia

Shulman & Post 1980; Kessing & Nilsson 2003; Shulman et al 1992

Pharmacotherapy of Manic and Mixed Episodes

- Limited evidence in elders
- Remove antidepressants and stimulants
- Lithium and divalproex are widely used
- Atypical antipsychotics are often used
- Adverse effect burden associated with polypharmacy may be more poorly tolerated in elders
- Lithium monotherapy can be beneficial in elders

AlJurdi et al 2008; Shulman 2010

Pharmacotherapy of Manic Episodes in Partial Remission

- Absence of evidence in elders
- Combined regimens are often used: addition of an atypical antipsychotic or a mood stabilizer

Pharmacotherapy of Bipolar Depression: Even Less Evidence

- Initiate or optimize dose of current mood stabilizer
- Rationale for use of lithium includes anti-suicide effect and efficacy in preventing recurrence
- Possible role for adjunctive lamotrigine based on data from mixed-age patients and small open trials in elders
- Some atypical antipsychotics are approved (quetiapine, olanzapine-fluoxetine combination) but risk-benefit ratio not defined in bipolar elders
- Adjunctive antidepressants: unclear benefits vs. potential risks; SSRI or bupropion may cause less ‘switching’ than tricyclics

Muller-Oerlinghausen & Lewitzka 2010; Sajatovic et al 2011

ECT in Bipolar Elders

- Some evidence supporting efficacy in manic and mixed episodes, and in bipolar depression
- Can be used in pharmacologically resistant or intolerant patients, and in severe cases
- Clinicians often select bilateral electrode placement in younger manic/mixed patients
- Most clinicians avoid using lithium during acute ECT course (due to risk of severe delirium)

APA Task Force 2001

Continuation and Maintenance Pharmacotherapy

Psychoeducation and social support are especially important in long-term management

Pharmacotherapy:

- Continuation treatment --Mood stabilizers and atypical antipsychotics usually continued at stable doses for ≥ 6 months
- Maintenance pharmacotherapy --Indications and optimal conditions poorly defined; if feasible, avoid prolonged use of antidepressants or antipsychotics
- In placebo controlled RCTs, there was evidence for long-term efficacy of lithium and lamotrigine in participants aged >55 yrs

Sajatovic et al 2005

Pharmacokinetic Issues in Bipolar Elders

- Impaired renal function associated with age or renal disease reduces lithium clearance
- Decreased volume of distribution for lithium and other hydrophilic drugs
- These changes lead to higher lithium concentration/dose and longer time to steady state
- Low albumin concentration and other factors may lead to higher proportion of nonbound (free) valproate

Satlin et al 2005

Pharmacodynamic Issues

- Bipolar elders may be slow to improve --the optimal duration of a first treatment trial is not clear
- Optimal doses/concentrations are not defined
- Some older patients respond to low concentrations of lithium
- Patients with mild cognitive impairment or dementia may have slower/attenuated benefit and greater neurocognitive adverse effects

Van Der Velde 1970; Himmelhoch 1980; Shaffer & Garvey 1984; Young & Falk 1989

Tolerability of Pharmacotherapy

Drug selection takes into account:

- differing adverse effect profiles, e.g., greater sedation with divalproex vs. lithium
- different relative contraindications
- Individual patient's treatment history

Dose-adverse effect relationships:

- generally linear
- patients who benefit from low doses may avoid toxicity
- some elders --e.g., with dementia-- experience adverse effects of lithium or divalproex at low doses/concentrations

Himmelhoch et al 1980; Tariot et al 2001

Drug-Drug Interactions

Pharmacokinetic:

- Lithium:
  - thiazide diuretics reduce renal clearance
  - xanthines increase renal clearance
- Valproate:
  - carbamazepine induces CYP 450 and thus reduces valproate levels
  - aspirin reduces protein binding

Pharmacodynamic

- lithium: antipsychotics potentiate motor side effects
- divalproex: antipsychotics potentiate sedation

Laboratory Monitoring of Lithium in Elders

- Monitoring of ambulatory lithium treatment is often not optimal in elders
- Specialized nurse can improve quality of management

Fielding et al 1999

Adherence

Among bipolar elders, non-adherence is associated with:

- Lack of social support
- Adverse effects
- Complex regimens
- Cognitive impairment

Lithium

- Best studied medication for geriatric bipolar disorder
- One review identified various outcome measures obtained in 137 elders: 66% improved at 0.3-2.0 mEq/L
- Monotherapy can be effective

Young et al 2004; AlJurdi et al 2008; Shulman 2010

Lithium in the Elderly

- Baseline screening: renal function, electrolytes, TSH, fasting glucose, ECG
- Reduce standard adult dose by 33-50%
  --i.e., typical doses do not exceed 900 mg per day
- Avoid concentrations >1.2 mEq/L
- Serum concentrations poorly correlated with brain concentrations determined by spectroscopy

Forester et al 2004; Forester et al 2009

Lithium in the Elderly: Adverse Effects

- Hypothyroidism
- Mental slowing
- Polyuria, polydipsia
- Ataxia
- Tremor
- Cerebellar abnormalities
- Urinary frequency, renal failure
- Increase serum glucose/weight gain
- Peripheral edema

Valproate

- In studies involving 137 patients, doses and blood levels ranged widely: 250-2250 mg/day and 25-120 mcg/ml
- 59% of patients improved irrespective of drug levels
- Effect on geriatric mania comparable to lithium in a retrospective study
- More often prescribed than lithium in some reports

