Lithium and Mood Stabilizers in the Elderly

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Disclosures

• Research funding from:
  ▫ The Canadian Institutes for Health Research (CIHR)
  ▫ Ontario Mental Health Foundation
  ▫ McGill University

• Most of my research has been “pro-lithium”
  ▫ Although not always

• Relationships with commercial interests:
  ▫ None

Discussion of off-label use of therapies

• There will be some talk of off-label uses of anticonvulsants in BD
  ▫ (but emphasis will be on evidence-based treatment)
    ▫ Geriatric-specific data quite limited: mainly from uncontrolled, retrospective, open label, or secondary analysis studies.

Objectives

• To review the effectiveness of lithium and other mood stabilizers in geriatric bipolar disorder
• To provide an overview of physical adverse effect profile of these medications
• To learn approaches to safely prescribe lithium and other mood stabilizers in the elderly, using a case-based approach.
Who do we use anticonvulsants on? (In late-life BD)

- 82 year old man, DM2, HTN, multiple somatic “medical” medications, previously a lithium responder, however now with chronic kidney disease: eGFR of 35mL/min/1.73m². Currently on an antipsychotic, but in a hypomanic state.

- Which Drug would you use?
  - Carbamazepine
  - Valproate
  - Lamotrigine
  - Pregabalin
  - Lithium

Who do we use anticonvulsants on? (In late-life BD)

- 69 year old woman, BD type1, 1st manic episode at age 41. No family history of BD. Unclear history of possible stroke. Chronic moderate-severe depression (failed lurasidone).

- Which Drug would you use?
  - Carbamazepine
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  - Lamotrigine
  - Buproprion
  - Lithium

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  - Valproate
  - Lamotrigine
  - Buproprion
  - Lithium
Bipolar Disorder (DSM V)

- Bipolar Disorder, Type 1
  - Manic Episode (3/7 Sx lasting >7 days)
    - Depression and Cognitive Symptoms most difficult to treat

- Bipolar Disorder, Type 2
  - Hypomanic Episode (3/7 Sx lasting >4 days)
  - Depressive Episode
    - Bipolar 2 (and bipolar depression) often difficult to treat

DSM V

What’s Unique About Late-Life BD?

- 0.5-1% of seniors have BD
- Amongst late life mental illness – one of highest users of psychiatric and physical health services
- Only 5-10% of geriatric BD started > 50yo
  - Assoc. with white matter disease, CVA, other neurological illness, poorer treatment response
- Cognitive Dysfunction 30%
  - Mostly executive, slow processing speed, visiospatial dysfunction (not Alzheimer’s etiology)
- Medical Comorbidity (mean 3-4 physical conditions)
  - Cardiovascular risk, 15-years less life expectancy
  - Medication tolerability

Sajatovic et al 2015; Rej, Al-Jurdi, Sajatovic 2014; Tamashiro et al. 2008, Yu et al. 2015

Epidemiology of Late-Life BD

- 0.5-1% of older adults have BD
- 6% and 10% of geriatric psychiatry outpatients and inpatients, respectively
- <5-10% have onset at age>50 (often related to cerebrovascular or other physical/neurological comorbidity)
- Grand majority of cases have onset <50 (90-95%)
- 25% of BD patients are currently aged >60 (2015)
- By 2030, >50% of BD patients will be aged >60

Sajatovic et al. 2015, Sajatovic et al. 2005

Late-Life Bipolar Psychopathology

- Overall, geriatric mania is qualitatively similar to mania in younger patients
  - Hyperactivity, aggression, insomnia, and self-neglect pose risks to self and others
  - Some evidence for negative association between age and overall severity of mania
- Delusions, hallucinations can be present, although psychosis less common in older adults compared to younger BD patients
- Lack of insight can be a challenge for patient management
- Elders may be more prone to have depression more often
  - Depression and cognitive dysfunction most disabling aspects of late-life BD

Young et al 2007; Oostervink et al 2009, Sajatovic et al. 2015
Etiology and Pathophysiology

- Abnormalities of brain morphology -- e.g., white matter hyperintensities -- are prevalent in elderly BD patients.
- In some but not all studies, late onset BD 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

  Roles for inflammation, oxidative stress, and mitochondrial dysfunctions have been proposed

