The Neuroprotective Effects of Mood Stabilizers

(page 101 in syllabus)

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Individual Disclosure Statement

Faculty Editor / Presenter

Rona J. Hu, MD, is a clinical associate professor in the department of psychiatry and behavioral sciences and medical director of the acute psychiatric inpatient unit at Stanford University School of Medicine in Standford, CA

Consultant/Advisor: Alexza/Biovail, Beta Healthcare, Sepracor/Sunovion
Learning Objectives

• Recognize bipolar disorder as a neuroprogressive illness

• Identify the biochemical processes involved in the neuroprogression of bipolar disorder

• Identify the mechanisms by which mood stabilizing treatment can target those biochemical processes to alter the course of bipolar disorder

• Select mood stabilizing treatment strategies that are consistent with evidence-based practice guidelines
?
Pretest Question 1

A 34-year-old man has recently been diagnosed with bipolar disorder, six years after his symptoms began. He has had no mood stabilizing treatment in that time. According to the kindling model and the allostatic load hypothesis, which progressive pattern of illness would you expect this patient to have exhibited over the last six years?

1. Longer interval between episodes, worsened emotionality, minimal change in cognitive impairment
2. Shorter interval between episodes, worsened emotionality, minimal change in cognitive impairment
3. Longer interval between episodes, worsened emotionality, worsened cognitive impairment
4. Shorter interval between episodes, worsened emotionality, worsened cognitive impairment
Pretest Question 2

A 28-year-old woman with bipolar disorder recently began taking a mood stabilizer and has experienced improvement in her symptoms. Which of the following are mechanisms by which different mood stabilizers may prevent mitochondrial dysfunction in bipolar disorder?

1. Increasing levels of anti-apoptotic proteins
2. Decreasing levels of pro-apoptotic proteins
3. Increasing levels of key antioxidants
4. 1 and 2
5. 1, 2, and 3
A 28-year-old woman presents with a depressive episode. She has previously been hospitalized and treated for a manic episode, but she is not currently taking any medication. Practice guidelines consistently agree on the preferential use of which of the following to treat bipolar depression?

1. Lamotrigine, quetiapine
2. Quetiapine, olanzapine
3. Olanzapine, lithium
4. Lithium, valproate
5. Valproate, lamotrigine
Progressive Course of Bipolar Disorder

Worsened cognitive impairment
Reduced treatment response

Chronic Bipolar Disorder: Structural Brain Changes

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Bipolar Disorder Is Neuroprogressive: Kindling Model

Bipolar Disorder Is Neuroprogressive: Allostatic Load Hypothesis

Biochemical Processes Underlying Neuroprogression in Bipolar Disorder

- Oxidative stress
- Mitochondrial dysfunction
- Alterations in dopamine
- Alterations in glutamate
- Increased inflammatory processes
- Decreased neurotrophins
Neuroprogression in Bipolar Disorder: Oxidative Stress (and Mitochondrial Dysfunction)

Neuroprogression in Bipolar Disorder: Mitochondrial Dysfunction (and Oxidative Stress)

Biochemical Processes Underlying Neuroprogression in Bipolar Disorder

- Oxidative stress
- Mitochondrial dysfunction
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- Alterations in glutamate
- Increased inflammatory processes
- Decreased neurotrophins
Neuroprogression in Bipolar Disorder: Oxidative Stress and Dopamine


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Biochemical Processes Underlying Neuroprogression in Bipolar Disorder

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Neuroprogression in Bipolar Disorder: Oxidative Stress and Glutamate

Biochemical Processes Underlying Neuroprogression in Bipolar Disorder

- Oxidative stress
- Mitochondrial dysfunction
- Alterations in dopamine
- Alterations in glutamate
- Increased inflammatory processes
- Decreased neurotrophins

