Bipolar Disorder Update

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Disclosures

• None

Lecture Outline

• Mood Disorder Overview
• Bipolar Disorder
  – Phenomenology, Epidemiology, Etiology, Course
  – Treatment Update
Bipolar Disorder Subtypes

- Bipolar I
- Bipolar II
- Bipolar NOS
- Cyclothymia

Bipolar Disorder Epidemiology

- Prevalence 3.7%
- 4% - 24% first degree relatives affected (BPD I, BPD II, and MDD)
- Peak age of onset – adolescence through early 20s
- Seasonal Variation
  - Autumn and Spring – Depression
  - Summer - Mania
Facts

• Almost half of all individuals with bipolar disorder struggle with substance dependence
• Approximate 35% of individuals with Bipolar Disorder attempt suicide
• Only about 1/3 receive treatment
• Average age of onset age 18

• What is Bipolar Disorder?
Contact with Health Care Provider

• The American Journal of Psychiatry demonstrated that on average 45% of suicide victims had contact with primary care providers within 1 month of committing suicide. Older adults had a higher rate of contact with their primary care providers prior to committing suicide.

• The British Journal of General Practice demonstrated that 91% of suicide victims contacted there general practitioner the year prior to committing suicide.

Reducing Suicide by Training Primary Care Physicians

• Primary Care Physicians in Hungary
  – Szanto K., Kalmar S., Hendin H., Rihmer Z. & Mann J.J. (2007). A suicide prevention program in a region with a very high suicide rate. [Research Support, Non-U.S. Gov't]. Arch Gen Psychiatry, 64(8), 914-920.
Relevant Changes in DSM 5

• There is not longer an AXIS I-V system
• We no longer have a “Not Otherwise Specified Diagnosis.” Mood Disorder NOS is gone.
• New Terminology- “Unspecified”
• “Mental Retardation” terminology changed to Intellectual Disability
• Asperger’s Disorder has been removed and replaced with Autism Spectrum Disorder
• Major Depressive Disorder and Bipolar Disorder are largely unchanged
DSM V Important Changes

• 1) adding a “with mixed features” for manic, hypomanic, and major depressive episodes
• 2) permitting a full manic or hypomanic episode that emerges during antidepressant treatment and persists beyond the physiological effect of that treatment to be sufficient evidence for a manic or hypomanic episode
• 3) adding a “with anxious distress” specifier for manic, hypomanic, and major depressive episodes

Case Review

• 46 y/o caucasian female was brought to the emergency room by police. Psychiatrically hospitalized 1 month ago, diagnosed with Bipolar Disorder. Patient’s husband recently left home with their 3 children because of concerns about the patients delusions and mental health. Patient left the home because “someone is hoarding things in my house.” She attempted to run over her friend who was driving around downtown Grand Rapids, randomly entering stores and rambling to employees and patrons. The police were contacted by the local library regard disruptive behavior. When police arrived she became combative with police insisting they allow her to speak with Betsy Devos and Hank Meijer. She was subsequently taken to the ED. She was agitated in the ED requiring emergency psychotropic medications. She was subsequently transitioned to the inpatient psychiatric hospital. During her assessment in the hospital she fluctuated from tearfulness to elation
Pathophysiology

• Neurotransmitter Theory- dysregulation of monoamine transmitter concentrations in the CNS.
  — Excessive catecholamines - NE and DA in mania
  — Functional deficit in depression- NE, 5HT, DA
• Dysregulation of intracellular second messenger systems.
### DSM-V Manic and Depressive Symptom Criteria for Diagnosis of Bipolar Disorder

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Manic Symptom Criteria</th>
<th>Depression Symptom Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar I disorder</td>
<td>Criteria met for at least one manic episode</td>
<td>Major depressive episodes typical but not required for diagnosis</td>
</tr>
<tr>
<td>Bipolar II disorder</td>
<td>Criteria met for at least one episode of hypomania</td>
<td>Criteria met for at least one episode of major depression</td>
</tr>
<tr>
<td>Cyclothymic disorder</td>
<td>For at least 2 years, the presence of numerous periods with hypomanic symptoms that do not meet criteria for a hypomanic episode</td>
<td>For at least 2 years numerous periods with depressive symptoms that do not meet criteria for a major depressive episode</td>
</tr>
</tbody>
</table>

**BIPOLAR I**

- **Manic**
- **Hypomania**
- **Depressive**
- **Dysthymia**
Major Depressive Episode