Steffens & Krishnan 1998; Wylie et al 1998; Cassidy & Carroll 2000; Vasudev and Thomas 2010; Berk 2011; Sajatovic et al 2014

Differential Diagnosis of Bipolar Disorder in Older Adults

- The differential diagnosis is broad and includes:
  - Bipolar manic and mixed episodes
  - Unipolar depression
  - Schizoaffective disorder - bipolar type
  - Schizophrenia
  - Major neurocognitive disorder (dementia)
  - Delirium
  - Substance intoxication, and
  - Substance/medication induced bipolar and related disorder
  - Bipolar and related disorder due to another medical condition

  Lack of detection and misdiagnosis may be more likely in some settings -- e.g., long term care homes

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
  - Hypercortisolism

- Infectious
  - HIV
  - Syphilis
  - Lyme disease
  - Viral encephalitis

- Toxic
  - Medications (corticosteroids, amphetamines, and other sympathomimetics, L-DOPA)
  - Other substances

Adapted from Forester et al 2004

Assessment

- Psychiatric, medical/neurological, treatment history;
- Mental status examination, including cognitive screen (e.g. Montreal Cognitive Assessment - MoCA)
- Physical/neurological examination;
- Clinical laboratory tests (for diagnosis and treatment planning) include TSH, CBC, liver function, renal function, electrolytes, calcium, folate, B12, EKG
- Neuroimaging when indicated -- e.g., focal neurological signs/symptoms, abrupt late onset, presentation different from prior episodes
What medications are being used in late-life BD?
- Canadian inpatient BD sample aged ≥66 (n=1433)
- Psychotropic polypharmacy highly prevalent (>81%)
  - Mean of 2.65 psychotropic medications
- Most common medications on psychiatric discharge:
  - Atypical antipsychotics (75.3%)
  - Benzodiazepines/zopiclone (42.3%)
  - Antidepressants (38.5%)
  - Valproate (35.4%) and lithium (23.4%).
  - 1.4% of patients on lithium monotherapy,
  - 4.4% and 15.7% on antidepressant or atypical monotherapy.
  - 8.9% using ≥2 atypical antipsychotics.
  - 6% lamotrigine, 4% carbamazepine

Rej et al presented at AAGP 2016

Pharmacokinetic Issues in Old Age
- 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 ratio and longer time to steady state
- Low albumin concentration and other factors may lead to higher proportion of non-bound (free) valproate
- Also drug interactions leading to toxicity are very common:

Satlin et al 2005, Rej et al. 2015

Drug-Drug Interactions

Pharmacokinetic:
- Lithium:
  - NSAIDs, ARBs, ACEIs, thiazide diuretics, loop diuretics can increase lithium levels up to 50%
- Valproate:
  - carbamazepine induces CYP 450 and thus reduces valproate levels
  - aspirin reduces protein binding
- Carbamazepine:
  - carbamazepine induces CYP 450 – poor choice for patients on many medications

Pharmacodynamic
- Lithium, valproate, antipsychotics - motor side effects
- Valproate, carbamazapine, antipsychotics – sedation/cognitive effects
- Lithium, valproate, antipsychotics – metabolic effects

Juurlink et al. 2004, Rej et al. 2015, Dols et al. 2014

Lithium
- Best studied medication for geriatric BD
- The gold-standard BD treatment: Helpful in mania, depression, and maintenance
- Monotherapy can be effective in up to 40% of late-life BD patients
- Some evidence for protective effects against suicide, neurocognitive disorder (dementia)

Young et al 2004; AlJurdi et al 2008; Shulman 2010; Cipriani et al 2013; Kessing 2008;
Prescribing Lithium

- Baseline screening: renal function, electrolytes, calcium, TSH, fasting glucose, urine osmolality, ECG
- Typical doses generally do not exceed
  - 600-900 mg per day at age >65
  - <300-600mg/day at age >75, and
  - <150-300mg/day at age >85
- Start at 150mg qhs
- Lithium levels: depression = 0.4-0.6, mania 0.4-0.8
- Avoid lithium levels >0.8 mEq/L
- Monitor lithium levels and eGFR every 3 months and 5-7 days after changing lithium dose/NSAID/ACEI/ARB/diuretic
- Serum lithium levels poorly correlated with brain concentrations determined by spectroscopy
  - i.e., To prevent neuro-toxicity, assess patient for cognitive dulling/fatigue, delirium, or neurological symptoms (e.g. tremor, rigidity)