Neuroprogression in Bipolar Disorder: Inflammatory Processes

Pro-inflammatory cytokines and chemokines

Episode-Dependent

Activated

Stage-Dependent

Tumor necrosis factor-α

Time

Biochemical Processes Underlying Neuroprogression in Bipolar Disorder

- Oxidative stress
- Mitochondrial dysfunction
- Alterations in dopamine
- Alterations in glutamate
- Increased inflammatory processes
- Decreased neurotrophins
Neuroprogression in Bipolar Disorder: Neurotrophins

Neuroprogression in Bipolar Disorder: Neurotrophins

Episode-Dependent

Stage-Dependent

BDNF

BDNF

Time

normal bipolar

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Can Early Treatment Prevent Neuroprogression in Bipolar Disorder?

Worsened cognitive impairment
Reduced treatment response

early treatment

HYPOMANIA

DYSTHYMIA

Neuroprogression in Bipolar Disorder: Linking Biochemical Processes to Mood Stabilizers

Clinical Effects of Acute and Maintenance Treatments


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# Bipolar Mania: What’s Available

<table>
<thead>
<tr>
<th>Lithium</th>
<th>Carbamazepine</th>
<th>Aripiprazole</th>
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<tr>
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<td>Chlorpromazine</td>
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Bipolar Mania: What’s (Relatively) Well Studied

- lithium
- carbamazepine
- aripiprazole
- asenapine
- valproate
- olanzapine
- quetiapine
- risperidone
- ziprasidone
- chlorpromazine
**Bipolar Mania:**
What’s Got Consistent Positive Evidence

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Bipolar Depression: What’s Available

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- carbamazepine
- lamotrigine
- oxcarbazepine
- valproate
- aripiprazole
- asenapine
- iloperidone
- lurasidone
- olanzapine
- paliperidone
- quetiapine
- risperidone
- ziprasidone
- bupropion
- fluoxetine
- paroxetine
- other ADs
- OFC
Bipolar Depression: What’s (Relatively) Well Studied

- lithium
- carbamazepine
- aripiprazole
- bupropion
- lamotrigine
- fluoxetine
- paroxetine
- valproate
- olanzapine
- quetiapine
- ziprasidone
- OFC


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Bipolar Depression: What’s Got Consistent Positive Evidence

Bipolar Depression: What’s Recommended First-Line

World Federation of Societies of Biological Psychiatry (WFSBP)

- lithium*
- lamotrigine
- valproate
- olanzapine
- quetiapine

*With lamotrigine

Bipolar Depression: What’s Recommended First-Line

British Association for Psychopharmacology (BAP)

- Lithium
- Lamotrigine
- Valproate
- Quetiapine
- ADs*

*Monotherapy if no mania; adjunct if mania

Bipolar Depression: What’s Recommended First-Line

Int’l Consensus Group on the Evidence-Based Pharmacologic Treatment of Bipolar I and II Depression (ISBD)

- lithium
- lamotrigine
- quetiapine

Bipolar Depression: What’s Recommended First-Line

Canadian Network for Mood and Anxiety Treatments and Int’l Society for Bipolar Disorders (CANMAT)

- **lithium**
- **bupropion**
- **lamotrigine**
- **valproate**
- **SSRIs**
- **olanzapine**
- **quetiapine**

*With lithium or valproate. *With SSRI. ***With lithium.

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Bipolar Depression: What’s Recommended First-Line

National Institute of Clinical Excellence (NICE)

*lamotrigine*

*SSRIs*

*olanzapine**

*quetiapine*

*risperidone**

*With “anti-manic.” **If psychosis is present.