• DSM-5 Criteria for Major Depressive Episode
  • Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
    – Note: Do not include symptoms that are clearly attributable to another medical condition.
    – Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
    – Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
    – Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
    – Insomnia or hypersomnia nearly every day.
    – Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
    – Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
    – Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
    – Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
  • The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
  • The episode is not attributable to the physiological effects of a substance or to another medical condition.
  • Note: Criteria A–C represent a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

PHQ-9 depression questionnaire

<table>
<thead>
<tr>
<th>Item</th>
<th>Not at all</th>
<th>Slightly</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Feeling bad about yourself, or that you are a failure, or have set yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Having or caring for friends that other people would have noticed the opposite, being as helpless or hopeless that you have been nearing around and a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Depression score range:

- 0 to 4: mild
- 5 to 14: moderate
- 15 to 21: moderately severe
- 22+: severe

If you checked all or any problems, how difficult have these problems made it for you to do your work, your chores, or get along with other people?

- Not difficult at all
- Slightly difficult
- Very difficult
- Extremely difficult

PHQ-9 Patient Health Questionnaire.

Developed by Drs. Robert W, Jacobson, Umphred, Berkowitz, and colleagues, with an educational grant from Pfizer. No permission required to reproduce, translate, adapt, or distribute.
Mania and Hypomania (Bipolar and Related Disorders)

Inclusion of increased energy/activity as a Criterion A symptom of mania and hypomania

- Rationale: This will make explicit the requirement of increased energy/activity in order to diagnose bipolar I or II disorder (which is not required under DSM-IV) and will improve the specificity of the diagnosis.

Manic Episode

- DSM-5 Criteria for Manic Episode
  - A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
  - During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
    - Inflated self-esteem or grandiosity.
    - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    - More talkative than usual or pressure to keep talking.
    - Flight of ideas or subjective experience that thoughts are racing.
    - Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
    - Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
    - Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
  - The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.
  - The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.
    - Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.
    - Note: Criteria A–D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.
Mixed Features for Depressive Episode

- DSM-5 Mixed Features Specifier for Depressive Episode
  - Full criteria are met for a major depressive episode, and at least three of the following manic/hypomanic symptoms are present during the majority of days of the current or most recent episode of depression:
    - Elevated, expansive mood.
    - Inflated self-esteem or grandiosity.
    - More talkative than usual or pressure to keep talking.
    - Flight of ideas or subjective experience that thoughts are racing.
    - Increase in energy or goal-directed activity (either socially, at work or school, or sexually).
    - Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
    - Decreased need for sleep (feeling rested despite sleeping less than usual; to be contrasted with insomnia).
  - Mixed symptoms are observable by others and represent a change from the person’s usual behavior.
  - For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features.
  - The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, or other treatment).
  - **Note:** Mixed features associated with a major depressive episode have been found to be a significant risk factor for the development of bipolar I or bipolar II disorder. As a result, it is clinically useful to note the presence of this specifier for treatment planning and monitoring of response to treatment.

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### Mixed disorder questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Were there ever a period of time when you were not your usual self?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...you felt so good or so happy that other people thought you were not your usual self or you were so happy that you got into trouble?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you were so irritable that you shouted at people or started fights or arguments?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you felt much more self-confident than usual?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you got much less sleep than usual and found you didn’t really need it?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you were much more talkative or spoke faster than usual?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...thoughts raced through your head so you couldn't slow down your mind?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you were so easily distracted that things around you that you had trouble concentrating or staying on topic?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you had much more energy than usual?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you were much more active or did many more things than usual?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...your moods were more up and down than usual, for example, you talked with friends in the middle of the night?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you were much more interested in sex than usual?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...spending money got you in trouble?</td>
<td>Yes</td>
<td>No</td>
</tr>
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### Mixed disorder questionnaire

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<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. If you checked YES to more than one of the above, have several of these ever happened during the current period of time? Please circle one response only.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>...you felt so good or so happy that other people thought you were not your usual self or you were so happy that you got into trouble?</td>
<td>Yes</td>
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<td>...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>...spending money got you in trouble?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

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*Please screen consistently for bipolar disorders if they answer “yes” to severe or more items in sections 1, yes in section 2, and “moderate problem” or “severe problem” or “serious problem” in section 3. The mixed disorder questionnaire should not be used to diagnose bipolar disorders in patients who screen positive should be interviewed to establish the diagnosis including family members or other keepers.*

