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 divalproex treatment of manic symptoms in dementia (Tariot et al, 2001) included which of the following:

a) Greater effect on psychotic symptoms with bid dosing

b) Response of demented patients to valproate at low dose

c) Positive association between psychosis and response

Self-Assessment Question 4

A post-hoc analysis (Sajatovic et al, 2005) of findings from randomized, placebo controlled trials of continuation-maintenance treatment in BP 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) Lower than expected rate of cognitive impairment/dementia

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.
- Data on pharmacotherapy are limited
- Some data are available to support use of lithium, divalproex, atypical antipsychotics in mania and lithium, lamotrigine, some antidepressants in bipolar depression.

GERIATRIC BIPOLAR DISORDER

- Primary Bipolar Disorder
  - Early Onset (recurring in later years)
  - Late Onset (e.g. first episode at age ≥50)
- Secondary Bipolar Disorder (Mood disorder related to Medical disorders or treatments)
  - Family history often negative for Bipolar Disorder
  - "Secondary mania" more commonly has late onset
    - Neurological disorders and other general medical conditions
    - Substance-induced mania
    - Medication-induced mania

Differential Diagnosis of Mania

The differential diagnosis of BP manic and mixed states in late life is broad and includes:

- delirium
- dementia
- schizophrenia
- schizoaffective disorder- BP type
- drug intoxication, and
- mood disorder due to medical disorders or treatments

❖ Lack of detection and misdiagnosis are likely in some settings.

Some Medical Causes of Secondary Mania

- **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**
  - Substances
  - Medications (corticosteroids, amphetamines, and other sympathomimetics, L-DOPA)

Adapted from Forester et al. 2004

Heterogeneity in BP Elders

In these patients, age-associated factors add to heterogeneity.

BP elders have a broad range of:

- clinical features
- prior illness course
- treatment history
- medical and psychiatric co-morbidity
- functional status
- psychosocial circumstances
- outcomes

Assessment

- Psychiatric, medical/neurological, treatment history;
- Mental status examination;
- Physical/neurological examination
- Routine clinical laboratory tests
  - Include TSH, folate, B12
- EKG
- Neuroimaging when indicated

Manic Psychopathology

- 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.
- Geriatric BP disorder is qualitatively similar to syndrome in younger patients. Differences in profile intensity with age have been suggested.

  - **Broadhead and Jacoby 1990;Young and Falk 1989**

Cognitive Impairments

- Frequent in elders with mania
- Can be detected by instruments such as Folstein Minimental State (MMSE) or Mattis Dementia Rating Scale (DRS)
- Can include 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; Bearden et al 2001; Gildengers et al 2004; Wylie et al 1999; Lyketsos et al 1995**

Mood Rating Scales

- Used in research
- May aid clinical management
- Utility of self-report not clear in elders
- Both depression (e.g.Hamilton; Montgomery Asberg) and mania instruments have roles
- Examples of mania rating scales used in elders:
  - Young
  - Blackburn
  - Bech-Rafaelsen

Utilization of Services

- High utilization by BP elders
- Greater than elders with unipolar depression
  - **Bartels et al 1997; Sajatovic et al 1997**

Comorbid Substance Abuse

In a retrospective study

- Frequently comorbid in elderly BP manic patients
- Associated with poor outcome of lithium treatment
  - **Himmelhoch et al 1980**

Epidemiology

- 5-10+ % among geropsychiatric admissions
- Low community prevalence (ECA study)
- Age of first mania in elderly patients is late on average, e.g. 6th decade
- Late-onset manic patients are often male

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

Behavioral Disability

- Common feature of early life bipolar illness
- Little studied in BP elders
- Associated with neurocognitive impairment
  - **Bartels et al 2000**

Etiology and Pathophysiology

- Abnormalities of brain morphology, e.g. signal hyperintensities, are prevalent in elderly BP patients.
- Late onset vs early onset BP elders:
  - Lower rate of familial mood disorder
  - Greater rate of vascular risk factors
  - More neurological and medical disorders
  - Greater abnormality on brain imaging