Young et al 2004

Valproate in the Elderly

- Baseline: weight, LFTs, CBC with platelets, ECG
- Starting dose: 125-250 mg/day
- Target dose: 500-1000 mg/day
- Usual therapeutic serum level range for geriatric mania overlaps younger patients,

  e.g., 60-100 mcg/ml
- A consideration in secondary mania

McDonald 2000

Valproate in the Elderly: Adverse Effects

- Sedation
- Nausea
- Tremor
- Weight gain
- Gait disturbance
- Hyperammonemia
- Delirium
- Hair Loss

Lamotrigine

- Adjunctive lamotrigine may be beneficial in geriatric bipolar I or II depression:
  - In one small series (n=5), 75-100 mg per day added to lithium or valproate; 3 had remission of symptoms, maintained at three months; well tolerated.
  - In another open study (n=57), at a mean dose of 151 mg/day, significant reduction in symptoms over 12 weeks; well tolerated.

Robillard et al 2002; Sajatovic et al 2011

Atypical Antipsychotics in Geriatric Bipolar Disorder

- Aripiprazole, clozapine, olanzapine, quetiapine, risperidone: benefit geriatric bipolar disorder in open label and retrospective reports
- Aripiprazole, asenapine, olanzapine, quetiapine, risperidone, or ziprasidone: approved by the FDA for the acute or maintenance treatment of bipolar mania in adults
- Quetiapine and olanzapine-fluoxetine combination: approved by the FDA for the acute treatment of bipolar depression in adults

Sajatovic et al 2005; Sajatovic et al 2008

Atypical Antipsychotics: FDA Indications for Adult Bipolar Disorder

	Mania and mixed episodes		Depressive episodes
	Monotherapy	Adjunct*	
aripiprazole	A & M	A &M	
asenapine	A	A	
olanzapine		A & M	
olanzapine-fluoxetine			A
quetiapine	A	A & M	A
risperidone	A	A	
ziprasidone	A	M	

* Adjunct to lithium or valproate

A: acute treatment; M: maintenance treatment

Atypical Antipsychotics in the Elderly: Adverse Effects

- Sedation
- Orthostatic hypotension
- Gait disturbance
- EPS/TD
- Weight gain/metabolic syndrome
- Cerebrovascular adverse events
- Increased mortality observed in patients with dementia

Young et al 2004; Mulsant & Pollock 2012

Tardive Dyskinesia: Rates in Adult vs. Elderly

- Conventional Antipsychotic Medications:
  - Year 1: Adult 5% Elderly 33%
  - Year 2: Adult 10% Elderly 50%
  - Year 3: Adult 15% Elderly 60%

- Atypical Antipsychotic Medications:
  - Year 1: Adult: 0.5% Elderly: 3%

Kane 1988; Jeste 1999; Jeste 2000; Csernansky 2002

2004 Consensus Recommendations on Treatment of Geriatric Mania

Severity	Psychosis	Mood Stabilizer	Antipsychotic	Antidepressant
Mild	No	Alone	No	D/C?
Severe	No	Alone or with antipsychotic	1st line: risperidone 1.25-3 mg/d olanzapine 5-15 mg/d 2nd line: quetiapine 50-250 mg/d	D/C
Severe	Yes	Combine with antipsychotic	As above	D/C

Alexopoulos et al 2004

Treatment Recommendations for Manic/Mixed States in Late Life

- 1st line: monotherapy - valproate or lithium
- Partial responders - add atypical antipsychotic
- For “treatment resistant” episode – consider clozapine or ECT
- No evidence-based guidance on duration of treatment, time to wait before augmentation, or use of other mood stabilizing anticonvulsants

Young et al 2004

Treatment Recommendations for Bipolar Depression in Late Life

- Monotherapy with mood stabilizer: e.g., lithium, divalproex, lamotrigine
- Quetiapine as monotherapy or adjunct
- Can combine mood stabilizer with antidepressant (SSRI, bupropion; avoid TCAs, SNRIs)
- ECT: especially for suicidal patient or patient with inadequate food/fluid intake

Young et al 2004

Main Points

1. Bipolar disorders in old age are heterogeneous.
2. Older bipolar patients frequently have vascular and neurological comorbidities, high service needs, and are at risk for poor outcomes.
3. Management typically focuses on pharmacotherapy with mood stabilizers, and use of simplest possible regimen.
4. Pharmacokinetic factors can alter drug dosing.
5. Dementia may reduce tolerability of treatment.

Suggested Readings

- Depp C and Jeste D: Bipolar disorder in older adults: a critical review. Bipolar Disorders, 2004. 6(5):343-67
- Mulsant BH and Pollock BG.: Psychopharmacology. In: Blazer DG, Steffens DC, (eds), Essentials of Geriatric Psychiatry, Second Edition. Arlington: American Psychiatric Publishing, 2012
- Young RC and Mahgoub N: Bipolar disorder. Mood Disorder in Late Life. Oxford Univ Press (in press)
- Young RC, Gyulai L, Mulsant BH, Flint A, Beyer JL, Shulman KI, and Reynolds CF: Pharmacotherapy of bipolar disorder in old age: review and recommendations. American Journal of Geriatric Psychiatry, 2004. 12(4): 342-357

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Self-Assessment Question 5

Which of the following does NOT characterize the long term outcome of elderly bipolar patients?

a) Preserved cognition

b) High mortality

c) Substantial utilization of services

d) Recurrent episodes

Self-Assessment Question Answers

1) d
2) d
3) b
4) c
5) a