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**Hypomanic Episode**

- **DSM-5 Criteria for Hypomanic Episode**
- A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
- During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behavior, and have been present to a significant degree:
  - Inflated self-esteem or grandiosity.
  - Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
  - More talkative than usual or pressure to keep talking.
  - Flight of ideas or subjective experience that thoughts are racing.
  - Distractibility (e.g., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
  - Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.
  - Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
- The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
- The disturbance in mood and the change in functioning are observable by others.
- The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.
- The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).
- **Note:** However, a full hypomanic episode that emerges during antidepressant treatment (e.g., tricyclic antidepressants) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.
- **Note:** Criteria A–F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

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**Mixed Features for Hypo/Mania**

- **DSM-5 Mixed Features Specifier for Manic or Hypomanic Episode**
- Full criteria are met for a manic episode or hypomanic episode, and at least three of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania:
  - Prominent dysphoria or depressed mood as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
  - Diminished interest or pleasure in all, or almost all, activities (as indicated by either subjective account or observation made by others).
  - Psychomotor retardation nearly every day (observable by others; not merely subjective feelings of being slowed down).
  - Fatigue or loss of energy.
  - Feelings of worthlessness or excessive or inappropriate guilt (not merely self-reproach or guilt about being sick).
  - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- Mixed symptoms are observable by others and represent a change from the person’s usual behavior.
- For individuals whose symptoms meet full episode criteria for both mania and depression simultaneously, the diagnosis should be manic episode, with mixed features, due to the marked impairment and clinical severity of full mania.
- The mixed symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment).
Mania and Hypomania

“With anxious distress” also added as a specifier for bipolar (and depressive) disorders

- Rationale: The co-occurrence of anxiety with depression is one of the most commonly seen comorbidities in clinical populations. Addition of this specifier will allow clinicians to indicate the presence of anxiety symptoms that are not reflected in the core criteria for depression and mania but nonetheless may be meaningful for treatment planning.

Bipolar I Disorder

- DSM-5 Criteria for Bipolar I Disorder
- Criteria have been met for at least one manic episode (Criteria A–D under “Manic Episode”).
- The occurrence of the manic and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
- Specify:
  - With anxious distress
  - With mixed features
  - With rapid cycling
  - With melancholic features
  - With atypical features
  - With mood-congruent psychotic features
  - With mood-incongruent psychotic features
  - With catatonia
  - With peripartum onset
  - With seasonal pattern
### Bipolar Symptoms

**Mania = mood is “12/10!”**
- **D** = Distractibility
- **I** = Impulsivity/Indiscretion
- **G** = Grandiosity
- **F** = Flight of ideas
- **A** = Activity/energy increased
- **S** = Sleep (decreased need for)
- **T** = Talkativeness (pressured speech)

**Depression = mood is “1/10”**
- **S** = Sleep (more or less)
- **I** = Interest
- **E** = Energy (down)
- **G** = Guilt/Worthlessness
- **C** = Concentration (poor)
- **A** = Appetite (up or down)
- **P** = Psychomotor agitation/slowness
- **S** = Suicidal ideation

### Bipolar II Disorder

- DSM-5 Criteria for Bipolar II Disorder
  - Criteria have been met for at least one hypomanic episode (Criteria A-F under “Hypomanic Episode”) and at least one major depressive episode (Criteria A-C under “Major Depressive Episode”).
  - There has never been a manic episode.
  - The occurrence of the hypomanic episode(s) and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
  - The symptoms of depression or the unpredictability caused by frequent alternation between periods of depression and hypomania causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- **Specify current or most recent episode:** Hypomanic
- **Depressed**
  - **Specify if:** With anxious distress
  - With mixed features
  - With rapid cycling
  - With mood-congruent psychotic features
  - With mood-incongruent psychotic features
  - With catatonia
  - With peripartum onset
  - With seasonal pattern
- **Specify course if full criteria for a mood episode are not currently met:** In partial remission
- **In full remission**
- **Specify severity if full criteria for a mood episode are currently met:** Mild, Moderate, or Severe
What is a Mood Stabilizer?