- **Wylie et al 1998; Cassidy and Carroll 2000; Steffens and Krishnan 1998**

Mania in Neurological Disorders

- Mania can accompany stroke or other focal brain diseases (especially 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

- Older BP patients report lack of social supports
- BP patients residing in nursing home lack spouses
- High caregiver burden
- Life events precede mania in some elders

Beyer et al 2000, Bartels et al 1997

Course

- Depression can precede mania by a decade
- High rate of relapse/recurrence, especially with neurological abnormality
- Excess non-suicide mortality on follow-up
- Excess emergent dementia

Shulman & Post 1980; Kessing & Nilsson 2003

Pharmacotherapy of Manic and Mixed Episodes

- Lithium and valproate are widely used
- Second generation antipsychotics are often used adjunctively in acute care
- Side effect burden associated with polypharmacy may be more poorly tolerated in elders

Pharmacotherapy of Manic Partial Responders

Co-therapy regimens

- Add atypical antipsychotic or additional mood stabilizer
- Novel approaches include
  - Cholinesterase inhibition
  - Omega-3-fatty acids
  - Dietary depletion of tyrosine

Pharmacotherapy of BP Depression

- Initiate and/or optimize dose of current mood stabilizer
- Antidepressant combined with mood stabilizer is first line approach, although clinicians may delay antidepressant
- Rationale for lithium salts includes anti-suicide effect and efficacy in preventing recurrence
- Possible role for lamotrigine is based on data from mixed-age patients
- SSRI or bupropion as antidepressant may avoid ‘switching’ more closely associated with tricyclics

ECT in BP Elders

- Effective in manic and mixed episodes, and in BP 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
- Many clinicians avoid using lithium during ECT

APA Task Force, 2001

Continuation and Maintenance Pharmacotherapy

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

Pharmacotherapy

- Continuation treatment--mood stabilizers usually maintained at stable doses for $\geq$ 6 mo
- Maintenance pharmacotherapy--Indications and optimal conditions poorly defined; if feasible, avoid prolonged antidepressant/antipsychotic co-therapy.
- In patients aged >55 yrs participating in placebo controlled RCTs, there was evidence for efficacy of lithium and lamotrigine

Sajatovic et al 2005

Pharmacokinetic Issues in BP Elders

- Reduced renal function with age or renal disease reduces lithium clearance
- Decreased volume of distribution for lithium and other hydrophilic drugs
- Lithium- lower dose/concentration and longer time to steady state
- Low albumin concentration and other factors may lead to higher proportion of nonbound valproate.

Satlin et al 2005

Pharmacodynamics in Aged

- Older BP patients may be slow to improve- the necessary duration of first treatment trial is not clear
- Optimal doses/concentrations are not defined.
- Some patients respond to low concentrations, e.g. of lithium.
- Patients with mild cognitive impairment or dementia may have slower/attenuated benefit and greater neurocognitive side effects.

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

Tolerability of Pharmacotherapy

Drug selection takes into account:

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

Dose-side effect relationships:

- generally linear
- patients who benefit from low doses may avoid toxicity
- some elders, e.g. with dementia, experience side effects of lithium or valproate 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 reduces metabolic clearance
  - aspirin reduces protein binding

Pharmacodynamic

- Lithium: antipsychotics potentiate motor side effects
- Valproate: antipsychotics potentiate sedation

Laboratory monitoring of lithium in elders

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

Fielding et al 1999

Adherence

Among BP elders, non-adherence is associated with:

- Lack of social support
- Side effects
- Complex regimens
- Cognitive dysfunction

Consensus Practice Guidelines on the Treatment of Bipolar Disorder 2000

- Mood stabilizer in all phases of treatment
- Start with atypicals, not conventional antipsychotics, for initial treatment when antipsychotic is indicated
- Treat mild depression with mood stabilizer monotherapy initially, severe depression with antidepressant plus mood stabilizer from the start
- Treat rapid-cycling mania or depression initially with mood stabilizer alone

Sachs et al. Postgrad Med Special Report, April 2000.

Lithium

- Best studied medication for geriatric bipolar disorder
  - 4 lithium studies in older aged samples
  - Total N= 137
  - Trial durations: 2-10 weeks
  - Various outcome measures
  - 66% of all patients improved at various levels (0.3 - 2.0 mEq/L)

Young 2004.