Forester et al 2004; Forester et al 2009; Rej et al. 2013 and 2014

Lithium in the Elderly: Adverse Effects

- Hypothyroidism (30%)
- Hypercalcemia (relatively rare <5%)
- Acute Neurotoxicity
  - Mental slowing/Fatigue, ataxia, cerebellar abnormalities, falls
- Ataxia
- Tremor
- ?Parkinsonism
- Nephrogenic Diabetes Insipidus, Acute kidney injury
- Chronic Kidney Disease
  - Controversial – Up to 2X increased risk, can lower risk by monitoring Li/eGFR q3months, Li level <0.8mmol/L
- Weight gain (but ? Anti-diabetes mellitus effects)


Valproate - Pros

- Effective in mania, depression, and maintenance
  - Both as monotherapy and combination Tx
- Has 2nd most data in geriatrics
  - Rated by 60% of pts as “efficacious” (n=35)
  - Of late-life patients: women, younger-old, tol. higher valproate levels, had less psychotic symptoms (n=39)
- May require similar therapeutic levels (12-hour 350-700micromol/L) and lower doses than adults
  - Anecdotally, can often get away with low-end of therapeutic range or slightly “sub-therapeutic”


Anti-Cancer effects of Valproate?

- Valproate associated with 30% less Head +Neck Cancer
  - ? Related to GSK-3Beta Inhibition (like lithium)

Kang et al. 2014, Cancer
Valproate Prescribing

- Baseline blood tests:
  - weight, LFTs, CBC with platelets, ECG
- Starting dose:
  - 250-500 mg/day (usually divided in two daily doses)
- Target dose:
  - 500-1500 mg/day (can be higher in certain patients)
- Usual valproate level
  - 347-866 micromol/L (50-125 microgram/mL)
  - Aim for low dose/level wherever possible


Valproate - Cons

- Believed to be less effective than Lithium
  - Partly has to do with who is started on valproate – non-Li-responders, poorer physical status
  - Less positive drug attitudes in late-life valproate users
- Cognitive Dysfunction
  - higher risk of dementia, delirium
- Weight Gain, Sedation, (Common), Nausea, Tremor, Gait disturbance, Hyperammonemia, Delirium, Hair Loss (Less common), Fulminant hepatic failure (rare)
  - Associated with diabetes mellitus (DM)
  - May be even worse for DM than antipsychotics in older adults

Valproate increases risk

- Diabetes Mellitus
  - 1.5-2X prevalence in BD
  - Lithium may be protective (strong GSK3Beta inhibitor)
- Carbamazepine, Lamotrigine more neutral across studies

Lamotrigine - Pros

- First-line for bipolar depression
- In a geriatric multi-site open-label study (n=57)
  - 57% depression remission and 65% response
  - Helpful in patients with cerebrovascular risk profile
- Similar results in geriatric secondary analysis of a Lamotrigine/Lithium/Placebo RCT
- Relatively weight neutral
- Less cognitive side effects

Table 2

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>Valproate and insulin</td>
<td>1.6 (0.9-2.8)</td>
<td>1.8 (0.9-3.4)</td>
<td>1.7 (0.9-3.3)</td>
</tr>
<tr>
<td>Lamotrigine and insulin</td>
<td>2.0 (1.3-3.3)</td>
<td>3.0 (1.8-4.9)</td>
<td>2.4 (1.6-3.8)</td>
</tr>
<tr>
<td>Carbamazepine and insulin</td>
<td>1.4 (0.9-2.1)</td>
<td>1.6 (1.1-2.6)</td>
<td>1.4 (0.9-2.1)</td>
</tr>
</tbody>
</table>

Table 4

<table>
<thead>
<tr>
<th>Model</th>
<th>B (SE)</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>0.36 (0.30)</td>
<td>0.30</td>
<td>0.65</td>
</tr>
<tr>
<td>Step 3</td>
<td>0.27 (0.27)</td>
<td>0.27</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Lamotrigine - Cons