## Bipolar Depression: What’s Recommended First-Line (Summary)

<table>
<thead>
<tr>
<th>WFSBP</th>
<th>BAP</th>
<th>ISBD</th>
<th>CANMAT</th>
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<tr>
<td>olanzapine</td>
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<td>olanzapine (w SSRI)</td>
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<tr>
<td>quetiapine</td>
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<td>quetiapine</td>
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</tr>
</tbody>
</table>

OFC

ADs

SSRIs, BUP (adj)

SSRIs (adj)

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Bipolar Depression: Practice Guideline Commonalities, First-Line

- Already taking MS
  - Optimize dose
  - Add quetiapine

- Not taking MS
  - Quetiapine
  - Lamotrigine
  - Lithium
  - Olanzapine + antidepressant
  - Other anti-manic + antidepressant

Bipolar Depression: Practice Guideline Commonalities, Second-Line

- Different first-line strategy
- Combination of first-line agents
- Addition of carbamazepine, modafinil, pramipexole
- Psychotherapy
- ECT for severe depression, catatonia, suicidality, psychotic features, pregnant women

Bipolar Maintenance: What’s Available

- Lithium
- Carbamazepine
- Lamotrigine
- Oxcarbazepine
- Valproate
- Aripiprazole
- Asenapine
- Iloperidone
- Lurasidone
- Olanzapine
- Paliperidone
- Quetiapine
- Risperidone
- Ziprasidone
- Psychotherapy
- Psychoeducation
- OFC
Bipolar Maintenance: What’s (Relatively) Well Studied

- lithium
- carbamazepine
- lamotrigine
- valproate
- aripiprazole
- psychotherapy
- olanzapine
- psychoeducation
- quetiapine
- risperidone
- ziprasidone


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Bipolar Maintenance: What’s Got Consistent Positive Evidence

- lithium
- aripiprazole
- psychotherapy
- lamotrigine
- psychoeducation
- valproate
- olanzapine
- quetiapine
- risperidone*

*Injectable

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Antipsychotics in Bipolar Maintenance

Number Needed to Treat (sig)

- Ari (Keck 2007)
- Olz (Tohen 2006)
- Que adj (Vieta 2008)
- Que adj (Suppes 2009)
- Que (Weisler 2009)
- Ris LA (Quiroz 2010)
- Ris LA (MacFadden 2009)
- Zip adj (Bowden 2010)

- Any Episode
- Mania
- Depression

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Anticonvulsants and Lithium in Bipolar Maintenance

Any Episode  Mania  Depression

Number Needed to Treat (sig)

Lam (Bowden 2003)  Lam (Calabrese 2000)  Li (Prien 1973)  Li (Goodwin 2004)  Li (Bowden 2003)  Li (Weisler 2009)  Val (Bowden 2000)

Bipolar Maintenance: What’s Recommended

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*Predominantly mania
**Predominantly depression
***Injectable

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Bipolar Maintenance

- Maintain medication
  - Educate on chronicity of disorder
  - Help establish routine for taking medication
- Maintain psychoeducation and psychotherapy
  - Include caregiver psychoeducation
- Monitor for and address adverse effects
- Encourage regular physical and social activity
- Encourage regular sleep pattern
- Address interepisode impairment
  - Neurocognitive, difficulty with sustained attention
  - Sleep disturbance

Bipolar Maintenance

- Train to monitor for prodromal symptoms
  - Change in motivated activity, sleep cycle, impulsivity, or interpersonal behavior
  - Change in affect (usually later in prodromal stage)
  - Usually consistent within individual

- Train to address prodromal symptoms
  - Small medication adjustment
  - Change in daily routine
  - Stress reduction
  - Increase in social interaction

Summary

- There is both clinical and pathophysiological evidence that bipolar disorder is neuroprogressive.
- Mitochondrial dysfunction and oxidative stress, perhaps related to alterations in dopamine and glutamate systems, may underlie the neuroprogressive changes that can occur during the course of bipolar disorder.
- Other proposed mechanisms include increased inflammatory processes and decreased expression of neurotrophins.
- Many of the existing medications for bipolar disorder, which have seemingly diverse mechanisms of action, share an ability to affect one or more of these factors.
- The key is to intervene early, before the disease progresses and positive treatment outcomes become less likely.
- Unfortunately, the evidence base for treating bipolar depression and for maintenance is relatively weak, and practice guidelines differ.