Proposed Nomenclature for Mood Stabilizers

| CLASS | 1. Agents that stabilize mood “from Above baseline”
|       | 2. Agents that possess marked antimanic properties without causing a worsening of depression (i.e., lithium, carbamazepine, divalproex, atypical antipsychotics, and electroconvulsive therapy) |
| CLASS | 1. Agents that stabilize mood “from Below baseline”
|       | 2. Agents that possess marked antidepressant properties without destabilizing the course of the illness by inducing switches into mania or episode acceleration (i.e., lamotrigine, lithium, |

FDA-Approved Treatment Options
- Lithium Salts
- Select Anticonvulsants
- Select Second Generation Antipsychotics
- Chlorpromazine

FDA-Approved Indications Vary by Agent
- Acute Mania/Mixed Treatment
- Maintenance
- Monotherapy
- Adjunctive Therapy
- Bipolar Depression

Mood Stabilizers
Foundation of Bipolar Symptom Management

Bipolar Mania or Mixed Episode Acute: FDA Indicated Medications

- Mood Stabilizers
  - Lithium
  - Valproic Acid
  - Carbamazepine
  - Oxcarbamazepine
  - Lamictal

- Atypical Antipsychotics
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Aripiprazole
  - Lurasidone
  - Paliperidone
  - Asenapine
  - Clozapine
  - Iloperidone
  - Chlorpromazine

Bipolar Mixed: Acute Treatment

- Stop Antidepressant
- Assess for substance abuse
- Assess for other medication use (stimulants)
- Assess for medical cause
- Use benzodiazepine, atypical antipsychotic, mood stabilizer
- Valproic Acid or Carbamazepine.
- Lithium less effective
Bipolar Rapid Cycling: Acute Treatment

- Stop antidepressant
- Assess for other med use: e.g., ephedrine
- Use benzodiazepine, atypical antipsychotic, mood stabilizer
- Optimize mood stabilization
  - Lithium less effective
- Check thyroid function

Bipolar I Disorder: Role of Antidepressants

- Acute Depressive Treatment with Antidepressants in Bipolar Disorder
  - May be a slight risk of destabilization with SSRI’s
  - But TCA’s probably are mood destabilizers
  - Should use a mood stabilizer with an antidepressant
Polarity Index = \frac{\text{NNT (Prevent Depression)}}{\text{NNT (Prevent Mania)}}

\text{PI} > 1 = \text{Greater Antimanic Value}, \text{PI} < 1 = \text{Greater Antidepressant Value}

Antipsychotic Agents and Bipolar Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Bipolar Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mania</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Acute &amp; Maintenance, Monotherapy &amp; Adjunct</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Acute, Monotherapy &amp; Adjunct</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Acute, Monotherapy</td>
</tr>
<tr>
<td>Clozapine</td>
<td>N/A</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>N/A</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>N/A</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Acute &amp; Maintenance, Monotherapy &amp; Adjunct</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Acute, Monotherapy &amp; Adjunct for Schizoaffective Disorder (po)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Acute as Monotherapy Maintenance as Adjunct</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Acute, Monotherapy &amp; Adjunct (PO) Maintenance, Monotherapy &amp; Adjunct (LAI)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Acute as Monotherapy Maintenance as Adjunct</td>
</tr>
</tbody>
</table>

Treatment Guidelines for Bipolar Disorder

- www.dshs.state.tx.us/mhprograms/TIMA.shm


American Psychiatric Association (2002)

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013
- Bipolar Disorders an International Journal of Psychiatry and Neurosciences 2013: 15: 1-44

The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for Bipolar disorder in adults (CINP-BD-2017), part 3

The International Society for Bipolar Disorders (ISBD) consensus guidelines for the safety monitoring of bipolar disorder treatments
- Bipolar Disorders an International Journal of Psychiatry and Neurosciences 2009: 11: 559-595

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Acute Manic or Mixed Episodes

<table>
<thead>
<tr>
<th>TIMA</th>
<th>ECG</th>
<th>APA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage I</strong></td>
<td>Lithium</td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Valproic Acid</td>
<td>Valproic Acid</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Quetiapine</td>
<td>Atypical Antipsychotic</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>(risperidone, quetiapine, olanzapine)</td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td></td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td>2 drug combination</td>
<td>2 drug combination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 drug combination</td>
</tr>
<tr>
<td><strong>Stage III</strong></td>
<td>Consider Clozapine or ECT</td>
<td>Consider Clozapine or ECT</td>
</tr>
<tr>
<td></td>
<td>3 drug combination</td>
<td></td>
</tr>
</tbody>
</table>

---
## Acute Depressive Episodes in Bipolar Disorder

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage Ia</td>
<td>Lamotrigine alone if not severe or recent mania</td>
<td>Lithotrigine or Lithium</td>
<td>Lithium or Lamotrigine Avoid antidepressants alone</td>
</tr>
<tr>
<td>Stage Ib</td>
<td>Combination treatment (M5 + lamotrigine)</td>
<td>Lithium + Lamotrigine Lithium + Antidepressant Psychotherapy</td>
<td>Lithium + SSRI If psychotic features add atypical antipsychotic</td>
</tr>
<tr>
<td>Stage II</td>
<td>Quetiapine Olanzapine-fluoxetine Lithium + Quetiapine or Lithium + Olanzapine-fluoxetine</td>
<td>Lithium + Lamotrigine Lithium + Antidepressant Psychotherapy</td>
<td>Consider addition of another antidepressant: Bupropion, paroxetine, venlafaxine, MAOI</td>
</tr>
</tbody>
</table>

## Lithium

- Lithium sodas advertisement from 1950s:
  - **7up** LITURATED LEMON SODA: Nothing does it like Seven-Up!
  - **7up** | 1950 print advertisement.
  - Why we have the youngest customer in the business.

