

# **Bipolar Disorders in Late Life**

**Robert C. Young, M.D.**

**Benoit H. Mulsant, M.D.**

***Departments of Psychiatry***

**Weill Medical College of Cornell University**

**University of Toronto**

# **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) Side effects at low dose in demented patients
- 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) 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.



# Differential Diagnosis of Mania in Elders

- ❖ The differential diagnosis is broad and includes:
  - BP manic and mixed states
  - delirium
  - dementia
  - schizophrenia
  - schizoaffective disorder- BP type
  - drug intoxication, and
  - mood disorder due to medical disorders or therapeutic agents
  
- ❖ Lack of detection and misdiagnosis are 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 depression episodes
    - ❖ new mania in recurrent major depression
    - ❖ family history often negative for bipolar disorder
- ❖ Mood disorder related to medical disorders or substances including therapeutic agents
  - ❖ 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**

- ❖ Drugs of abuse
- ❖ Medications (corticosteroids, amphetamines, and other sympathomimetics, L-DOPA)

# 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;
- ⌘ Clinical laboratory tests include TSH, folate, B12  
EKG
- ⌘ Neuroimaging when indicated e.g., neurological signs/symptoms, late onset, different presentation from prior episodes

# 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 mania is qualitatively similar to syndrome in younger patients.
- ❖ Effects of age *per se* on severity may be small

**Broadhead & Jacoby 1990; Young et al 2007**

# 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)
- ❖ 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; Lyketsos et al 1995; Wylie et al 1999; Bearden et al 2001; Gildengers et al 2004**

# Mood Rating Scales

- ❖ Used in research
- ❖ 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 BP elders:

- ❖ High utilization
- ❖ Greater than in 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

- ❖ 5-19 % among geropsychiatric admissions
- ❖ Low community prevalence (ECA study)
- ❖ Age of first mania in elderly patients is late on average, i.e., 6<sup>th</sup> decade
- ❖ Late-onset manic patients are often male

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

# Behavioral Disability

- ❖ Common feature of early-life bipolar illness
- ❖ Little studied in BP elders
- ❖ Associated with neurocognitive impairment

**Bartels et al 2000; Gildengers et al 2007**

# 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 structural neuroimaging

**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

- ❖ Older BP patients report lack of social support
- ❖ BP patients residing in nursing home lack spouses
- ❖ BP elders generate high caregiver burden
- ❖ Life events precede mania in some BP elders

**Bartels et al 1997; Beyer et al 2000**

# Course

- ❖ Depression 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**



# Pharmacotherapy of Manic and Mixed Episodes

- ❖ Limited evidence-base
- ❖ Remove antidepressants and stimulants
- ❖ Lithium and valproate are widely used
- ❖ Second generation antipsychotics are often used
- ❖ Side effect burden associated with polypharmacy may be more poorly tolerated in elders

# Pharmacotherapy of Manic Partial Responders

- ❖ Lack of empirical data
- ❖ Co-therapy regimens are used: add atypical antipsychotic or additional mood stabilizer
- ❖ Novel approaches
  - ❖ Cholinesterase inhibition
  - ❖ Omega-3-fatty acids
  - ❖ Dietary depletion of tyrosine

# Pharmacotherapy of BP Depression: Even Less Empirical Data

- ❖ Initiate and/or optimize dose of current mood stabilizer
- ❖ Rationale for lithium salts includes anti-suicide effect and efficacy in preventing recurrence
- ❖ Possible role for adjunctive lamotrigine is based on data from mixed-age patients
- ❖ Atypical antipsychotics (quetiapine, olanzapine-fluoxetine combination) are approved as monotherapy; risk-benefit ratio not defined in elderly BP patients.
- ❖ Adjunctive antidepressants: unclear benefits vs potential risks; SSRI or bupropion may cause less 'switching' than 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
- ❖ Most clinicians avoid using lithium during acute ECT course

**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  $\geq 6$  months
- ❖ 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 long-term efficacy of lithium and lamotrigine

**Sajatovic et al 2005**

# Pharmacokinetic Issues in BP Elders

- ❖ Impaired renal function associated 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 (free) 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 older patients respond to low concentrations of lithium.
- ❖ Patients with mild cognitive impairment or dementia may have slower/attenuated benefit and greater neurocognitive side effects.