Lithium in Elderly

- Reduce standard adult dose by 33-50%, i.e. often not exceeding 900 mg per day
- Baseline screening: renal function, electrolytes, TSH, fasting glucose, ECG

Forester et al. 2004

Adverse Effects of Lithium in the Elderly

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

Valproate

- Only 5 studies have assessed > 10 patients
- Total N studied = 137 elderly patients
- Dose range: 250 - 2250 mg/d (25 -120 mcg/ml)
- 59% of patients improved irrespective of drug levels.
- Effect on geriatric mania comparable to lithium in one retrospective report

Young 2004

Valproate in Elderly

- Screening labs: 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

  Eg 60-100 mcg/ml
- A consideration in secondary mania

McDonald 2000

Valproate in Elderly: Adverse Effects

- Sedation
- Nausea
- Tremor
- Weight Gain
- Gait disturbance
- Delirium
- Hyperammonemia

Lamotrigine

- Lamotrigine in geriatric bipolar depression[1]
  - Open label, 5 female inpatients (mean age = 71.5 years)
  - 75-100 mg per day added to lithium or divalproex
  - 3/5 had remission of symptoms, maintained at 3 months
  - Well tolerated, without rash

1. Robillard et al: *Can J Psychiatry* 2002;47:767-770

Atypical Antipsychotics in Geriatric Bipolar Disorder

- Open label and retrospective reports
- Clozapine, olanzapine, quetiapine, risperidone reported to benefit geriatric bipolar disorder
- Olanzapine, risperidone, quetiapine all FDA approved for mania (adults studied)
- Clozapine for treatment refractory illness, severe mania

Sajatovic, AAGP meeting, Baltimore, February 2004

Consensus Recommendation on Antipsychotics in Geriatric Mania

Severity	Psychosis	Mood Stabilizer	Antipsychotic	Antidepressant
Mild	No	Alone	No	D/C?
Severe	No	Alone or with APD	**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 APD	As above	D/C

Alexopoulos GS et al: J Clin Psychiatry 2004;65 Suppl 2:5-99.

Atypical Antipsychotics in Elderly: Side Effects

- Sedation
- Orthostatic Hypotension
- Gait Disturbance
- EPS/TD
- Weight gain/metabolic syndrome
- Cerebrovascular adverse events
- Increased mortality

Young 2004 and FDA

Tardive Dyskinesia: Rates in Adult vs. Elderly

- Conventional Antipsychotic Medications[1,2] :
  - Year 1: Adult 5% Elderly 33%
  - Year 2: Adult 10% Elderly 50%
  - Year 3: Adult 15% Elderly 60%
- Atypical Antipsychotic Medications[3,4]
  - Year 1 Adult: 0.3-0.6%
  - Year 1 Elderly: 2.6%

1. Kane 1988; 2. Jeste 1999; 3. Csemansky 2002; 4. Jeste 2000

Treatment Recommendations For Mania/Mixed States

- 1st line: Monotherapy - divalproex or lithium
- Partial responders - add atypical antipsychotic medication - olanzapine, risperidone, quetiapine (possibly aripiprazole)
- 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 2004

Treatment Recommendations for Bipolar Depression

- Monotherapy with mood stabilizer: lithium, lamotrigine, possibly valproate
- Partial responder: cautious addition of antidepressant (SSRI, bupropion, avoid TCA)
- ECT: especially for suicidal patient or patient with inadequate food/fluid intake

Young 2004

Main Points

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

Suggested Readings

- Evans DL. Bipolar disorder: diagnostic challenges and treatment considerations. Journal of Clinical Psychiatry 2000;61[Suppl 13]:26-31.
- McDonald WM. Epidemiology, etiology and treatment of geriatric mania. J Clin Psychiatry 2000;61[S13]:3-11.
- Shulman KI. Disinhibition syndromes, secondary mania, and bipolar disorder in late life. J Affective Disorders 1997;46:175-182.
- Young RC et al. Pharmacological management of bipolar disorder in old age. Am.J. Ger. Psychiatry 2004;12: 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?

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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