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7/31/2017
Lithium

- lithium carbonate: tablet: 300 mg, capsule: 150 mg, 300 mg, 600 mg extended-release tablet: 300 mg, 450 mg.
- Lithium citrate: liquid: 8 mEq/5 mL (=300 mg LiCO₃)
  FDA approved: Acute and maintenance treatment of mania
- Dosing, Acute 900–1,800
- Dosing, Maintenance 600–1,200
- TDM, Acute 0.8–1.5 mEq/L
- TDM, Maintenance 0.8–1.2 mEq/L

### Lithium Adverse Effects

<table>
<thead>
<tr>
<th>Organ System (teratogenic)</th>
<th>Clinical Presentation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>ECG Changes</td>
<td>T wave suppression, delayed or irregular rhythm, increased PVCs, SSNS, Myocarditis</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acne, Psoriasis, Rash</td>
<td>Worsens Treatment-refractory worsening, Maculopapular and Follicular</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroid state, Hyperparathyroid state</td>
<td>5% goiter; 4% clinically significant hypothyroidism</td>
</tr>
<tr>
<td>Fetus</td>
<td>Tricuspid valve malformation, Atrial septal defect</td>
<td>Epstein’s Anomaly</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia, Nausea (10 – 30%), Vomiting, Diarrhea</td>
<td>Early in treatment and transient; may be early sign of toxicity, Slow-release preps may help</td>
</tr>
<tr>
<td>Hematological</td>
<td>Granulocytosis</td>
<td>May be useful in disorders such as Felty’s syndrome, iatrogenic neutropenia, and clozapine-associated neutropenia</td>
</tr>
<tr>
<td>Neurological</td>
<td>Tremors, Delirium</td>
<td>Worsen with high doses, Toxicity</td>
</tr>
<tr>
<td>Renal</td>
<td>Polyuria-polydipsia, Nephrogenic diabetes insipidus</td>
<td>May be an indication of morphologic changes; Requires hydration</td>
</tr>
</tbody>
</table>
Lithium Monitoring

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History: Comorbidities, smoking status, alcohol use, pregnancy status, family history of CVD</td>
<td>• Li⁺ level, BUN, sCr, &amp; electrolytes every 3-6 months</td>
</tr>
<tr>
<td>• Investigations: Waist circumference, BMI, BP, CBC, BUN, sCr, electrolytes, LFT, FBS, fasting lipid profile</td>
<td>• Ca, TSH, &amp; weight after 6 months, then annually</td>
</tr>
<tr>
<td>• Additional: TSH, Ca**</td>
<td>• Polyuria</td>
</tr>
<tr>
<td></td>
<td>• Drug interactions: NSAIDs, ACEIs, thiazide diuretics</td>
</tr>
</tbody>
</table>


Lithium Monitoring

<table>
<thead>
<tr>
<th>Monitoring Measurement</th>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy status</td>
<td>Pregnancy category D. Lithium is teratogenic, it has been linked to an increase in congenital defects of the CV system.</td>
</tr>
<tr>
<td>Waist circumference/BMI</td>
<td>While weight loss may be seen initially, weight gain is often a long-term side effect.</td>
</tr>
<tr>
<td>CBC</td>
<td>Leukocytosis is usually benign and there is no reason to discontinue therapy unless it rises to 100,000 cells/mm³, as there have been rare reports of lithium-induced secondary malignancy (including acute leukemia).</td>
</tr>
<tr>
<td>BUN, sCr, &amp; electrolytes</td>
<td>Although lithium may cause nephrogenic diabetes insipidus at any point in therapy, it is more associated with long-term use. Generally the slow decline in renal function enables safety monitoring to detect progressive renal disease in its earlier stages.</td>
</tr>
<tr>
<td>TSH</td>
<td>Clinically significant hypothyroidism occurs in ~5% of patients. Hyperparathyroidism may also occur, but is less common than hypothyroidism. Of note, minor changes in thyroid function tests can occur during an acute affective episode &amp; on initiation of lithium therapy, so it is often warranted to repeat tests after a few weeks to determine whether treatment or referral is indicated.</td>
</tr>
<tr>
<td>Ca**</td>
<td>Lithium can cause an increase in serum Ca, an association with hyperparathyroidism is possible.</td>
</tr>
</tbody>
</table>
Valproate