- Lack of Efficacy in mania
- Side effects
  - Hyponatremia (<130mmol/L: < 2%)
  - Hair loss, psoriasis, acne,
  - Rash
    - Benign “morbiliform” rash in 8-13% of pts
    - Risk minimized by slow dose titration
    - Often can have no rash with re-challenge (87%)
    - Steven’s Johnson syndrome – rare <0.1%

Carbamazepine - Pros

- Effective in mania, depression, and maintenance
  - More data for mania
- Very limited geriatric data
  - One case series (n=3)
- Anecdotally – have seen geriatric pts on monotherapy/bi-therapy, stable for decades
- Relatively weight neutral

Carbamazepine - Cons

- **Multiple P450 Drug interactions**
  - Auto-inducer (3A4) and others (e.g. 2C19)
  - Grapefruit juice increases CBZ
- Side effects:
  - Hyponatremia
  - Arrhythmias (OR 3.2 in epilepsy)
  - Rashes
  - Blood dyscrasias - rare <1/10,000

Oxcarbazepine

- Similar effectiveness and safety profile as carbamazepine
- Less data than CBZ, mostly mania studies
- No geriatric data
Gabapentin, Pregabalin, Topiramate, Phenytoin

- Some agents potentially harmful
  - Sedation, cognitive dysfunction (Topiramate), skin, liver, cardiac, drug interactions (Phenytoin), etc
- Very limited geriatric data
- Gabapentin
  - 2 Open-label case series, n=12 total
  - Well-tolerated
  - Somewhat “clinically helpful” in acute mania, in combination with other agents.
- Pregabalin
  - ? Helpful in concurrent generalized anxiety, neuropathic pain
  - No adult RCT for GAD +BD (no geriatric BD data)

Atypical Antipsychotics: FDA Indications for Adult Bipolar Disorder (2015)

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug</th>
<th>Year</th>
<th>Drug</th>
<th>Year</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>Lithium</td>
<td>2003</td>
<td>Olanzapine + fluoxetine</td>
<td>1974</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>combination</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>Olanzapine*</td>
<td>2005</td>
<td>Aripiprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Risperidone*</td>
<td>2008</td>
<td>Quetiapine, XR (adjunct)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Quetiapine, XR (2008)*</td>
<td>2009</td>
<td>Risperidone LAI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Ziprasidone</td>
<td>2009</td>
<td>Ziprasidone (adjunct)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Aripiprazole*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>Carbamazepine ERC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Asenapine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Atypical Antipsychotics in Geriatric BD

- 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
- Lurasidone, Quetiapine and olanzapine-fluoxetine combination: approved by the FDA for the acute treatment of bipolar depression in adults

Young et al 2004; Mulsant & Pollock 2012

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 concurrent dementia

Young et al 2004; Mulsant & Pollock 2012
A Case

An 82 year old woman with bipolar disorder, type 1 is stable for >25yrs on lithium. However, because of kidney problems (eGFR<30mL/min/1.73m2), lithium had to be discontinued. She was tried on valproate monotherapy, but had little effect, with predominantly depressive symptoms. She had a history of rashes with lamotrigine. Based on the current geriatric evidence, what may be the most useful treatment to try next in this case?

a) Buproprion
b) Lurasidone
c) Electroconvulsive Therapy
d) Lamotrigine
e) Aripiprazole

Special Issues” in Late-Life BD

• Physical/ “Medical” Comorbidity

• Cognition

Anticonvulsants and Physical Health Outcomes

• Some anticonvulsants assoc. with:
  ◦ Weight gain, DM2, other physical effects
  ◦ Especially valproate
  ◦ Is Valproate associated with higher rates of poor physical health outcomes?
    • Mortality
    • “Medical” ER/Hospital Visits
Physical Health Outcomes and Late-Life BD Pharmacotherapy