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

# 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 induces CYP 450 and thus reduces valproate levels
- ❖ 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 is 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

# Lithium

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

# Lithium in Elderly

- ❖ Baseline screening: renal function, electrolytes, TSH, fasting glucose, ECG
- ❖ Reduce standard adult dose by 33-50%, i.e., often not exceeding 900 mg per day
- ❖ Avoid concentrations  $> 1.2$  mEq/L
- ❖ Concentrations 0.60 - 0.99 mEq/L may provide benefit

# Adverse Effects of Lithium in the Elderly

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

# Valproate

- ❖ Only 5 studies have assessed > 10 elderly patients
- ❖ Total N studied = 137
- ❖ 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

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



# Valproate in Elderly: Adverse Effects

- ❖ Sedation
- ❖ Nausea
- ❖ Tremor
- ❖ Weight Gain
- ❖ Gait disturbance
- ❖ Delirium
- ❖ Hyperammonemia
- ❖ Hair Loss

# Lamotrigine

- ❖ Open-lamotrigine in geriatric bipolar I or II depression
  - ❖ In one 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 a recent preliminary report (n = 51) there was significant reduction in symptoms over 12 weeks; well tolerated.

# Atypical Antipsychotics in Geriatric Bipolar Disorder

- ❖ Open label and retrospective reports
- ❖ Clozapine, olanzapine, quetiapine, risperidone aripirazole reported to benefit geriatric bipolar disorder
- ❖ Olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone all FDA approved for mania (adults studied)
- ❖ Clozapine for treatment refractory illness, severe mania
- ❖ Quetiapine and olanzapine-fluoxetine combination approved for depression (adults)

# Atypical Antipsychotics in Elderly: Side Effects

- ❖ Sedation
- ❖ Orthostatic Hypotension
- ❖ Gait Disturbance
- ❖ EPS/TD
- ❖ Cerebrovascular adverse events

# Antipsychotics: Excess Mortality

- ❖ “Clinical studies of ‘atypical antipsychotic drugs’ used ‘off-label’ to treat behavioral disorders in elderly patients with dementia have shown a 1.6-1.7 times higher death rate associated with their use compared to patients receiving a placebo.” Absolute risks not reported
- ❖ Aripiprazole, olanzapine, quetiapine, risperidone, clozapine, ziprasidone, and combination olanzapine and fluoxetine; all antipsychotics may be affected
- ❖ Death causes varied—most heart related (heart failure, sudden death) or infections (pneumonia)
- ❖ Implications for nondemented elderly are not clear

# Antipsychotics: Metabolic Effects

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/-	-	-
Ziprasidone	+/-	-	-

+ = increased effect      - = no effect      D = discrepant results<sup>1</sup>

▶ Diabetes and weight effects may attenuate with age<sup>2,3</sup>

1. American Diabetes Association. 2004.
2. Hammerman A, et al. 2008.
3. Trifirò G, et al.

# 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: 0.3-0.6%      Elderly: 2.6%

# Treatment Recommendations for Manic/Mixed States in Late Life

- ❖ 1st line: monotherapy - divalproex or lithium
- ❖ Partial responders - add atypical antipsychotic medication - risperidone, quetiapine, olanzapine, 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



# Treatment Recommendations for Bipolar Depression in Late Life

- ❖ Monotherapy with mood stabilizer: lithium, lamotrigine, possibly valproate when appropriate
- ❖ Atypical antipsychotics, e.g., quetiapine may have role as monotherapy or adjunct
- ❖ Can add/combine with mood stabilizer with antidepressant (SSRI, bupropion, avoid TCA)
- ❖ ECT: especially for suicidal patient or patient with inadequate food/fluid intake

# 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 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

- ❖ Evans DL. Bipolar disorder: diagnostic challenges and treatment considerations. *Journal of Clinical Psychiatry* 2000;61[S13]: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

# 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) Side effects at low dose in demented patients
- 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 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



# Self-Assessment Question Answers

1) d

2) d

3) b

4) c

5) a