- divalproex: Immediate release: 125 mg [tablet, sprinkle], 250 mg, 500 mg Extended release: 250 mg, 500 mg
- valproic acid: Capsule: 250 mg, oral solution: 250 mg/5 mL

- FDA approved: Acute manic or mixed episodes in bipolar disorder
- Dosing: 10–60 mg/kg/day divided (loading strategy: 20 mg/kg day 1)
- Oral bioavailability of ER 20% < IR (1000 mg ER ≈ 750 mg IR)
- TDM: 85–125 µg/mL

Valproate Adverse Effects

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Clinical Presentation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Reversible alopecia</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td>Fetus (teratogenic)</td>
<td>Neural tube defects from first-trimester exposure</td>
<td>(FDA Preg Risk Category D &amp; X) Folic acid supplementation in childbearing-potential women</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, hepatotoxicity, pancreatitis</td>
<td>Black box for pancreatitis</td>
</tr>
<tr>
<td>Hematological</td>
<td>Thrombocytopenia, rare blood dyscrasias</td>
<td>Dose dependent thrombocytopenia</td>
</tr>
<tr>
<td>Neurological</td>
<td>Reversible tremor</td>
<td>Dose-dependent</td>
</tr>
<tr>
<td>Renal</td>
<td>Polycystic ovary syndrome</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Drug Interactions (Inhibitor)</td>
<td>Inhibits glucuronidation (lamotrigine) Albumin displacement (phenytoin)</td>
</tr>
</tbody>
</table>
### Valproate Monitoring

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>History: Comorbidities, smoking status, alcohol use, pregnancy status, family history of CVD</td>
<td>Weight, FBC, LFT, menstrual history every 3 months for the first year, then annually</td>
</tr>
<tr>
<td>Investigations: Waist circumference, BMI, BP, CBC, BUN, SCR, electrolytes, LFT, FBS, fasting lipid profile</td>
<td>BP, &amp; FBG, lipid profile &amp; bone density if risk factors</td>
</tr>
<tr>
<td>Additional: Hematological &amp; hepatic history</td>
<td>Supplement Folic Acid 3mg daily in childbearing-potential women</td>
</tr>
</tbody>
</table>


### Valproate Monitoring

<table>
<thead>
<tr>
<th>Monitoring Measurement</th>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy status</td>
<td>Pregnancy category D and X (migraine indication). Manifestations of valproic acid teratogenesis have included major and minor congenital abnormalities, intrauterine growth retardation, hyperbilirubinemia, hepatotoxicity, and afibrinogenemia.</td>
</tr>
<tr>
<td>Waist circumference/BMI</td>
<td>While weight loss may be seen initially, weight gain is often a long-term side effect.</td>
</tr>
<tr>
<td>CBC/Hematological history</td>
<td>Abnormalities such as leukopenia, eosinophilia, anemia, <strong>thrombocytopenia</strong>, pancytopenia, aplastic anemia, &amp; agranulocytosis are possible, but rare.</td>
</tr>
<tr>
<td>LFT/Hepatic history</td>
<td>Minor, dose-related elevations in LFTs are common with valporate therapy, but hepatotoxicity and pancreatitis may also occur, and cases have been described with rapid progression from initial symptoms to death. If pancreatitis or hepatic dysfunction has been diagnosed, valporate should be discontinued.</td>
</tr>
<tr>
<td>Menstrual history</td>
<td>Dysmenorrhea, amenorrhea, and metrorrhagia are all possible with valproate use. These may be a sign of PCOS, which is usually seen within the first year of therapy.</td>
</tr>
<tr>
<td>Bone density</td>
<td>There is an incomplete understanding of this process, therefore no agreement on an optimal approach to monitoring.</td>
</tr>
</tbody>
</table>
Carbamazepine

- Extended-release capsule: 100 mg, 200 mg, 300 mg
- Chewable tablet: 100 mg, 200 mg
- Extended-release tablet: 100 mg, 200 mg, 400 mg
- Oral solution: 100 mg/5 mL