<table>
<thead>
<tr>
<th>Medical Comorbidity in Late-Life BD</th>
<th>Lithium (n=259)</th>
<th>Valproate (n=452)</th>
<th>Other (n=657)</th>
<th>Uncorrected p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>12.5%</td>
<td>15.3%</td>
<td>11.6%</td>
<td>0.19</td>
</tr>
<tr>
<td>Ischemic Heart Disease</td>
<td>16.1%</td>
<td>20.8%</td>
<td>20.2%</td>
<td>0.26</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>31.9%</td>
<td>36.1%</td>
<td>31.8%</td>
<td>0.29</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>50.2%</td>
<td>54.2%</td>
<td>49.0%</td>
<td>0.23</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57.3%</td>
<td>74.6%</td>
<td>69.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>4.3%</td>
<td>6.0%</td>
<td>6.7%</td>
<td>0.37</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9%</td>
<td>4.2%</td>
<td>3.3%</td>
<td>0.60</td>
</tr>
<tr>
<td>COPD</td>
<td>29.4%</td>
<td>30.8%</td>
<td>30.7%</td>
<td>0.91</td>
</tr>
<tr>
<td>Dementia</td>
<td>35.1%</td>
<td>36.7%</td>
<td>35.9%</td>
<td>0.91</td>
</tr>
<tr>
<td>Delirium</td>
<td>12.9%</td>
<td>12.4%</td>
<td>11.9%</td>
<td>0.90</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>11.5%</td>
<td>15.9%</td>
<td>12.0%</td>
<td>0.11</td>
</tr>
</tbody>
</table>

In 1,388 older adults psychiatrically admitted for BD, baseline medical comorbidity not different between lithium, valproate, and non Li/Valproate groups.

Rej et al. 2015 – Gen Hosp Psychiatry

Paradox: Physical Health and Late-Life BD Pharmacotherapy

- Late-Life: Medical comorbidity common, but consequences of BD Pharmacotherapy less important?
  - “Survivor effect” – most medically ill and side effect prone pts already dead in late life
  - Genetic effect – if were going to get a chronic medical illness (e.g. diabetes mellitus), would have often gotten it already
  - Effect of mental illness severity on physical illness may trump pharmacofX effects

- Lifestyle, Inherent BD biology

Lala + Sajatovic 2012 – J Geri Psych Neurol; Abitbol et al. 2014 Psychogeriatrics; Sylvestre et al. 2015 J Psychosom Res

Medical Health Utilization, Mortality not different w/ late-life BD pharmacoTx

- In 1,388 BD patients >66y
  - 1-year Acute Med Hospitalizations and ER visits very similar across medication groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Lithium Users (n=279)</th>
<th>Valproate Users (n=452)</th>
<th>Non-Lithium, Non-Valproate Users (n=657)</th>
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<td>Inpatient medical hospitalization, N (%)</td>
<td>58 (20.8%)</td>
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<td>151 (23.0%)</td>
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<td>Medical ER visit, N (%)</td>
<td>98 (35.1%)</td>
<td>167 (36.9%)</td>
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- Time-to-hospitalization not independently affected by lithium, valproate, atypical APs

<table>
<thead>
<tr>
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<th>Univariate Hazard Ratio [95% CI]</th>
<th>Multivariate Hazard Ratio [95% CI]</th>
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<tr>
<td>Lithium Use</td>
<td>0.83[0.71-1.0]</td>
<td>0.83[0.71-1.2]</td>
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<tr>
<td>Valproate Use</td>
<td>0.93[0.73-1.1]</td>
<td>0.93[0.71-1.1]</td>
</tr>
<tr>
<td>Concurrent Antipsychotic Use</td>
<td>0.85[0.66-1.09]</td>
<td>0.85[0.71-1.1]</td>
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- Mortality did not differ significantly (3.5%/yr)

Rej et al. 2015 – Gen Hosp Psychiatry

Admin Retrospective Cohort Study

- 45,000 valproate and lithium users
- 1 year follow-up, HDPS-matching

Compared to valproate:

- Lithium users had lowered mortality up to 90-day f/u (intent-to-treat)
- When considering persistent lithium users, lowered mortality throughout up to 365-day f/u (as-treated)
- Li discontinuation assoc. w/ higher mortality

Smith et al. 2015 – Br J Psychiatry

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<td>Concurrent Antipsychotic Use</td>
<td>0.85[0.66-1.09]</td>
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</tr>
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</table>

- Mortality did not differ significantly (3.5%/yr)