- FDA approved (ER tabs): Acute manic or mixed episodes in bipolar disorder

- Daily Dosing: 400 mg–1600 mg in divided doses.
- TDM: use epilepsy range of 4 - 12 μg/mL

Carbamazepine Adverse Effects

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Clinical Presentation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Severe dermatological reactions (e.g., SJS/TENs)</td>
<td>Especially with HLA-B*1502 allele. FDA requires testing before use in patients of Asian ancestry.</td>
</tr>
<tr>
<td></td>
<td>DRESS (Drug Reaction (or Rash) with Eosinophilia and Systemic Symptoms)</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hyponatremia</td>
<td>SIADH</td>
</tr>
<tr>
<td>Fetus (teratogenic)</td>
<td>Neural tube defects from first-trimester exposure</td>
<td>FDA Preg Risk Category D</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, constipation</td>
<td></td>
</tr>
<tr>
<td>Hematological</td>
<td>Agranulocytosis</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>Dizziness, ataxia, drowsiness</td>
<td>Especially rapid dose titration</td>
</tr>
<tr>
<td>Other</td>
<td>Drug interactions (Inducer)</td>
<td>Induces uridine diphosphate glucuronyltransferase (lamotrigine) induces CYP2C9 (autoinduction)</td>
</tr>
</tbody>
</table>

7/31/2017
### Carbamazepine Monitoring

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Longitudinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History:</strong> Comorbidities, smoking status, alcohol use, pregnancy status, family history of CVD</td>
<td>CBC, LFT, BUN, SCr, &amp; electrolytes (esp Na⁺) monthly for the first 3 months, then annually</td>
</tr>
<tr>
<td><strong>Investigations:</strong> Waist circumference, BMI, BP, CBC, BUN, SCr, electrolytes, LFT, FBS, fasting lipid profile</td>
<td>Alert to rash in the first few months</td>
</tr>
<tr>
<td><strong>Additional:</strong> Hematological &amp; hepatic history</td>
<td>Bone density if risk factors</td>
</tr>
<tr>
<td></td>
<td>Review contraceptive efficacy where applicable</td>
</tr>
<tr>
<td></td>
<td>Drug interactions: Hormonal contraceptives</td>
</tr>
</tbody>
</table>


### Carbamazepine Monitoring

<table>
<thead>
<tr>
<th>Monitoring Measurement</th>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy status</td>
<td>Pregnancy category D. Epidemiologic studies have associated it with congenital malformation, including spina bifida, craniofacial defects, &amp; developmental delay.</td>
</tr>
<tr>
<td>Waist circumference/BMI</td>
<td>Weight gain can be seen with carbamazepine, but to a lesser extent than valproate.</td>
</tr>
<tr>
<td>FBC/Hematological history</td>
<td>Leukopenia, thrombocytopenia, leukocytosis, &amp; eosinophilia are possible, but rare, occurring in ~0.004% of patients.</td>
</tr>
<tr>
<td>BUN, SCr, &amp; electrolytes</td>
<td>Hyponatremia can occur (usually within the first three months, although it can occur at any time). Renal failure has also been seen with carbamazepine.</td>
</tr>
<tr>
<td>LFT/Hepatic history</td>
<td>Hepatic effects can range from asymptomatic elevated LFTs to hepatitis (rare).</td>
</tr>
<tr>
<td>Bone density</td>
<td>There’s an incomplete understanding of this process, therefore no agreement on an optimal approach to monitoring.</td>
</tr>
</tbody>
</table>
Lamotrigine

- Tablet: 25 mg, 100 mg, 150 mg, 200 mg
- Chewable tablet: 2 mg, 5 mg, 25 mg
- Orally dissolving tablet (ODT): 25 mg, 50 mg, 100 mg, 200 mg

- FDA Approved: Maintenance treatment of bipolar I disorder to delay time to depressed, manic, hypomanic, or mixed episodes

- Daily Dosing Target: 200 mg (100 mg with valproate; 400 mg with carbamazepine)
- Strict titration schedule to reduce risk of severe rash

Lamotrigine Adverse Effects

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Clinical Presentation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Pruritus, rash (benign to rare—Stevens Johnson syndrome)</td>
<td>SJS risked increased by rapid dose titration</td>
</tr>
<tr>
<td>Fetus (teratogenic)</td>
<td>Small increased risk of cleft palate</td>
<td>FDA Preg Risk Category C</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>diarrhea</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>Headache, dizziness</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Drug interactions</td>
<td>Lamotrigine metabolism: Induced by carbamazepine &amp; phenytoin Inhibited by Valproate</td>
</tr>
</tbody>
</table>
### Mood-Stabilizing Anticonvulsants