Rej et al. 2015 – Gen Hosp Psychiatry

Physical Health Outcomes and Late-Life BD Pharmacotherapy

- Compared to valproate:
  - Lithium users had lowered mortality up to 90-day f/u (intent-to-treat)
  - When considering persistent lithium users, lowered mortality throughout up to 365-day f/u (as-treated)
  - Li discontinuation assoc. w/ higher mortality

- Admin Retrospective Cohort Study
  - 45,000 valproate and lithium users
  - 1 year follow-up, HDPS-matching

Smith et al. 2015 – Br J Psychiatry

Medical Health Utilization, Mortality not different w/ late-life BD pharmacoTx

- In 1,388 BD patients >66y
  - 1-year Acute Med Hospitalizations and ER visits very similar across medication groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Lithium Users (n=279)</th>
<th>Valproate Users (n=452)</th>
<th>Non-Lithium, Non-Valproate Users (n=657)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient medical hospitalization, N (%)</td>
<td>58 (20.8%)</td>
<td>96 (21.2%)</td>
<td>151 (23.0%)</td>
</tr>
<tr>
<td>Medical ER visit, N (%)</td>
<td>98 (35.1%)</td>
<td>167 (36.9%)</td>
<td>270 (41.1%)</td>
</tr>
</tbody>
</table>

- Time-to-hospitalization not independently affected by lithium, valproate, atypical APs

<table>
<thead>
<tr>
<th></th>
<th>Univariate Hazard Ratio [95% CI]</th>
<th>Multivariate Hazard Ratio [95% CI]</th>
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- Mortality did not differ significantly (3.5%/yr)

Rej et al. 2015 – Gen Hosp Psychiatry
Cognitive Dysfunction in Late-Life BD

- >30% of late-life BD pts have cognitive dysfunction
  - Executive function, attention, memory, and processing speed affected in mania, depression, and euthymic periods, but not necessarily progressive over 2-5yr follow-up
  - Cholinesterase Inhibitors not found to be helpful
- Anticonvulsants (and antipsychotics) have high cognitive risk vs. lithium
  - OR 1.25-2 of dementia, valproate most associated, carbamazapine also implicated
  - Less white matter integrity (vs. lithium)
- Aside from Lithium, Lamotrigine may be somewhat protective
  - May be driven by lamotrigine’s effect in bipolar depression, which greatly affects cognition (no lamotrigine RCT, test/re-test effects)
- Can use instruments like Montreal Cognitive Assessment (MoCA) to quantify cognitive dysfunction


Key Points about Late-Life Bipolar Disorder

- By 2030, more than half of bipolar disorder (BD) patients will be aged >60
- Episodes of BD in the elderly are heterogeneous and require careful differential diagnosis.
- Medical assessment is essential for diagnosis, as well as for the comprehensive treatment of late-life BD since medical comorbidity is very frequent.
- Cognitive dysfunction is frequently observed in late-life BD and is disabling, but is not necessarily progressive.

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

- Limited geriatric BD pharmacotherapy data in all phases of illness

Sajatovic et al. 2015; Young et al 2004

Treatment Recommendations for Bipolar Depression in Late Life

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

- Maintenance:
  - Little geriatric data – lithium/valproate best adult data. “Whatever gets you well, keeps you well”

Sajatovic et al. 2015, Young et al 2004
Lithium and Anticonvulsants in Late-Life Bipolar Disorder - Punch Lines

- Lithium
  - Gold standard: 42% of older adults though may respond to Li monotherapy
  - Safe prescribing can avoid most adverse effects (e.g. CKD)

- Valproate, Lamotrigine, and Carbamazepine
  - Despite challenges, Useful medications
  - Esp. considering polypharmacy usually used

- Pregabalin, gabapentin
  - well-tolerated, but ?efficacy
  - Role needs to be clarified in geriatric mania, and concurrent disorders (anxiety, chronic pain)

“Punch Lines” (cont.)

- Physical Health/Medical Comorbidity
  - Lamotrigine, Carbamazepine more weight neutral
  - Is weight gain as important in late-life?
  - ?Increased mortality with valproate (controversial)
  - Physical Health Service Use similar in Valproate, Lithium, and Other Pts with Late-life BD

- Cognition
  - Lamotrigine (and properly-dosed lithium) probably safer than valproate and carbamazapine

Thank You!