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Daily Dosage Range</th>
<th>Acute Mania Therapeutic Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Divalproex</td>
<td>Depakote Depakote ER Depakene</td>
<td>1000 – 3000 mg Once daily or divided doses</td>
<td>80 – 120 mcg/mL</td>
<td>Wt. gain, Tremors, Hyperammonemia, Hepatotoxicity, Pancreatitis, Teratogenicity, PCOS?</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Tegretol Tegretol XR Equetro Carbatrol</td>
<td>400 – 1600 mg Divided doses</td>
<td>8 – 12 mcg/mL</td>
<td>Ataxia, confusion, headache, nausea, hepatotoxicity, neutropenia Teratogenicity</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Lamictal</td>
<td>100 – 300 mg BID Dosing Slow Titratioon</td>
<td>NA</td>
<td>Stevens-Johnsons Syndrome</td>
</tr>
<tr>
<td>Oxcarbazepine (off-label)</td>
<td>Trileptal</td>
<td>1200 – 2400 mg BID Dosing</td>
<td>NA</td>
<td>Drowsiness, Hyponatremia, ataxia</td>
</tr>
</tbody>
</table>

**Mood Stabilizer Warnings**

- **watch your back**
- **out to get you**
Aripiprazole (Abilify)

- Acute episodes of mania or mixed as monotherapy or adjunct to lithium or VPA
- Bipolar maintenance as monotherapy or adjunct to lithium or VPA
- Bipolar Depression: Not FDA approved
- Dosing
  - 15mg – 30mg once daily

Asenapine (Saphris)

- Acute treatment of Bipolar I manic or mixed episodes with or without psychotic features. Monotherapy or adjunct to lithium or VPA.
- Bipolar Depression: Not FDA approved
- Dosing
  - Mania/Mixed- 10mg SL BID
  - Schizophrenia- 5mg SL BID
  - Max-20mg/day
**Clozapine (Clozaril, Fazaclo)**

- Not FDA approved for Bipolar Disorders
- Can be effective anti-manic when other atypical antipsychotics fail
- WBC/ANC monitoring
- Lower seizure threshold
- Initial dosing 25mg – 50mg daily
- Titrate to clinical effect (max daily dose-900mg)

**Lurasidone (Latuda)**

- Bipolar Mania/Mixed: Not FDA approved

- Bipolar Depression: FDA approved for monotherapy and adjunct to lithium or valproate

- Bipolar Depression Dosing
  - 20 mg – 60 mg/day with food (350 calories)
Olanzapine (Zyprexa)

• Acute and maintenance, monotherapy or adjunct to lithium or VPA for acute mania
• Dosing:
  – Initial 10mg - 15mg/day
  – Titrate to 20mg/day (max 40mg/day)
• In combination with fluoxetine (Symbyax®) for bipolar depression
  – Effective dosage range: 6/25 – 18/50

Quetiapine (Seroquel)

• Acute as monotherapy or in maintenance as adjunct with lithium or VPA
• Bipolar Depression as monotherapy
• Mania Dosing (ER)
  – 300 mg PO once daily in the evening on Day 1 followed by 600 mg PO once daily in the evening on Day 2. Beginning on Day 3, the daily dosage may be adjusted to 400—800 mg/day depending upon response and tolerability
  – Mania Dosing (IR)
    • Initially, 50 mg PO twice daily on Day 1. Increase in increments of up to 100 mg/day in two divided doses as tolerated to 400 mg/day on Day 4. If needed, may further titrate up to 800 mg/day by Day 6 in increments of no greater than 200 mg/day.
  – Depression Dosing (ER & IR): maximum 300 mg/day
Risperidone (Risperdal)

- PO: Acute as monotherapy or adjunct to lithium or VPA
- LAI: Maintenance as monotherapy or adjunct to lithium or VPA
- Dosing (PO):
  - Initial 0.5 mg – 1 mg once or twice daily
  - Titrate up to 6 mg/day
- Consider in patients with aggressive and/or psychotic features

Ziprasidone (Geodon)

- Acute as monotherapy or adjunct with lithium or VPA
- Maintenance as adjunct with lithium or VPA
- Bipolar Depression: Not FDA approved
- Dosing
  - 40mg BID with food (350 calories)
  - FDA approved up to 80mg BID with food
  - High dose- 120mg BID with food
Walmart $4 Bipolar Medications

- Lamictal (Lamotrigine)
- Lithium (Lithium Carbonate)
- Walmart Medications
- Wallgreen's